THE JOURNAL

OF THE

AMERICAN CHEMICAL SOCIETY

VOL. LXIV

JULY—DECEMBER

1942

Editor

ARTHUR B. LAMB

Associate Editors

W. E. BACHMANN
FARRINGTON DANIELS
PAUL H. EMMETT
N. HOWELL FURMAN
REYNOLD C. FUSON
HENRY GILMAN
C. S. HUDSON
FREDERICK G. KEYES
EDWARD MACK, JR.
R. H. F. MANSKE
LINUS PAULING
JOHN E. RICCI
LEE IRVIN SMITH
H. B. VICKERY
VINCENT DU VIGNEAUD

EASTON, PA.
MACK PRINTING COMPANY
1942

JOURNAL OF THE
AMERICAN CHEMICAL SOCIETY

VOLUME 64 JULY 6, 1942 NUMBER 7

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

1,2,3,4-Dibenzylidene-D-sorbitol

BY JOHN K. WOLFE, RAYMOND M. HANN AND C. S. HUDSON

In 1890 Meunier[1] reported that two dibenzylidene-D-sorbitols could be obtained by the condensing action of strong mineral acids on a mixture of benzaldehyde and sirupy D-sorbitol. One of these diacetals was a colorless powder (m. p. 162°) which was insoluble even in boiling water; the second one was soluble in boiling water and deposited from the cooled aqueous solution in the form of a gel, which could be dried to a powder melting at 200°. The present communication outlines the experimental procedures necessary to obtain the latter compound in pure condition and describes the reactions which lead to the definitive conclusion that its structure is that of 1,2,3,4-dibenzylidene-D-sorbitol. Under the experimental conditions which were employed, we did not encounter the compound reported as melting at 162°.

Initial efforts to obtain a dibenzylidene-D-sorbitol by condensation of *two* molecular equivalents of benzaldehyde with one equivalent of D-sorbitol through the influence of various concentrations of hydrochloric acid yielded a mixture of tribenzylidene-D-sorbitol and a gel which could not be readily separated into its components. However, when only *one* equivalent of benzaldehyde was employed and the condensing agent was 4 *N* hydrochloric acid, no formation of tribenzylidene-sorbitol was observed and the resulting condensate contained a small amount of the 2,4-monobenzylidene-D-sorbitol described by Vargha,[2] together with a second product which could be converted in high yield (88%) to a crystalline dibenzoyl-dibenzylidene-D-sorbitol. This pure recrystallized dibenzoate, upon debenzoylation in chloroform solution with sodium methylate, yielded a gel which could be dried to a cryptocrystalline powder analyzing correctly for a dibenzylidene-hexitol and showing a melting point of 219–221° (cor.) and a specific rotation $[\alpha]^{20}D$ of +21.6° in pyridine. A second portion of the crude dibenzylidene-D-sorbitol was converted to a crystalline diacetyl-dibenzylidene-D-sorbitol, and the latter compound, upon deacetylation, regenerated dibenzylidene-D-sorbitol agreeing in melting point and rotation with that obtained from the dibenzoate. The diacetal that was obtained from the crystalline diacetate was in turn converted in high yield (95%) to dibenzoyl-dibenzylidene-D-sorbitol which was identical with the dibenzoate previously mentioned. These interconversions leave no doubt that the dibenzylidene-D-sorbitol of m. p. 219–221° is a single chemical entity and not a mixture of isomers. The problem of establishing its structure was first studied through its reaction with lead tetraacetate in glacial acetic acid solution. It was observed that one molecular equivalent of lead tetraacetate was reduced in three hours and that an additional four molecular equivalents were slowly consumed over a period of twelve days; these results suggested that a glycol group was oxidized in the

(1) Meunier, *Ann. chim. phys.*, [6] **22**, 412 (1891).

(2) Vargha, *Ber.*, **68**, 23, 1337 (1935).

initial stage of the reaction and that the primary oxidation products were then slowly attacked by the reagents and further oxidized. A second oxidation was therefore interrupted at the end of four hours, and the oxidation products isolated at once; they proved to be formaldehyde and an aldehydo-dibenzylidene-pentose (isolated as a crystalline methyl hemiacetal). These results limited the structure of the dibenzylidene-D-sorbitol to 1,2,3,4-dibenzylidene-D-sorbitol or 3,4,5,6-dibenzylidene-D-sorbitol. Decision between these two structures depended upon whether the aldehydo-dibenzylidene-pentose was aldehydo-2,3,4,5-dibenzylidene-L-xylose or aldehydo-2,3,4,5-dibenzylidene-D-arabinose. The methyl hemiacetal was therefore subjected to acid hydrolysis; the resulting pentose sugar proved to be L-xylose as shown by its melting point, final rotation and mutarotation rate; the L-xylose was further characterized by conversion to its phenylosazone and phenylosazone triacetate, which were found to be enantiomorphs of the corresponding derivatives of D-xylose. The identity of the pentose with L-xylose is a definite proof that the aldehydo-dibenzylidene-pentose, obtained by oxidation of dibenzylidene-D-sorbitol, is aldehydo-2,3,4,5-dibenzylidene-L-xylose and this fact limits the structure of the dibenzylidene-hexitol to that of 1,2,3,4-dibenzylidene-D-sorbitol. Supporting evidence for this structure was obtained by the observation that dibenzylidene-D-sorbitol, upon reaction with two equivalents of triphenylmethyl chloride under mild conditions, yielded a mono-trityl derivative, a result which indicated that a single primary hydroxyl group was present in the diacetal. Attention has previously[3] been directed to the difficulty of assigning a definitive structural and stereochemical formula to a dibenzylidene-hexitol. Although Vargha[2] has demonstrated that monobenzylidene-D-sorbitol is 2,4-monobenzylidene-D-sorbitol, we have not succeeded in condensing it with further amounts of benzaldehyde to yield the dibenzylidene-D-sorbitol melting at 219–221° (cor.), and it is possible at the present time, therefore, to designate the latter compound only as 1,2,3,4-dibenzylidene-D-sorbitol.

We express our appreciation to Dr. A. T. Ness for performing the microchemical analyses and to Dr. C. P. Saylor, of the National Bureau of Standards, for assistance in the microscopic examination of 1,2,3,4-dibenzylidene-D-sorbitol, which showed the substance to be cryptocrystalline.

(3) Haskins, Hann and Hudson, THIS JOURNAL, **64**, 138 (1942).

Experimental

5,6-Dibenzoyl-1,2,3,4-dibenzylidene-D-sorbitol.—To a solution of 10.0 g. of crystalline D-sorbitol in a mixture of 10 cc. of water and 5 cc. of concentrated hydrochloric acid, 5 cc. of benzaldehyde (1.1 molecular equivalents) was added; the reaction mixture, upon agitation at room temperature, formed a homogeneous solution which set to a gel after one hour. The next day the mass was broken into small pieces, transferred to a Büchner funnel, washed successively with water and ether, and dried; the dry powder was pulverized and leached with 100 cc. of boiling water and the undissolved solid was separated by filtration and dried to constant weight. The yield was 7.1 g. (70% based on the benzaldehyde used). The substance was dissolved in 35 cc. of pyridine and after addition of 15 cc. of benzoyl chloride the mixture was allowed to stand overnight at room temperature; the next day 200 g. of ice was added and the gummy precipitate of dibenzoate which formed, crystallized slowly. The compound deposited from its solution in 10 parts of alcohol in the form of long silky needles, which melted at 195–196° (cor.) and exhibited a specific rotation[4] of −41.5° (*c*, 0.69) in chloroform.

Anal. Calcd. for $C_{34}H_{30}O_8$: C, 72.06; H, 5.34; C_6H_5CO, 37.1. Found: C, 72.14; H, 5.28; C_6H_5CO, 36.4.

1,2,3,4-Dibenzylidene-D-sorbitol.—A solution of 91.0 g. of 5,6-dibenzoyl-1,2,3,4-dibenzylidene-D-sorbitol in 700 cc. of chloroform was cooled in ice and 50 cc. of 0.1 *N* sodium methylate in methanol solution was added. After eighteen hours the gel which had formed was dried *in vacuo* at 65° to remove the chloroform and methyl benzoate, and the residual powder was washed with water and dried. The yield was 57.0 g. (99%). The compound melted at 219–221° (cor.) and showed a specific rotation of +21.6° (*c*, 1.04) in pyridine. The substance was soluble in warm ethyl alcohol, methyl alcohol, acetone, and acetic acid, but the solutions on cooling deposited gels. The homogeneity of the material was demonstrated, however, by repeated solution and recovery from 65 parts of alcohol; the material recovered after three such treatments, agreed in melting point and rotation with the original sample and also with 1,2,3,4-dibenzylidene-D-sorbitol obtained by the deacetylation of the crystalline 5,6-diacetyl-1,2,3,4-dibenzylidene-D-sorbitol that is described in the following paragraph.

Examination of the substance under the petrographic microscope by Dr. C. P. Saylor of the National Bureau of Standards revealed that little or no birefringence was detectable in mounts prepared with aqueous media, presumably because of extensive scattering of light by dust of the compound covering the surface of the crystals. However, mounts in liquids of higher refractive index (methyl phthalate, aniline) allowed observation of the high birefringence characteristic of the compound. Since there were complex changes of optical crystallographic direction within the crystal units, the compound may be designated as cryptocrystalline.

(4) All of the crystalline compounds described in the experimental part were recrystallized to constant melting point and specific rotation, $[\alpha]^{20}D$; *c* is the concentration in grams in 100 cc. of solution; the tube length was 4 dm.

Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.04; H, 6.19. Found: C, 67.08; H, 6.23.

5,6-Diacetyl-1,2,3,4-dibenzylidene-D-sorbitol.— A solution of 2.0 g. of 1,2,3,4-dibenzylidene-D-sorbitol (obtained by debenzoylation of 5,6-dibenzoyl-1,2,3,4-D-sorbitol) in a mixture of 5 cc. of pyridine and 5 cc. of acetic anhydride was heated on the steam-bath for one hour and then cooled and poured upon crushed ice. The yield of 2.35 g. (95%) of diacetate was recrystallized from 15 parts of acetone and it deposited in prisms which melted at 202–205° (cor.) and rotated +4.1° (*c*, 0.95) in chloroform. Upon deacetylation with sodium methylate, 1,2,3,4-dibenzylidene-D-sorbitol, agreeing in rotation and melting point with the compound prepared from the dibenzoate, was obtained in a 93% yield.

Anal. Calcd. for $C_{24}H_{26}O_8$: C, 65.15; H, 5.92; CH_3CO, 19.4. Found: C, 65.25; H, 5.94; CH_3CO, 19.2.

5,6-Dibenzoyl-1,2,3,4-tetraacetyl-D-sorbitol.—A solution of 1.25 g. of 5,6-dibenzoyl-1,2,3,4-dibenzylidene-D-sorbitol in 50 cc. of an acid acetylating solution (prepared by adding 1 cc. of concentrated sulfuric acid dropwise to an ice-cold mixture of 35 cc. of acetic anhydride and 15 cc. of acetic acid) was allowed to stand at 20° for twenty-four hours. The reaction mixture was poured upon crushed ice and the thick sirup which precipitated was washed several times with water and dissolved in warm alcohol. As the solution cooled it deposited 5,6-dibenzoyl-1,2,3,4-tetraacetyl-D-sorbitol (0.95 g., 73%) in the form of prisms. After two recrystallizations from 6 parts of alcohol, the substance melted at 96–97° (cor.) and showed a specific rotation of +14.4° (*c*, 0.48) in chloroform.

Anal. Calcd. for $C_{24}H_{26}O_8$: C, 60.21; H, 5.42; sapn. titer, 10.7 cc. of 0.1 *N* alkali for 100 mg. Found: C, 60.34; H, 5.43; sapn. titer, 10.5 cc. of 0.1 *N* alkali for 100 mg.

5,6-Ditosyl-1,2,3,4-dibenzylidene-D-sorbitol.—Five grams of 1,2,3,4-dibenzylidene-D-sorbitol was dissolved in 15 cc. of absolute pyridine on the steam-bath and the solution was then cooled to 0° to form a gel; to this gel an ice-cold solution of 6.0 g. of *p*-toluenesulfonyl chloride in 10 cc. of pyridine was added and the reaction mixture was agitated vigorously at 0° for three hours and then allowed to stand at 15° for a further eighteen hours. The solution was then poured over crushed ice and the precipitated ditosylate (7.9 g., 84%) was recrystallized from a mixture of 10 parts of alcohol and 4.5 parts of acetone. The compound crystallized in cotton-like needles, which showed a specific rotation of +1.2° (*c*, 0.6) in acetone. The melting point of the compound varied with the rate of heating; when the bath was heated at a rate of 1° in three minutes, it melted at 155–156°, at a rate of 2° in one minute the melting point was 159–160° (cor.). When the tosylation was conducted at a temperature higher than 15°, the mixture of products which was obtained gave a strong Beilstein test for halogen, indicating that some substitution of chlorine had occurred.

Anal. Calcd. for $C_{34}H_{34}O_{10}S_2$: C, 61.24; H, 5.14. Found: C, 61.12; H, 5.29.

6-Trityl-1,2,3,4-dibenzylidene-D-sorbitol.—A solution of 2.0 g. of 1,2,3,4-dibenzylidene-D-sorbitol and 3.4 g. (2.2 molecular equivalents) of triphenylmethyl chloride in 15 cc. of pyridine was allowed to stand at room temperature for seventy-two hours. The mixture was poured into 100 cc. of ice water and the supernatant liquor, which contained crystalline triphenylcarbinol, was decanted from the insoluble gummy trityl derivative. The latter material was suspended in 50 cc. of cold alcohol and in the course of one week it crystallized in a yield of 3.3 g. (96%). This product was recrystallized twice from 10 parts of ethyl acetate and formed elongated prisms which melted slowly over a range of 110–115° (cor.) to a clear oil, then solidified in the form of needles and remelted at 182–183° (cor.). This behavior is exhibited only by material freshly crystallized from ethyl acetate; after drying at 50° overnight, the transition to the needle form is complete and only the higher melting point is observed; apparently the substance is dimorphic. The needles gave a specific rotation of +16.8° (*c*, 0.6) in ethyl acetate.

Anal. Calcd. for $C_{42}H_{38}O_7$: C, 76.61; H, 5.96. Found: C, 76.54; H, 6.01.

5-Acetyl-6-trityl-1,2,3,4-dibenzylidene-D-sorbitol.—This compound was obtained in quantitative yield by the action of acetic anhydride and pyridine on 6-trityl-1,2,3,4-dibenzylidene-D-sorbitol. It deposited from its solution in 80 parts of alcohol in long needles which melted at 117–119° (cor.) to a clear oil, then resolidified in the form of plates and remelted at 186–187° (cor.). The lower melting form showed no change on preservation at room temperature for several months. It exhibited specific rotations of −41.8° (*c*, 0.6) in ethyl acetate and −46.5° (*c*, 0.4) in chloroform.

Anal. Calcd. for $C_{42}H_{38}O_7$: C, 76.61; H, 5.96; CH_3CO, 6.58. Found: C, 76.54; H, 6.01; CH_3CO, 6.25.

Lead Tetraacetate Oxidation of 1,2,3,4-Dibenzylidene-D-sorbitol.—A sample of 0.1198 g. of 1,2,3,4-dibenzylidene-D-sorbitol was dissolved in 20 cc. of glacial acetic acid, and after the addition of 16.22 cc. of 0.0904 *M* lead tetraacetate (2.2 molecular equivalents) in glacial acetic acid, the volume was adjusted to 50 cc. with glacial acetic acid. Analysis of 5-cc. aliquots at the expiration of fifteen and thirty minutes, one, three and nineteen hours showed that 0.43, 0.63, 0.79, 0.97 and 1.15 molecular equivalents of oxidant had been consumed. In a second experiment, 5.5 molecular equivalents of lead tetraacetate were added and it was observed that 1.0 equivalent was reduced in a period of three hours and a further 4.0 equivalents was reduced very slowly over a period of twelve days. The rapid reaction was due to the oxidation of the glycol grouping at carbons five and six (see the following section) and the slower one occurred presumably as a result of a slow hydrolysis of the benzylidene groups and subsequent oxidation of the hydrolysis products. The final consumption of lead tetraacetate (5.0 molecular equivalents) agreed with that expected for such a series of reactions.

Isolation of Aldehydo-2,3,4,5-dibenzylidene-L-xylose Methyl Hemiacetal.—A suspension of 21.5 g. of 1,2,3,4-dibenzylidene-D-sorbitol and 40 g. of pulverized lead tetraacetate (1.1 molecular equivalents) in 400 cc. of glacial acetic acid was agitated vigorously for four hours with occasional cooling to maintain the temperature below 25°; the amorphous reaction product was separated by filtration, pulverized and dried over potassium hydroxide until free of acetic acid. The product (21.2 g.), which was

sufficiently pure for synthetic operations, was dissolved in a warm mixture of 100 cc. of methyl alcohol and 100 cc. of chloroform and as the solution cooled it deposited the methyl hemiacetal of aldehydo-2,3,4,5-dibenzylidene-L-xylose in the form of needles. The compound, after recrystallization to constant rotation from 80 parts of a 1:1 mixture of methyl alcohol and chloroform, melted at 187–188° (cor.) and exhibited a rotation of +40.4° (*c*, 0.46) in pyridine. The yield of hemiacetal was 15.0 g. (70%).

Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19; OCH_3, 8.65. Found: C, 67.05; H, 6.38; OCH_3, 8.38.

Identification of Formaldehyde as an Oxidation Product.—The acetic acid filtrate from the oxidation mixture was refluxed while a gentle current of carbon dioxide was passed through it; the gas was led through an efficient condenser and into 100 cc. of ice-cold water. At the end of six hours, an aliquot of the aqueous solution was tested with dimethyl-dihydroresorcinol; the characteristic formaldimethone which formed, melted at 189–190° (cor.) and no depression of the melting point was observed upon admixture with authentic formaldimethone.

Aldehydo-2,3,4,5-dibenzylidene-L-xylose.—A sample of the methyl hemiacetal of aldehydo-2,3,4,5-dibenzylidene-L-xylose was sublimed in a vacuum at 140–145° and the sublimate, which was partially crystalline, was recrystallized from 5 parts of dioxane. The compound was obtained in the form of small needles which melted at 186–187° (cor.) and showed a rotation of −33.4° (*c*, 0.52) in pyridine.

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.84; H, 5.66.

Aldehydo-2,3,4,5-dibenzylidene-L-xylose Oxime.—A suspension of 1.0 g. of aldehydo-2,3,4,5-dibenzylidene-L-xylose in a solution containing 25 cc. of methanol, 5 cc. of water, 1.0 g. of hydroxylamine hydrochloride and 1.0 g. of fused sodium acetate was refluxed for twenty minutes, during which period complete solution occurred; the crystalline product, which deposited as the solution cooled, was recrystallized from 240 parts of alcohol and yielded 0.9 g. (86%) of oxime in the form of colorless needles which melted with decomposition at 239–240° (cor.) and gave a rotation of −108.9° (*c*, 0.41) in pyridine.

Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.86; H, 5.57; N, 4.28.

L-Xylose from Aldehydo-2,3,4,5-dibenzylidene-L-xylose Methyl Hemiacetal.—A suspension of 10.6 g. of 1,2,3,4-dibenzylidene-L-xylose methyl hemiacetal in a mixture of 280 cc. of methyl alcohol, 15 cc. of water and 3 cc. of concentrated hydrochloric acid was refluxed for one hour, during which time complete solution occurred and a strong odor of benzaldehyde developed. The solution, following the removal of the hydrochloric acid by silver carbonate in the usual manner, was concentrated *in vacuo* to a sirup, presumably a mixture of α- and β-methyl-L-xylosides. The sirup, which resisted crystallization, was dissolved in 100 cc. of 1% sulfuric acid and hydrolyzed for two hours on the steam-bath. The acid was neutralized with barium hydroxide and the neutral solution concentrated *in vacuo* to a sirup, which deposited crystalline L-xylose upon treatment with 3 cc. of glacial acetic acid. The yield was 1.7 g. (40%). The pentose melted at 143–145° (cor.) and gave an extrapolated initial rotation of −92° and an equilibrium value of −19.4° (*c*, 0.88) in aqueous solution. Its mutarotation rate at 20° was 20.2 × 10^{-3}, which agrees with the known rate for D-xylose. Vargha[2] records a melting point of 144° and initial and equilibrium rotations of −79.3° and −18.6°, respectively, for the L-xylose which he prepared by the lead tetraacetate oxidation of 2,4-benzylidene-D-sorbitol. Isbell[5] reports an initial rotation of +94.8° and an equilibrium rotation of +18.3° for a 4.4% aqueous solution of D-xylose.

Anal. Calcd. for $C_5H_{10}O_5$: C, 40.00; H, 6.71. Found: C, 39.86; H, 6.57.

D,L-Xylose.—A mixture of 100 mg. each of D-xylose and L-xylose was dissolved in 2 cc. of warm methanol and diluted with 5 cc. of glacial acetic acid. The D,L-xylose (110 mg., 55%) obtained was optically inactive in aqueous solution and melted at 128–130° (cor.) in good agreement with the value of 129–131° recorded by Fischer[6] for D,L-xylose.

Racemic Xylose Phenylosazone.—A mixture of 0.5 g. of L-xylose, 1.5 cc. of phenylhydrazine, 1.0 cc. of acetic acid and 5 cc. of water was heated on the steam-bath for one hour. The L-xylose phenylosazone (yield, 0.8 g.; 74%) was recrystallized from aqueous acetone and obtained as fine yellow needles melting at 161–163° (cor.). Reichstein, Grüssner and Oppenauer[7] reported a melting point of 160–162° (cor.) for D-xylose phenylosazone. A mixture of 100 mg. each of D- and L-xylose phenylosazones was dissolved in 10 cc. of warm acetone; the precipitate (171 mg.; 85%), which formed on cooling the solution, was recrystallized from 10 cc. of acetone and obtained as fine needles which decomposed at 207° (cor.) and were devoid of optical activity in pyridine solution. These properties are in substantial agreement with those reported by Fischer[6] for the racemic xylose phenylosazone which he obtained from D,L-xylose and also from the oxidation of xylitol.

Anal. Calcd. for $C_{17}H_{20}O_3N_2$: C, 62.18; H, 6.14. Found: C, 62.30; H, 6.13.

L-Xylose Phenylosazone Triacetate.—This compound was obtained in a yield of 0.672 g. (97%) by acetylation of L-xylose phenylosazone (0.5 g.) in a mixture of 3 cc. of pyridine and 2 cc. of acetic anhydride. The substance was recrystallized by solution in 12 parts of alcohol and the gradual addition of 8 parts of water. It was obtained in fine yellow needles which melted at 116–117° (cor.) and rotated +44.3° (*c*, 0.34) in chloroform. Percival and Percival[8] reported a melting point of 116–117° and a specific rotation $[\alpha]^{16}D$ of −46° for the D-form. We find a melting point of 116–117° (cor.) and a specific rotation $[\alpha]^{20}D$ of −44.2° (*c*, 0.47) for D-xylose phenylosazone triacetate.

Racemic Xylose Phenylosazone Triacetate.—A mixture of 100 mg. each of the D- and L-forms of xylose phenylosazone triacetate was dissolved in 2 cc. of warm alcohol; upon addition of 1 cc. of water the racemate deposited from the solution in the form of fine yellow needles. The yield was 165 mg. (82%). The recrystallized compound was

(5) Isbell, *J. Research Natl. Bur. Standards*, **13**, 515 (1934).

(6) Fischer, *Ber.*, **27**, 2488 (1894).

(7) Reichstein, Grüssner and Oppenauer, *Helv. Chim. Acta*, **16**, 1024 (1933).

(8) Percival and Percival, *J. Chem. Soc.*, 1320 (1937).

devoid of optical activity in chloroform solution; it melted at 131–132° (cor.), which is much higher than the melting point of its components, from which fact it is evident that the crystalline substance is a true racemate.

Summary

D-Sorbitol, in solution with 4 *N* hydrochloric acid and *one* molecular equivalent of benzaldehyde, condenses to yield principally a cryptocrystalline dibenzylidene-D-sorbitol melting at 219–221°. The latter substance, upon oxidation with lead tetraacetate in glacial acetic acid, produces formaldehyde and aldehydo-2,3,4,5-dibenzylidene-L-xylose, which is conveniently isolated as a crystalline methyl hemiacetal. This hemiacetal is converted by acid hydrolysis to L-xylose, which was isolated as the crystalline sugar and further characterized by preparation of L-xylose phenylosazone; the latter compound combines with D-xylose phenylosazone to yield the long known racemic xylose phenylosazone. Also, L-xylose phenylosazone triacetate forms a true racemate with D-xylose phenylosazone triacetate.

The work constitutes a definitive proof that the structure of dibenzylidene-D-sorbitol is that of 1,2,3,4-dibenzylidene-D-sorbitol.

BETHESDA, MD. RECEIVED APRIL 10, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF MISSOURI]

The Action of Alkali on Cyclohexenecarbonals[1]

BY H. E. FRENCH AND D. M. GALLAGHER

Although the cyclohexenecarbonals possess alpha hydrogens, one might reasonably expect reactions like those of the aromatic series toward alkaline reagents, because of the steric effect of the large radical attached to the alpha carbon. In order to test this supposition, we have investigated the reactions with several 3-cyclohexenecarbonals, particularly the 3,4,6-trimethyl derivative. Concentrated aqueous solutions of sodium or potassium hydroxide acted on this aldehyde forming a tripolymer. Similar tripolymers of cyclohexanecarbonal and of 3-cyclohexenecarbonal had previously been prepared by the action of mineral acids.[2] Saturated aqueous solutions of barium hydroxide gave very small yields of the polymer, most of the aldehyde being recovered. A cold 10% solution of potassium hydroxide in methyl alcohol was also without action on the aldehyde. At 70°, using a methyl alcohol–water solution, reaction took place with the formation of the corresponding acid and the alcohol. The acid had previously been prepared from ethyl crotonate and 2,3-dimethylbutadiene.[3] The structure of the alcohol was shown by its synthesis from the aldehyde using aluminum *iso*propoxide, and by carbon and hydrogen analyses of the naphthyl urethan.

Under similar conditions, 3,4-dimethyl-6-phenyl-3-cyclohexenecarbonal, 6-methyl-3-cyclohexenecarbonal, and 3-cyclohexenecarbonal were found to give the Cannizzaro reaction. In all cases the acids formed were known compounds[4] but the alcohols had not previously been reported. These were identified by their syntheses from the aldehydes using aluminum isopropoxide, and analyses of their phenyl or naphthyl urethans. Yields of the pure acids were of the order of 80%. Varying amounts of polymerization products were obtained if the temperature of reaction was much in excess of 70°.

Freshly distilled 6-methyl-3-cyclohexenecarbonal gave but a trace of reaction in the usual reaction time, while aldehyde used after long standing, or through which air had been bubbled, readily entered into the reaction. This is in accord with the observation that peroxide is a catalyst for the Cannizzaro reaction.[5]

Each of the aldehydes was dissolved in aqueous methyl alcohol and heated to approximately 70° with potassium hydroxide and formalin solution. Diols, in yields of from 50 to 60% of the pure redistilled or recrystallized compounds, were obtained in all cases. The formation of these compounds presumably follows the course indicated by the equation

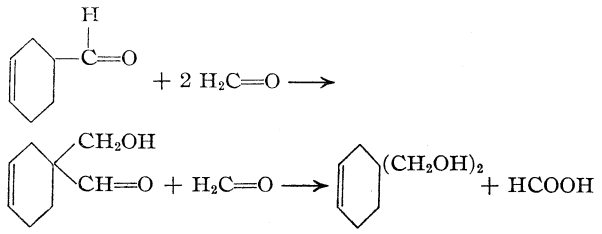
(1) This work is part of the thesis material to be submitted by Mr. Gallagher to the graduate faculty of the University of Missouri.

(2) Wallach, *Ann.*, **347**, 336 (1906); Zelinsky and Gutt, *Ber.*, **40**, 3051 (1907); Chayanov, *J. Gen. Chem.* (U. S. S. R.), **8**, 460 (1938).

(3) Farmer and Pitkethly, *J. Chem. Soc.*, 11 (1938).

(4) Fujisi, Horiuchi, and Takahashi, *Ber.*, **69**, 2102 (1936); Chayanov and Grishiu, *Colloid J.* (U. S. S. R.), **3**, 461 (1937); Perkin, *J. Chem. Soc.*, **85**, 416 (1904).

(5) Kharasch and Foy, THIS JOURNAL, **57**, 1510 (1935).



The molecular weight of 3,4,6-trimethyl-3-cyclohexene-1,1-dicarbonol in camphor and in dioxane was found to be 184 and 183.5, respectively, and in the Grignard machine was found to possess two active hydrogens. Each of the diols combined with two molecules of phenyl isocyanate to yield crystalline urethans. The ring unsaturation of the 3-cyclohexene-1,1-dicarbonol was reduced, and on oxidation the known cyclohexane-1,1-dioic acid was obtained.[6]

Experimental

The cyclohexenecarbonals were prepared by the Diels–Alder condensation, and their properties corresponded to those given in the literature for the pure compounds.

3,4,6-Trimethyl-3-cyclohexenecarbonal with Alkali.—Twelve and one-half grams of the aldehyde was allowed to stand for twenty-four hours at room temperature with a solution of 20 g. of potassium hydroxide in 12.5 cc. of water. An insoluble oil was then separated from the aqueous layer and washed with water. In the course of a month this oily material partly solidified. The pasty mass was filtered with suction and was washed with ethyl alcohol. The white solid thus obtained was found to be soluble in benzene and in acetone, and insoluble in ethyl alcohol and in ether; white, powdery material from acetone; m. p. 132–134°; molecular weight in benzene, 482; molecular weight of the original aldehyde, 152; yield of polymer, 2 g.

A solution containing 20 g. of the aldehyde in 20 cc. of ether was shaken for forty-eight hours at room temperature with 20 cc. of a saturated solution of barium hydroxide in water. Practically all of the aldehyde was recovered from the ether solution as the bisulfite compound, together with a trace of an oily material, presumably a polymer of the aldehyde.

A solution of 10 g. of the aldehyde in 20 cc. of methyl alcohol was shaken for three days at room temperature with 10 cc. of a 10% solution of potassium hydroxide in methyl alcohol. Eight and a half grams of the aldehyde was recovered.

The Cannizzaro Reaction.—The following procedure is typical for the Cannizzaro reactions using the various aldehydes. A solution of 9 g. of potassium hydroxide in 5.5 cc. of water was added rapidly to 8.5 g. of the aldehyde in 11 cc. of methyl alcohol, with mechanical stirring at 65–75° for two hours. At temperatures much in excess of 75°, considerable polymerization occurred. Addition of an equal volume of water caused the separation of a second layer, which was extracted with ether. After drying, the ether and methyl alcohol were removed on the water-bath. Vacuum distillation of the residue gave the carbinols as colorless liquids which readily formed urethans with α naphthyl isocyanate. In each case the identity of the carbinol was demonstrated by its synthesis from the aldehyde with aluminum isopropoxide and a comparison of the urethans. The acids were obtained from the alkaline solutions remaining after the ether extraction, in yields which were generally of the order of 78%. Melting points of the acids were found to correspond to those given in the literature for those compounds.

3,4-Dimethyl-6-phenyl-3-cyclohexenecarbonol.—Naphthyl urethan; white crystals from petroleum ether; m. p. 110–111°.

Anal. Calcd. for $C_{26}H_{27}O_2N$: C, 81.03; H, 7.01. Found: C, 80.84; H, 7.32.

6-Methyl-3-cyclohexenecarbonol.—Phenyl urethan; white crystals; m. p. 83°. *Anal.* Calcd. for $C_{15}H_{19}O_2N$: N, 5.71. Found: N, 5.86.

3-Cyclohexenecarbonol.—Naphthyl urethan; white crystals from petroleum ether; m. p. 106°.

Anal. Calcd. for $C_{18}H_{19}O_2N$: C, 76.86; H, 6.76. Found: C, 76.92; H, 6.94.

3,4,6-Trimethyl-3-cyclohexenecarbonol.—Naphthyl urethan; white crystals from petroleum ether; m. p. 112°.

Anal. Calcd. for $C_{21}H_{25}O_2N$: C, 78.01; H, 7.74. Found: C, 78.35; H, 8.05.

The Cross Cannizzaro Reaction.—The following represents a typical reaction for these aldehydes. A mixture of 8 g. of the aldehyde, 10 cc. of methyl alcohol, and 5 cc. of formalin in a 3-neck flask equipped with dropping funnel, motor stirrer, and reflux condenser was heated to 70°, and maintained at that temperature while a solution of 8.4 g. of potassium hydroxide in 6 cc. of water was added. The mixture was heated at 70° for forty minutes, then refluxed for one hour. The reaction mixture was cooled, diluted with an equal volume of water, and extracted with ether. From this ether solution the diol was obtained. The unsubstituted and the monomethyl substituted compounds were obtained as oils which solidified after vacuum distillation and standing for several hours in an ice chest. The others were obtained as crystalline compounds, and were recrystallized from petroleum ether. The diols were obtained in yields of 50–60% of the pure compounds. In each case the diol combined with two molecules of phenyl isocyanate, yielding crystalline urethans which were recrystallized from dilute alcohol.

3,4,6-Trimethyl-3-cyclohexene-1,1-dicarbonol.—White crystals; m. p. 86.5°; molecular weight in camphor, 184; in dioxane, 183.5; calcd. for $C_{11}H_{20}O_2$, 184; active hydrogens, 1.91; urethan, m. p. 121.5–123°.

Anal. Calcd. for $C_{25}H_{30}O_4N_2$: C, 71.09; H, 7.10. Found: C, 71.01; H, 7.34.

3,4-Dimethyl-6-phenyl-3-cyclohexene-1,1-dicarbonol.—White crystals; m. p. 131.5°; phenyl urethan, m. p. 166°.

Anal. Calcd. for $C_{30}H_{32}O_4N_2$: C, 74.36; H, 6.61. Found: C, 74.22; H, 6.85.

6-Methyl-3-cyclohexene-1,1-dicarbonol.—White crystals; m. p. 45°; phenyl urethan, m. p. 150°.

Anal. Calcd. for $C_{23}H_{26}O_4N_2$: C, 70.05; H, 6.59; N, 7.10. Found: C, 70.28; H, 6.53; N, 7.06.

(6) Wightman, *J. Chem. Soc.*, 2541 (1926).

3-Cyclohexene-1,1-dicarbonol.—White crystals; m. p. 92.5°; phenyl urethan, m. p. 118.5°.

Anal. Calcd. for $C_{22}H_{24}O_4N_2$: C, 69.45; H, 6.36. Found: C, 69.29; H, 6.57. Active hydrogens in the diol, 1.81.

Hydrogenation of 3,4,6-Trimethyl-3-cyclohexene-1,1-dicarbonol.—The compound was reduced at 2500 lb. pressure at 150°, using Raney nickel, to the known cyclohexane-1,1-dicarbonol, m. p. 95–96°.[7]

Oxidation of Cyclohexane-1,1-dicarbonol.—Oxidation with potassium permanganate in neutral and in alkaline solutions, using water and water–acetone solvents, gave only uncrystallizable oils. Nitric acid oxidation gave a small yield of a solid acid which was not identified.

1.7 g. of the diol was dissolved in 10 cc. of pyridine. A solution of 5.5 g. of potassium permanganate in 110 cc. of water was added with stirring, at a temperature of 0°. The mixture was stirred for eight hours at that temperature and allowed to warm slowly to room temperature. The excess permanganate was discharged with 1 cc. of ethyl alcohol. After filtering, the solution was concentrated on a water-bath to 10 cc. using vacuum. Hydrochloric acid was added and the solution placed in the ice chest. A yield of 0.8 g. of the known cyclohexane-1,1-dioic acid was obtained.

(7) Franke and Sigmund, *Monatsh.*, **46**, 61 (1925).

Summary

1. The action of alkaline solutions on certain cyclohexenecarbonals has been studied.

2. These aldehydes were found to undergo the Cannizzaro reaction, and to react with formaldehyde to yield cyclohexene-1,1-dicarbonols.

COLUMBIA, MISSOURI RECEIVED MARCH 30, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Sulfanilamido Derivatives of Nitrogen Bases from California Petroleum[1]

BY LESLIE M. SCHENCK[2] AND HENRY R. HENZE

Bobranski[3] and Winterbottom[4] have reported syntheses in the sulfanilamidoquinoline series; however, no alkylation in the quinoline nucleus higher than methyl was included. Since detailed pharmacological tests of their compounds have not been published, it was considered of interest to prepare sulfanilamido derivatives of a series of alkylated quinoline homologs encountered in nitrogen bases extracted from California petroleum. Since quinolines substituted in positions 2, 3 and 8 occur in appreciable quantity among the complex petroleum base fractions, this series was selected for investigation. The compounds prepared in this work are sulfanilamido and acetylated sulfanilamido derivatives of 5-amino-2,3,8-trimethylquinoline, and of the hitherto unreported 5-amino-8-ethyl-2,3-dimethylquinoline and 5-amino-2,3-dimethyl-8-*n*-propylquinoline.

Through the courtesy and coöperation of Parke, Davis and Company, the 2,3,8-trimethyl and 2,3-dimethyl-8-*n*-propylquinoline sulfanilamido derivatives have received preliminary testing for possible pharmacological activity. No activity was found in mice infected with experimental Type I pneumococcus, *Staph. aureus* or *Strep. viridans*. The slight activity toward hemolytic streptococci indicates that the activity of sulfanilamide is lowered by substitution of the quinoline heterocycle at the N^1 position. Certainly the compounds here reported do not have the desirable properties obtained with other heterocycles such as pyridine, thiazole and pyrimidine.

Two of the new compounds reported herein have received preliminary testing for antimalarial activity (through the courtesy of Parke, Davis and Company). It is of interest to note the activity against avian malaria of 5-sulfanilamido-2,3,8-trimethylquinoline in the *blood*, whereas larger doses of this material are inactive in the tissue.

	Stage tested	Dose, mg.	Result
5-Sulfanilamido-2,3,8-trimethylquinoline	Blood	50	Active
	Tissue	100	Inactive
5-(N^4-Acetylsulfanilamido)-2,3-dimethyl-8-*n*-propylquinoline	Blood	50	Inactive

Experimental

2,3,8-Trimethyl-5-nitroquinoline.—Fourteen grams of 2,3,8-trimethylquinoline,[5] isolated from petroleum nitrogen bases, was converted to 2,3,8-trimethyl-5-nitroquinoline in accordance with Burger and Modlin.[6] There was obtained 13 g. of purified product, crystallizing from petroleum ether as pale yellow needles melting at 124° (cor.).

(1) Constructed from a portion of a thesis presented to the Graduate Faculty of the University of Texas by Leslie M. Schenck in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1942.

(2) Parke, Davis Fellow, 1941–1942; present address, General Aniline and Film Corporation, Grasselli, N. J.

(3) Bobranski, *Arch. Pharm.*, **277**, 75 (1939).

(4) Winterbottom, THIS JOURNAL, **62**, 160 (1940).

(5) Poth, Schultze, King, Thompson, Slagle, Floyd and Bailey, *ibid.*, **52**, 1239 (1930).

(6) Burger and Modlin, *ibid.*, **62**, 1079 (1940).

2,3,8-Trimethyl-5-aminoquinoline.—Burger and Modlin[6] report the preparation of this compound by reduction of the corresponding nitro derivative with stannous chloride and 17% hydrochloric acid. When their method was tried upon larger quantities of 2,3,8-trimethyl-5-nitroquinoline, the isolation was found unsatisfactory, and it was necessary to steam distil the amine from the reduction mixture and to recover it from the large volume of distillate by ether extraction.

As an alternate method, promising less difficulties in isolation and purification of the desired intermediate, 12.5 g. of 2,3,8-trimethyl-5-nitroquinoline (0.058 mole) was hydrogenated over Raney nickel catalyst at 70° and 1000 lb./sq. in. pressure for thirty minutes, employing ethyl alcohol as the solvent. The catalyst was removed by filtration, the solvent diluted with water and the precipitated amine crystallized from dilute ethyl alcohol to give a quantitative yield of 2,3,8-trimethyl-5-aminoquinoline melting at 110–111° (cor.) identical with that prepared by the more laborious method of Burger and Modlin.

5-(N_4-Acetylsulfanilamido)-2,3,8-trimethylquinoline.—The amine (0.059 mole) was dissolved in 100 cc. of pyridine which had been dried by prolonged contact with potassium hydroxide pellets. To the solution was added 18 g. (0.077 mole) of acetylsulfanilyl chloride which had been purified by crystallization from acetone–benzene and thoroughly dried through vacuum desiccation over calcium chloride. Heat was immediately developed, and the solution was agitated until all the acid chloride was in solution. At this point, the reaction mixture was heated three hours on the steam-bath, a calcium chloride tube being employed to protect against atmospheric moisture.

The crude 5-(N^4-acetylsulfanilamido)-2,3,8-trimethylquinoline was precipitated by pouring its pyridine solution into 500 cc. of ice water. Separating first as a highly discolored oil, the product soon solidified and was removed by filtration. One-half the product was purified by repeated treatment with Norite in boiling ethyl alcohol. The purified compound, prepared in 47% yield, crystallized from this solvent as hair-like needles melting undecomposed at 260.5–261.5° (cor.).

Anal. Calcd. for $C_{20}H_{21}N_3O_3S$: N, 10.95. Found: N, 10.78.

5-Sulfanilamido-2,3,8-trimethylquinoline.—One-half of the crude 5-(N^4-acetylsulfanilamido)-2,3,8-trimethylquinoline described above was dissolved in 100 cc. of 4 *N* hydrochloric acid and hydrolyzed by refluxing thirty minutes. After cooling, the acid solution was neutralized with ammonium hydroxide and the product removed by filtration. Purification was effected by three crystallizations from ethyl alcohol, Norite being employed during the initial process. The final product, realized in 58% yield, was in the form of fine colorless needles melting without decomposition at 225.5–226° (cor.).

Anal. Calcd. for $C_{18}H_{19}N_3O_2S$: N, 12.31. Found: N, 12.26.

8-Ethyl-2,3-dimethyl-5-nitroquinoline.—Six grams of 8-ethyl-2,3-dimethylquinoline[7] (0.032 mole) was added slowly to 60 cc. of fuming nitric acid (sp. gr. 1.49) and heated on the steam-bath for five hours. Upon neutralization of the diluted acid with sodium carbonate, the nitrated base was recovered by filtration and crystallized in 83% yield from ethyl alcohol as fine needles melting undecomposed at 107–109° (cor.).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13. Found: C, 67.88; H, 6.37.

5-Amino-8-ethyl-2,3-dimethylquinoline.—Six grams of the nitro compound was hydrogenated under the identical conditions used in the reduction of the trimethyl analog to yield 5 g. (94%) of amine which crystallized from ligroin as irregular shaped needles melting at 101–102° (cor.).

Anal. Calcd. for $C_{13}H_{16}N_2$: N, 13.99. Found: N, 13.97.

5-(N^4-Acetylsulfanilamido)-8-ethyl-2,3-dimethylquinoline.—In the manner previously described, 5 g. of 5-amino-8-ethyl-2,3-dimethylquinoline was dissolved in 50 cc. of dry pyridine and heated with acetylsulfanilyl chloride for three hours on the steam-bath. The product was recovered from the pyridine by dilution with water, and crystallized only after prolonged standing. The crude material was divided into two equal portions, one of which was purified. Unlike its 2,3,8-lower homolog, 5-(N^4-acetylsulfanilamido)-8-ethyl-2,3-dimethylquinoline is extremely soluble in alcohol. Since no suitable solvent for recrystallization was found, purification was achieved by repeatedly dissolving the discolored compound in boiling ethyl alcohol, treating with Norite, and precipitating the colorless acetyl derivative by addition of water. Only 1 g. (20%) of pure material, melting at 244–245° (cor.), was obtained.

Anal. Calcd. for $C_{21}H_{23}N_3O_3S$: N, 10.57; S, 8.07. Found: N, 10.74; S, 8.20.

5-Sulfanilamido-8-ethyl-2,3-dimethylquinoline.—The second portion of the crude product referred to above was hydrolyzed as in the previous case by thirty minutes of refluxing with 60 cc. of 6 *N* hydrochloric acid. The product, precipitated by the addition of ammonium hydroxide, was purified to the constant melting point of 241–242° (cor.) by recrystallization from ethyl alcohol, from which solvent it crystallizes in fine needles.

Anal. Calcd. for $C_{19}H_{21}N_3O_2S$: N, 11.83. Found: N, 11.81.

2,3-Dimethyl-5-nitro-8-*n*-propylquinoline.—Fifteen grams (0.075 mole) of 2,3-dimethyl-8-*n*-propylquinoline[8] was nitrated by heating at steam-bath temperature with 150 cc. of nitric acid (sp. gr. 1.49) for three hours. The nitro derivative, precipitated by neutralizing the diluted solution with sodium carbonate, was recrystallized from petroleum ether in 93% yield. A small sample was further purified to a constant melting point of 97–99° (cor.).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: N, 11.47. Found: N, 11.51.

5-Amino-2,3-dimethyl-8-*n*-propylquinoline.—Reduction was realized in 95% yield by hydrogenating the nitro compound (17 g.) over Raney nickel at 70–100° and 1000 lb./sq. in. pressure. Following crystallization from petroleum ether, the amine melted at 90–92° (cor.).

Anal. Calcd. for $C_{14}H_{18}N_2$: N, 13.08. Found: N, 13.15.

(7) Key and Bailey, THIS JOURNAL, **60**, 3028 (1938).

(8) Axe and Bailey, *ibid.*, **60**, 3028 (1938).

5-(N^4-Acetylsulfanilamido)-2,3-dimethyl-8-*n*-propylquinoline.—Fourteen grams of 5-amino-2,3-dimethyl-8-*n*-propylquinoline (0.065 mole) reacted with 22 g. of acetylsulfanilyl chloride (0.094 mole) in 140 cc. of dry pyridine for three hours. The product, recovered by dilution with water, separated as an oil which did not crystallize upon standing. The aqueous layer was decanted, and the tarry product divided into two fractions of approximate equality. By repeatedly dissolving one portion of the oil in ethyl alcohol, refluxing with Norite, and precipitating the product with water, the acetyl derivative was obtained (in 15% yield) and melted at 208–209° (cor.).

Anal. Calcd. for $C_{22}H_{25}N_3O_3S$: N, 10.21. Found: N, 10.26.

5-Sulfanilamido-2,3-dimethyl-8-*n*-propylquinoline.—The residual oil referred to above was refluxed for one hour with 150 cc. of 4 *N* hydrochloric acid. Following neutralization with ammonium hydroxide, the hydrolysis product was filtered and crystallized from ethyl alcohol with the aid of Norite as fine needles in 70% yield; melting point 237–238° (cor.).

Anal. Calcd. for $C_{20}H_{23}N_3O_2S$: N, 11.38; S, 8.66. Found: N, 11.46; S, 8.48.

Summary

The preparation of a series of sulfanilamido derivatives of nitrogen bases from California petroleum has been described. Preliminary pharmacological tests of these 2,3,8-trialkyl-5-sulfanilamidoquinolines show them to be practically inactive as sulfa drugs, indicating that such substitution of the quinoline nucleus for hydrogen of the amide group reduces the therapeutic effectiveness of sulfanilamide. One of the compounds exhibits some activity against avian malaria at the blood stage.

AUSTIN, TEXAS RECEIVED MARCH 23, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE STATE UNIVERSITY OF IOWA]

Azoyl Derivatives of Sugars and Separation by Chromatographic Adsorption[1]

BY GEORGE H. COLEMAN, ALFORD G. FARNHAM AND AARON MILLER

Reich[2] has reported the chromatographic separation of the *p*-phenylazobenzoyl esters of α-D-glucose and β-D-fructose on both alumina and silica as adsorbents.

The present work was undertaken to determine the applicability of the chromatographic adsorption method to similar derivatives of other sugars with the thought of applying the procedure to mixtures such as "hydrol."

p-Phenylazobenzoyl derivatives were prepared from the following sugars by the method described in the experimental part: α-D-glucose, β-D-glucose β-D-fructose, α-D-galactose, α-lactose, trehalose, sucrose, β-cellobiose, β-gentiobiose, β-maltose, D-xylose and melezitose. The compounds were analyzed for percentage azoyl and the specific rotations were measured in chloroform solution using both sodium and cadmium vapor lamps.

Several pairs of the sugar esters were separated by the chromatographic adsorption method. The following pairs of azoates were separated using Magnesol[3] as adsorbent with Dicalite as a filter aid: α-lactose and α-D-galactose, trehalose and β-D-glucose, α-lactose and sucrose, α-D-glucose and β-D-fructose, β-maltose and α-D-glucose, sucrose and α-D-glucose. On silicic acid[4] as adsorbent α-D-glucose and β-D-fructose, α-D-galactose and β-D-fructose, sucrose and β-D-fructose, α-D-glucose and melezitose were separated. Several other pairs of derivatives did not give satisfactory separation under the conditions employed.

Experimental

Preparation of Azoyl Derivatives.—The *p*-phenylazobenzoyl or "azoyl" derivatives were prepared by allowing the sugars to react in pyridine solution at 0° with *p*-phenylazobenzoyl chloride over a period of eight to twenty days. The mole ratio of azoyl chloride to sugar was about eight to one for monosaccharides and twelve to one for disaccharides. At the end of this time the excess acid chloride was decomposed by adding methanol. The products were precipitated by pouring the reaction mixture into water. The precipitate, after drying, was purified by dissolving in chloroform and reprecipitating by pouring into alcohol. The monosaccharide derivatives were recrystallized, the glucose derivatives from dioxane and the galactose and fructose derivatives from mixtures of chloroform and carbon tetrachloride. The disaccharide esters were purified by several reprecipitations.

Specific Rotations.—The specific rotations were measured at 25° in chloroform solution at a concentration of 0.5 g. per 100 ml. of solvent using a water-jacketed 2-decimeter tube. Two light sources were used, the sodium and cadmium vapor lamps, giving, respectively, the readings for the sodium D line and the cadmium 6438 Å. line.

(1) Presented at the meeting of the American Chemical Society, St. Louis, Missouri, April, 1941.

(2) Reich, *Compt. rend.*, **208**, 589, 748 (1939); *Biochem. J.*, **33**, 1000 (1939).

(3) "Magnesol" is a hydrous magnesium silicate manufactured by the Magnesol Co.

(4) Merck Reagent Silicic Acid.

The cadmium lamp gave more satisfactory readings, especially at higher concentrations. Physical constants are listed in Table I.

TABLE I

SPECIFIC DATA ON AZOYL DERIVATIVES

Sugar azoate	M. p., °C.[a]	$[\alpha]^{25}D$	$[\alpha]^{25}_{6438}$	% Azoyl
α-D-Glucose	234–236	+282°	+226°	85.14
β-D-Glucose	204–206	+111	+ 86	86.00
β-D-Fructose	128–130	−511	−394	82.64
α-D-Galactose	224–226	+504	+399	85.77
α-Lactose	218–220	+355	+274	83.32
Trehalose	123–125	+276	+217	82.89
Sucrose	125–126	+ 43	+ 35	82.92
β-Cellobiose	206–208		+101	82.00
β-Gentiobiose	159–161		+ 28	82.03
D-Xylose	146–148	+285	+225	84.83
β-Maltose	242–244	− 30	− 22	78.50
	253–255			80.20
Melezitose	135–137	+110	+ 81	

Calculated per cent of azoyl:

Hexose pentaazoate = 85.66
Hexose tetraazoate = 82.61
Pentose tetraazoate = 85.13
Pentose triazoate = 81.01
Disaccharide octaazoate = 83.35
Disaccharide heptaazoate = 81.37

[a] The melting points were determined between cover glasses using a Fisher Johns apparatus.

Some of these constants may be revised when perfectly pure derivatives unmixed with isomers are prepared. In certain cases complete azoylation and purification of the product was difficult by the methods used. Since the primary interest in the present work was to determine the value of these derivatives in the separation of sugars, extended study was not given to methods of preparation and purification. The work is being continued and special attention given to modification of the method of preparation and the characterization of the pure compounds.

Analysis for Percentage of Azoyl.—The derivatives were analyzed by hydrolyzing the esters and weighing the free *p*-phenylazobenzoic acid formed. The azoyl derivative was dissolved in 20 ml. of dioxane, and 15 ml. of methanol containing about 12 mg. of sodium methylate was added. The mixture was refluxed for thirty minutes and then 3 ml. of sodium hydroxide (6 *N*) and 30 ml. of water were added. Refluxing was continued for another half hour and the solution was diluted to about 200 ml. with water and 125–150 ml. removed by distillation. The residual solution was filtered, cooled, and made slightly acid with dilute hydrochloric acid. After cooling for some time to allow complete precipitation, the solid acid was collected in a crucible with sintered glass bottom, dried and weighed.

Chromatographic Adsorption.—For chromatographic adsorption a column (23 mm. by 30 cm.) was packed by suspending the solid adsorbent in petroleum ether containing about 10% of benzene and filtering under a pressure of 10 cm. of mercury. A solvent mixture of equal volumes of chloroform, benzene and petroleum ether was passed down the column followed by a solution of the azoyl derivatives. The solution contained 120 mg. of each of a pair of sugar azoates dissolved in 35–50 ml. of chloroform to which were then added corresponding volumes of benzene and petroleum ether. The solutions were all filtered through the column under a nitrogen pressure of 10 cm. of mercury and the column was not allowed to run dry, as this caused channeling.

After adding all of the solution of sugar derivatives the chromatogram was developed using a solvent mixture of the same composition as the solution. When development was complete the column was allowed to run partially dry, the adsorbent was removed, and the bands were separated. Elution of the adsorbed materials was accomplished by extracting the adsorbent layers with hot chloroform containing a small amount of methanol. The solvent was evaporated from the eluted materials, which were then transferred in chloroform to volumetric flasks. The optical rotations were measured and the weights determined by evaporating aliquot portions of the solutions.

Typical Chromatographic Adsorption Separations

α-D-Glucose and Sucrose Azoates.—From 100 mg. of each derivative was obtained an upper band of 106.7 mg. $[\alpha]^{25}_{6438}$ +47° as compared to +35° for the pure sucrose derivative; calcd. sucrose azoate, 93.8%. The lower band of 88.1 mg. had a specific rotation of $[\alpha]^{25}_{6438}$ +212° as compared to +225° for the pure α-D-glucose derivative; calcd. α-D-glucose azoate, 93.2%.

β-D-Fructose and α-D-Galactose Azoates.—From 120 mg. of each derivative was obtained an upper band of 128 mg. $[\alpha]^{25}_{6438}$ −340° as compared to −394° for the pure fructose derivative; calcd. fructose azoate, 93.2%. The lower band contained 104 mg.; $[\alpha]^{25}_{6438}$ +413° as compared to +399° for the pure galactose derivative; calcd. galactose azoate, 101.6%.

α-Lactose and Sucrose Azoates.—From 120 mg. of each azoate was obtained an upper band of 144.5 mg., $[\alpha]^{25}_{6438}$ +206° as compared to +274° for the pure lactose derivative; calcd. lactose azoate, 71.6%. The lower band contained 89.2 mg., $[\alpha]^{25}_{6438}$ +36° as compared to +35° for the pure sucrose derivative; calcd. sucrose azoate, 99.4%.

α-D-Glucose and Melezitose Azoates.—From 55 mg. of each derivative was obtained an upper band of 52.5 mg., $[\alpha]^{25}D$ + 115° as compared to +110° for the pure melezitose azoate; calcd. melezitose azoate, 82.8%. The lower band of 50.5 mg. had a specific rotation of $[\alpha]^{25}D$ + 261° as compared to + 282° for the pure α-D-glucose azoate; calcd. α-D-glucose azoate, 89.3%.

Summary

1. The *p*-phenylazobenzoyl esters of several sugars have been prepared. These derivatives were analyzed for percentage azoyl and the specific rotations measured in chloroform solution.

2. Several pairs of these sugar esters have been separated by the chromatographic adsorption method using silicic acid and mixtures of Magnesol and Dicalite as adsorbents. This included the separation of two monosaccharides, a monosaccharide and disaccharide, two disaccharides, and the separation of a monosaccharide and trisaccharide.

IOWA CITY, IOWA RECEIVED MARCH 18, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

Synthesis of 2-Alkylaminoethanols from Ethanolamine

BY ARTHUR C. COPE AND EVELYN M. HANCOCK

Certain disadvantages are inherent in the methods which are available for the preparation of 2-alkylaminoethanols, $RNHCH_2CH_2OH$. The reaction of primary amines with ethylene oxide[1] and with ethylene chlorohydrin[2] produces a mixture of mono and dialkylaminoethanols. The reaction of ethanolamine with alkyl halides[3] may lead to either secondary or tertiary amino compounds. The method described by Goldberg and W. F. Whitmore,[4] in which an alkyl aniline is converted into a dialkylaminoethanol with ethylene oxide, and then cleaved to a monoalkylaminoethanol by nitrosation and hydrolysis, leads to pure products but involves several steps.

We have investigated the preparation of 2-alkylaminoethanols by the reduction of mixtures of ethanolamine with ketones and aldehydes.

The catalytic reduction of mixtures of ethanolamine with various ketones proved to be a remarkably successful method for the preparation of 2-alkylaminoethanols containing secondary alkyl groups. Of the aminoalcohols listed in Table I, seventeen were prepared in this manner, from ketones containing three to ten carbon atoms. The yields in many cases are nearly quantitative. The 2-alkylaminoethanols are produced in a state of exceptional purity, as indicated by constant boiling points and refractive indexes, and uniform agreement between calculated and observed molecular refractions.

Adams platinum oxide-platinum catalyst was used in preparing all of the aminoalcohols. Most of the reductions were exothermic and proceeded rapidly without heating in alcohol solution, the rates of the various reductions corresponding to the reactivity of the ketones. The reductions were much slower in acetic acid, and still slower when palladinized charcoal was used as the catalyst. Raney nickel and copper chromite proved to be suitable catalysts at elevated temperatures and pressures.

(1) Knorr and Matthes, *Ber.*, **31**, 1069 (1898); Knorr and Schmidt, *ibid.*, **31**, 1072 (1898); Matthes, *Ann.*, **315**, 104 (1901); Bain and Pollard, THIS JOURNAL, **61**, 2704 (1939).

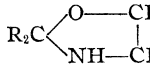
(2) Knorr, *Ber.*, **22**, 2081 (1889); *cf.* Adams and Segur, THIS JOURNAL, **45**, 785 (1923).

(3) Goldberg, U. S. Patent 2,139,818; English Patent 482,886; *cf.* Fränkel and Cornelius, *Ber.*, **51**, 1660 (1918).

(4) Goldberg and W. F. Whitmore, THIS JOURNAL, **59**, 2280 (1937).

Five 2-*primary* alkylaminoethanols were prepared in a similar manner in 60 to 90% yield by reducing mixtures of aldehydes with ethanolamine. By-products were formed from the aldehydes, but they could be removed by distillation, or by dissolving the amino-alcohols in dilute hydrochloric acid and extracting with ether or benzene.

Skita[5] has prepared a number of amines (different in type from the aminoalcohols herein described) by the reduction of aldehydes and ketones in the presence of ammonia and amines, or by the reduction of the alkylidene amines (Schiff bases) which are the intermediates. We have isolated the products formed by the reaction of four ketones with ethanolamine and found that in three cases the compounds formed by elimination of water are not alkylidene aminoalcohols, $R_2C{=}NCH_2CH_2OH$, I, but oxazolidines,


, II.

By refluxing a benzene solution of cyclohexanone and ethanolamine under a constant water separator until the separation of water became very slow, an anhydro compound was formed in about 90% yield. It is very readily hydrolyzed back to ethanolamine and cyclohexanone. Catalytic reduction converts the anhydro compound into 2-cyclohexylaminoethanol. The low boiling point of the anhydro compound [89–90° (16 mm.)] compared to that of 2-cyclohexylaminoethanol [122–123.5 (13 mm.)] suggests a more fundamental change in structure on reduction than simple saturation of a double bond.[6] The molecular refraction of the anhydro compound (39.55) is in much better agreement with the value calculated for the oxazolidine (40.00) than the calculated value for the alkylidene aminoalcohol (41.48). A similar easily hydrolyzed anhydro compound regarded as an oxazolidine was formed from methyl amyl ketone and ethanolamine; b. p. 88–90° (7 mm.), in contrast to the b. p. of 115–116° (10 mm.) observed for its reduction product, 2-(2-heptylamino)-ethanol; M_D found 46.86, calculated for the oxazolidine 46.82, for the alkylidene aminoalcohol 48.30.

(5) Skita and Keil, *Ber.*, **61**, 1452 (1928), and subsequent papers.

(6) Alkylidene amines derived from citral (ref. 5) boil *higher* than the corresponding saturated amines.

TABLE I: 2-ALKYLAMINOETHANOLS, $RNHCH_2CH_2OH$

Alkyl group	Prepared from (ketone or aldehyde)	Yield, %	Boiling point, °C. (uncor.)	mm.	$n^{25}D$	d^{25}_{25}	Molecular refraction Calcd.	Found	Formula	Nitrogen, % Calcd.	Found[f]	Picrate, m. p., °C. (uncor.)	Formula	Nitrogen, % Calcd.	Found[f]
Isopropyl[a]	Acetone	95	76–77	15	1.4390	0.8977	30.42	30.29	$C_5H_{13}ON$			127–128.5[a]	$C_{11}H_{16}O_8N_4$		
s-Butyl	Methyl ethyl ketone	98	88–88.5	17	1.4435	.8953	35.04	34.82	$C_6H_{15}ON$	11.96	11.80	98–100	$C_{12}H_{18}O_8N_4$	16.18	16.25
2-Pentyl	Methyl propyl ketone	95	98–99	15	1.4445	.8868	39.66	39.44	$C_7H_{17}ON$	10.68	10.74	90–92	$C_{13}H_{20}O_8N_4$	15.55	15.59
3-Pentyl	Diethyl ketone	97	85–85.5	8	1.4463	.8931	39.66	39.32	$C_7H_{17}ON$	10.68	10.67	98–99	$C_{13}H_{20}O_8N_4$	15.55	15.48
2-(4-Methylpentyl)	Methyl isobutyl ketone	98	102–102.5	13	1.4440	.8770	44.28	44.12	$C_8H_{19}ON$	9.65	9.41	105–106	$C_{14}H_{22}O_8N_4$	14.97	14.97
2-Heptyl	Methyl amyl ketone	98	115–116	10	1.4485	.8791	48.90	48.69	$C_8H_{19}ON$	8.79	8.64	70–71	$C_{13}H_{24}O_8N_4$	14.43	14.41
4-Heptyl	Dipropyl ketone	96	104–105	8	1.4479	.8788	48.90	48.65	$C_9H_{21}ON$	8.79	8.96	112–113	$C_{15}H_{24}O_8N_4$	14.43	14.27
2-Octyl	Methyl hexyl ketone	96	130–130.5	12	1.4501	.8751	53.52	53.57	$C_{10}H_{23}ON$	8.08	8.03	67–69	$C_{16}H_{26}O_8N_4$	13.93	13.97
2-Nonyl	Methyl heptyl ketone	92	138–139	10	1.4516	.8729	58.14	58.02	$C_{11}H_{25}ON$	7.48	7.39	73–74	$C_{17}H_{28}O_8N_4$	13.46	13.34
5-Nonyl	Dibutyl ketone	94	130.5–131	9	1.4509	.8732	58.14	57.92	$C_{11}H_{25}ON$	7.48	7.50	112–113	$C_{17}H_{28}O_8N_4$	13.46	13.34
4-(2,6-Dimethylheptyl)	Diisobutyl ketone	94	113–114	7	1.4456	.8639	58.14	57.95	$C_{11}H_{25}ON$	7.48	7.50	150–151	$C_{17}H_{28}O_8N_4$	13.46	13.40
2-Decyl	Methyl octyl ketone	97	149–150	9	1.4528	.8712	62.76	62.62	$C_{12}H_{27}ON$	6.96	7.05	66–68	$C_{18}H_{30}O_8N_4$	13.02	12.96
Cyclohexyl[d]	Cyclohexanone	96	122–123.5[d]	13	1.4843	.9811	42.08	41.87	$C_8H_{17}ON$	9.78	9.84	128–129	$C_{14}H_{20}O_8N_4$	15.05	15.04
2-Methylcyclohexyl	2-Methylcyclohexanone	88	123.5–124	13	1.4827	.9714	46.70	46.34	$C_9H_{19}ON$	8.91	8.86	120–122	$C_{15}H_{22}O_8N_4$	14.49	14.49
4-Methylcyclohexyl	4-Methylcyclohexanone	98	129.5–130	14	1.4792	.9607	46.70	46.57	$C_9H_{19}ON$	8.91	8.99	116–117	$C_{15}H_{22}O_8N_4$	14.49	14.59
2,2,6-Trimethylcyclohexyl	2,2,6-Trimethylcyclohexanone	98	123–123.5	7	1.4729	.9329	55.94	55.87	$C_{11}H_{23}ON$	7.56	7.53	142–142.5	$C_{17}H_{26}O_8N_4$	13.52	13.31
l-Menthyl	*l*-Menthone	80	134.5–136	7	1.4779	.9393	60.56	60.23	$C_{12}H_{25}ON$	7.03	7.00	118–120	$C_{18}H_{32}O_8N_4$	13.08	12.94
1-(1-Phenylethyl)	Acetophenone	95	139–140	9	1.5326	1.0311	49.91	49.85	$C_{10}H_{15}ON$	8.48	8.37	139–140	$C_{16}H_{18}O_8N_4$	13.88	13.86
Butyl[e]	Butyraldehyde	68	91–92	11	1.4427	0.8905	35.04	34.97	$C_6H_{15}ON$			86–88[b]	$C_{12}H_{18}O_8N_4$	16.18	16.25
Isobutyl[e]	Isobutyraldehyde	62	89–90	16	1.4389				$C_6H_{15}ON$						
Amyl[e]	Valeraldehyde	70	114–115	19	1.4446	.8834	39.66	39.62	$C_7H_{17}ON$	10.68	10.57	64–65	$C_{13}H_{20}O_8N_4$	15.55	15.42
Heptyl	Heptaldehyde	71	120–121[e]	7	1.4488	.8782	48.90	48.77	$C_9H_{21}ON$	8.79	8.68	69–70	$C_{15}H_{24}O_8N_4$	14.43	14.33
1-(2-Ethylhexyl)	2-Ethylhexanal	91	119–120	8	1.4519	.8808	53.52	53.22	$C_{10}H_{23}ON$	8.08	7.88	104–106	$C_{16}H_{26}O_8N_4$	13.93	13.77

[a] Previously prepared by Matthes (ref. 1). [b] Matthes (ref. 1) reports m. p. 98°. M. p. of the picrolonate 211–213°, in fairly good agreement with the value of 218° reported by Matthes. [c] Reported by Goldberg (ref. 4) as having b. p. 214–216°; refractive index (conditions unspecified) 1.4508; sp. gr. 0.8814; picrate m. p. 57–58°. [d] Reported by Bain and Pollard (ref. 1), whose physical constants are in good agreement with ours. Our sample solidified on standing, m. p. 40–41°. Physical constants were determined on the supercooled liquid. [e] Solidified on standing, m. p. 30–32°. Physical constants were determined on the supercooled liquid. [f] We are indebted to Mr. C. S. Miller and Mr. J. P. Lutz for semi-micro Kjeldahl analyses.

The reaction of methyl propyl ketone and ethanolamine also gave an anhydro compound with physical properties indicating an oxazolidine structure; b. p. 62–62.5° (16 mm.) compared to 98–99° (15 mm.) for its reduction product; M_D found 37.06, calculated for the oxazolidine 37.58, for the alkylidene aminoalcohol 39.06. The refractive index of this compound increased rapidly on standing for a few hours from an initial value of 1.4400 to a final value of 1.4502, which remained practically constant for two months. Redistillation reconverted the material into the form with the original refractive index, which again increased to 1.4502 on standing. These data are interpreted as meaning that this particular anhydro compound exists as an oxazolidine (II) in fairly mobile equilibrium with an alkylidene aminoalcohol (I). The freshly distilled material is the lower boiling oxazolidine, which reaches an equilibrium with I on standing. The conversion is apparently not complete, for the molecular refraction of the material at equilibrium is 37.81, a value too low for structure I.

The condensation of diisobutyl ketone with ethanolamine produced an anhydro compound which boiled only slightly lower than its reduction product [110–111° (8 mm.)] compared to [113–114 (7 mm.)], and had a molecular refraction (57.21) closer to the value for the alkylidene aminoalcohol (57.54) than the oxazolidine (56.06). Presumably it is largely or completely in the form of the alkylidene aminoalcohol.

It is of interest to note that the three anhydro compounds which appear to exist predominantly in the form of oxazolidines are derived from the three reactive, relatively unhindered ketones. Presumably the first step in the reaction is the formation of an addition product, $R_2C(OH)NHCH_2CH_2OH$. Whether the oxazolidines are formed directly from these intermediates by the elimina-

tion of water, or whether the reaction takes the course of dehydration to an alkylidene amino-alcohol followed by an intramolecular addition to give the oxazolidines, the presence of large branched alkyl groups would be expected to retard or prevent their formation.

Knorr and Matthes[7] have prepared anhydro compounds from aldehydes and ethanolamine, and considered that their low boiling points and ease of hydrolysis proved them to be oxazolidines. Knorr and Rössler[8] obtained anhydro compounds formulated as oxazolidines from the reaction of ethanolamine with acetyl acetone and aceto-acetic ester. They did not obtain pure products from either acetone or acetophenone. Oxazolidines derived from ketones and ethanolamine are mentioned as intermediates in the patent literature,[9] but were not isolated.

Experimental Part

Most of the ketones and all of the aldehydes listed in Table I were obtained from commercial sources and purified by distillation before use. Methyl heptyl ketone was prepared from caprylyl chloride and methyl zinc iodide; dibutyl ketone from valeronitrile and butylmagnesium bromide; methyl octyl ketone from ethyl *n*-heptylaceto-acetate; 2,2,6-trimethylcyclohexanone by reducing isophorone in the presence of palladinized charcoal.

Preparation of 2-*s*-Alkylaminoethanols.—Details of the preparation of 2-(2-octylamino)-ethanol may be cited to illustrate the method used for the 2-*s*-alkylamino-ethanols listed in Table I, with one exception. Platinum oxide catalyst (0.5 g.) was placed in a one-liter bottle containing 50 cc. of absolute alcohol and reduced to platinum by shaking in an atmosphere of hydrogen. Ethanolamine (61 g., 1 mole) was dissolved in 100 cc. of absolute alcohol and methyl hexyl ketone (166 g., 1.3 mole) was added. The mixture became warm from the heat of reaction. The solution was rinsed into the bottle containing the platinum catalyst with 50 cc. of alcohol and reduced by shaking with hydrogen at one to two atmospheres pressure for seven hours. The reduction was rapid and exothermic. The catalyst was removed by filtration and the bottle and catalyst rinsed with 75 cc. of benzene. The benzene and alcohol were removed from the filtrate by distillation at atmospheric pressure, and the residue was distilled in vacuum through a Widmer column. The excess ketone was recovered as a fore-run. There was practically no distillation residue.

Mixtures of ethanolamine with all of the methyl ketones except acetophenone reduced rapidly, preparations of one-half to one mole requiring three to ten hours for completion. The cyclic ketones, except *l*-menthone, gave equally rapid reductions. The reduction was slightly slower in the case of diethyl ketone, but went to completion without heating. The mixtures of ethanolamine and acetophenone, dipropyl ketone, dibutyl ketone and *l*-menthone were heated to 50 to 60°, and complete reduction of one-half mole quantities required 20 to 30 hours. No reduction occurred with diisobutyl ketone under these conditions. An excess of ketone was used in each reduction in order to eliminate the possibility that the products might be contaminated with ethanolamine. It is noteworthy that no dialkylaminoethanols were formed through further reaction of the monoalkylaminoethanols with the ketones present in excess.

The following facts concerning the reductions were established during the development of the procedure illustrated above. It is advantageous to reduce the catalyst separately before adding the mixture of ethanolamine and carbonyl compound, in order to avoid a long induction period which otherwise occurs before the catalyst reduces. Palladinized charcoal[10] is a much less effective catalyst for the reduction. Thus a half-mole preparation of 2-*s*-butylaminoethanol required a total of 3 g. of palladinized charcoal added in three portions and thirty-one hours for complete reduction at 60°. A number of reductions were carried out in acetic acid (2 moles per mole of ethanolamine). With platinum catalyst under these conditions the reductions required twenty to thirty hours at 60°, while palladium gave even slower reductions. The yields were also 10 to 20% lower than those obtained by the above procedure, due to the loss of the aminoalcohols which occurred because of their solubility in water when they were liberated from their acetate salts by treatment with alkali. Raney nickel and copper chromite are satisfactory catalysts for the reductions either in alcohol solution or without a solvent. Thus the reduction of 28 g. of methyl ethyl ketone and 18 g. of ethanolamine in the presence of 3 g. of Raney nickel at 150° and 1000 to 2000 lb. hydrogen pressure gave 27.2 g. (86%) of 2-*s*-butylaminoethanol. A similar reduction in the presence of 1 g. of copper–barium chromite[11] at 160° gave 28.5 g. (88%) of the aminoalcohol.

Preparation of 2-*primary*-Alkylaminoethanols.—The method described in detail above was followed, except that the alcohol solution of ethanolamine was cooled in ice while the aldehyde (15% molar excess) was added slowly, in order to avoid polymerization. One attempt to prepare 2-butylaminoethanol in acetic acid solution was unsuccessful due to extensive polymerization of the aldehyde under these conditions.

The picrates described in Table I were prepared by heating to boiling alcohol solutions of the aminoalcohols with equivalent quantities of picric acid, followed by cooling. Water was added if necessary. They were recrystallized from alcohol or alcohol and water.

Condensation of Ketones with Ethanolamine. Spiro-[cyclohexane-1,2′-oxazolidine].—A mixture of 30.5 g. of ethanolamine, 63.7 g. of cyclohexanone and 100 cc. of benzene was refluxed under a constant water separator[12] for thirty minutes, while 9.4 cc. of water collected. The benzene was removed in vacuum and the residue distilled in vacuum through a Widmer column. The yield of spiro-[cyclohexane-1,2′-oxazolidine] was 66.8 g. (94%); b. p.

(7) Knorr and Matthes, *Ber.*, **34**, 3484 (1901).
(8) Knorr and Rössler, *ibid.*, **36**, 1282 (1903).
(9) French Patent 730,760; English Patent 388,874.
(10) Hartung, THIS JOURNAL, **50**, 3372 (1928).
(11) Connor, Folkers and Adkins, *ibid.*, **54**, 1140 (1932).
(12) Cope, Hofmann, Wyckoff and Hardenbergh, *ibid.*, **63**, 3452 (1941).

89–90° (16 mm.); $n^{25}D$ 1.4803; d^{25}_{25} 1.0178; M_D calcd. 40.00, found 39.55.[13]

Anal. Calcd. for $C_8H_{15}ON$: N, 9.92. Found: N, 9.81.

Reduction of 28.2 g. of the oxazolidine in 40 cc. of alcohol with the platinum from 0.3 g. of platinum oxide gave 26.3 g. (92%) of 2-cyclohexylaminoethanol.

2-Methyl-2-amyloxazolidine.—Ethanolamine (30.5 g.), methyl amyl ketone (74 g.) and 100 cc. of benzene were refluxed under a water separator. After thirty-five minutes 9.2 cc. of water had collected. Distillation gave 50 g. (64%) of the oxazolidine; b. p. 88–90° (7 mm.); $n^{25}D$ 1.4501; d^{25}_{25} 0.9047; M_D calcd. 46.82, found 46.86.

Anal. Calcd. for $C_9H_{19}ON$: N, 8.92. Found: N, 9.16.

2-Methyl-2-propyloxazolidine.—Ethanolamine (30.5 g.), methyl propyl ketone (56 g.) and 100 cc. of benzene were refluxed under a water separator for one hour, when 9.0 cc. of water had collected. Distillation gave 49.5 g. (85%) of the oxazolidine; b. p. 62–62.5° (16 mm.); $n^{25}D$ 1.4400; d^{25}_{25} 0.9215; M_D calcd. 37.58, found 37.06.

Anal. Calcd. for $C_7H_{15}ON$: N, 10.84. Found: N, 11.01.

The refractive index of this oxazolidine increased noticeably on the refractometer. After one day its refractive index was 1.4502, after two months, 1.4510. The density remained constant; d^{25}_{25} 0.9216. Redistillation converted the sample without appreciable loss into material with $n^{25}D$ of 1.4400, which again increased to 1.4502 after standing for one day.

In a quantitative reduction with platinum catalyst 2.50 g. of this oxazolidine took up 99.3% of one molecular equivalent of hydrogen. Distillation gave 2.0 g. of 2-(2-pentylamino)-ethanol, identified by its physical properties and the melting point of its picrate.

2-[4-(2,6-Dimethylheptylidene)-amino]-ethanol.—A mixture of 30.6 g. of ethanolamine, 92 g. of diisobutyl ketone and 150 cc. of benzene was refluxed under a constant water separator for thirteen hours, during which time 12 4 cc. of water collected. The mixture was not homogeneous at the beginning of the reaction, but was at the end. The water which collected in the separator contained some ethanolamine. After the benzene had been removed in vacuum, the residue was distilled through a Widmer column. The yield of the alkylidene aminoalcohol was 52 g. (56%); b. p. 110–111° (8 mm.); $n^{25}D$ 1.4568; d^{25}_{25} 0.8844; M_D calcd. 57.54, found 57.21.

Anal. Calcd. for $C_{11}H_{23}ON$: N, 7.56. Found: N, 7.66.

Reduction of 29.6 g. of the above anhydro compound with platinum catalyst in alcohol solution gave 28 g. (94%) of 2-[4-(2,6-dimethylheptyl)-amino]-ethanol (Table I).

All of the above anhydro compounds were very readily hydrolyzed. Samples which were freshly distilled or stored in sealed containers had a distinct amine-like odor, but after exposure to moist air for a few minutes the odor of the ketones appeared.

Methyl hexyl ketone and acetophenone were also condensed with ethanolamine in benzene solution. A molecular equivalent of water was formed in both cases, but the condensation products did not have constant boiling points and appeared to polymerize slightly on distillation in vacuum.

In order to determine whether condensation products could be prepared from ketones and 2-alkylaminoethanols, 32.8 g. of 2-(2-pentylamino)-ethanol, 28 g. of methyl propyl ketone, 1.5 g. of acetic acid and 50 cc. of benzene were refluxed under a constant water separator for 48 hours. Although 1.4 cc. of water collected, on distillation 29 g. (88%) of the aminoalcohol was recovered.

Summary

The reduction of mixtures of ethanolamine with ketones and with aldehydes provides a convenient synthesis for 2-alkylaminoethanols. Nearly quantitative yields of 2-*s*-alkylaminoethanols are obtained from ketones and ethanolamine.

The substances which are presumably intermediates in this synthesis were isolated in four cases by condensing four ketones with ethanolamine. The condensation products obtained from cyclohexanone and methyl amyl ketone had physical properties which indicated that they were not alkylidene aminoalcohols (I) but oxazolidines (II). The product obtained from methyl propyl ketone and ethanolamine had the properties of an oxazolidine when distilled, but rapidly changed in refractive index on standing, probably because of ring-chain tautomerism and the establishment of an equilibrium between I and II. The condensation product obtained from diisobutyl ketone and ethanolamine had physical properties indicating that it was largely in the alkylidene aminoalcohol form.

BRYN MAWR, PENNSYLVANIA RECEIVED MARCH 5, 1942

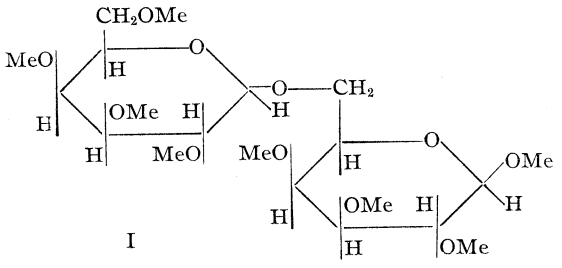
(13) The following atomic refractions were used in obtaining calculated molecular refractions: nitrogen in the oxazolidines, 2.50 as in secondary amines; Eisenlohr, *Z. phys. Chem.*, **79**, 134 (1912). Double bond-nitrogen in the Schiff bases, 4.10 as in alkylidene amines; von Auwers, *ibid.*, **147**, 436 (1930). Other values (C, 2.42; H, 1.10; O, 1.64) are the usual Eisenlohr values; *ibid.*, **75**, 605 (1910). "Optical depression" is frequently observed in (unsaturated) heterocyclic compounds [see Brühl, *ibid.*, **79**, 38 (1912); von Auwers, *Ber.*, **57**, 461 (1924)]. Consequently it is probable that the low molecular refractions observed for spiro[cyclohexane-1,2′-oxazolidine] (deviation −0.45) and 2-methyl-2-propyl-oxazolidine (−0.52) are characteristic of the oxazolidine ring system, while the agreement of calculated and found values for 2-methyl-2-amyl-oxazolidine (deviation +0.04) is fortuitous and may indicate the presence of some of the corresponding Schiff base.

[CONTRIBUTION FROM THE WOOD CONVERSION LABORATORY OF THE UNIVERSITY OF IDAHO]

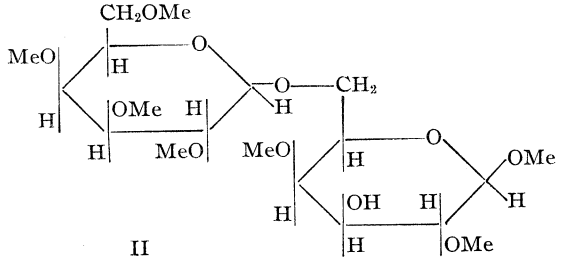
The Constitution of Arabo-galactan. III. The Location of the Arabinose Component

BY E. V. WHITE

It has been shown that the water-soluble gum[1] of the western larch, *Larix occidentalis*, yields the glycosides of 2,4-dimethyl-*d*-galactose, 2,3,4-trimethyl-*d*-galactose, 2,3,4,6-tetramethyl-*d*-galactose, and 2,3,5-trimethyl-*l*-arabinose in the approximate molecular ratio 3:1:2:1 upon alcoholysis of the methyl ether derivative.[2] Furthermore, by partial methanolysis of arabo-galactan methyl ether,[3] two methylated disaccharides have been obtained in crystalline form. These are, respectively, octamethyl-6-*d*-galactosidogalactose (I)and heptamethyl-6-*d*-galactosidogalactose (II).[3a]



I



II

Apparently the terminal galactose anhydride units of the polysaccharide are engaged by oxygen linkage through the 1 position to the 6 position of adjacent galactose residues and the question arises as to the mode of union of the terminal arabofuranose unit.

As is well known, the furanopentosides are considerably more susceptible to acid hydrolysis than are the corresponding derivatives of the pyranopentoses and especially the pyranohexoses, although, under similar conditions, the rate of hydrolysis is a function of the particular saccharide under consideration. Advantage has been taken of this phenomenon in the investigation of certain oligosaccharides,[4a,b] xylan[5] and arabic acid.[6] Hirst and co-workers[7] report its successful application to arabo-galactan but do not give details of the experiment.

The relative rates of hydrolysis of the galactopyranosides as compared with those of the corresponding arabofuranosides under similar conditions are not known, although it is indicated indirectly that the difference is not as large as might be expected. Thus, since the methyl arabopyranosides are hydrolyzed about 1.5 times as rapidly as the methyl galactopyranosides[8] and since the only known methyl arabofuranoside is hydrolyzed about 10 times as rapidly as the corresponding pyranoside,[9] it is to be expected that the arabofuranosides would hydrolyze about 15 times as rapidly as the galactopyranosides. In the case of arabo-galactan, therefore, wherein six molecules of galactose are associated with one residue of arabofuranose, hydrolysis of the furanopentose unit should be accompanied theoretically by concomitant hydrolysis of 0.4 unit of galactose.

The strictly preferential hydrolysis of the arabofuranose component of arabo-galactan is thus a matter of some difficulty. However, after mild treatment, any substantial change in the ratio of the components isolated upon alcoholysis of a partially hydrolyzed, fully methylated material as compared with those obtained upon similar treatment of the methyl ether derivative would indicate the method of linkage of the pentose unit.

With these considerations in mind, a quantity of arabo-galactan was separated from larch sawdust and divided into two portions. One of these was subjected to partial hydrolysis. Samples of the hydrolyzing solution were removed at intervals and analyzed for residual polysaccharide. The non-hydrolyzed pentose fraction of the latter was then determined by the Tollens method. The

(1) Schorger and Smith, *Ind. Eng. Chem.*, **8**, 494 (1916).
(2) White, THIS JOURNAL, **63**, 2871 (1941).
(3) White, *ibid.*, **64**, 302 (1942).
(3a) In Part II the structures (I) and (II) are incorrectly represented in the relative location of H and OMe at position 4 of the monosaccharide units involved.
(4) (a) Bourguelot and co-workers, *Comp. rend.*, **126**, 280 (1898); **132**, 571 (1901); (b) Kuhn and Grundherr, *Ber.*, **59**, 1655 (1926).
(5) Hirst and Peat, *J. Chem. Soc.*, 1983 (1937).
(6) Smith, *ibid.*, 744 (1939).
(7) Hirst, Jones and Campbell, *Nature*, **147**, 25 (1941).
(8) Isbell and Frush, *J. Research N.B.S.*, **24**, 125 (1940).
(9) Montgomery and Hudson, THIS JOURNAL, **59**, 992 (1937).

TABLE I

PARTIAL HYDROLYSIS OF ARABO-GALACTAN

Acidity, 0.020 N H_2SO_4; temp., 90°

Time, hours	% Residual polysaccharide	% Arabinose in residual polysaccharide
0	100	13.6
7	94.2	9.91
16	90.0	7.24
23	88.4	6.16

results obtained, given in Table I, are represented graphically in Fig. 1.

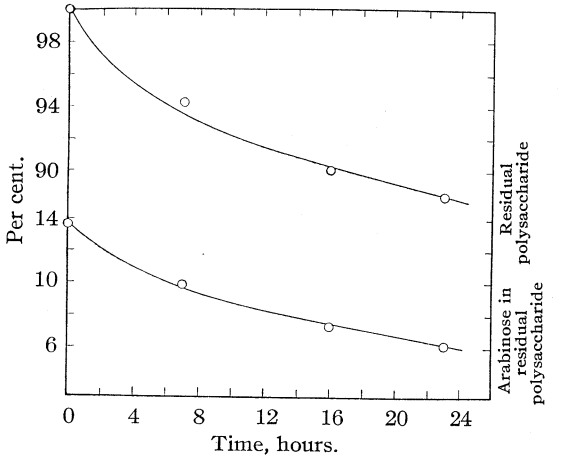


Fig. 1.—The hydrolysis of arabo-galactan (acidity, 0.02 N H_2SO_4; temp., 90°).

Hydrolysis of the gum obviously proceeds with gradual decrease in the pentose fraction of the residual polysaccharide and apparently tends toward a final value. Furthermore, within the range investigated, the decrease in yield of residual polysaccharide parallels approximately the loss of pentose, indicating that simultaneous galactose fission was relatively slight under the conditions employed.[10] No attempt was made to completely remove the arabinose component lest prolonged treatment promote undue galactose hydrolysis. The hydrolyzate, therefore, is to be regarded as a mixture of unchanged arabo-galactan and arabinose-free arabo-galactan together with some more extensively hydrolyzed material. The partially hydrolyzed product was methylated with dimethyl sulfate and alkali and subjected to simultaneous complete hydrolysis and glycoside formation with methanolic hydrogen chloride. The resulting sirup was distilled fractionally and the yield of the components compared with those obtained from the second portion of arabo-galactan which was methylated directly and subjected to alcoholysis.

An analysis of the results obtained is given in Table II as taken from Tables III and IV, respectively.

An examination of this table shows a sharp decrease in the amount of dimethyl-galactoside obtained from the glycosidic sirup of the partially hydrolyzed, fully methylated product as compared with that obtained from the ether of the original polysaccharide. Correspondingly, an increase is noted in the yield of trimethyl-galactoside. When correction is made in the glycosidic sirup for those components resulting from unchanged arabo-galactan in the partially hydrolyzed product, a substantially equimolecular ratio is obtained for the di-, tri- and tetramethyl-galactoside components[7] derived from methylated, arabinose-free arabo-galactan. The conclusion is reached, therefore, that the arabinose fraction of the polysaccharide is joined by oxygen linkage to an already di-linked galactose residue and that the new hydroxyl group formed by hydrolysis of the furanopentose residue and substituted in subsequent methylation contributes to the increased proportion of the trimethylated component in the glycosidic sirup from the partially hydrolyzed, fully methylated product.

The location of the new hydroxyl group, and therefore of the arabinose residue, was revealed by an examination of the trimethyl galactoside component of the glycosidic sirup. Thus, while arabo-galactan methyl ether yields only 2,3,4-trimethyl-methyl-galactoside as trimethyl component upon methanolysis, the partially hydrolyzed, methylated and hydrolyzed material provides a trimethyl galactoside fraction which furnishes 2,3,4-trimethyl-galactose and 2,4,6-trimethyl-galactose. The latter evidently originates through methylation of a hydroxyl group in the 6-position of a galactose residue formed during partial hydrolysis by removal of the arabinose unit. The same galactose residue normally occurs in the alcoholysis products of arabo-galactan methyl ether as 2,4-dimethyl-methyl-galactoside. In the original arabo-galactan, therefore, the arabinose

(10) After twenty-three hours of treatment, arabinose removed by hydrolysis = 13.6 − (6.16 × 88.4/100) = 8.2%; residual galactan = (88.4 − 5.4) = 83.0%; hydrolysis ratio galactose : arabinose = $\left(\frac{8.2}{13.6} \div \frac{86.4 - 83.0}{86.4} \times \frac{180}{160}\right)$ = 13.6:1. The experimental value approximates the theoretical hydrolysis ratio 15:1 and indicates 4.5% galactose fission under conditions hydrolyzing 62% of the arabinose component. Similar calculations made after sixteen and seven hours of hydrolysis yield the ratios 13.8:1 and 16.2:1, respectively. However, these evaluations of hydrolysis ratio must be regarded as approximations since galactan hydrolysis may occur leaving an alcohol insoluble residue without formation of galactose.

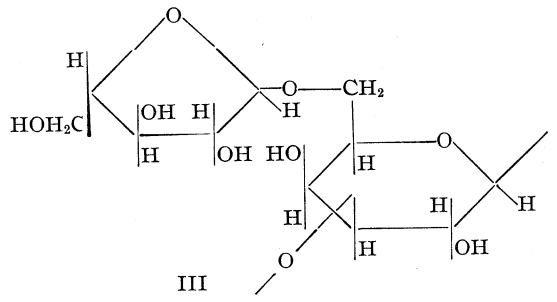
TABLE II

GLYCOSIDIC SIRUP ANALYSIS

	From arabo-galactan Me ether			From partially hydrolyzed, fully methylated arabo-galactan				
		Total yield			Total yield	Unchanged[b] arabo-galactan, grams	Arabinose-free arabo-galactan	
	Grams	%	Mol. ratio	Grams	%		Grams	Mol. ratio
Trimethyl-methyl-arabinoside	9.6[a]	12.9	1.00	3.6[b]	5.9	3.6	0	0
Tetramethyl-methyl-galactoside	21.2	28.2	1.82	20.2	33.0	8.7	11.5	1.97
Trimethyl-methyl-galactoside	12.5	16.7	1.14	15.3	2 5.0	4.1	11.2	2.01
Dimethyl-methyl-galactoside	31.5	42.2	3.04	22.1	36.1	11.5	10.6	2.02
Totals	74.7	100.0	7.00	61.2	100.0	27.9	33.3	6.00

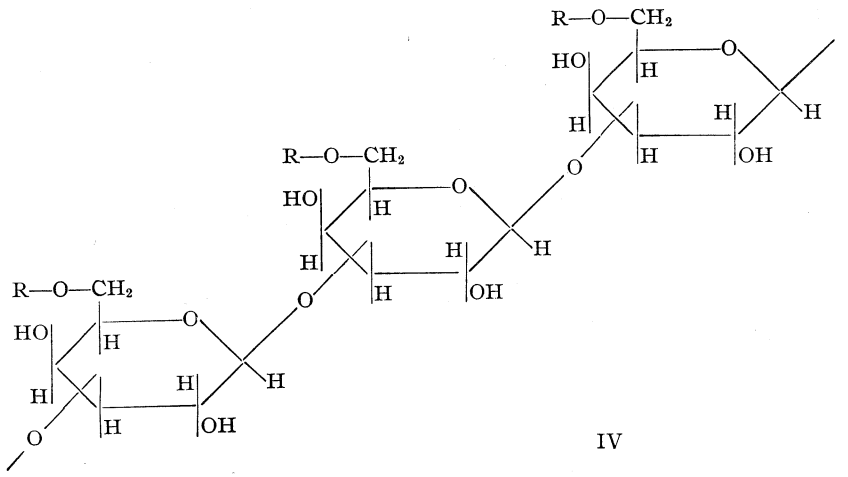
[a] Calcd. from arabinose content of arabo-galactan. [b] Calcd. from arabinose content of arabo-galactan and that of the hydrolyzed product.

fraction occurs as a 1-6 linked arabofuranosido-galactan III.



III

A consideration of these facts, together with the knowledge that octamethyl- and heptamethyl-6-*d*-galactosidogalactose have been isolated through partial methanolysis of arabo-galactan methyl ether, furnishes direct information concerning six monosaccharide units of the polysaccharide wherein six galactose residues are associated with one unit of arabinose. The remaining galactose anhydride occurs as the 2,4-dimethyl derivative in arabo-galactan methyl ether and is thus tri-linked in the original polysaccharide. The exact location of this unit is not known, although the problem resolves itself into two possibilities. Thus, the tri-linked residue may be situated in the main chain of the branched structure previously indicated,[3] whereupon the constitution of the polysaccharide is represented by a "backbone" or main chain of 1-3 linked galactose anhydride units IV each substituted in the 6 position by the radical R. The repeating unit of arabo-galactan then becomes one of three main chain units bearing the radicals R, respectively, *l*-arabinose, *d*-galactose, and 6-*d*-galactosidogalactose. In the event, however, that the final tri-linked galactose anhydride is not part of the main chain but that one or more such units are engaged in side-chain linkage, a portion or all of the radicals R become of polysaccharide character and the nature of the main chain linkage is unknown. This phase of the investigation is now being extended.



IV

Experimental

Extraction and Purification of Arabo-galactan.—Larch sawdust was extracted with water and the extract, purified by filtration through norite and Super-Cel, fractionally precipitated with ethyl alcohol.[2] The precipitate thus obtained was dissolved in water, evaporated under reduced pressure at 50° to remove residual alcohol, and divided into Parts A and B, respectively. Part A was fully methylated under nitrogen with dimethyl sulfate and alkali, as described previously.[3] Part B was subjected to partial hydrolysis.

Partial Hydrolysis of Arabo-galactan.—A number of preliminary experiments indicated that hydrolysis of arabo-galactan took place rapidly when the gum was heated in sulfuric acid solutions of greater concentration than 0.05 *N*. In more dilute solutions hydrolysis proceeded progressively slower until in 0.01 *N* acid solution only slight change was noted over long periods of time. Accordingly, Part B (72.6 g. of solid) of the arabo-galactan extract was heated at 90° on the water-bath in 750 cc. of 0.02 *N* sulfuric acid.

Samples of the hydrolyzing solution were removed at intervals, cooled, and a 25-cc. portion precipitated into excess rapidly stirred ethyl alcohol. The precipitate was washed with fresh alcohol to remove residual monosaccharide, dissolved in water, and made up to 100 cc. volume. Aliquot portions of this solution were then analyzed for total solid and for furfural distilled by the Tollens method. The results are given in Table I and are illustrated graphically in Fig. 1.

Methylation of Partially Hydrolyzed Arabo-galactan.—The hydrolyzing solution of arabo-galactan after twenty-three hours of treatment was cooled (635 cc.) and precipitated into excess rapidly stirred ethyl alcohol. The precipitate was removed from the supernatant liquor (C), washed with fresh alcohol, dissolved in water, and evaporated to a thin sirup. The latter was methylated at 25° under nitrogen using 300 cc. of methyl sulfate and 900 cc. of 30% sodium hydroxide. The reagents were added dropwise and simultaneously over a period of five hours. Acetone (200 cc.) was added over the interval to reduce foaming. After complete hydrolysis of the methyl sulfate the partially methylated product separated from the inorganic reaction components. The latter were removed and the residue remethylated under similar conditions. After four methylations, retreatment effected no increase in methoxyl content of the product, which was isolated by extraction of the methylation liquors with chloroform. The extract, dried over magnesium sulfate, decolorized with norite and filtered, was evaporated to a sirup and precipitated into excess rapidly stirred petroleum ether (30–60°). The precipitate, taken up in ether, filtered and evaporated to dryness, yielded a friable glassy solid of light yellow color; yield, 57 g. (Found: MeO, 44.7.).

Isolation and Identification of Arabinose.—The supernatant alcoholic liquor (C) was neutralized with barium carbonate, decolorized with norite, and evaporated to small volume. The resulting solution was precipitated into excess alcohol and a small quantity (1.5 g.) of residual gum removed. The solution, containing 5.6 g. of arabinose by the Tollens method, evaporated to a sirup and taken up in fresh alcohol, crystallized, yielding crude arabinose identified as the benzyl-phenylhydrazone: m. p. 174°.

Methanolysis of Fully Methylated, Partially Hydrolyzed, Arabo-galactan and of Arabo-galactan Methyl Ether.—Fifty-six grams of fully methylated, partially hydrolyzed arabo-galactan was dissolved in 360 cc. of anhydrous pure methyl alcohol containing 2% of dry hydrogen chloride. After reaction in sealed tubes[4] maintained at 115° for five and one-half hours, excess acidity was neutralized with silver carbonate. The filtered solution was decolorized with norite, evaporated to a sirup, and taken up in anhydrous ether. Filtration of the solution and evaporation of solvent gave a sirupy mixture of variously methoxylated glycosidic components; yield, 62.0 g. A similar experiment performed on the methyl ether of non-hydrolyzed arabogalactan (66.0 g.) gave a similar glycosidic sirup; yield, 75.2 g.

Examination of the Glycosidic Sirups.—The sirup obtained upon methanolysis of arabo-galactan methyl ether was distilled fractionally under high vacuum, yielding the portions indicated in Table III. No attempt was made to separate trimethyl-methyl-arabinoside from tetramethyl-methyl-galactoside, although the separation of these components from trimethyl-methyl-galactoside and the latter from dimethyl-methyl-galactoside was relatively complete. In calculation of the components, the arabinoside fraction was determined upon the basis of the 6:1 molecular ratio of galactose to arabinose in arabo-galactan, while the small intermediate portions and the trimethyl fraction were apportioned on the basis of methoxyl content.

TABLE III

FRACTIONAL DISTILLATION OF THE GLYCOSIDIC SIRUP FROM ARABO-GALACTAN METHYL ETHER

Distillate	Grams	OMe	Components			
			[a]	[b]	[c]	[d]
Fraction I	28.3	61.3	9.6	18.7		
Fraction II	3.2	55.0		2.4	0.8	
Fraction III	12.2	51.5			10.9	1.3
Fraction IV	5.8	43.4			0.8	5.0
Fraction V	25.2	41.9				25.2
Total	74.7		9.6	21.1	12.5	31.5

[a] Trimethyl-methyl-arabinoside. [b] Tetramethyl-methyl-galactoside. [c] Trimethyl-methyl-galactoside. [d] Dimethyl-methyl-galactoside.

A similar fractional distillation was performed upon the glycosidic sirup resulting from methanolysis of the partially hydrolyzed, fully methylated material. The results obtained are listed in Table IV, wherein calculation of fraction composition was again determined as previously. In this case, the arabinose component is based upon unchanged arabo-galactan in the partially hydrolyzed product as determined from the arabinose content thereof.

TABLE IV

FRACTIONAL DISTILLATION OF THE GLYCOSIDIC SIRUP FROM PARTIALLY HYDROLYZED, FULLY METHYLATED ARABO-GALACTAN

Distillate	Grams	OMe	Components			
			[a]	[b]	[c]	[d]
Fraction I	23.2	61.5	3.6	19.6		
Fraction II	2.9	54.5		0.6	2.3	
Fraction III	12.9	51.6			11.8	1.1
Fraction IV	6.7	43.8			1.2	5.5
Fraction V	15.5	41.9				15.5
Total	61.2		3.6	20.2	15.3	22.1

[a] Trimethyl-methyl-arabinoside. [b] Tetramethyl-methyl-galactoside. [c] Trimethyl-methyl-galactoside. [d] Dimethyl-methyl-galactoside.

Separation of 2,4,6-Trimethyl-galactose from 2,3,4-Trimethyl-galactose.—The distilled fraction containing the major portion of trimethylgalactoside, Fraction III, Table IV, was hydrolyzed (5.0 g.) in 50 cc. *N* sulfuric acid on the boiling water-bath for twelve hours. The product was isolated in the usual manner and distilled under high vacuum [b. p. 150° (0.1 mm.)] yielding trimethyl galactose as a sirup; yield, 4.8 g. (Found: OMe, 41.8. Calcd. for $C_9H_{18}O_6$: OMe, 41.9).

A partial separation of 2,3,4-trimethyl-galactose from 2,4,6-trimethyl-galactose can be achieved through fractional crystallization of the corresponding anilides from ether–alcohol solution. A more satisfactory method was developed through the preferential reaction of the 2,3,4-

trimethyl derivative with triphenylchloromethane. Accordingly, 2.5 g. of the sirup was treated with 3.0 g. of triphenylchloromethane in 12 cc. of pyridine solution at room temperature for two days. The reaction mixture was then triturated with a small quantity of water to dissolve pyridine hydrochloride and the solution poured into an excess of rapidly stirred ice-water. The insoluble trityl derivative settled out as a gum along with residual reactant. After standing in the icebox with occasional stirring, the solution (A) was decanted from the granular residue. The latter, washed with fresh ice-water, dissolved in acetone, dried over magnesium sulfate, decolorized with norite, filtered and evaporated to a thin sirup, deposited crystals of triphenylcarbinol. The mother liquor, upon evaporation to a sirup (0.9 g.) and treatment with aniline (0.4 g.) in absolute ethanol under reflux for three hours, crystallized upon removal of solvent. Recrystallization from absolute ethanol gave the anilide of 2,3,4-trimethyl-6-trityl-galactose; yield, 0.7 g., m. p. 152°. (Found: OMe, 17.1. Calcd. for $C_{34}H_{37}O_5N$; OMe, 17.2).

The solution (A) containing unreacted 2,4,6-trimethyl-galactose was neutralized with silver carbonate and filtered. Silver ion was removed with hydrogen sulfide, and, after filtering, decolorizing with norite, and evaporating excess solvent, a sirupy residue was obtained; yield, 1.0 g. (Found: OMe, 52.2. Calcd. for $C_9H_{18}O_6$: MeO, 52.5).

The sirup, upon treatment with aniline (0.5 g.) in the usual manner crystallized upon removal of solvent. Recrystallization from ether–alcohol solution gave 2,4,6-trimethyl-galactose anilide; yield, 0.9 g., m. p. 178°.[11] (Found: OMe, 31.4. Calcd. for $C_{15}H_{24}O_5N$: OMe, 31.4.)

Summary

1. Fractional distillation of the glycosidic sirup obtained upon methanolysis of arabo-galactan methyl ether yields three main fractions. These are, respectively, dimethyl-methyl-galactoside, trimethyl-methyl-galactoside, and a mixture of tetramethyl-methyl-galactoside and trimethyl-methyl-arabinoside.

2. Based upon the 6:1 molecular ratio of galactose to arabinose in the original polysaccharide, the molecular ratio of the glycosidic components is 3:1:2:1, respectively.

3. The arabinose component of arabo-galactan is joined to a tri-linked galactose residue.

4. The position of such linkage is through the 1 position of the arabinose component to the 6 position of the galactose residue.

(11) McCreath and Smith, *J. Chem. Soc.*, 390 (1939).

MOSCOW, IDAHO RECEIVED MARCH 4, 1942

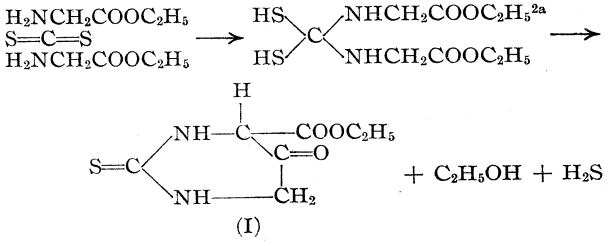
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

2-Thio-5-keto-4-carbethoxy-1,3-dihydropyrimidine and Related Compounds

BY JOHN H. YOE AND GEORGE R. BOYD, JR.

Sheppard and Brigham[1] described the preparation of a heterocyclic compound which gave a deep purple colored precipitate in the presence of silver ions and suggested that it might be used as a sensitive reagent for silver. Recently Yoe and Overholser[2] have employed this compound for the colorimetric determination of silver.

The compound, 2-thio-5-keto-4-carbethoxy-1,3-dihydropyrimidine, was prepared by the action of carbon disulfide on the ethyl ester of glycine. An intermediate product was formed, diethylaminoacetate dithiocarbamate, which upon further treatment with carbon disulfide eliminated hydrogen sulfide and ethyl alcohol, closing the ring and forming the desired product. The reaction as outlined by Sheppard and Brigham[1] is as follows



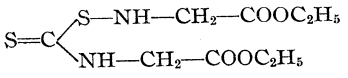
(I)

M. L. Huggins prefers to regard the structure (I) not as a closed heterocyclic ring, but as a chain which is chelated through a hydrogen bridge,[3] thus

(1) S. E. Sheppard and H. R. Brigham, THIS JOURNAL, **58**, 1046 (1936).

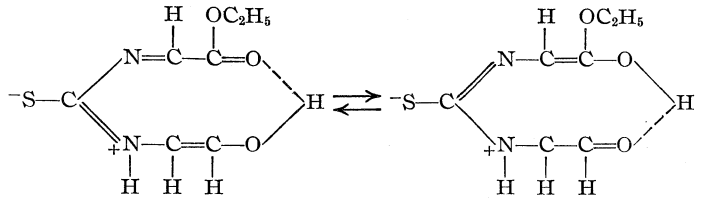
(2) J. H. Yoe and L. G. Overholser, *Ind. Eng. Chem., Anal. Ed.*, **14**, 148 (1942).

(2a) Sheppard and Brigham wrote the formula of this intermediate product with the following structure



Consideration of the arrangement of the electrons about the atoms, however, suggests that the structure first given is more likely.

(3) Private communication to the authors from Dr. S. E. Sheppard, Eastman Kodak Company.



The compound prepared in this manner is an orange solid which is very soluble in aniline, phenol, thymol, and hot ethylenechlorohydrin. It is soluble in hot acetophenone and slightly soluble in acetone, acetic acid, and hot benzene. It is insoluble in carbon tetrachloride, ligroin, and water. Its melting point is 276–280°.

In an attempt to confirm the structure of this silver reagent, Sheppard and Brigham[1] attempted to synthesize it by the condensation of thiourea with α,γ-dichloracetoacetate, but obtained only "a red oil which could not be crystallized."

First attempts to synthesize the compound in this Laboratory were made according to the published directions of Sheppard and Brigham,[1] but as the reaction gives only very small yields (on the order of 1%) and since only small amounts of ethyl glycinate were used, it was impossible to isolate any crystalline material by this means.

In a private communication to the authors, Sheppard and Brigham revised their procedure slightly, saying that it gave somewhat higher yields than their older one. Both procedures required the use of absolute alcohol, but it has been found in this Laboratory that the presence of a small amount (1%) of water in the alcohol is essential for the preparation of the cyclic compound.

Preparation of 2-Thio-5-keto-4-carbethoxy-1,3-dihydropyrimidine.—The best method of synthesis was found to be as follows: 50 g. of ethyl glycinate hydrochloride was suspended in 25 ml. of water in a separatory funnel and 30 ml. of a 40% solution of sodium hydroxide was added while shaking and cooling under running water. This was saturated with anhydrous potassium carbonate and then extracted with ether, using four 25-ml. portions. The extract was allowed to dry over anhydrous potassium carbonate for twenty-four hours. At the end of this time, the potassium carbonate was filtered off and washed twice with ether that had been dried over sodium. The filtrate was cooled in ice.

Eight milliliters of carbon disulfide was added to the ether solution of ethyl glycinate while stirring and cooling in ice. The diethylaminoacetate dithiocarbamate settled out as an oil and froze to a white solid upon further cooling. The ether was decanted and poured on 50 ml. of 99% alcohol at once (the intermediate product changed into a red oil upon prolonged contact with the air); 2 ml. of carbon disulfide was added and the solution was refluxed for forty-eight hours.[4] At the end of this time, the solution was quite dark in color. When the solution was cooled in ice and stirred, a large amount of precipitate appeared and was filtered off. The solution from this precipitation was evaporated to about one-half of its original volume; an orange red precipitate settled out, and this was filtered off and recrystallized from ethylene chlorohydrin. The compound so formed melted at 275° and gave a very intense purple color when a 0.025% solution in acetone was treated with silver nitrate solution. The amount of the orange compound thus obtained was about 0.3 g.

Following the same procedure except for the use of absolutely dry reagents (absolute alcohol was prepared by distilling alcohol dried over lime from sodium methylate and ethyl phthalate; carbon disulfide dried over "Drierite") and with the reactions carried out in an atmosphere of nitrogen, a yellow compound was obtained. This compound was purified by recrystallizing from dioxane. The melting point was 181° and the compound gave a red color reaction with silver.

If more than 1% of water is present in the alcohol, the yield of (I) is decreased; only about 150 mg. was obtained using alcohol containing 1.5% of water.

Additional Compounds

Since the above procedures for the synthesis of the silver reagent gave, at best, only very poor yields of the desired product, several related compounds were prepared in an attempt to find some compound which would be comparable in sensitivity toward silver, but which could be more easily prepared. The starting material in every case was diaminoacetone which was synthesized from citric acid by the method of Kalischer[5] as improved by Koessler and Hanke.[6]

The diamine, in the form of its dihydrochloride, can be purified by recrystallizing from water. *Anal.* Calcd. for $C_3H_8ON_2 \cdot 2HCl$: N, 17.39. Found: N (Dumas), 17.24; (Kjeldahl), 17.31.

Diaminoacetone is quite reactive and can be coupled with several reagents to give cyclic compounds. These were investigated as possible sensitive reagents for silver.

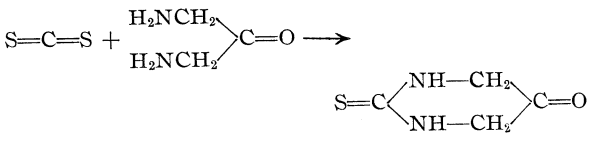
Van Alphen[7] has shown that diamines react with carbon disulfide forming cyclic compounds, and so it was thought that diaminoacetone should react with carbon disulfide according to the scheme.

(4) S. E. Sheppard reports that the yield of 2-thio-5-keto-4-carbethoxy-1,3-dihydropyrimidine may be greatly increased by adding hydrogen peroxide in aqueous solution just before refluxing the alcoholic solution of diethylaminoacetate dithiocarbamate. In one experiment in which 20 ml. of 2.5% aqueous solution of hydrogen peroxide was added to 80 ml. of an alcoholic solution of the dithiocarbamate (obtained from 13 g. of ethylglycinate hydrochloride) before refluxing, a 12.6% yield of the purified orange compound was obtained. This is about a ten-fold increase in the yield previously obtained. Stronger solutions of hydrogen peroxide and also sodium peroxide are now being tried. Private communication from Dr. S. E. Sheppard.

(5) G. Kalischer *Ber.*, **28**, 1519 (1895).

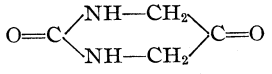
(6) K. K. Koessler and M. T. Hanke, THIS JOURNAL, **40**, 1716 (1918).

(7) J. Van Alphen, *Rec. trav. chim.*, **55**, 412 (1936).



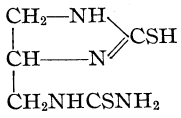
Diaminoacetone dihydrochloride was dissolved in hot alcohol and hot alcoholic sodium hydroxide then added in sufficient quantity to neutralize all hydrochloric acid. An equivalent amount of carbon disulfide was then poured into the solution, causing a vigorous reaction. A brown precipitate formed immediately, which was filtered off and dried at 110°. This compound gives a white precipitate with silver ions which decomposes into silver sulfide upon standing.[8] The compound decomposes without melting at about 150°.

Chloroformic ester was added to a hot alkaline solution of diaminoacetone, yielding a white precipitate which Rügheimer and Mischel[9] say is probably a derivative of urea having the formula

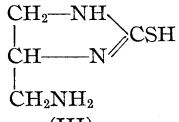


This compound gives a white precipitate with silver ions.

According to Pyman[10] two products are obtained when diaminoacetone is treated with potassium thiocyanate



(II)



(III)

Diaminoacetone dihydrochloride was heated on a water-bath for ninety minutes with the theoretical amount of potassium thiocyanate causing the formation of a white precipitate. The two products were separated by heating with water in which most of the precipitate dissolved leaving only a small residue. This residue, which melts at 212° with decomposition, is only very slightly soluble in acetone and alcohol. In acid solution, however, it gives a yellow precipitate with silver ions. This seems to be compound (II).

If the aqueous solution is allowed to crystallize, another compound is obtained which darkens at 240° but does not melt even when heated to 350°. This compound gives a white precipitate with silver and presumably is compound (III).

It is apparent from the reactions of the various compounds with silver ions that those with simpler structures give white or light colored precipitates and that only compound (I) gives a highly colored precipitate and hence is the most sensitive reagent for silver.

Rhodanine, which is closely related to these compounds, behaves in an analogous manner. Thus, Feigl[11] found that the condensation product of rhodanine with *p*-dimethylaminobenzaldehyde gave a more highly colored precipitate with silver ions than did rhodanine itself.

Acknowledgment.—Our thanks are expressed to Professors Robert E. Lutz and Alfred Burger for helpful suggestions during the course of this investigation.

Summary

2-Thio-5-keto-4-carbethoxy-1,3-dihydropyrimidine has been prepared by a modification of the Sheppard and Brigham method. Several related compounds have also been made. The reactions of these compounds with silver ions have been studied; only the former is a sensitive reagent for silver.

(8) Sheppard and Brigham[1] also prepared this compound by another method and report this reaction with silver.

(9) S. E. Rügheimer and E. Mischel, *Ber.*, **25**, 1562 (1892).

(10) F. L. Pyman, *J. Chem. Soc.*, **99**, 668 (1911).

(11) F. Feigl, *Z. anal. Chem.*, **74**, 380 (1938).

UNIVERSITY, VA. RECEIVED MARCH 31, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS]

Adsorption of Organic Compounds. I. Adsorption of Ampholytes on an Activated Charcoal*

BY VERNON H. CHELDELIN AND ROGER J. WILLIAMS

During recent years charcoal adsorption has become an important operation in the purification of materials of biological importance. It has been especially useful in the concentration and isolation of several of the water-soluble vitamins, the wound hormone traumatin[1] and the amino acid methionine.[2]

Amino acids as a class might be expected to be adsorbed considerably less than the parent carboxylic acids, due to their salt forming properties and high water solubilities. A few experiments by Phelps and Peters[3] and Bartell and Miller[4] indicate that glycine and alanine are not adsorbed at all on Norite or sugar charcoal, and that aspartic acid and glutamic acid are only slightly adsorbed, with a maximum near the isoelectric point. Ito[5] observed marked adsorption of the

* Original manuscript received August 5, 1941.

(1) English and Bonner, *J. Biol. Chem.*, **121**, 791 (1937).

(2) Mueller, *Proc. Soc. Exptl. Biol. Med.*, **18**, 14 (1921).

(3) Phelps and Peters, *Proc. Roy. Soc.* (London), **124A**, 554 (1929).

(4) Bartell and Miller, THIS JOURNAL, **45**, 1106 (1923).

(5) Ito, *J. Agr. Chem. Soc., Japan*, **12**, 204 (1936); through *Chemical Abstracts*, **30**, 6265[2] (1936).

basic amino acids lysine, histidine and arginine. Wunderly[6] obtained adsorption isotherms for phenylalanine, leucine, alanine, serine and aspartic acid on animal and sugar charcoals.

Further information regarding the charcoal adsorption of organic ampholytes is lacking. It was therefore decided to begin a systematic study of the problem by obtaining adsorption isotherms for thirty-three amino acids, vitamins and related compounds on one charcoal, with emphasis upon discovering differences in adsorption produced by constitutive differences within the molecules of the different adsorbates.

Experimental

Adsorbent.—The adsorbent used in the present investigation was Darco G-60, a commercial grade lignite charcoal which is in general a very effective adsorbent.[6a] Its ash content (practically all non-leachable) is 4% and the charcoal was used as received since information was first desired with respect to an adsorbent which finds common laboratory and commercial use. Adsorption studies using other charcoals will be discussed in another communication.

Method of Measuring Concentrations.—Measurements of all amino acid solutions and some of the others were made by the interferometric method.[7] The instrument used was of the Zeiss portable water type and was calibrated for each adsorbate by obtaining readings of several solutions of known concentrations. After adsorption and centrifuging, readings were made and the residual concentrations were calculated by comparison with the standards. The inorganic constituents of the charcoal were not leached away by this procedure, so that it was possible to detect concentration changes as small as 10 mg. per liter.

The lower concentrations of calcium pantothenate, β-alanine, biotin, pyridoxin and thiamin after adsorption were determined by microbiological assay methods developed in this Laboratory.[8,9]

Duplicate determinations were made for each experimental point. The number of duplicate experiments ranged from three to ten for each substance tested, averaging five or six.

Procedure.—Samples of the adsorbent were weighed into 50-cc. Erlenmeyer flasks. To these were added the desired volumes of various concentrations of a given solution. The amounts varied from 25 ml. to 2 liters per gram of carbon, depending upon the solute used. The flasks were stoppered and shaken for thirty minutes, after which the solutions were centrifuged, decanted and their concentrations determined in the interferometer.

Experiments were run at room temperature, which was usually about 25° but at times rose to 35°. Other workers[10] have found little change in adsorption over this temperature range.

Preliminary experiments with asparagine showed that adsorption was essentially complete in a very few minutes. This is in line with general experience in so far as adsorption is a reversible process.

The substances tested were adsorbed from pure solutions with no special effort being made in most instances to control their *p*H, since ampholytes in solution tend to maintain *p*H values near their isoelectric points. Comparison of the *p*H values of many amino acid solutions before and after adsorption revealed relatively little change in *p*H (Table I). In the cases of pantothenic acid and biotin dilute solutions of aspartic acid (0.0025 *M*) were added to buffer the systems near the isoelectric points of these substances.

Treatment of Adsorption Data.—Any attempt to reduce adsorption behavior to a simple mathematical expression usually results in the adoption of the well-known Freundlich equation.[11] In almost all cases in the present study the Freundlich equation was found applicable. The Langmuir equation[12] has been found in our work to be less useful.

Data and Results

The data obtained for each adsorbate are listed in Table II. The values of $1/n$ and k were determined from adsorption isotherms (not shown) derived from the experimental data.

It may be observed from Table II that, contrary to previous reports,[3,4] glycine and alanine are definitely adsorbed, although only slightly. The amounts adsorbed are less than for the parent carboxylic acids, but increase with increasing members of a homologous series. This is in accordance with adsorption experience in general.

The introduction of an amino group into the carboxylic acid molecule more than doubles the values of $1/n$ in the Freundlich equation. The

TABLE I

*p*H OF AMINO ACID SOLUTIONS BEFORE AND AFTER ADSORPTION

Substance	Maximum concn., g./l.	*p*H Before adsorption	*p*H After adsorption	Minimum concn., g./l.	*p*H Before adsorption	*p*H After adsorption
Serine	13.4	6.0	6.2	0.84	6.1	6.7
Aspartic acid	7.2	3.3	3.3	.90	3.4	3.8
Threonine	14.6	5.7	5.5	.91	5.6	6.0
Glycine	50.0	5.8	5.7	3.1	6.1	5.9
Nicotinic acid	1.00	3.4	3.4	0.250	3.6	3.7
Valine	3.94	6.2	6.2	.246	6.6	6.4
Creatine	5.00	7.1	6.8	.313	6.9	6.2
Leucine	2.50	5.9	5.8	.156	6.2	5.8

(6) Wunderly, *Helv. Chim. Acta*, **17**, 523 (1934).

(6a) Thanks are extended the Darco Corporation for their donations of materials used in this work.

(7) Bartell and Sloan, THIS JOURNAL, **51**, 1637 (1929).

(8) Williams, Lyman, Goodyear, Truesdail and Holaday, *ibid.*, **55**, 2912 (1933).

(9) Williams, *et al.*, *The University of Texas Publications*, No. 4137 (1941).

(10) Yajnik and Rana, *J. Phys. Chem.*, **28**, 267 (1924).

(11) Freundlich, *Z. physik. Chem.*, **57**, 385 (1906).

(12) Langmuir, THIS JOURNAL, **40**, 1361 (1918).

TABLE II

ADSORPTION OF AMPHOLYTES ON DARCO G-60

Substance	Equilibrium concn., moles/liter Maximum	Minimum	Mg. carbon per cc. of solution	$1/n$	k	Average dev., %
Acetic acid	1.69	0.0070	20	0.34[e]	0.0032	±0.8[a]
Propionic acid	1.26	.0201	20	.31[e]	.0044	±0.5
Glycine	0.659	.082	50[b], 20	.76	.00023	±5
dl-Alanine	.225	.0145	20	.86	.00083	±2
β-Alanine	.394	.0000057	20[c], 40	.64	.00050	±7
dl-α-Aminobutyric acid	.280	.0168	20	.75	.0015	±1.7
dl-Norleucine	.0402	.00079	20	.45	.0048	±0.4
dl-Valine	.0276	.00156	20	.82	.0056	±1
dl-Leucine	.0124	.00051	20[d], 10	.50	.0054	±0.3
dl-Isoleucine	.137	.00092	20	.50	.0054	±0.5
dl-Serine	.125	.0076	20	.63	.00051	±8
dl-Threonine	.125	.0098	20	.83	.0014	±2
dl-Methionine	.0161	.00055	10	.61	.011	±0.4
l-Lysine	.0446	.00522	10	.68[e]	.0051	±2
l-Aspartic acid	.0414	.00315	20	.70	.0059	±0.8
	.0360	.00377		.66[f]	.0041	±0.1
l-Asparagine	.164	.00377	20	.64	.0022	±0.3
				.65	.0023	±2
Benzoic acid	.0081	.00042	2	.24	.013	±0.6
Aniline	.164	.0041	10	.26	.010	±0.2
o-Aminobenzoic acid	.0113	.00090	2	.16	.0071	±0.5
m-Aminobenzoic acid	.0125	.00145	2	.16	.0057	±0.3
p-Aminobenzoic acid	.0117	.00140	2	.12	.0045	±0.3
Nicotinic acid	.00593	.00067	1	.22	.0069	±3
dl-Phenylalanine	.0489	.00075	1	.10[e]	.0023	±1.3
l-Tyrosine	.00014	.000031	0.5	.30[g]	.011	±10
dl-Tryptophan	.00340	.00284	0.5	.10[e]	.0032	±0.3
Urea	.762	.0419	40	.66	.0021	±1
d-Glucose	.093	.0042	20	.54	.0033	±0.4
i-Inositol	.0570	.00536	20	.86	.0042	±1
l-Hydroxyproline	.0500	.00250	20	.79	.0032	±1
Caffeine	.0145	.00124	2	.10	.0033	±1
Creatine	.0367	.00170	1	.15	.0023	±4
Creatinine	.0862	.00448	1	.26	.0044	0
Calcium pantothenate (dextro)	.024	.00000019	0.5	.69	.39	±10
Calcium pantothenate (from liver extract)	.00334	.000000230	.5	.56	.026	±10
Biotin	.000000037	.000000000092	.1	.69	.53	±10
Pyridoxin hydrochloride	.00335	.00000097	2	.38	.0062	±15
Thiamin hydrochloride	.00107	.00000013	0.3	.66	.30	±10

[a] The per cent. average deviation is the average of the deviations obtained at all concentrations. [b] 50 mg. carbon per cc. solution in the first two cases, 20 mg. per cc. in the last three. [c] 20 mg. carbon per cc. solution for the five highest concentration levels, 40 mg. per cc. for the lower five. [d] 20 mg. carbon per cc. solution at the highest concentration, 10 mg. per cc. in the others. [e] In this case the logarithmic plot is not a straight line. The value of $1/n$ increases with dilution. [f] Duplicate determinations made nine months later with a different sample of charcoal. [g] This value does not fit in well with generalizations presented later, but is only very approximate due to experimental difficulties involved in obtaining sufficient data regarding a compound of such low solubility. In several similar cases the $1/n$ values increased with dilution.

higher homologous alpha amino acids have somewhat lower $1/n$ values compared to the lower members and branched chain amino acids seem to have higher $1/n$ values than the corresponding straight chain acids. The position of the amino group appears to be important, for β-alanine has a lower $1/n$ value than either α-alanine or α-aminobutyric acid.

The introduction of additional functional groups causes at most a slight rise in the $1/n$ value. The effect of these additional groups on the *amount* of adsorption is in the opposite direction, however, as was the case with the monoamino monocarboxylic acids mentioned above.

Striking differences exist between aromatic and

aliphatic compounds, both in the values of $1/n$ and in the amounts adsorbed.

While the difference in $1/n$ for the representative carboxylic acids (acetic, benzoic) is not large, the difference becomes much greater when amino groups are introduced; for whereas among aliphatic acids the $1/n$ values are increased by the presence of polar groups, the effect of these groups when placed on the aromatic nucleus is to *lower* the $1/n$ values. The difference in $1/n$ for alanine and phenylalanine is most striking, and illustrates the influence of the benzene nucleus on adsorption.

The relation between the amounts of adsorption and the trend in $1/n$ values is opposite in aromatic compounds to that found among the aliphatic compounds.

The adsorption data for various nutrilites is as varied as might be expected on the basis of the structures of the nutrilites themselves.

Calcium pantothenate, β-alanine, thiamin hydrochloride and inositol are all non-aromatic compounds with several polar groups. Their $1/n$ values are high (above 0.6) in accordance with the previous discussion. The aromatic compounds nicotinic and p-aminobenzoic acids and pyridoxin hydrochloride have low $1/n$ values (below 0.4). Biotin, the structure of which is unknown, on this basis would be expected to be non-aromatic ($1/n = 0.69$), provided of course that the extrapolated curve is valid over the extremely wide range for which as yet no experimental data are available.

It is worthy of note that the adsorption data for several of the nutrilites follow the Freundlich equation through extremely wide concentration ranges. By using microbiological tests it has been possible in some cases to measure adsorption from solutions far more dilute than has hitherto been possible in dealing with organic compounds. The application of the Freundlich equation through a wide range is somewhat contrary to results obtained with certain other substances studied within a much narrower range.

Summary

1. Adsorption isotherms have been obtained for thirty-three amino acids, vitamins and related substances using Darco G-60 as the adsorbent. The experimental data fit the equation commonly known as the Freundlich adsorption isotherm.

2. Several generalizations have been evolved from the data which show certain trends (based upon structure) in adsorption and in the $1/n$ values of the Freundlich equation. The presence and position of polar groups and the presence or absence of aromatic nuclei are important factors.

AUSTIN, TEXAS RECEIVED MARCH 23, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

Studies on High Molecular Weight Aliphatic Amines and their Salts. VII. The Systems Octylamine–, Dodecylamine– and Octadecylamine–Water

BY A. W. RALSTON, CHARLES W. HOERR AND EVERETT J. HOFFMAN

Previous studies upon the behavior of aliphatic amines in water have been concerned only with amines of low molecular weight, and the literature pertaining to the higher homologs in water is confined to statements regarding their solubility. Preceding papers of this series have reported some aspects of the behavior of the hydrochlorides and acetates of primary aliphatic amines containing from 8 to 18 carbon atoms in the paraffin chain. This paper reports the behavior of octyl-, dodecyl- and octadecylamines in water. Since these three amines represent a cross-section of the series of normal primary aliphatic amines, a comparison of their water systems illustrates the effect of increased length of the alkyl chain upon such systems.

The applicability of the phase rule to colloidal systems has been demonstrated with respect to soap phases by McBain and his co-workers.[1] While they have shown that the phase rule can be applied in its usual form without the introduction of any new variable, they point out several of the assumptions and interpretations which must necessarily be made to fit the phase rule to some of the phenomena encountered in colloid chemistry. Of course, the original Gibbs deduction of the phase rule specifically excludes the effects of surface and boundary forces which are so important in connection with colloidal behavior; hence, in some cases certain observations must be omitted

(1) McBain, Vold and Vold, THIS JOURNAL, **60**, 1866 (1938).

or ignored. In other cases relative importances must be determined before an interpretation can be made. For example, no absolute meaning can be attached to the definitions of homogeneity and heterogeneity, since in dealing with colloids the degree of dispersion of the various phases has considerable bearing on their behavior.

Further complexities in the application of the phase rule to colloidal systems, aside from the confusion of the terminology, arise from the experimental difficulties encountered in dealing with these systems. The problem of establishing and maintaining equilibrium conditions is often an obstacle presented by the nature of the substances under observation. At certain temperatures the liquid phases may possess a very high viscosity, or the solid phases may exist in gelatinous or mesomorphic states. Hence, there is a problem of maintaining intimate admixture of the phases to bring about an equilibrium between them. In some cases, too rapid cooling may introduce a false phase which may not disappear for such a length of time that it would appear to be a true equilibrium phase. While these metastable phases have a given place in the phase diagram, they are misleading in the investigation of the stable phases. Thus it is essential, in studying a given phase, to demonstrate that equilibrium can be attained from higher and lower temperatures, and from higher and lower concentrations.

Procedure

Preparation of Materials.—Caprylonitrile, lauronitrile and stearonitrile were prepared by the action of ammonia upon the respective acids.[2] The caprylonitrile and lauronitrile ($n^{25}D$ 1.4184 and 1.4342, respectively) were purified by vacuum distillation,[3] and the stearonitrile (m. p. 42.0–43.0°) was crystallized from 95% ethanol. These nitriles were hydrogenated to the corresponding amines, which were then purified by fractional distillation *in vacuo*.[4] The amines used in this investigation had the following boiling points: octylamine, 46.5° (4 mm.); dodecylamine, 81.4° (1 mm.); and octadecylamine, 153.2° (1 mm.). Their freezing points, determined by the cooling curve method (*vide infra*), were −1.0, 28.0 and 52.5°, respectively. Titration with standard hydrochloric acid solution using methyl red as the indicator, in all cases yielded values exceeding 99.95% amine. These compounds were exposed to the atmosphere as little as possible in order to minimize absorption of carbon dioxide.

The water used in most of these experiments was distilled from an alkaline potassium permanganate solution in an all-Pyrex glass still, and was used in making up the amine samples directly after cooling without access to the air. Its specific conductance was 0.8×10^{-6} mho at 25°. The carbon dioxide content, therefore, was at a minimum. For the cooling curve measurements, boiled distilled water was used.

Experimental.—Five methods of investigation were followed. In every case, each amine–water sample prepared was first heated until it became a homogeneous liquid, or, in the ranges of concentrations where the systems do not become homogeneous at ordinary temperatures, until both components were liquefied and could be intimately mixed by shaking or stirring. This precaution has been stressed as a most desirable prerequisite in dealing with colloidal substances.[1]

The first experimental procedure was a synthetic method in which weighed amounts of the two components were sealed in glass tubes. After preliminary heating, the samples were suspended in a constant temperature water-bath and shaken regularly. The temperature of the bath was changed 0.1 to 0.2° about every half hour and the samples were observed visually to determine what phases were present. Since the various phases were arrived at both from higher and lower temperatures, and since the observed transition temperatures obtained in this manner could be duplicated within ±0.1°, it was considered that equilibrium had been attained.

The second method was an analytical procedure. Various compositions of amines and water (of approximately 50 g. total weight) were prepared in tightly stoppered flasks and, after preliminary heating, were placed in a constant temperature water-bath at several given temperatures. The flasks were shaken intermittently for two to three hours to allow the samples to attain equilibrium. Preliminary experimentation indicated that equilibrium was reached well within this time. After this interval, the separate phases were removed by means of a pipet and analyzed for amine content by titration with standard hydrochloric acid solution using methyl red as the indicator. The results obtained by this method showed that the analyses of samples existing in given phases at given temperatures gave calculated compositions of amine which agreed within 0.1% of those predicted by the synthetic method.

Cooling curves were run on amine–water mixtures in the following manner: an amine–water sample (10 g.), after being prepared in a tightly stoppered flask and heated to liquefaction, was transferred to a transparent Dewar flask (100 ml.) fitted with a rubber stopper through which were inserted a glass stirrer and a glass thermocouple well. This flask was swept with nitrogen before the introduction of the sample, and the stirrer was sealed at its insertion through the stopper with stopcock lubricant to minimize diffusion of carbon dioxide into the sample. Iron–constantan thermocouples were employed, and the reference junction was immersed in melting ice kept in a silvered Dewar flask (2 l.). Ice and water were used as the cooling bath for the amine–water samples above 0°, and acetone and solid carbon dioxide were used below this temperature. The thermal analyses thus obtained, for the most part, gave transition temperatures which agreed within ±0.1° of those obtained from the visual observations. However, in the cases in which samples containing the most highly hydrated forms of the two higher amines went through

(2) Ralston, Harwood and Pool, THIS JOURNAL, **59**, 986 (1937).
(3) Ralston, Selby and Pool, *Ind. Eng. Chem.*, **33**, 682 (1941).
(4) Ralston, Selby, Pool and Potts, *ibid.*, **32**, 1093 (1940).

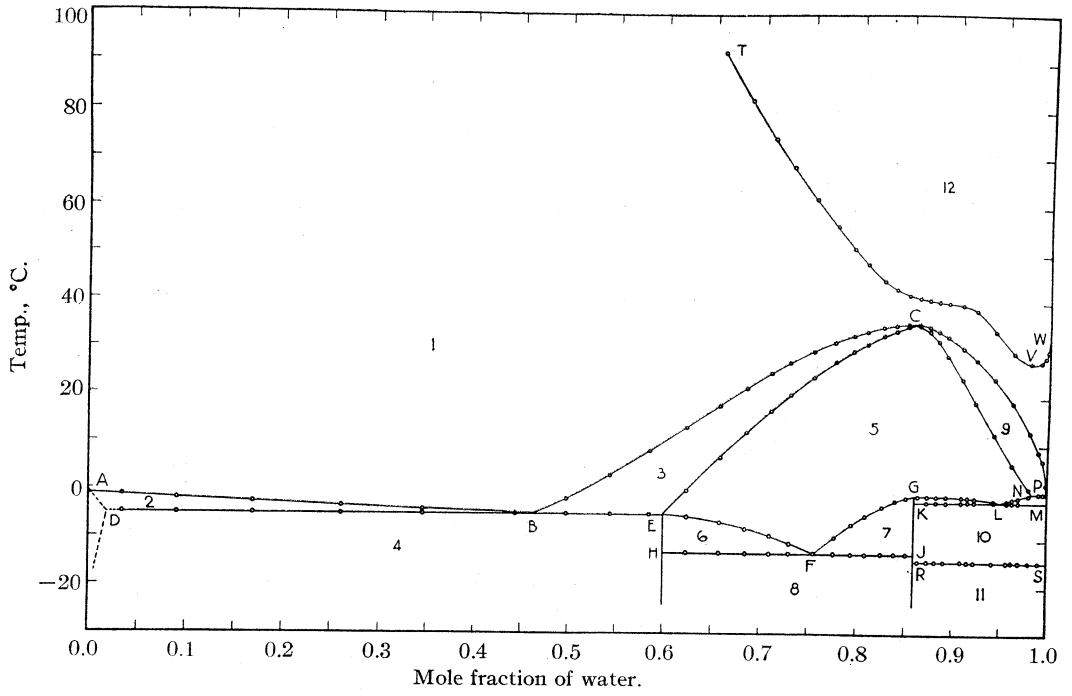


Fig. 1.—Transition temperatures of the system octylamine–water.

mesomorphic changes before crystallization, the cooling curves gave less accurate results because of the slower rate of heat transfer within the samples and the slow rate of formation of the crystalline phases.

Several of the transitions, chiefly the lowering of the freezing point of water by solution of the amines, were determined with a Beckmann thermometer in the usual manner. The transition temperatures obtained by this method agreed well within 0.1° of those obtained by the above procedures.

Finally, microscopic examinations with polarized light were made on a number of samples of varying composition in order to determine more definitely what phases were present. The samples were placed on ordinary glass slides and inclosed with thin glass cover slips sealed with paraffin. Observations were made chiefly at room temperature. However, some samples were heated gently over a small flame and were examined as they cooled. These observations verified the existence of the various phases in their given order as previously found by gross examination. Further observations of the order of appearance of certain phases were made by cooling the stage of the microscope below room temperature by means of a small piece of solid carbon dioxide.

Since transition temperatures could, in general, be duplicated to ±0.1°, and since the agreement of the results obtained by the various experimental procedures was also within ±0.1°, the transitions shown in the phase diagrams presented in this paper are probably accurate to ±0.2°.

Experimental Results

Octylamine–Water.—The temperature–composition relations of octylamine and water are shown graphically in Fig. 1. On this diagram, point A represents the freezing point of octylamine (−1.0°). Area 1 is isotropic solution. Two hydrates are formed, one having a composition of $(C_8H_{17}NH_2)_2 \cdot 3H_2O$ and the other $C_8H_{17}NH_2 \cdot 6H_2O$. The sesquihydrate exists as a crystalline solid below −5.0°, and above this temperature it breaks down to a mixture of hexahydrate and solution (area 3). The hexahydrate changes from a crystalline solid to a mesomorphic state at −14.5° (R). Between this temperature and −0.4° (G) it exists as a firm semi-solid of the smectic type of liquid crystal. From −0.4° (G) to its melting point, 34.6° (C), it exists as a nematic type of liquid crystal.

The portion of the diagram ABCED represents the equilibrium between octylamine and its hexahydrate. Octylamine precipitates from the isotropic solution (area 1) along AB and the hydrate precipitates along BC, giving a eutectic at B. Thus area 2 consists of a two-phase mixture of solid amine and solution, and area 3 of mesomorphic hydrate and solution. Below DBE (area 4) the system consists of a heterogeneous mixture of crystals. Microscopic examination of solutions at temperatures just below BC with polarized light shows the presence of inverted focal conics, indicating that the hydrate molecules are beginning to aggregate in liquid crystalline arrangements as the system cools below BC.

Examination of samples in area 5 shows a microscopically homogeneous fluid of a viscosity such that it will barely flow under its own weight at the lower temperatures, but of lower viscosity as the temperature is increased. Under polarized light, samples in this region reveal delicate thread-like lines of light, showing the presence of molecular layers in the liquid. The samples in this region can be considered to be one phase in accordance with the phase rule, analogous to the solid solutions of mixtures of metallic elements. In this case, however, instead of being a crystalline solid, the system consists of a highly dispersed mixture of amine and hydrated amine molecules in a mesomorphic state.

Octylamine sesquihydrate crystallizes from the isotropic solid solution (area 5) along EF while one of the forms of the hexahydrate precipitates out along FG, giving a eutectoid at F. Below HFJ (area 8) the system consists of a heterogeneous mixture of crystals.

The equilibria between the several forms of octylamine hexahydrate and water are in the concentration range of 0.857 to 1.0 mole fraction of water. The equilibrium between the nematic form of the hexahydrate and water is not shown clearly in the diagram. The eutectic between them (P) is located near 0.9996 mole fraction of water. Investigations in this neighborhood were considered relatively inaccurate since it was impossible to prevent contamination of such necessarily small amounts of amine with some carbon dioxide. However, measurement of the lowering of the freezing point of water along NP indicated that 0.0004 mole fraction of amine was in solution. The nematic octylamine hexahydrate precipitates from the isotropic solution (area 1) along CP, giving a two-phase mixture in area 9. On crossing CN, the microscopically homogeneous solid solution (area 5) is obtained.

On further cooling of the solid solution, smectic hexahydrate precipitates along GL, while water freezes along LN, giving a eutectoid at L. Thus below KLM (area 10) the system consists of a heterogeneous mixture of mesomorphic hydrate and ice. Since the crystalline hexahydrate forms at $-14.5°$, the system consists of a mixture of ice and hydrate crystals in area 11.

On being heated above TVW, the isotropic solution separates into two conjugate solutions, the layer of lower density being rich in amine, and the more dense one being water-rich. Analysis of the amine-rich layer by titration showed that the amount of octylamine at any given temperature was of the composition corresponding to that temperature on TV. The composition of the water-rich layer could not be determined accurately by analysis because small amounts of amine remained as a suspension of microscopic droplets in the water-rich layer.

Dodecylamine–Water.—The temperature–composition relations of dodecylamine and water are shown graphically in Fig. 2. On this diagram A represents the freezing point of dodecylamine (28.0°). Area 1 is isotropic solution. Three hydrates are formed, one having a composition of $(C_{12}H_{25}NH_2)_3 \cdot 2H_2O$, another $C_{12}H_{25}NH_2 \cdot 2H_2O$ and the third $C_{12}H_{25}NH_2 \cdot 4H_2O$. The lowest hydrate exists as a crystalline solid below 24.4° (F), while above this temperature it breaks down to a mixture of higher hydrate and solution. The dihydrate exists as crystalline solid below 15.4° (H), while between this temperature and 35.5° it exists as a smectic type of liquid crystal. At 35.5° the mesomorphic hydrate begins to liquefy, while at 36.5° (C) this mixture of hydrate and solution changes to isotropic solution. The dodecylamine tetrahydrate exists as crystalline solid below 14.0° (R), while above this temperature it exists as a smectic type of liquid crystal, changing to a form of the nematic type at 34.2° (P) and to another form of the latter type at 38.0° (O). At 48.0° (M) the tetrahydrate decomposes.

The equilibrium between dodecylamine and its dihydrate is similar to that between octylamine and its hexahydrate. Dodecylamine precipitates out of the isotropic solution (area 1) along AB, while the dihydrate freezes out along BC, giving a eutectic at B. Thus areas 2 and 3 consist of two phase mixtures, solid amine and solution, and solid dihydrate and solution, respectively. Below EBF (area 4) the system consists of a heterogeneous mixture of crystals of dodecylamine and its dihydrate.

Area 5 of this diagram is similar to area 5 of the octylamine–water system. Again the solid solution consists of a microscopically homogeneous mesomorphic mixture of amine and amine hydrate. As samples in this area are cooled, the lower hydrate precipitates out along FG and dihydrate freezes out along GH, giving a eutectoid at G. Below JGK (area 6) the system consists of a heterogeneous mixture of crystals of the two hydrates.

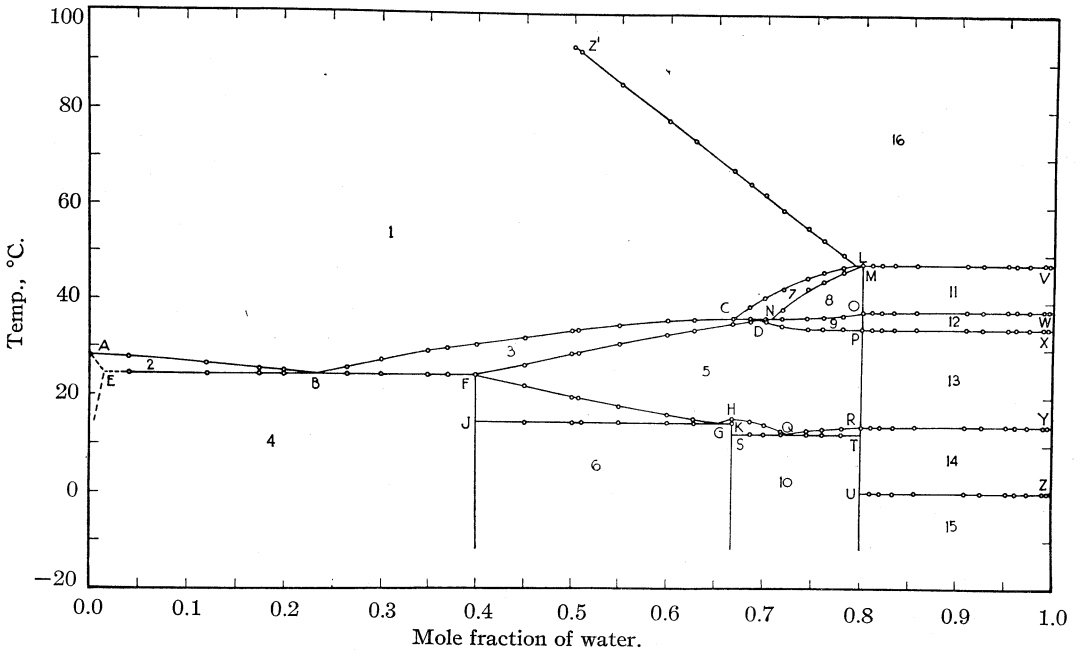


Fig. 2.—Transition temperatures of the system dodecylamine–water.

As the isotropic solution above CL is cooled, dodecylamine tetrahydrate freezes out, giving a two phase mixture of solid hydrate and solution in area 7. Below NM this mixture changes to a solid solution similar to that in area 5, while along NO the tetrahydrate transforms to another mesomorphic form giving a two phase mixture (area 9). On cooling this mixture, solid solution (area 5) is obtained.

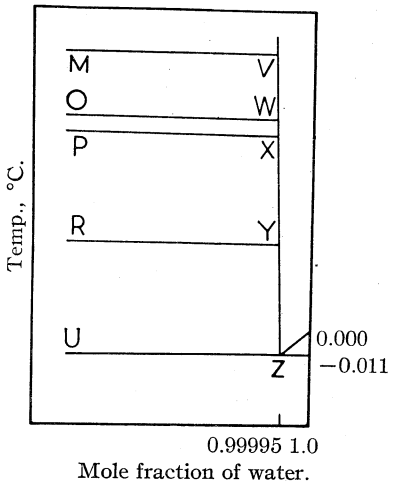


Fig. 3.—Diagram of eutectic between dodecylamine tetrahydrate and water (not drawn to scale).

Along HQ crystalline dodecylamine dihydrate freezes from the solid solution, while crystalline tetrahydrate appears along QR, giving a eutectoid at Q. Below SQT (area 10) the system consists of a mixture of these crystalline hydrates.

Beyond 0.8 mole fraction of water (MOPRTU), Fig. 2 shows the practically independent behavior of the various forms of dodecylamine tetrahydrate and of water. Measurements of the freezing point of water (along UZ) indicated that the eutectic between the tetrahydrate and water lies in the neighborhood of 0.99995 mole fraction of water. Hence, the isothermals (LMV, OW, PX, RY and UZ) intersect a curve (VWXYZ) representing the solubility of dodecylamine tetrahydrate in water. This region is illustrated by the enlarged diagram in Fig. 3. Thus, beyond 0.99995 mole fraction of water above Z to 0.0°, the system exists as isotropic solution.

In the part of the diagram between Z'LMOPRTU and VWXYZ in the temperature range investigated the system exists in all regions as two phases. In areas 11, 12 and 13 one of the phases is solution, and the other is the appropriate mesomorphic form of tetrahydrate (*vide supra*). In area 14 one of the phases is crystalline tetrahydrate, and the other is solution. In area 15 one phase is crystalline tetrahydrate, and the other is ice. Above LMV the system exists as two conjugate solutions similar to those occurring in the octylamine–water system (area 12, Fig. 1). The lines LMV, OW, PX and RY are isothermals. Their depression with increasing concentration is

well within the experimental accuracy of their measurement.

The portion of the diagram in the neighborhood of area 12 is a region of formation of a fibrous, curd-like solid of hydrated amine. This is a metastable compound which is frequently obtained on cooling the two phase mixture of mesomorphic tetrahydrate and solution, and is never obtained on heating the system. It is not found in the octylamine– and octadecylamine–water systems. If samples in which this metastable product is obtained are held at room temperature, transformation to the smectic form of the tetrahydrate and solution takes place slowly. The metastable compound, in some cases, has remained for several months.

In Fig. 4 are shown photomicrographs of the crystalline forms of dodecylamine and of its three hydrates, together with the appearance of the metastable curd-like compound.

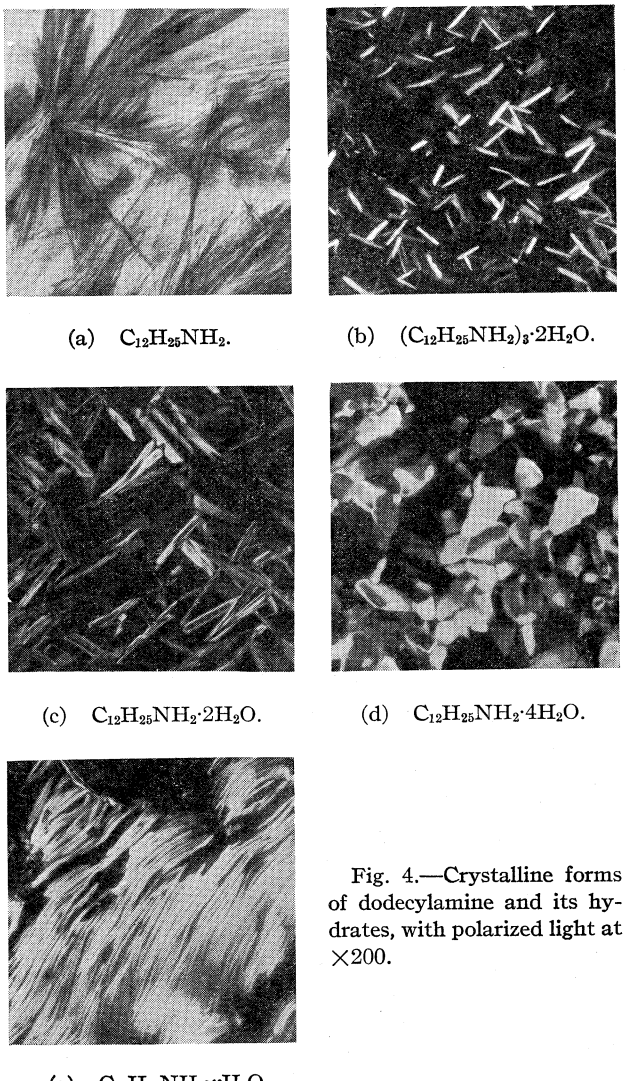
Octadecylamine–Water.—The temperature–composition relations of octadecylamine and water are shown graphically in Fig. 5. On this diagram A represents the freezing point of octadecylamine (52.5°). Area 1 is isotropic solution. Two hydrates are formed, one having a composition $(C_{18}H_{37}NH_2)_3 \cdot H_2O$, and the other $C_{18}H_{37}NH_2 \cdot 2H_2O$. The lower hydrate exists as crystalline solid below 50.5°, while above this temperature it breaks down to a mixture of dihydrate and solution. The dihydrate exists as crystalline solid below 43.3°, while above this temperature it transforms to a smectic state. At 64.0° the dihydrate decomposes.

In Fig. 5 octadecylamine crystallizes from the isotropic solution (area 1) along AB, while the dihydrate precipitates along BC, giving a eutectic at B. Thus areas 2 and 3 consist of two-phase mixtures of solid amine and solid dihydrate, respectively, and solution. Below EBF (area 4) the system consists of a heterogeneous mixture of crystals.

Samples in area 5 are solid solutions microscopically indistinguishable from the corresponding phase of the other amines (area 5, Figs. 1 and 2). On cooling this solid solution, the lower octadecylamine hydrate freezes out along FG and the dihydrate along GH, giving a eutectoid at G. Below JGK (area 6) the system consists of a mixture of the two crystalline hydrates.

The part of the diagram beyond 0.667 mole fraction of water (DHKL) represents the behavior of the several forms of the dihydrate with water. As in the case of dodecylamine tetrahydrate, there is a eutectic between the octadecylamine dihydrate and water similar to that shown in Fig. 3. As far as was determined, the solubility of this dihydrate in water must be less than 1.8×10^{-6} g./liter, since this amount must be in solution to lower the freezing point of water 0.001°. However, no such depression was observed by measurement with a Beckmann thermometer. Hence, the eutectic in this case is beyond 0.999991 mole fraction of water. No further attempt was made to determine more accurately the location of the solubility curve through MNP in Fig. 5.

Between DHKL and MNP the octadecyla-



(a) $C_{12}H_{25}NH_2$. (b) $(C_{12}H_{25}NH_2)_3 \cdot 2H_2O$.

(c) $C_{12}H_{25}NH_2 \cdot 2H_2O$. (d) $C_{12}H_{25}NH_2 \cdot 4H_2O$.

(e) $C_{12}H_{25}NH_2 \cdot xH_2O$.

Fig. 4.—Crystalline forms of dodecylamine and its hydrates, with polarized light at ×200.

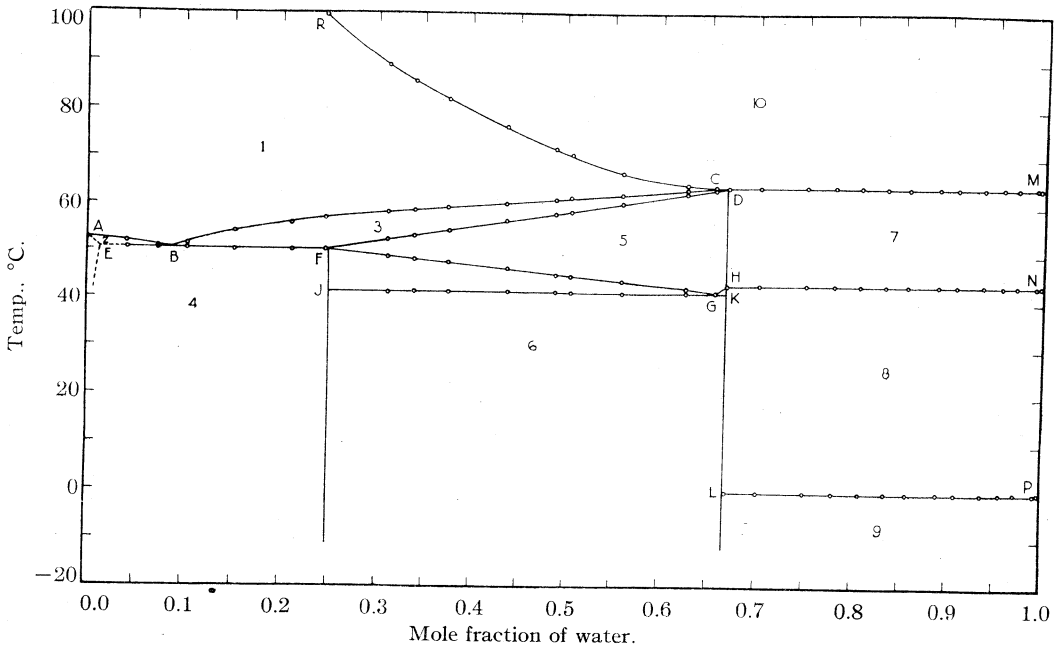
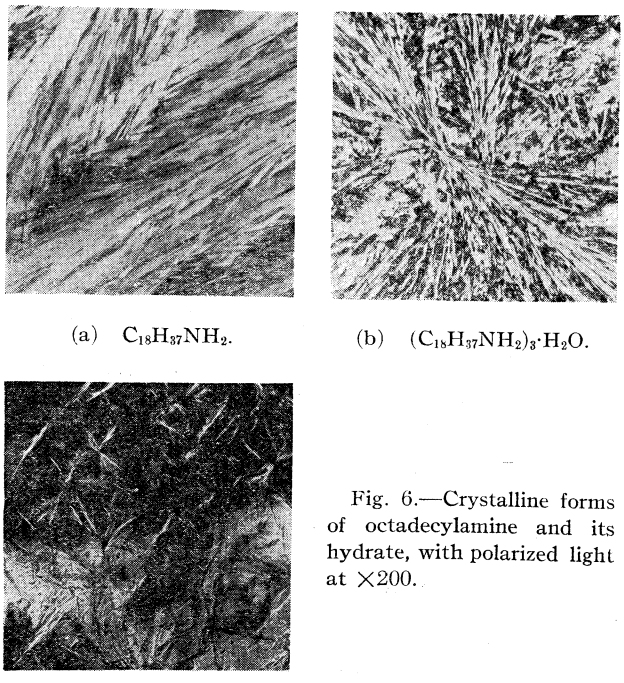


Fig. 5.—Transition temperatures of the system octadecylamine–water.

mine–water system exists as two phases in the temperature range investigated. In areas 7 and 8 one of these phases is solution and the others are mesomorphic dihydrate and crystalline dihydrate, respectively. Area 9 consists of a mixture of ice and dihydrate crystals. Above RCDM the system exists as two conjugate solutions similar to those in the other two systems investigated. The lines DM and HN are isothermals.

In Fig. 6 are shown photomicrographs of the crystalline forms of octadecylamine and its hydrates.



(a) $C_{18}H_{37}NH_2$. (b) $(C_{18}H_{37}NH_2)_3 \cdot H_2O$.

(c) $C_{18}H_{37}NH_2 \cdot 2H_2O$.

Fig. 6.—Crystalline forms of octadecylamine and its hydrate, with polarized light at ×200.

Discussion

Qualitatively the three systems investigated are similar. All three amines form hydrates; the higher the molecular weight, the lower the degree of hydration. Microscopic examinations indicated that hydrates of the lower amines tend to form more nearly perfect crystals than hydrates of the higher amines. As would be expected, the lower amines and their hydrates are considerably more soluble in water than the higher homologs. Of the systems investigated, that of octylamine–water is the only one in which there is an isotropic liquid region across the whole range of concentrations.

The amine hydrates found, with the exception of the lowest hydrate of each amine, pass through one or more mesomorphic states before their melting or decomposition points are reached. The hydrates of the lower members of the series tend toward the nematic type of liquid crystal, while those of the higher members tend toward the smectic type.

In the case of octylamine, the hexahydrate is relatively unstable, the water of hydration being very loosely bound to the amine molecules.

This is shown by the relative flattening of the curve as the melting point of the hydrate is approached from higher and lower concentrations, indicating that considerable change in the water content of the hydrate is necessary to change the melting point to any great extent. Since the addition of an impurity (in this case one of the decomposition products) tends to cause lowering of the melting point of a given compound, and since the lowering is greater with greater compound stability, the relative instability of this hydrate is indicated. The decomposition of the other amine hydrates is evidence of their instability.

The fibrous, curd-like, metastable compound formed only in the dodecylamine system suggests the behavior of dodecylamine hydrochloride in water.[5] In the latter system, also, a similar fibrous, curd-like, metastable compound was found on rapid cooling of systems containing large amounts of water. This behavior is not observed in the case of the octadecylamine hydrochloride–water system, and likewise it is absent in the present case of octadecylamine–water.

In each of the three diagrams presented the dotted lines at the left of the figures show the existence of a small region of solid solution of amine and amine hydrate. While these areas were indicated, their exact location was not verified by direct measurement.

With the interpretations and limitations which have been placed upon the mesomorphic states, and since equilibrium conditions have been evidenced by the agreement of the transition temperatures obtained by several different experimental methods, the applicability of the phase rule to these colloidal systems has been demonstrated. The equilibria between the amines and their respective hydrates are similar to phase diagrams for ordinary crystalloidal compounds. In the case of the higher amine hydrates, their insolubility and their mesomorphic changes account for the numerous isothermals which are present in their diagrams.

(5) Ralston, Hoffman, Hoerr and Selby, THIS JOURNAL, **63**, 1598 (1941).

The authors are indebted to Drs. J. A. Wilkinson and H. A. Wilhelm of Iowa State College for their assistance and helpful suggestions during the course of this investigation.

Summary

1. The systems octylamine–water, dodecylamine–water and octadecylamine–water have been investigated.

2. The phase rule has been applied to these systems.

3. The following hydrates have been found: $(C_8H_{17}NH_2)_2 \cdot 3H_2O$ (dec. −5.0°); $C_8H_{17}NH_2 \cdot 6H_2O$ (m. p. 35.6°); $(C_{12}H_{25}NH_2)_3 \cdot 2H_2O$ (dec. 24.4°); $C_{12}H_{25}NH_2 \cdot 2H_2O$ (m. p. 36.5°); $C_{12}H_{25}NH_2 \cdot 4H_2O$ (dec. 48.0°); $(C_{18}H_{37}NH_2)_3 \cdot H_2O$ (dec. 50.5°); and $C_{18}H_{37}NH_2 \cdot 2H_2O$ (dec. 64.0°).

CHICAGO, ILLINOIS RECEIVED JANUARY 12, 1942

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

Plumbic Acetate–Anhydrous Acetic Acid Solutions

BY ARTHUR W. DAVIDSON, W. CLARENCE LANNING AND SR. M. MAXINE ZELLER

It is well known that whenever a comparison is made between two hydroxides of the same metal, the one in which the metal is in the lower state of oxidation is the more basic and the more soluble in water. A partial qualitative explanation of this fact may be based upon the distribution of electrons about the metal atom.[1] Evidence of an analogous relationship in non-aqueous systems has hitherto been limited to observations on the solubilities of sulfates in sulfuric acid.[2]

The fact that plumbic acetate (lead tetraacetate), unlike most plumbic salts, is stable at ordinary temperatures and may, in fact, be prepared rather readily, affords an opportunity for a comparison of the solubilities of the two acetates of lead in anhydrous acetic acid, solutions of plumbous acetate in this medium having already been studied.[3] Hutchinson and Pollard,[4] who were the first to make an extensive study of the properties of plumbic acetate, reported that it is

(1) See, for example, O. K. Rice, "Electronic Structure and Chemical Binding," McGraw-Hill Book Company, Inc., New York, N. Y., 1940, pp. 428–9.

(2) Kendall and Davidson, THIS JOURNAL, **43**, 979 (1921).

(3) (a) Davidson and McAllister, *ibid.*, **52**, 507 (1930); (b) Davidson and Chappell, *ibid.*, **55**, 4524 (1933).

(4) Hutchinson and Pollard, (a) *J. Chem. Soc.*, **63**, 1136 (1893); (b) *ibid.*, **69**, 212 (1896).

not acted upon at ordinary temperatures by concentrated sulfuric acid, and it was confirmed in this Laboratory that plumbic acetate in acetic acid solution, unlike the plumbous salt, does not take part in rapid metathetic reactions (except with water); the compound behaves in this respect like a non-electrolyte. It seemed of interest, therefore, to compare the electrical conductivities of the two solutions.[5,6] Another property of the acetates which might be expected to vary greatly with the valence state of the lead is the tendency to form addition compounds with alkali acetates. Griswold and Olson[7] found the solubility of plumbous acetate in acetic acid to be increased in the presence of sodium acetate, although they were unable to obtain an addition compound of the two acetates in the solid state; Lehrman and Leifer,[8] however, showed the existence of potassium acetatoplumbites analogous to the hydroxoplumbites of the aqueous system.

In the present work, the solubility of plumbic acetate in acetic acid over a range of temperatures has been determined, the conductances at 30° of both plumbous and plumbic acetates have been measured, and the effect of sodium acetate upon the solubility of the plumbic compound has been studied. The results, in every case, were in accord with the hypothesis that plumbic acetate is an extremely weak electrolyte in this solvent.

Method

Preparation of Materials.—Anhydrous acetic acid, and sodium and plumbous acetates, were prepared as described in previous papers from this Laboratory. Plumbic acetate was prepared by crystallization from a solution made by adding red lead to hot glacial acetic acid, as described by Hutchinson and Pollard[4b]; their method was slightly modified, however, in that the product was recrystallized from anhydrous acetic acid and was dried over phosphorus pentoxide in a current of dry air. The product was analyzed by treatment with water to give lead dioxide and acetic acid; the precipitate was filtered off and weighed, while the filtrate was titrated with sodium hydroxide solution. A typical analysis gave: PbO_2, 54.00%; $(CH_3CO)_2O$, 46.07% (calculated for $Pb(C_2H_3O_2)_4$: PbO_2, 53.95; $(CH_3CO)_2O$, 46.05%).[9]

Solubility of Plumbic Acetate in Acetic Acid.—The solubility at various temperatures was determined both by synthetic and by analytic methods. In the former method, equilibrium temperatures were determined for samples of known composition as described in previous papers. The chief source of error in these determinations lay in the difficulty of preventing hydrolysis of the plumbic acetate by atmospheric moisture. Because of the extraordinary sensitiveness of the dry salt to hydrolysis, samples which had been moistened with acetic acid and subsequently analyzed were used in many of the determinations. It may be of interest to mention that the atmospheric humidity was an important factor in determining whether or not the dry salt could be handled successfully. When the humidity was high, even the briefest exposure to the atmosphere brought about appreciable discoloration, whereas at low humidity several samples could be removed successively from the same weighing bottle without discoloration of the residue. At several temperatures, also, mixtures containing an excess of solid salt were allowed to come to equilibrium, from both higher and lower temperatures, in a constant temperature bath. Samples of the liquid phase were drawn off, weighed, and analyzed for plumbic acetate content. Points obtained by both methods fall upon the same smooth curve.

Conductance Measurements.—These were all made at 30°, by means of a Leeds and Northrup bridge, an audio oscillator as a source of alternating current, and a type A Washburn cell; the conventional method was suitably modified for the measurement of low conductances. The specific conductivity of the acetic acid used was 3.8×10^{-8} reciprocal ohm, which is within the range of variation of the values given in the literature.

Solutions were made up by weight in stoppered 50-ml. flasks; each such solution was diluted several times with known weights of acetic acid, and the conductance measured after each dilution. In the case of plumbic acetate, the conductivity of the solutions differed so little from that of pure solvent that only specific conductivities have been reported. For plumbous acetate, which was found to approximate a weak binary electrolyte in behavior, the molar conductances were calculated.[10] Since the conductance of the solvent would probably be greatly decreased in acetate solutions, because of the common ion effect,[11] no solvent correction was applied.

Solubility of Plumbic Acetate in Sodium Acetate Solutions.—The method used for these determinations was the same as that described in a previous paper[12] for a similar study on zinc acetate. Acetic acid solutions were prepared containing six different concentrations of sodium acetate, and the solubility of plumbic acetate in each of these solutions, over a limited range of temperature (22 to 46°), was determined just as in the binary solutions. From these solubility curves data were obtained, by interpolation, to show the isothermal variation of solubility of plumbic acetate with sodium acetate concentration.

(5) Conductance data for solutions of plumbous acetate in 99.4% acetic acid are given by Schall and Meltzer, *Z. Elektrochem.*, **28**, 474 (1922). Molar conductances observed by them for this medium, however, are very much higher than for the anhydrous acid.

(6) A determination of the conductance of plumbous acetate in pure acetic acid at a single concentration is reported by Kolthoff and Willman, THIS JOURNAL, **56**, 1014 (1934).

(7) Griswold and Olson, *ibid.*, **59**, 1894 (1937).

(8) Lehrman and Leifer, *ibid.*, **60**, 142 (1938).

(9) Since the completion of the experimental work here described, an improved method of preparation of lead tetraacetate, similar to the above, has been described by Bailar, in "Inorganic Syntheses," Vol. I, McGraw-Hill Book Co., Inc., New York, N. Y., 1939, p. 47.

(10) In this calculation, the molar concentration was taken as the molality multiplied by 1.039, the density of acetic acid at 30°. Since the highest concentration used was less than 0.1 molar, no significant error was introduced by this simplification.

(11) Kolthoff and Willman, THIS JOURNAL, **56**, 1007 (1934).

(12) Davidson and McAllister, *ibid.*, **52**, 519 (1930).

Results

1. Solubility of Plumbic Acetate in Acetic Acid.—In the following table, S denotes the mole percentage of plumbic acetate, and T the corresponding equilibrium temperature. The synthetic method was used except as otherwise noted. The data are presented graphically in Fig. 1.

TABLE I

PLUMBIC ACETATE—ACETIC ACID

S	T	S	T
Solid phase $HC_2H_3O_2$		Solid phase $Pb(C_2H_3O_2)_4$ (cont.)	
0	16.60		
0.088	16.52		
.193	16.45	0.638[a]	37.0
.280	16.40	.798[a]	45.0
		1.03	53.0
Solid phase $Pb(C_2H_3O_2)_4$		1.29	59.8
		1.64	68.4
0.354	18.2	1.96	74.6
.427	25.2	2.55	82.3
.512[a]	29.9	3.31	90.7
.582	33.5	3.74	94.4

[a] These data were obtained by the analysis of solutions saturated at the given temperature.

Since analysis by the method already described had already shown that crystallization from acetic acid at ordinary temperatures yielded pure unsolvated plumbic acetate, and since there was no indication of a break in the curve except at the eutectic point, no further analysis of solid phases was necessary.

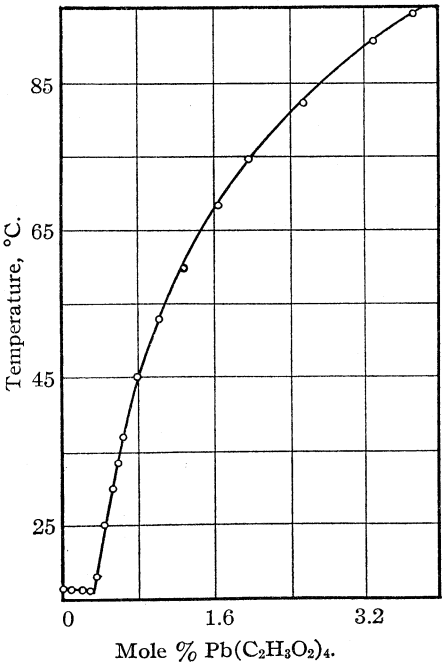


Fig. 1.—Solubility of plumbic acetate in acetic acid.

The solubility of plumbic acetate in anhydrous acetic acid at 25° is found by interpolation to be 0.43 mole %, or 0.072 molal; this is in marked contrast to the solubility of the plumbous salt (hemisolvate) at the same temperature, 16.75 mole %, or 3.35 molal. By a very short extrapolation, the solubility of the plumbic compound at 17° is found to be 0.34 mole %, or 0.057 molal; the latter figure may be compared with Hutchinson and Pollard's[4b] value of 0.062 molal, which, however, applies to the solubility in "glacial" (not anhydrous) acetic acid.

2. Conductance Data.—Specific conductivities, κ, of solutions of plumbic acetate of molality m are shown in Table II, and of plumbous acetate in Table III. Here c is the concentration in moles of solute per liter of solution, Λ the molar conductance. The data for plumbous acetate are shown in a log c–log Λ plot in Fig. 2.

TABLE II

CONDUCTANCE OF PLUMBIC ACETATE SOLUTIONS AT 30°

m	$\kappa \times 10^8$
0	3.80
0.00593	3.80
.0186	4.05
.0262	4.82
.0616	5.56

TABLE III

CONDUCTANCE OF PLUMBOUS ACETATE SOLUTIONS AT 30°

c	$\kappa \times 10^7$	Λ
0.00195	0.556	0.0286
.00626	.880	.0141
.00705	.937	.0133
.0181	1.76	.00973
.0284	2.62	.00921
.0432	3.83	.00887
.0822	8.03	.00977
.0866	8.80	.0102

It is evident from the data of Table II that the specific conductivities of plumbic acetate solutions differ so little from that of the pure solvent that any attempt to calculate molar conductances

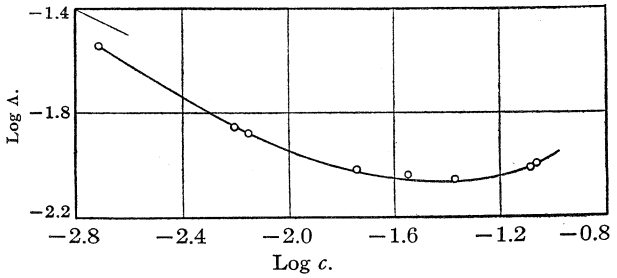


Fig. 2.—Molar conductance of solutions of plumbous acetate in acetic acid.

would have been meaningless. In Table III, the value of Λ is found to go through a minimum (at about 0.04 molar), as is usual in this solvent[13] and in others of low dielectric constant. The molar conductance of a 0.02 molar solution obtained from these data by interpolation is 0.00942; Kolthoff and Willman[11] found the value of 0.00855 for a similar solution at 25°.

3. Solubility of Plumbic Acetate in Sodium Acetate Solutions.—In Table IV, the mole fraction of sodium acetate in the binary solvent is represented by R, while S denotes the mole percentage of plumbic acetate in the ternary solution in equilibrium with solid plumbic acetate at the temperature T.

TABLE IV

SOLUBILITY OF PLUMBIC ACETATE IN SODIUM ACETATE SOLUTIONS

S	T	S	T	S	T
R = 0.003		R = 0.007		R = 0.015	
0.390	24.1	0.404	25.2	0.394	25.7
.417	26.2	.425	27.3	.445	28.3
.460	28.3	.523	34.5	.457	30.2
.501	31.7	.589	38.3	.489	31.6
.525	32.8	.654	40.8	.524	34.7
.560	34.7	.688	42.6	.586	38.1
.638	38.8	.772	46.0	.607	39.3
R = 0.025		R = 0.050		R = 0.07[a]	
0.321	22.5	0.266	23.1	0.339	32.1
.446	32.7	.294	26.3	.368	34.3
.507	36.2	.356	31.9	.379	36.3
.597	41.3	.451	37.8	.429	40.5
.634	43.2	.471	39.0	.461	42.8

[a] This mole fraction is barely below the solubility of sodium acetate (7.06%) in acetic acid at 25°. Hence, in the ternary solutions, $NaC_2H_3O_2 \cdot 2HC_2H_3O_2$ appeared as solid phase at temperatures in the neighborhood of 25°.

Samples of the solid phase from several different solutions were filtered off, dried between porous tiles, and analyzed. The percentages of lead dioxide were found to vary only between 53.6 and 53.9%; hence the solid phase was undoubtedly unsolvated plumbic acetate.

The data of Table IV were plotted in a series of curves, not reproduced here, none of which showed any discontinuity of slope. From these curves were obtained, by interpolation, the isothermal data shown in Table V, where R and S have the same significance as in Table IV.

Thus, contrary to the statement of Schall and Meltzer,[5] the solubility of plumbic acetate is not increased by the presence of sodium acetate, but

(13) Weidner, Hutchison and Chandlee, THIS JOURNAL, **60**, 2877 (1938).

TABLE V

SOLUBILITY OF PLUMBIC ACETATE IN SODIUM ACETATE-ACETIC ACID SOLUTIONS AT 30°

R	S
0	0.51
0.003	.48
.007	.46
.015	.45
.025	.41
.050	.33
.070	.31

decreases markedly with increasing concentration of the sodium salt.

Discussion

A comparison of the behavior of plumbous and plumbic acetates in acetic acid brings out the following differences.

1. The plumbic compound forms no solvate, and its solubility is little more than one-fortieth as great as that of the plumbous salt. This variation corresponds to the difference between plumbous and plumbic oxides in water; the solubility of the former, at 25°, is about 0.0002 mole per 1000 g. of water,[14] while that of the latter is so small (less than 1×10^{-6} mole per 1000 g.)[15] that it has never been accurately determined.

2. As was pointed out by Kolthoff and Willman,[6] plumbous acetate is a much poorer conductor in acetic acid than are the acetates of the alkali metals; the lead salt must be regarded as being but very slightly dissociated. The course of the log Λ–log c curve, with its slope of $-1/2$ at the lowest concentrations measured (as indicated by the straight line in Fig. 2), is characteristic of the behavior of electrolytes in solutions of low dielectric constant,[13,16] while the minimum molar conductance at a concentration of 0.04 molar, and the increase in Λ with increasing concentration beyond this point, may be attributed to the formation of triple ions.[17] In the case of plumbic acetate, however, the increase in specific conductance brought about by its addition to acetic acid is so small that this solute appears to be altogether non-ionic in character.

3. Although no compound of sodium and plumbous acetates has as yet been isolated from acetic acid solutions, it has been shown[7] that the solubility of plumbous acetate increases with in-

(14) Garrett, Vellenga and Fontana, *ibid.*, **61**, 367(1939).

(15) Topleman, *J. prakt. Chem.*, **229**, 320 (1929).

(16) Kraus and Fuoss, THIS JOURNAL, **55**, 21 (1933); Fuoss and Kraus, *ibid.*, **55**, 476 (1933).

(17) Fuoss and Kraus, *ibid.*, **55**, 2387 (1933).

creasing concentration of sodium acetate. In the case of plumbic acetate, the solubility is *decreased* by the addition of the sodium salt. There is no evidence for the existence of compounds corresponding to the plumbates of the aqueous system. The absence of amphoteric properties of plumbic acetate would, by itself, be difficult to reconcile with the generally analogous behavior of corresponding compounds of the water and the acetic acid systems. In view of the other facts here presented, however, the decrease in solubility of plumbic acetate in the presence of sodium acetate appears merely as an instance of the "salting out" of a non-electrolyte.

Summary

1. The solubility of plumbic acetate in acetic acid over a wide range of temperature was determined. No solvate was isolated.

2. The conductivities of solutions of plumbous and plumbic acetates in acetic acid at 30°, over a range of concentrations, were measured. The former was found to behave as a typical weak base, the latter as a non-electrolyte.

3. The solubility of plumbic acetate was found to decrease with increasing concentration of sodium acetate. There was no evidence of amphoteric behavior.

LAWRENCE, KANSAS RECEIVED MARCH 20, 1942

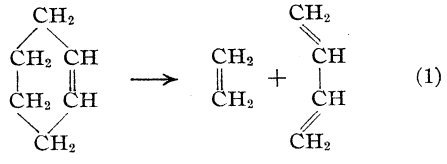
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE CATHOLIC UNIVERSITY]

The Decomposition of Cyclohexene Oxide and 1,4-Cyclohexadiene from the Standpoint of the Principle of Least Motion[1]

BY FRANCIS OWEN RICE AND ADRIAN L. STALLBAUMER

(I) Cyclohexene Oxide.—In this paper we propose to discuss the homogeneous thermal decomposition of organic compounds in the gaseous state, more particularly with reference to two compounds which we have investigated experimentally. The principle of least motion which we use to interpret our results has been discussed in a recent paper.[2a]

Before taking up in detail the decomposition of cyclohexene oxide, we should like to point out that under certain conditions[2b] cyclohexene decomposes according to the following equation, in which ethylene and butadiene are the sole products



(1)

This decomposition illustrates the value of the principle of least motion because this reaction obviously requires less motion of the constituent atoms and involves less disturbance of the electronic system than any other thermodynamically possible reaction that can be written.

A second reaction that we wish to discuss in this connection is the decomposition of ethylene oxide.[3] The decomposition is obviously complicated yielding methane and carbon monoxide as the final products presumably produced from the decomposition of acetaldehyde which appears as an intermediate product. We exclude a direct migration of a hydrogen atom according to the equation



(2)

both from the principle of least motion (attack of a hydrogen atom on a shielded carbon atom) and also on the experimental basis that ethylene oxide produces free radicals (Paneth effect) under conditions[4] where acetaldehyde is stable. Accordingly we are forced to assume that the change of ethylene oxide into acetaldehyde is not a single step reaction merely involving the migration of a hydrogen atom.

The first step of the decomposition of ethylene oxide may occur in two ways. The first way represented by the equation



(3)

seems unlikely because migration of a hydrogen atom to the exposed end carbon atom could read-

(1) This is taken from the dissertation presented by Adrian L. Stallbaumer for the Degree of Doctor of Philosophy in the Catholic University.

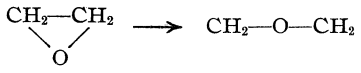
(2a) Rice and Teller, *J. Chem. Physics*, **6**, 489 (1938); **7**, 199 (1939).

(2b) Rice, Ruoff and Rodowskas, THIS JOURNAL, **60**, 955 (1938).

(3) Heckert and Mack, *ibid.*, **51**, 2706 (1929).

(4) Rice and Rice, "The Aliphatic Free Radicals," The Johns Hopkins Press, Baltimore, Md., 1935, p. 160.

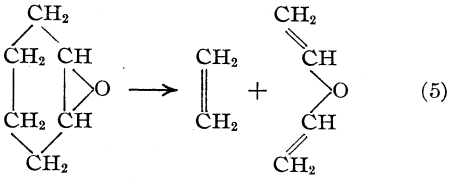
ily occur and acetaldehyde would form in the same way that ethylene forms from diazoethane.[4a] The second possible method of decomposition may be represented by the equation



(4)

and is, we believe, followed by a radical chain decomposition leading to the formation of acetaldehyde. The radical $CH_2—O—CH_2$ cannot isomerize to any molecule unless the constituent atoms undergo a very large amount of motion indeed.

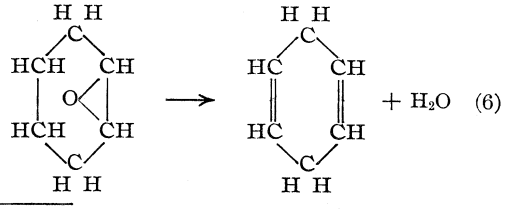
We are now prepared to discuss the thermal decomposition of cyclohexene oxide. If we assume that the decomposition occurs by rupture of a carbon–carbon bond in a manner similar to that shown in Eq. 4, we may expect the production of ethylene and divinyl ether according to the equation



(5)

Actually no divinyl ether was found in the decomposition so that we may assume that incorporating the two carbon atoms of ethylene oxide into a six-membered ring somewhat strengthens the bond between them.

On the other hand, if the carbon–oxygen bond breaks in a manner similar to that shown for ethylene oxide in Eq. 3, we may expect that this will be followed by exceedingly rapid isomerization to cyclohexanone. Our experiments show that there is indeed extensive formation of cyclohexanone. However, this decomposition is accompanied by another because we find in the products appreciable quantities of water, acetylene, butadiene and a hydrocarbon which we believe is 1,4-cyclohexadiene. The appearance of these products would seem to indicate that the following reaction occurs



(6)

(4a) Rice and Glasebrook, THIS JOURNAL, **56**, 741 (1934).

The occurrence of small amounts of water and a C_6 diolefin would not appear to be unreasonable in spite of the relatively large hydrogen–oxygen distances in cyclohexene oxide since these distances become smaller during the normal vibrations of the molecule. The partial decomposition of 1,4-cyclohexadiene into acetylene and butadiene is exactly parallel to the decomposition of cyclohexene into ethylene and butadiene shown in Eq. 1.

Experimental

The cyclohexene oxide was prepared according to a method given in "Organic Syntheses."[5] A second sample was prepared by oxidizing cyclohexene with perbenzoic acid in chloroform solution.[6] The only point requiring special notice in this preparation is that after both reactants have been added, the homogeneous solution must not be allowed to rise above 0° and must be stirred for about ten hours. This is because the reaction is slow and exothermic and, even if kept in an ice-bath, stirring is necessary to prevent local heating. The pyrolytic apparatus used was essentially the same as that described in a preceding article.[2b] The cyclohexene oxide was passed through a quartz tube at a known temperature, the condensable products were caught in traps and the permanent gases were collected over saturated aqueous zinc sulfate solution after leaving the glycerol pump. Podbielniak distillations supplemented by gas analysis enabled us to make a satisfactory analysis of the products and obtain a weight balance. Table I shows the results of three experiments in which cyclohexene oxide was decomposed.

TABLE I

THERMAL DECOMPOSITION OF CYCLOHEXENE OXIDE

	I	II	III
Moles used	1.00	1.15	0.95
Decomposed, %	25	6	27.6
Press., mm.	10	10	6
Temperature, °C.	780	630	735
Contact time, sec.	0.030	0.038	0.048
Water recovered, g.	2.0	1.3	3.6
"1,4-Cyclohexadiene," g.		1.1	4.9
Cyclohexanone, g.			22.3
Butadiene, moles	0.016	0.001	0.005
Acetylene	.015	.003	.016

The cyclohexanone was identified by its boiling point, refractive index and conversion into the oxime. We did not make a satisfactory identification of the material, which we assumed to be 1,4-cyclohexadiene. However, this material had two double bonds, boiled at 88°, was liquid at −80° and its refractive index was $n^{20}D$ 1.4680. The hydrocarbon, 1,4-cyclohexadiene, does not seem to have been very well characterized and its boiling point is variously reported[7] from 84–89° (760 mm.) and $n^{20}D$ 1.47 ± 0.003.

(5) "Organic Syntheses," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1925, pp. 31, 35.

(6) Godchot and Bedas, *Compt. rend.*, **174**, 462 (1922); see also, Bartlett and Bavley, THIS JOURNAL, **60**, 2418 (1938).

(7) Egloff, "Physical Constants of Hydrocarbons," Reinhold Publishing Corp., New York, N. Y., 1940, Vol. 2, p. 407.

(II) **1,3-Cyclohexadiene.**—We studied this compound because we hoped it would throw light on the decomposition of ethane which yields ethylene and hydrogen according to the equation

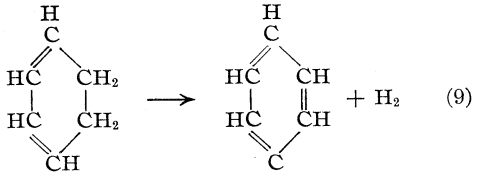
$$C_2H_6 \longrightarrow CH_2{=}CH_2 + H_2 \qquad (7)$$

This may occur by the direct separation of molecular hydrogen in a single elementary act or it may occur by the primary separation into two methyl radicals according to the equation

$$C_2H_6 \longrightarrow 2CH_3 \qquad (8)$$

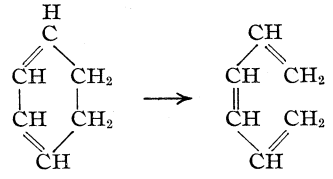
followed by a radical chain.

It seemed at the commencement of this investigation that we could distinguish between these two possibilities in the case of 1,3-cyclohexadiene because the final product would be different depending upon whether the process represented by Eq. 7 or that of Eq. 8 was followed. The process analogous to Eq. 7 would be



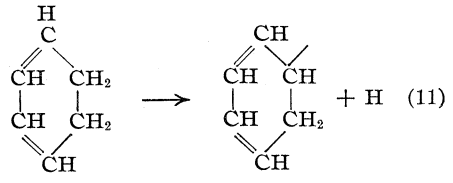
(9)

in which the separation of hydrogen occurs in a single elementary act; on the other hand, the process analogous to Eq. 8 is



(10)

Actually the experimental results showed that benzene and hydrogen are the only products and that there is no 1,3,5-hexatriene formed. However, after further consideration we concluded that our experiment is not after all decisive, and the reaction shown by Eq. 9 may not be the separation of a hydrogen molecule in a single elementary act. This is because the separation of a hydrogen atom from 1,3-cyclohexadiene according to the equation



(11)

results in a large gain of resonance energy in the ring so that the C–H bond may be as weak or even weaker than a C–C bond. Consequently reaction 9 may also occur by a hydrogen atom chain in a manner similar to that postulated for ethane.

It is not even necessary to assume the initial separation of a hydrogen atom as shown in Eq. 11 because a trace of free radicals produced by impurities or initiated at the wall could start a hydrogen atom chain.

Experimental

Six moles of a commercial sample of *o*-cyclohexanediol was acetylated according to standard procedure and 4.4 moles of diacetate [b. p. 240° (760 mm.) and 133° (33 mm.)] were obtained; the yield was 73%. The decomposition of the diacetate to 1,3-cyclohexadiene and acetic acid was performed in the apparatus previously described in which 820 g. (4.1 moles) was pyrolyzed at 750° and 6 mm., the time of the run being six hours; a 50% yield was obtained.

In Table II we show the results of a preliminary experiment on the decomposition of cyclohexane diacetate in which we made an over-all balance and established the fact that hydrogen is formed to the extent of less than 5% and that the main product is 1,3-cyclohexadiene.

TABLE II

PYROLYSIS OF CYCLOHEXANE DIACETATE AND 1,3-CYCLOHEXADIENE

	Cyclohexane diacetate	1,3-Cyclohexadiene
Moles used	0.897	0.67
Moles recovered		None
Decomposed, %	84	100
Mm. Hg	6	4–6
Temperature, °C.	660	960
Moles permanent gas	0.123	0.518
Contact time, sec.	.186	.157
Gaseous products (moles per mole decomposed)		
Hydrogen	0.034	0.53
Methane	.054	.15
Carbon monoxide	.031	...
Ethylene	.021	.05
Carbon dioxide	.012	...
Propylene	.009	.13
Acetylenes	.004	.07
Liquid products (moles per mole decomposed)		
Cyclohexadiene	0.45	...
Benzene	Trace	0.70

In Table II we also give the results of the pyrolysis of 1,3-cyclohexadiene. We performed the experiment at high temperature because we wanted to attain 100% decomposition and thus avoid the difficulty of separating the products from undecomposed substrate; since we anticipated that all the possible products would be very stable we felt that in this particular experiment the procedure would not lead to difficulties due to decomposition of the products. Furthermore, we performed the experiment at a rather low pressure in an attempt to avoid as far as possible the initiation of chain decompositions by the adventitious formation of traces of free radicals. As will be seen in the table we ob-

tained a 70% yield of benzene and 53% of hydrogen. Since 15% of methane was formed it is evident that some sort of secondary chain reaction accompanies the main decomposition into benzene and hydrogen in spite of the low pressure. In these circumstances we feel that we cannot neglect the possibility that 1,3-cyclohexadiene may have been formed by a chain reaction in which a hydrogen atom is one of the chain carriers.

Summary

1. We have discussed the thermal decomposition of organic compounds from the standpoint of the principle of least motion and have pointed out that organic decompositions may consist of a comparatively few elementary (*i. e.*, single step) reactions.

2. On heating cyclohexene oxide the main change is a rearrangement to cyclohexanone. This is accompanied by a decomposition of the cyclohexene oxide into water and a hydrocarbon, probably 1,4-cyclohexadiene.

3. 1,3-Cyclohexadiene decomposes into benzene and hydrogen.

WASHINGTON, D. C. RECEIVED JANUARY 14, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

Reproducible Contact Angles on Reproducible Metal Surfaces. II. Interfacial Contact Angles between Water and Organic Liquids on Surfaces of Silver and Gold

BY F. E. BARTELL AND PAUL H. CARDWELL

The angle formed at the line of contact of two liquids, such as water and an organic liquid, against a solid phase is generally referred to as an *interfacial contact angle.* Reliable data pertaining to interfacial contact angles could be of much importance, but such data as do exist are for the most part of questionable value, for seldom do data presented by different investigators show good agreement.

One difficulty which besets the investigator is that, for a given system, he may obtain different and *apparently* stable angles anywhere between two fairly wide limits. The limits of variation are the values of the angles which have usually been referred to as "advancing" and "receding" contact angles. This same variation exists also with contact angles of solid–liquid–air systems and has been discussed in an earlier paper.[1]

In the majority of investigations the fact that the two liquids of a solid–liquid–liquid system possess at least limited miscibility has been largely disregarded. Furthermore, it appears that no one has given much consideration to the possibility that adsorption of the dissolved material might occur at either or both of the solid–liquid interfaces, nor to the fact that highly condensed and firmly held layers might be formed which could not easily be removed and which, by their presence, would cause considerable alteration of interfacial tension.

In the present investigation it has been quite conclusively demonstrated that all of the factors mentioned above must be taken into consideration. In addition it has been shown that time must be allowed for any given system to attain equilibrium. Moreover, in case the experimental procedure is such as to bring about a slight displacement of the liquid–liquid interface at the line of contact with the solid, there then exists a tendency for a comparatively great readjustment of conditions at and near the line of intersection of the interfaces. Such readjustment would involve partial or total removal or deposition of condensed layers as well as both adsorption and desorption processes and might require considerable time before the reattainment of equilibrium.

The solid surfaces selected for study in the present investigation were silver and gold surfaces formed by vaporization and subsequent condensation on Pyrex tips.[1] The liquids were "conductivity" water and purified isoamyl alcohol, *n*-butyl acetate, benzene, α-bromonaphthalene and heptane. The interfacial contact angles were formed with each of these different organic liquids against water on the solids. To save time in attaining equilibrium conditions each pair of liquids (*i. e.*, water and each of the organic liquids) used in this research were mutually saturated before use and it is to be understood that when reference is made to one of the liquids it refers to that liquid as being saturated with the other liquid of the pair.

(1) Bartell and Cardwell, THIS JOURNAL, **64**, 494 (1942).

The apparatus used for the formation of the interfacial contact angles was described in an earlier paper.[1] This apparatus made possible the formation of water drops on metal surfaces immersed in organic liquid as well as of organic liquid drops on metal surfaces immersed in water. In recording contact angles *the convention has been observed of expressing the value as that obtained when measured through the water phase.*

The results obtained in this investigation have shown that for a given solid–liquid–liquid drop system there exist two definite, stable, closely reproducible, contact angles.

Stable Solid–Organic Liquid–Water Contact Angles.—In order to obtain a stable and reproducible contact angle with a drop of water on a solid immersed in an organic liquid, one must form the drop on a solid which was in a fresh and clean condition when it was immersed in the organic liquid and which had been allowed to remain for a sufficient time in the organic liquid before the water drop was formed. If left undisturbed after its formation, the water drop will spontaneously adjust itself so as to reach the *stable* water advancing angle provided the drop as initially formed had an initial advancing angle greater in value than the value of the *stable* water advancing angle. In case the water drop as initially formed had an advancing angle smaller in value than that of the *stable* water advancing angle, no movement of the drop will occur spontaneously until the system has stood awhile longer and the volume of the drop has been expanded by addition of water to such an extent that the contact angle becomes greater than the stable water advancing angle. The drop will then adjust itself so as to form the *stable water advancing* angle. This stable angle does not change with time nor with further addition of water to the drop.

If, after one obtains a *stable water advancing* (solid–organic liquid–water drop) contact angle, one progressively withdraws liquid from the water drop, causing it to decrease in volume, the angle will progressively decrease until finally a definite and *stable water receding* angle is obtained. The value of this angle remains constant even though the volume of the drop is materially altered by withdrawal of liquid and even though the line of contact of solid–liquid–liquid drop is caused to move inward to a considerable extent. This angle we have designated as the *stable water receding contact angle.*

The values obtained for stable angles of water drops are presented in Table I. The stable water advancing angles for each of the organic liquid–water systems have practically identical values for a given metal. For silver this value is approximately 128° and for gold approximately 117°. Earlier investigators have found a similar constancy of interfacial angles for corresponding systems with other solids.[2] The stable water receding angles for the different organic liquid systems on a given metal were not identical and, moreover, in each case they were considerably different from the stable advancing angle.

TABLE I

STABLE SOLID–ORGANIC LIQUID–WATER DROP CONTACT ANGLES

Organic liquid	Water angle on silver Advancing	Receding	Water angle on gold Advancing	Receding
Isoamyl alcohol	127	72	117	61
n-Butyl acetate	129	68	116	57
Benzene	129	58	116.5	45
α-Bromo-naphthalene	127	65	118	55
Heptane	127	58	116.5	45

TABLE II

STABLE SOLID–WATER–ORGANIC LIQUID DROP CONTACT ANGLES

Organic liquid	Water angle on silver Advancing	Receding	Water angle on gold Advancing	Receding
Isoamyl alcohol	126	71	117	59
n-Butyl acetate	129	68	115.5	57
Benzene	129	57	116	45
α-Bromo-naphthalene	126	65	116	55
Heptane	127	57	115.5	45

In the formation of stable interfacial contact angles by organic liquid drops on solids immersed in water the instructions for the formation of stable angles with drops of water can be used. For the use with the organic liquid drops the terms advancing and receding must be interchanged, however, since an advancing (*i. e.*, expanding) organic liquid drop produces a receding water angle. It must be kept in mind also that a spontaneous movement of the organic liquid drop, while giving a smaller angle through the organic liquid phase, will give a larger angle through the water phase which is the phase through which the contact angle measurements must be made.

The results obtained with organic liquid drops are given in Table II. It will be noted that for the different organic liquids on a given metal the water advancing angles were all practically iden-

(2) Bartell and Bartell, THIS JOURNAL, **56**, 2205 (1934).

tical. The angles obtained for silver were, as before, somewhat larger than those obtained for gold. The water receding contact angle values were considerably smaller than the water advancing angle values and were not identical for all the different organic liquids. As was the case also for the water drop measurements, with the non-polar liquids benzene and heptane the receding angle values were the same for a given solid while with the heteropolar organic liquids the receding angle values varied according to the solubility of the organic liquids in water, the greater the solubility the larger the stable receding angle.

A comparison of the data of Tables I and II obtained by the two methods, the one using the water drop and the other using the organic liquid drop, shows that all the corresponding values for the two methods of operation agree within the limit of two degrees. Each value reported in the tables or in the text is the average of at least twenty measurements. The maximum deviation for individual measurements was $\pm 1.5°$, but the deviation of many of the measurements was not more than $\pm 0.5°$. Maximum deviation occurred in the measurement of angles having maximum difference in advancing and receding angle values.

Initial Solid–Liquid–Liquid Contact Angles.—When a water drop was formed upon a new and clean metal surface immediately after immersion of the metal in one of the organic liquids, the water advancing contact angle thus initially obtained was not the same as the stable water advancing angle. On the other hand, when a drop of one of the organic liquids was formed upon a new and clean metal surface immediately after immersion of the metal in water the water receding contact angle thus initially obtained was in all cases, except that of isoamyl alcohol, the same as the corresponding stable angle. Values obtained from measurements made on drops formed within two minutes after immersion of the metal are shown in Table III and are designated *initial angles*.

TABLE III

INITIAL INTERFACIAL CONTACT ANGLES

	Solid–organic liquid–water drop Water advancing angle on		Solid–water–organic liquid drop Water receding angle on	
Organic liquid	Silver	Gold	Silver	Gold
Isoamyl alcohol	107	83	79	65
n-Butyl acetate	111	88	69	58
Benzene	180	95	57	45
α-Bromo-naphthalene	151	108	65	55
Heptane	180	107	58	45

These initial angles were closely reproducible when identical methods of procedure were used, but they were not in all cases stable angles since some of them changed upon standing or upon addition of liquid.

Theory of Condensed Liquid Layers on Solids.—The experiments on stable interfacial angles and on initial interfacial angles demonstrate clearly that there are two, and only two, stable contact angles for any one of these solid–liquid–liquid systems. One stable angle, the water receding angle, can be obtained (except for the liquid systems containing isoamyl alcohol which has the highest solubility in water of any of the organic liquids used) immediately after the mutually saturated immiscible liquids are brought into contact with the solid surface. The other stable angle, the water advancing angle, can be obtained only after these liquids have been allowed to stand in contact with the surface for an optimum period of time which is different for different systems. This indicates that alteration of surface properties at the solid–liquid interfaces must occur before *stable* water advancing interfacial angles can be obtained.

In the case of the stable receding angles, which are obtained immediately, the interface is moving over an area previously occupied by water. In the case of the advancing angles, where the stable advancing angle cannot be obtained immediately, the interface is moving over an area previously occupied by organic liquid. It seems probable that the organic liquids produce on the metals highly condensed and firmly held layers which take time for their formation, whereas water produces no such layers on the metals. The organic liquids used, with the exception of alpha bromonaphthalene which forms small angles, do not form contact angles when placed upon silver or gold in air. The work of adhesion of silver or gold against one of these liquids is greater than the work of cohesion of the liquid. As a result of the attraction of the liquid molecules to the solid phase, the liquid immediately adjacent to the solid apparently tends to become denser and to form, in effect, a condensed layer. The force of attraction may extend through a distance representing a number of molecular diameters. Water, which forms a fairly large contact angle both on silver and gold in air, apparently does not tend to form condensed layers on these metals since the work of adhesion of water against the metals is less than the work of cohesion of water.

Condensed layers formed on solids by the non-angle-forming liquids appear to be tenaciously held and not quickly removed from the solid surface by water. The time that elapsed between the measurements of the initial water advancing angles of Table III and the stable water advancing angles of Table I, shown in Table IV, appears to

TABLE IV

TIME NECESSARY FOR TRANSFORMATION OF INITIAL ADVANCING ANGLES TO STABLE ADVANCING ANGLES FOR SYSTEM SOLID–ORGANIC LIQUID–WATER DROP

Liquid–liquid system	Silver, hours	Gold, hours
Isoamyl alcohol–water	2	1
n-Butyl acetate–water	4	1
Benzene–water	>72	11
α-Bromonaphthalene–water	12	2
Heptane–water	12	2

be approximately the length of time which was necessary for formation of the fully condensed organic liquid layers on the solid plus the time (*i. e.*, in those cases in which the initial contact angles are larger than the stable contact angles) for the water to partially remove this condensed organic liquid so as to give the stable water advancing contact angle. The shortest time was required for isoamyl alcohol (slightly less than one hour with gold) and the longest time was required for benzene (over 72 hours with silver). The water drop in the silver–benzene–water system had not broken through the benzene layer at the end of seventy-two hours as was evidenced by the fact that at the end of that time the contact angle was still approximately 180°. The value of 129° reported in Table I for the stable water advancing angle of the silver–benzene–water system was obtained on a silver surface which had been immersed in benzene no longer than half a minute before the water drop was formed.

The time required for producing stable interfacial water advancing angles formed by receding drops of organic liquids upon the metal surfaces immersed in water was much shorter than the time required for producing the corresponding angles by means of advancing water drops. In general it was found that the systems which required the shortest time to give the stable water advancing angle when the water drop was used required the longest time to give the stable water advancing angle when a corresponding organic liquid drop was used. Drops of heptane, α-bromonaphthalene and benzene on silver gave stable angle values if the organic liquid drops were receded within a few seconds, while with drops of *n*-butyl acetate and isoamyl alcohol it was necessary to let the drops stand for a period of about one minute. If the drops of benzene and heptane were allowed to stand on the solid for an hour or more before being withdrawn, the water advancing contact angles thus obtained approached 180°. As with the water drop system, if the benzene was allowed to remain in contact with the metal too long before the water was advanced over it, the water did not sufficiently remove the firmly held organic liquid layer, at least within any reasonable period of time, to give the stable advancing interfacial contact angles.

Adsorption Effects.—Some adsorption of water from the organic liquid phase at the solid–organic liquid interface probably occurs, but in the systems studied such adsorption is probably less than the adsorption of organic liquid from the water phase at the solid–water interface. Any effect due to adsorption appears to be of much smaller magnitude than the effects due to condensed layers, but the exceptional effects obtained with isoamyl alcohol may be due to its greater solubility in water and the consequently greater amount of this solute available for adsorption at the water–solid interface.

"Hysteresis" of Contact Angles.—The causes for the "hysteresis" of contact angles, that effect responsible for the existence of a definite advancing and a definite receding angle, have been obscure.[3] A rational explanation of the "hysteresis" of contact angles can be made if it is assumed that formation of condensed layers does occur, and if, in addition, consideration is given to the fact that there is adsorption from the fluid phases in contact with the solid. The changes brought about at the various solid–liquid interfaces by adsorption and by the formation of condensed liquid layers would be sufficient to provide very different conditions at the line of contact of the phases when the water is caused to advance and when it is caused to recede. These different conditions account for the existence of stable advancing and stable receding angles. It is probable that both the advancing and the receding angles are equilibrium angles for the system as it exists at the moment of measurement, and that there is no single "equilibrium" angle for any system unless the system is so arranged that the

(3) Adam, "The Physics and Chemistry of Surfaces," Oxford Univ. Press, New York, N. Y., 1938, 2nd ed., p. 180.

same conditions prevail whether the water is advancing or receding.

During the course of this work it was demonstrated that for many systems one can obtain receding angles which have the same value as the advancing angles (including the stable advancing angles). This can be accomplished by permitting the solid to stand in contact with the organic liquid for a comparatively long period of time before forming the water drop, then by immediately receding the drop after its formation. It seems probable that the advancing angles (including the stable advancing angles) thus obtained are formed by water drops advancing over a condensed organic liquid layer, and that the receding angles are formed by water drops withdrawn before the water has an opportunity to remove the condensed organic liquid layer. If the water drop is allowed to stand it begins to remove the condensed layer and not only is the receding angle then obtained different from the advancing angle, but a new advancing angle, immediately reformed over the area that had been under the drop, is not the same as the advancing angle previously obtained.

With metal surfaces and other solid surfaces less inert chemically than gold and silver other complicating factors are introduced which affect the magnitude of contact angles and of interfacial contact angles. Studies carried out in this Laboratory on antimony, bismuth and cadmium have shown that for these more active substances still further factors must be considered in explaining differences between advancing and receding angles. The results of the work on antimony, bismuth and cadmium will be presented in a later paper.

Summary

1. With the sessile drop apparatus described in a previous paper interfacial contact angles were measured for water drops on silver and on gold immersed in organic liquids and for organic liquid drops on these solids immersed in water.

2. For each of the solid–organic liquid–water systems it was possible to produce two stable and reproducible interfacial contact angles. These two angles have been designated as "stable advancing" and "stable receding" interfacial contact angles.

3. The stable advancing and stable receding interfacial contact angles given by water drops on silver and on gold immersed in organic liquids were the same (*i. e.*, within the limits of experimental error, 2° or less) as the corresponding angles obtained by using organic liquid drops on the solids in water.

4. The values of the stable advancing interfacial contact angles were found to be approximately the same for all the different organic liquids on a given metal, silver or gold. For silver this value was 128° and for gold 117°.

5. The stable receding interfacial contact angles were smaller than the stable advancing interfacial contact angles of the same system. For the non-polar organic liquids (benzene and heptane) the stable receding angles were practically of the same value against a given solid. For silver this value was 57.5° and for gold 45°. For the heteropolar organic liquids on silver and gold the stable receding contact angle values of the different liquids were not the same for a given solid but varied according to the solubility of the organic liquids in water. The greater the solubility of the organic liquids in water the larger were the stable receding angles.

6. The existence of two different stable interfacial contact angles for a given system has been explained by the theory that the solid surfaces, or interfaces, contiguous to the fluid phases become altered through adsorption from the fluids or by formation of condensed layers of fluid upon the surfaces. The experimental evidence obtained supports this view.

7. When a given system could be so acted upon by special manipulation that conditions at the interfaces were the same whether the water was advancing or receding, the water advancing angle was the same as the water receding angle.

ANN ARBOR, MICHIGAN RECEIVED MARCH 16, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF PHYSICAL CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, NO. 499]

Magnetism and the Third Law of Thermodynamics. The Heat Capacity of Manganous Fluoride from 13 to 320°K.

BY J. W. STOUT AND H. E. ADAMS

The multiple electronic states present in paramagnetic compounds cause at sufficiently low temperatures a contribution to the heat capacity due to the changing population of the magnetic ions among the various states. Calorimetric investigation yields information about the number and separation in energy of the electronic states in the solid. For example, from low temperature heat capacity measurements on $NiSO_4 \cdot 7H_2O$[1] it has been possible to infer the magnetic energy spectrum in the solid. At high temperatures the random distribution of the magnetic ions among the various states gives rise to a magnetic contribution to the entropy. In order to apply the third law of thermodynamics to the calculation of entropies from low temperature heat capacity measurements, it is necessary to correct for any magnetic entropy remaining at the lowest temperature of measurement. The investigation of the thermal behavior of typical paramagnetic salts contributes to our knowledge of and ability to allow for such magnetic entropy.

The measurements of Bizette and Belling[2] and of de Haas, Schultz and Koolhaas[3] show that the magnetic susceptibility of anhydrous manganous fluoride exhibits a sharp maximum at 72°K. At the temperatures of liquid hydrogen the susceptibility varies with the field strength and there is a small remanent magnetization when the field is removed. We have measured the low temperature heat capacity of manganous fluoride in order to investigate the calorimetric phenomena associated with the behavior of the susceptibility curve as well as to obtain, through the application of the third law of thermodynamics, the entropy at 298°K. for use in thermodynamic calculations.

Apparatus.—The calorimeter consisted of a cylindrical copper can 5.1 cm. in diameter and 10.2 cm. long. An open copper tube, 1.27 cm. i. d., extended axially along the center of the calorimeter. The resistance thermometer made a snug fit inside this tube. A chamber of volume 11 cc. in the top of the calorimeter was connected to a reflux tube in thermal contact with the shield and the liquid hydrogen and nitrogen reservoirs. The portion of the reflux tube between the calorimeter and the surrounding shield consisted of a nickel–silver tube, 6.5 cm. long, 0.32 cm. o. d. and 0.010 cm. in wall thickness. The reflux tube and chamber were used to cool the calorimeter before the start of measurements. The volume of the sample chamber in the calorimeter was 169.5 cc. The sample was introduced through a nickel–silver tube, 0.63 cm. i. d., opening into the bottom of the sample chamber. After the introduction of the sample a copper cap with a small pinhole was soldered on the filling tube. The air was removed from the sample chamber and helium gas at one atmosphere pressure introduced through the pinhole which was then closed with solder. The outside of the calorimeter was gold plated in order to reduce the radiation loss and to prevent tarnishing. The weight of the empty calorimeter was 126.8 g. and of the resistance thermometer 46.6 g.

The calorimeter was mounted in the cryostat which has been described by Blue and Hicks.[4] The inside of the shield surrounding the calorimeter was covered with aluminum foil to decrease the heat radiated to the calorimeter and the lead wires were heat stationed at the top of the shield. A copper–constantan difference thermocouple read the temperature difference between the shield and the calorimeter and another couple measured the difference between the top and bottom of the shield. The current in the shield heaters was manually controlled so as to keep the shield always at the same temperature as the calorimeter. The readings of the difference couples were recorded and corrections have been applied when necessary for the small heat interchange between the shield and calorimeter when the conditions were not completely adiabatic. The maximum correction for non-adiabaticity between 25 and 310°K. was 0.2% of the measured heat capacity. Below 25°K. the shield was not kept at exactly the same temperature as the calorimeter and the corrections for heat interchange were made as in the Nernst-type apparatus. Above 200°K., where radiation is important, the adiabatic apparatus permits a more accurate determination of heat capacities than does the Nernst-type apparatus since the heat interchange can be made very small and corrected for accurately. Furthermore, the temperature difference between the outside radiating surface of the calorimeter and the surrounding shield is measured directly and no assumptions as to the temperature distribution throughout the calorimeter during energy input are necessary. This is particularly important when the thermometer-heater is on the inside of the calorimeter, as in the present case.

Energy was introduced and the temperatures measured by means of the platinum–rhodium resistance thermometer of laboratory designation R222. The calibration of the thermometer has been described by Blue and Hicks.[4] During the present measurements the thermometer was

(1) Stout and Giauque, THIS JOURNAL, **63**, 714 (1941).
(2) Bizette and Belling, *Compt. rend.*, **209**, 205 (1939).
(3) de Haas, Schultz and Koolhaas, *Physica*, **7**, 57 (1940).
(4) Blue and Hicks, THIS JOURNAL, **59**, 1962 (1937).

checked at the ice point and at the triple point of hydrogen and found to agree with the original calibration to within 0.01°. The leads to the resistance thermometer (No. 30 B. and S. gage D. S. C. copper) were wrapped once around the calorimeter. Each of the four lead wires was connected to a corresponding lead from the heat station on the shield by one inch of No. 40 B. and S. gage copper wire so as to minimize the heat conduction. Electrical measurements were made with a Leeds and Northrup Wenner potentiometer.

The method of measurement and the corrections applied to the heat capacities, other than those discussed above, followed the standard practice[5] in low temperature calorimetry. The ice point was taken as 273.16°K. The temperatures calculated from the resistance thermometer calibration of Blue and Hicks[4] were corrected for the change in the choice of the ice point. The defined calorie, 4.1833 international joules, was used throughout.

Material.—The manganous fluoride used for the heat capacity measurements was prepared by the method described by Kurtenacker, Finger and Hey.[6] Manganous carbonate was precipitated from a solution of analytical reagent manganous sulfate by means of a solution of sodium carbonate containing sufficient sodium bicarbonate to prevent the formation of basic carbonates. Only about 90% of the available manganese was precipitated as the carbonate in order to avoid precipitating any magnesium which was a probable impurity in the original manganous sulfate. The manganous carbonate, after being washed free of soluble impurities, was added to a 50% solution of hydrofluoric acid contained in a platinum dish. A fine precipitate of pink manganous fluoride was obtained. In order to remove all the volatile impurities from the precipitated manganous fluoride it was necessary to heat the sample at 250° for five hours. During the heating the manganous fluoride was kept in an atmosphere of carbon dioxide in order to prevent reaction with the oxygen of the air. When the resulting material was examined under a microscope individual crystals could not be distinguished but from the extinction of polarized light it was estimated that the crystals were between 10^{-5} and 10^{-6} cm. in size. A sample of the manganous fluoride was analysed for manganese by Professor G. G. Marvin of this Laboratory. He obtained 58.9% Mn; calcd. for MnF_2 59.11%. Two of the heat capacity points just below the ice-point are about 0.3% high. If this is due to the fusion of ice it would correspond to 0.01% by weight of water in the sample. The presence of this amount of water would produce a negligible effect upon the observed heat capacities so no correction has been made for it.

The Heat Capacity of Manganous Fluoride.—The calorimeter contained 1.7604 moles (163.593 g. *in vacuo*) of manganous fluoride. The heat capacity measurements are presented in Table I and represented graphically in Fig. 1. In Table I Series I and II are exploratory runs. The measurements of Series III extend from 13°K. to above the maximum in the heat capacity curve. In the neighborhood of the maximum the temperature increments were made small in order to determine the shape of the curve. Series IV consists of measurements with small temperature increments extending through the region of the maximum. Immediately before the start of Series IV the calorimeter was cooled from above 80°K. to 65.86°K. The good agreement with the points of Series III shows that there was no supercooling of the heat effect associated with the maximum in the curve. At no time during the measurements was there evidence of thermal hysteresis or slowness in the attainment of equilibrium. Series V and VI extend the measurements to room temperatures. The point in Series VII was measured after the completion of

TABLE I

THE HEAT CAPACITY OF MANGANOUS FLUORIDE
0°C. = 273.16°K. Molecular weight 92.93

T, °K.	Approx. ΔT	C_p, cal. deg.$^{-1}$ mole^{-1}
	Series I	
264.62	7.12	15.61
271.67	6.98	15.78
278.61	6.88	15.87
	Series II	
61.94	2.99	8.419
65.53	4.17	9.333
70.04	4.84	7.053
74.81	4.70	6.902
79.40	4.47	7.057
	Series III	
13.18	0.53	0.458
14.68	1.39	.622
16.60	1.59	.802
18.82	2.40	1.050
21.56	2.93	1.384
24.49	3.15	1.762
27.49	2.84	2.182
30.36	2.90	2.605
33.16	2.91	3.024
36.44	3.63	3.514
40.32	4.14	4.121
44.33	3.90	4.780
48.68	4.67	5.551
53.47	4.91	6.460
58.51	5.19	7.536
62.29	2.36	8.520
64.08	1.26	9.076
65.23	1.05	9.550
66.05	0.58	9.892
66.55	.43	9.987
66.99	.45	9.332
67.47	.50	7.903
67.98	.52	7.385
68.59	.71	7.194
69.48	1.06	7.036
70.72	1.42	6.926
72.67	2.48	6.875
75.77	3.73	6.925
	Series IV	
66.11	0.49	9.932
66.50	.29	9.996
66.83	.36	9.802
67.25	0.48	8.532
67.74	.52	7.520
68.27	.52	7.309
68.79	.53	7.164
	Series V	
80.12	5.05	7.091
85.60	5.90	7.426
91.85	6.61	7.865
98.98	7.44	8.388
106.35	7.29	8.939
113.78	7.57	9.474
121.47	7.80	10.01
129.06	7.38	10.50
136.29	7.23	10.94
143.72	7.66	11.37
151.23	7.33	11.79
158.77	7.73	12.20
166.35	7.45	12.56
173.67	7.20	12.89
181.11	7.77	13.19
188.77	7.54	13.48
196.56	8.04	13.78
204.57	7.82	14.03
212.28	7.62	14.29
220.14	8.10	14.53
	Series VI	
221.52	5.31	14.59
228.09	7.85	14.75
235.84	7.65	14.99
243.44	7.54	15.14
250.96	7.37	15.35
258.26	7.22	15.55
265.77	7.80	15.71
273.38	7.67	15.80
280.98	7.54	15.93
288.46	7.41	16.07
295.60	7.28	16.20
303.11	7.17	16.32
310.22	7.05	16.45
	Series VII	
78.02	3.52	6.999

(5) (a) Giauque and Wiebe, THIS JOURNAL, **50**, 101 (1928) Giauque and Johnston, *ibid.*, **51**, 2300 (1929); (c) Hicks, *ibid.*, **60**,; 1000 (1938).

(6) Kurtenacker, Finger and Hey, *Z. anorg. Chem.*, **211**, 83 (1933).

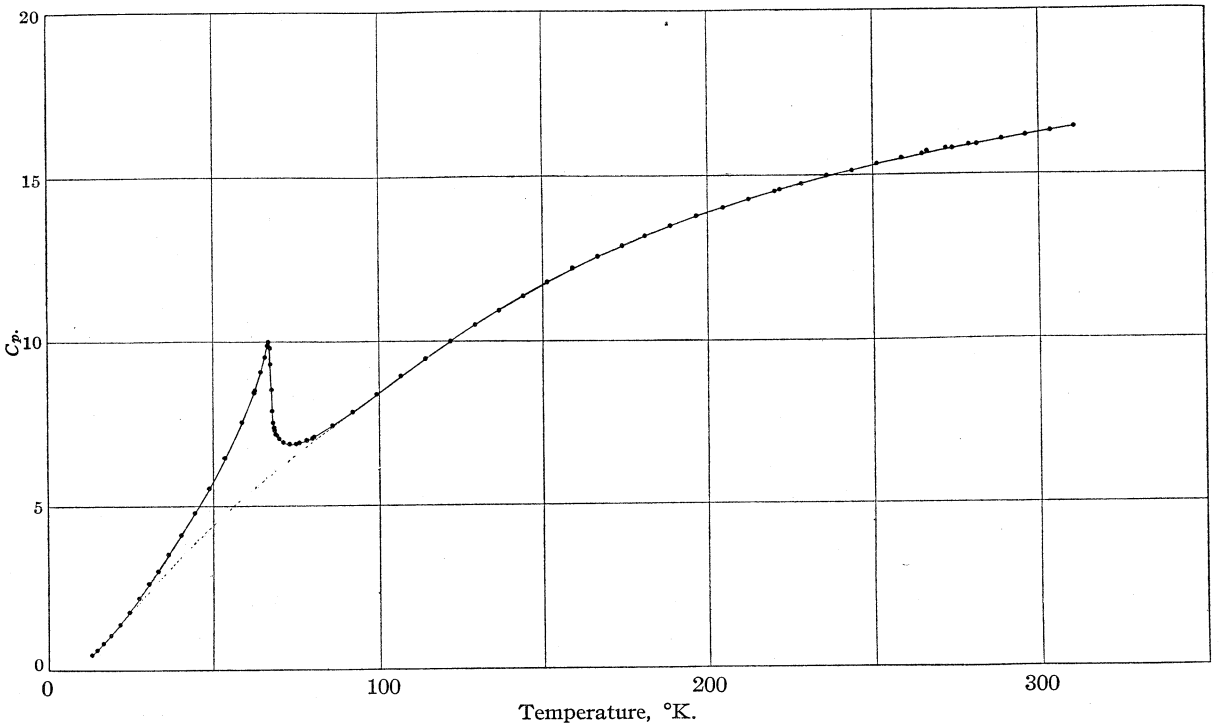


Fig. 1.—Heat capacity in calories per degree per mole of manganous fluoride.

Integral Heat No. 2 mentioned below. During each series of measurements the calorimeter was under continuous observation.

Values of the heat capacity read from a smooth curve through the observations are given in Table II. These values are believed accurate to 0.2% above 35°K., to 1% at 20°K. and to 5% at 15°K.

TABLE II

THE HEAT CAPACITY OF MANGANOUS FLUORIDE. VALUES FROM A SMOOTH CURVE THROUGH THE OBSERVATIONS

0°C. = 273.16°K. Molecular weight, 92.93

T, °K.	C_p, cal. deg.$^{-1}$ mole^{-1}	T, °K.	C_p, cal. deg.$^{-1}$ mole^{-1}
15	0.638	140	11.16
20	1.189	150	11.73
25	1.830	160	12.25
30	2.551	170	12.73
35	3.297	180	13.14
40	4.067	190	13.52
45	4.895	200	13.88
50	5.791	210	14.22
55	6.769	220	14.53
60	7.896	230	14.82
66.5	10.0 (max.)	240	15.08
70	6.978	250	15.32
75	6.900	260	15.54
80	7.086	270	15.73
90	7.733	280	15.91
100	8.471	290	16.10
110	9.207	300	16.27
120	9.908	310	16.44
130	10.56	320	16.60

The heat capacity measurements listed in Table I are values of $\Delta H/\Delta T$ and when ΔT and the curvature of the heat capacity–temperature curve are large, as is the case with some of the measurements in Series II, may differ appreciably from the differential heat capacity. The values in Table II represent the true differential heat capacity.

The heat capacity curve of manganous fluoride rises smoothly to a maximum of about 10.0 cal. deg.$^{-1}$ mole^{-1} at 66.5°K. and then falls rapidly, but not discontinuously, on the high temperature side of the maximum. The measurements indicate that the maximum is rounded at the top, that is, there is no discontinuity in the slope of the heat capacity curve. Measurements of the rate of warming under a small temperature head qualitatively confirmed the shape of the curve given by the short heat capacity measurements. The maximum in the magnetic susceptibility curve[2,3] is at 72°K.

Two measurements were made of the total energy necessary to heat the sample from 61.00 to 76.50°K. In Table III these values are compared with those obtained from the heat capacity measurements. Corrections have been applied in order to convert the different measurements to a common temperature interval for comparison.

TABLE III

CHANGE OF HEAT CONTENT OF MANGANOUS FLUORIDE BETWEEN 61.00° AND 76.50°K.

Measurement	Temp. interval, °K.	H (76.50) − H (61.00), cal. mole^{-1}
Integral heat no. 1	61.34–76.67	121.76
Integral heat no. 2	60.97–76.26	121.79
$\Sigma C_p \Delta T$, Series II	60.46–77.17	121.72
$\Sigma C_p \Delta T$, Series III	61.12–77.64	121.61
	Accepted value	121.8

The entropy was evaluated by graphical integration of $\int C_p \, d \ln T$. The calculation is summarized in Table IV. In making the entropy extrapolation to the absolute zero the function 3/4 D (119.6°K.) per mole of manganous fluoride, which gave the best representation of the lowest temperature heat capacity data, was used. D is the Debye function.

TABLE IV

THE ENTROPY OF MANGANOUS FLUORIDE

0–15°K., Debye extrapolation	0.22
15–298.16°K., graphical integration	22.03
S at 298.16°K.	22.25 ± 0.10 cal. deg.$^{-1}$ mole^{-1}

Discussion.—The ground state of the free Mn^{++} ion is, according to Hund,[7] a ^6S. The magnetic susceptibility measurements as well as theoretical considerations[8] show that in solid manganous salts at high temperatures the magnetic ions are randomly distributed among the six states per ion. As the temperature is lowered the distribution of the magnetic ions among the states changes until at the absolute zero they are all in a completely ordered arrangement of zero entropy. The maximum in the heat capacity curve of manganous fluoride as well as the anomalous behavior of the magnetic susceptibility[2,3] of this substance is associated with the loss of the magnetic entropy. The dotted line in Fig. 1 is an estimate of the "normal" heat capacity curve due to the crystalline vibrations. The entropy contributed by that portion of the measured heat capacity lying above this curve is 1.2 cal. deg.$^{-1}$ mole^{-1}. This is to be compared with $R \ln 6 =$ 3.56 cal. deg.$^{-1}$ mole^{-1} which is the total amount of magnetic entropy present at high temperatures which must be acquired as the temperature increases from the absolute zero. It is apparent that a large portion of the magnetic entropy must be acquired in regions of temperature other than that in which there is the evident anomaly in the heat capacity curve. It seems most probable that there is a gradual increase in the magnetic entropy at temperatures above the region of the maximum so that the magnetic contribution to the heat capacity cannot be distinguished from that due to the crystalline vibrations. A similar conclusion was drawn in the case of anhydrous copper sulfate[9] which also exhibits a maximum in its heat capacity curve. Another possibility, which we believe to be very unlikely, is that even at 13°K. there remains a large amount of magnetic entropy which would be lost at lower temperatures.

The maximum in the heat capacity curve is much sharper and narrower than would be the case if the energy states available to each magnetic ion were independent of the situation of its neighbors as is the case in $NiSO_4 \cdot 7H_2O$.[1] The name antiferromagnetism has been given to such a cooperative phenomenon which occurs frequently at low temperatures in concentrated paramagnetic salts. Van Vleck[10] has proposed a theory of antiferromagnetism which is formally similar to the Weiss theory of ferromagnetism. The theory predicts that the magnetic heat capacity would rise gradually to a maximum and then drop discontinuously to zero. At the temperature of the maximum the complete magnetic entropy of $R \ln 6$ would have been acquired. These predictions are not in agreement with our results.

Summary

The heat capacity of manganous fluoride has been measured from 13 to 320°K. There is a maximum in the heat capacity curve, due to the changing distribution of the magnetic manganous ions among the available energy states, at 66.5°K. Short heat capacity measurements were taken in the region of the maximum in order to define accurately the shape of the curve. Measurements were also made of the total heat absorbed between 61.00 and 76.50°K.

The entropy of manganous fluoride calculated from the heat capacity measurements is 22.25 cal. deg.$^{-1}$ mole^{-1} at 298.16°K.

CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 3, 1942

(7) Hund, "Linienspektren," Berlin, 1927, p. 161.

(8) Van Vleck, "Electric and Magnetic Susceptibilities," 1932, p. 301.

(9) Stout, *J. Chem. Phys.*, **9**, 285 (1941).

(10) Van Vleck, *ibid.*, **9**, 85 (1941).

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, NO. 267]

The Distribution of Acetyl Groups in a Technical Acetone-Soluble Cellulose Acetate[1]

BY THOMAS S. GARDNER[2] AND C. B. PURVES

The *p*-toluenesulfonyl (tosyl) esters of primary, as opposed to secondary, alcoholic groups in carbohydrates are quantitatively converted to the corresponding halides by heating with sodium iodide dissolved in a suitable solvent.[3] This analytical method made it possible to determine the molar amount of unsubstituted primary hydroxyl group in the sixth positions of acetone-soluble cellulose acetate, to estimate the corresponding rate of tosylation under standard conditions and to obtain, by difference, the total amount of secondary alcoholic groups distributed in the second and third positions of the anhydroglucose residues.[4] More recent work with a partly ethylated cellulose showed that hydroxyl groups in the second position were tosylated very much more rapidly than those in the third and that a mathematical analysis of their combined tosylation rate plot gave the molar amount of each.[5] The improved experimental and mathematical methods developed in this ethylcellulose study have now been applied to the high grade, commercial acetone-soluble cellulose acetate II used in the previous work.[4]

Experimental

Materials.—Acetyl analysis of the cellulose acetate by a modification of a standard method,[6] as yet unpublished, gave values of 39.73, 39.72, 39.79, 39.60%, corresponding to an average substitution of 2.44. The substitution value of 2.33 formerly accepted as correct for du Pont sample II was accordingly too low.[7] All samples were dried before use or before analysis over phosphorus pentoxide *in vacuo* at 65°.

High grade pyridine was dried over barium oxide and redistilled shortly before use. Commercial *p*-toluenesulfonyl chloride was purified by washing the benzene solution with cold water, drying and decolorizing with carbon. After recovery, the acid chloride was recrystallized from ether–petroleum ether until the colorless product melted at 69°.

The acetonylacetone was freshly distilled under diminished pressure and the sodium iodide was a carefully dried C. P. specimen.

Rate of Tosylation.—The experiment was carried out as formerly[4] but on a four-fold scale. The mixture of 80 g. of the cellulose acetate (1 mole hydroxyl) and 424 g. of tosyl chloride (13.1 moles), dissolved in a total of 1420 ml. of pyridine, was contained in a large, glass stoppered bottle kept in the dark at 20 ± 0.5°. Discoloration of the solution set in very slowly. From time to time a 30 to 50 ml. sample was withdrawn in a glass dipper and the tosylated product was isolated and prepared for analysis as previously described.[4] The first samples were colorless and fibrous but those withdrawn after one week, when replacement of tosyl by chlorine began to be apparent (Notes *e*, *f*, *g*, Table I) had a little color and gave light brown solutions in acetone.

Sulfur analyses were conveniently carried out on the semi-micro scale by a recently published method.[8] Acetyl was determined by the modified technique, in which the carefully shredded sample was heated in alcoholic sodium methylate before the mixture was acidified with excess *p*-toluenesulfonic acid and acetyl was recovered in the form of methyl acetate by distillation. The analyses in Table I, columns 3 and 4, are the mean of closely concordant duplicates and obvious simultaneous equations made it possible to calculate the moles of acetyl present at each stage of the tosylation. The data (column 5) show that the acetyl substitution did not change during the first five days from the original value of 2.44 and the reliability and accuracy of the analytical methods were thereby confirmed. After seven days, when the presence of combined chlorine rendered the acetyl values high, an acetyl content of 2.44 was assumed and the total substitution was calculated from the sulfur and halogen values (Table I, notes *f* and *g*). The last sample isolated (eighty days) was a light brown fibrous material that was soluble in pyridine, acetonylacetone and acetone. Tests for nitrogen were negative. The assumption that this sample had the usual acetyl substitution of 2.44 was justified because on this basis the 1.65% of chlorine and 3.89% of sulfur gave a combined acetyl, chloro and tosyl substitution of 2.99 where theory was 3.00. A Staudinger viscosity determination made with this sample dissolved in glacial acetic acid at 25 ± 0.1°, gave an η_{sp}/c value of 54.8. This value checked very well with those of 53.3 and 52.5 previously found for a 6-chlorotosyl acetate and for the original cellulose acetate II.[4,9] The absence of degradation during prolonged tosylation and the consistency of the acetyl analyses justified the calculation of the molar tosyl substitution (column 6) from the observed sulfur content (column 4) and the average acetyl substitution of 2.44 (column 5).

(1) Presented before the Division of Cellulose Chemistry at the Memphis Meeting of the American Chemical Society, April, 1942.

(2) du Pont Cellulose Research Fellow, 1941–1942.

(3) Oldham and Rutherford, THIS JOURNAL, **54**, 366 (1932).

(4) Cramer and Purves, *ibid.*, **61**, 3458 (1939).

(5) Mahoney and Purves, *ibid.*, **64**, 9 (1942).

(6) Freudenberg and Harder, *Ann.*, **433**, 230 (1923).

(7) We are indebted to Doctors J. W. Hill and F. Schulze, of the du Pont Company, for the gift of this acetate. The quoted acetyl content was 39.3%. Cramer and Purves[4] found 38.6%.

(8) Mahoney and Michell, *Ind. Eng. Chem., Anal. Ed.*, **14**, 97 (1942).

(9) Cramer and Purves' η_{sp}/c values[4] become 54.0 and 53.3 when based on an acetyl substitution of 2.44 instead of 2.33.

TABLE I

ANALYTICAL DATA OF TOSYLATION AND IODINATION REACTIONS

	Tosylation					Iodination					
Sample (1)	Tosylated, hours (2)	Acetyl, % (3)	Sulfur, % (4)	Acetyl,[a] moles (5)	Tosyl,[a] moles (6)	Iodine, % (7)	Sulfur, % (8)	Calcd.[b] S, % (9)	Iodine, moles (10)	Tosyl, moles (Z_S) (11)	Calcd. tosyl[c] moles ($Z_A + Z_B$) (12)
1	0.25	37.85	0.92	2.443	0.079	3.76	0.10	0.00	0.081		0.007
2	0.50	36.52	1.66	2.441	.149	5.98	.28	.20	.133	0.016	.015
3	0.75	35.78	2.02	2.437	.185	6.94	.42	.31	.157	.028	.021
4	1.00	35.43	2.26	2.448	.210	7.60	.55	.45	.170	.040	.029
5	2.00	34.43	2.69	2.428	.255	8.51	.65	.61	.198	.057	.052
6	3.00	34.05	2.94	2.439	.290					.092[d]	.071
7	4.00	33.97	3.01	2.445	.291	8.42	1.08	.95	.200	.093	.088
8	5.00	33.92	3.09	2.457	.301					.103[d]	.100
9	6.00	33.76	3.17	2.449	.310					.112[d]	.112
10	7.00	33.73	3.22	2.464	.316					.118[d]	.122
11	8.00	33.66	3.27	2.468	.322	8.05	1.25	1.33	.194	.124[d]	.129
12	9.00	33.57	3.38	2.483	.336					.138[d]	.136
13	10.00	33.38	3.42	2.469	.338					.140[d]	.143
14	11.00	33.07	3.49	2.443	.347					.149[d]	.149
15	12.00	32.73	3.65	2.444	.366					.168[d]	.153
	Days										
16	0.71	32.48	3.72	2.428	.374	7.98	1.73	1.81	.196	.176[d]	.174
17	1.11	32.23	3.84	2.427	.389					.191[d]	.192
18	1.57	31.97	3.97	2.425	.405					.207[d]	.210
19	2.08	31.56	4.17	2.422	.430	7.95	2.39	2.38	.203	.232[d]	.228
20	2.58	31.52	4.26	2.453	.444					.246[d]	.243
21	3.08	31.33	4.33	2.432	.451					.253[d]	.257
22	5.16	30.90	4.59	2.440	.487					.289[d]	.299
23	7.08	30.95[e]	[4.60]	2.448	.489					.291[d]	.322
24	9.12	31.60[e]	[4.51]	2.493	.471					....	...
25	11.12		[4.42]		....					.323[d]	.361
26[f]	21.12		4.17		.521[f]					.355[d]	.362
27[g]	80.12		3.89		.553[g]						

[a] Calcd. from columns (3) and (4) by means of simultaneous equations. [b] Calcd. from % iodine and acetyl substitution of 2.44. [c] Calcd. by $(0.56 - 0.198) = Z_S = Z_A + Z_B$; $\log 0.139/(0.139 - Z_A) = 2.16\,t$; $\log 0.223/(0.223 - Z_B) = 0.106\,t$. [d] Column 11 was obtained by subtracting a constant iodine substitution of 0.198 (average value) from column 6. [e] Replacement of tosyl by chlorine gives high acetyl values. [f] % Cl = 0.93, giving 0.434 mole of tosyl and 0.087 mole of chlorine, and if acetyl is 2.44; total = 2.961 moles. [g] % Cl = 1.65, giving 0.400 mole of tosyl, and 0.153 mole of chlorine, and if acetyl is 2.44 moles; total = 2.993 moles.

Chlorine in later tosylated acetates was determined by heating 20–30 mg. samples under reflux for two hours with 100 ml. of 95% ethanol containing 2 g. of chloride-free sodium hydroxide (made from metallic sodium). Nitrite-free, 6 *N* nitric acid was used to acidify the mixture before the halogen was estimated by the Volhard method[10] with nitrobenzene to coagulate the silver chloride.

Iodination.—The dry, tosylated sample, 1 g., sodium iodide, 2 g., and acetonylacetone, 75 ml., were heated together to 120°, when solution was complete in all cases. After two hours at that temperature, which was again shown to be sufficient[4,5] for maximum iodination, the solution was cooled, poured into 1 liter of ice water, allowed to stand for one hour and filtered. The residue was washed with distilled water, dried and purified by reprecipitation from aqueous acetone. A final drying at 65° *in vacuo* over phosphorus pentoxide preceded the analyses for sulfur and for iodine. Iodine analyses were carried out as described in the work on ethylcellulose.[5]

The assumption that iodination replaced a portion of the tosyl groups by iodine without altering the original acetyl substitution was checked by calculating the per cent. of sulfur in the iodinated specimens from the observed iodine content (Table I, column 7) and an assumed acetyl substitution of 2.44. Calculated sulfur values (column 9) agreed well with the observed ones (column 8) except with the first four samples, in which the sulfur content was too small to be estimated accurately. The corresponding data for the molar substitution of iodine (column 10) were therefore accepted as reliable. All attempts to iodinate later specimens containing chlorine gave dark colored products which were not amenable to purification and were not further examined.

(10) Kolthoff and Sandell, "Textbook of Quantitative Inorganic Analysis," The Macmillan Company, New York, N. Y., 1938, p. 543.

Results

The molar amount of tosyl groups replaced by iodine (Z) corresponded to the primary hydroxyl groups that had been esterified at any given time. Reference to Table I, column 10, shows that a total of 0.198 mole of hydroxyl was originally present in the sixth position of the cellulose acetate and that all were tosylated within two hours. The total agreed excellently with the earlier value of 0.197 mole,[4] and, as the cellulose acetate averaged 0.56 mole per glucose unit, about 35% of the hydroxyl groups were primary. The earlier work showed that the amount lay between one-third and one-half. Substitution in the first order rate

equation, $\log 0.198/(0.198 - Z) = kt$, of the data in columns 2 and 10 gave values for k of (21.4), 23.2, 21.9 and 25.0 corresponding to (0.25), 0.50, 0.75 and 1.00 hour, respectively. The average rate constant for the last three samples was 23.4 when reckoned in days and decimal logarithms. Calculation by the method of least squares, using the same time intervals, gave 24.9 when most weight was given to the hour interval. No advantage was gained by assuming a second order rather than a first order equation for the tosylation.

Subtraction of 0.198 from 0.56 gave 0.362 as the total moles of hydroxyl group in the second and third positions of the cellulose acetate. Subtraction of the data in column 10 from those in column 6 gave the amount of tosylation, Z_S, in both of these secondary positions at various times. Points corresponding to the function $\log 0.362/(0.362 - Z_S)$ were plotted against time t (in days) and those within the limits 0.71 to 3.08 days inclusive were found to lie about a straight line whose position was determined by the method of least squares[5] (Fig. 1). The conclusion was that the amount of tosylation, Z_B, of 0.223 mole of the secondary hydroxyl groups at any time was given by the equation

$$\log 0.223/(0.223 - Z_B) = 0.106\, t \qquad (1)$$

The remaining 0.139 mole was esterified at a faster rate. If Z_A represented the amount of this more rapid tosylation at any time, $Z_A + Z_B = Z_S$. By the use of Eq. 1, the amount of Z_B was calculated for times between 0.125 and 0.5 days and was subtracted from Z_S (column 11). The values of Z_A so obtained were found to fit the following first order rate equation

$$\log 0.139(0.139 - Z_A) = 2.16\, t \qquad (2)$$

In order to check the data, the sums $Z_A + Z_B$, as calculated from Eqs. 1 and 2, were tabulated in Table I, column 12. The agreement with the observed values of Z_S (column 11) was always within 0.02 mole, and usually within 0.01 mole, until the replacement of tosyl by chlorine became appreciable from sample 23 onward. It is interesting to note that no such replacement complicated the equally prolonged tosylation of the ethylcellulose.[5]

Discussion

The above work was an experimental duplicate of that on the ethylcellulose, when it was demonstrated that hydroxyl groups in the sixth, second and third positions of the anhydroglucose units were tosylated at rates in the approximate ratio of 15:2.3:0.07. Rates for acetone-soluble cellulose acetate were 23.4 for the sixth position with 2.16 and 0.106 for the two kinds of hydroxyl groups occupying the other two positions. Comparison with ethylcellulose values justified the conclusion that the faster rate (2.16) was characteristic of the second position in the acetyl cellulose and the slower one (0.106) pertained to the third. There was no reason to expect that the rates for ethylcellulose and acetyl cellulose would be absolutely the same in magnitude, because steric and other effects caused by the different substituents would not necessarily be the same in the two cases. These effects, however, could hardly be large enough to obliterate or reverse a ratio of rates, one of which was twenty or thirty times the other. It therefore appeared that the deacetylation of cellulose triacetate to the acetone-soluble condition removed 0.223 mole of acetyl from the third position and only 0.139 mole from the second, which was more than twenty times as reactive in tosylation. While it is possible that the reactivities displayed toward acetylation and deacetylation may be reversed, it seems probable that the original "triacetate" contained a few unacetylated hydroxyl groups in the sluggishly reacting position three. Further experiments are required to decide between the alternative explanations.

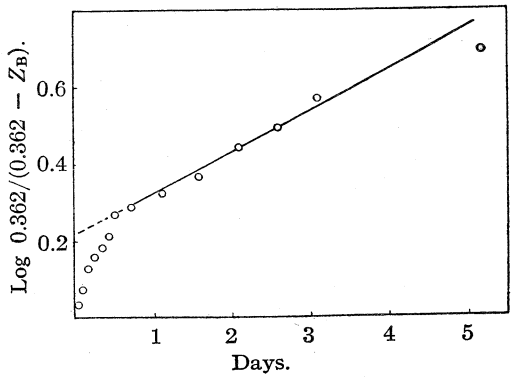


Fig. 1.—Logarithmic plot of rate of tosylation of 0.362 mole of secondary hydroxyl group. Solid line is calculated relationship $\log 0.223/(0.223 - Z_B) = 0.106$ day.

If secondary hydroxyl groups in the acetone-soluble cellulose acetate were distributed in random order but with uniform average density along the length of the macromolecules, the probability of a particular glucose residue containing a completely unsubstituted 2,3 glycol group was 0.139 ×

0.223 or 0.031.[11] If the hydroxyl groups occurred in sharply localized patches along the macromolecule, the probability of a glycol grouping was obviously 0.139 and if deacetylation in one position tended to preclude deacetylation in the other, the probability was 0.139 + 0.223 − 1 or zero.[5]

The oxidation of the cellulose acetate with lead tetraacetate was carried out as before[5] and the results (Table II) showed that 0.0071 to 0.0079, or almost zero, moles of glycol were actually present. This confirmation of the earlier low value of 0.0067 to 0.01 mole[11] supports the inference that the number of 2,3 glycol groups in acetone soluble cellulose acetate, as well as in the partly ethylated cellulose,[5] is depressed by factors still unknown. It also suggests that the partial deacetylation of the triacetate was carried out in a practically homogeneous system and that the loss of acetyl from one of the two secondary alcoholic positions had a marked tendency to stabilize the adjacent group in the same anhydroglucose residue.

TABLE II

OXIDATION OF 0.01 MOLE OF CELLULOSE ACETATE WITH EXCESS LEAD TETRAACETATE AT 20°

Hours (t)	0.01 N Thio., ml.	Moles $Pb(OAc)_4$ $\times 10^2$	$\Delta M/\Delta t$ ($10^5 y$)	Moles glycol[a] ($10^3 x$)
0	0			
24	0.81	0.41		
48	1.50	0.75		
72	2.07	1.04		
82.5	2.42	1.21		
102	2.65	1.33	6.2	7.9
120	2.76	1.38	(2.7)	7.4
168	3.22	1.61	4.7	7.1
192	3.45	1.73	5.0	7.1
		Average	5.3	7.4

[a] Per glucose residue. Calcd. as previously described.[5]

(11) Cramer, Hockett and Purves, THIS JOURNAL, **61**, 3463 (1939).

Summary

1. A technical cellulose acetate, averaging 2.44 acetyl and 0.56 hydroxyl groups per glucose residue, was esterified by *p*-toluenesulfonyl chloride. Analyses of samples removed at intervals showed that 0.198 mole of hydroxyl groups was present in the sixth or primary positions of the original cellulose acetate.

2. The data in (1) give, by difference, a value of 0.362 mole of total secondary hydroxyl in the cellulose acetate and mathematical analyses of the rate of esterification showed that there was a first order, fairly rapid tosylation of 0.139 mole of hydroxyl, on which was superimposed a slow tosylation of 0.223 mole. The 0.139 mole was assigned to the second position and the 0.223 mole to the third by analogy with previous experience on an ethylated cellulose.

3. The first order rate constants for the tosylation of unsubstituted hydroxyl groups in the cellulose acetate were found to be in the ratio of 2.16 for the second, 0.106 for the third and 23.4 for the sixth position.

4. Lead tetraacetate oxidation of the cellulose acetate indicated that 7.4×10^{-3} mole of unsubstituted 2,3 glycol was present per glucose residue. The amount calculated for a random distribution of hydroxyl groups in the two positions was 3.1×10^{-2} mole and for localized concentrations of hydroxyl, 13.9×10^{-2} mole. If deacetylation in either the second or third position of cellulose triacetate stabilized the adjacent acetyl group, the probability of 2,3 glycol groups in the resulting acetone-soluble acetate was zero.

CAMBRIDGE, MASS. RECEIVED APRIL 4, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY]

The Preparation of Several Deuterium Derivatives of Pyrrole

BY FOIL A. MILLER[1]

In the course of some studies on the vibrational spectrum of pyrrole[2] it became necessary to prepare several of the symmetrically substituted deuterium derivatives. Inasmuch as the methods of preparing these compounds add some interesting facts to our knowledge of pyrrole chemistry, and since other workers may have occasion to prepare deuteropyrroles, it seems worth while to describe the preparations in some detail.

Very little earlier research has been reported on this subject. Pyrrole-N-*d* has been prepared by Redlich and Stricks[3] and by Bonino and Manzoni-Ansidei.[4] The extent of exchange between pyrrole and heavy water has been determined by Koizumi and Titani.[5] They conclude that at *p*H $\geqq$ 2 only one hydrogen exchanges, but that at *p*H $\leqq$ 1 all five hydrogens exchange rapidly. However, no attempt was made to prepare and isolate an isotopically pure product. This paper reports the application of Koizumi and Titani's findings to the preparation of 8 ml. quantities of pyrrole-N-*d*, *sym*-pyrrole-d_4, and pyrrole-d_5. Spectroscopic evidence is offered as convincing proof for the course of the exchanges.

Experimental

Pyrrole-N-*d*. 1. Preparation from Potassium Pyrrole.—This is the method used by both Redlich and Stricks and by Bonino and Manzoni-Ansidei. It was deemed necessary to repeat the work, however, because the Raman spectra of the two samples differed considerably,[3,4] and because pyrrole-N-*d* was needed for purposes of comparison in a later experiment.

The reactions involved are

$$2C_4H_4NH + 2K \longrightarrow 2C_4H_4NK + H_2$$
$$C_4H_4NK + D_2O \longrightarrow C_4H_4ND + KOD$$

Clean potassium was added slowly in slight excess to 10 ml. of freshly-distilled pyrrole[6] dissolved in 80 ml. of toluene. The mixture was warmed and later refluxed in a water-free atmosphere until the precipitate became white. Most of the excess potassium was removed mechanically. The solid was filtered off on a sintered glass funnel in a gas box, washed with ether which was sufficiently dry to give a blue color with sodium and benzophenone, and dried; yield of potassium pyrrole, 80%. The solid was suspended in 40 ml. of dry ether, and heavy water (99.6%) was added dropwise with continued shaking until a second layer of liquid was formed. Five and one-half ml. of heavy water was used, which is about 2.5 times the theoretical amount. The ether-pyrrole-N-*d* solution was filtered through a sintered glass funnel and removed from the gas box, and the ether was evaporated with a stream of dry nitrogen. The pyrrole-N-*d* was dried over sodium carbonate and distilled four times in succession at low pressure in an all-glass apparatus; yield on the second reaction, 70%.

This synthesis, while extremely wasteful of heavy water and pyrrole, is useful because one knows that the deuterium atom introduced into the molecule has bonded to the nitrogen atom of the ring.

Pyrrole-N-*d*. 2. Preparation by Exchange.—Koizumi and Titani suggest that the one hydrogen which exchanges in solutions of *p*H $\geqq$ 2 is the N-hydrogen. It was necessary to confirm this, however, for it was hoped that the suggestion could be applied later to the preparation of *sym*-pyrrole-d_4. One can test the suggestion by carrying out an exchange between pyrrole and neutral heavy water. Comparison of the Raman spectrum of the resulting compound with that of the pyrrole-N-*d* prepared from potassium pyrrole will show whether the exchange proceeds on the nitrogen atom alone. An experiment of this kind has been performed.

Four 2.5-ml. samples of freshly-distilled pyrrole were shaken for one hour with 2-ml. portions of heavy water (99.6%) in 6-ml. cylindrically-shaped separatory funnels. Each portion of the heavy water was used with each of the pyrrole samples in turn. The exchange was continued until calculation indicated that the deuterium content was at least 99% of the total exchangeable hydrogen. The united product was dried over sodium carbonate and distilled as before. Practically no pyrrole was lost.

The Raman spectrum of this product agreed exactly with that of the pyrrole-N-*d* prepared from potassium pyrrole. Hence exchange between pyrrole and neutral water involves only the N-hydrogen.

Pyrrole-d_5.—Koizumi and Titani[5c] have pointed out that *p*H 1 is optimum for exchanging

(1) Chemical Foundation Fellow, 1938–1942.

(2) R. C. Lord, Jr., and Foil A. Miller, *J. Chem. Phys.*, **10**, June (1942).

(3) O. Redlich and W. Stricks, *Monatsh.*, **68**, 47 (1936).

(4) G. B. Bonino and R. Manzoni-Ansidei, *Ricerca sci.*, **7**, II, Nos. 3–4 (1936); *or Atti accad. Lincei, Classe sci. fis. mat. nat.*, **25**, 494 (1937).

(5) (a) M. Harada and T. Titani, *Bull. Chem. Soc. Japan*, **11**, 465–474 (1936); (b) M. Koizumi and T. Titani, *ibid.*, **12**, 107–108 (1937); (c) M. Koizumi and T. Titani, *ibid.*, **13**, 85–94 (1938).

(6) The pyrrole was obtained through the kindness of Dr. Saul R. Buc, formerly of this Department. It had been prepared from ammonium mucate according to the method of Blicke and Powers [*Ind. Eng. Chem.*, **19**, 1334 (1927)].

all five hydrogens of pyrrole. At pH > 1.5, all the hydrogens do not exchange; at pH < 1, acid-induced decomposition of the pyrrole becomes serious. Pyrrole-d_5 was prepared by an exchange between pyrrole and heavy water at this optimum pH.

Adjusting the heavy water to pH 1 without contaminating it with light hydrogen required special methods. Deuterium chloride was made from heavy water and thionyl chloride, using the apparatus of Langseth and Klit.[7] The deuterium chloride was bubbled into heavy water to which had been added a trace of dry methyl violet, until the color of the solution matched that of a comparison solution of ordinary hydrochloric acid whose pH had been adjusted to 1.0. Trials with ordinary water and hydrogen chloride showed that the pH could readily be adjusted in this manner to 1.0 ± 0.2 unit, which is sufficiently close. The procedure for exchange was similar to that for pyrrole-N-*d*. Because decomposition of the pyrrole resulted in the formation of a scum, and because the liquids did not separate as nicely as in the former case, the separatory funnels were rotated rather slowly in a large centrifuge to hasten the separation. The product was dried and distilled as before. About 1 ml. of pyrrole was lost during the exchange.

Symmetrical Pyrrole-d_4.—This compound was prepared from pyrrole-d_5 by an exchange with neutral water. It has already been shown that under these conditions only the N-deuterium will be involved. The procedure for carrying out the exchange and purifying the product was identical with that for pyrrole-N-*d*. There was practically no loss of material.

(7) A. Langseth and A. Klit, *Kgl. Danske Videnskab Selskab, Math. fys. Medd.*, **15**, No. 13, p. 7 (1937).

Spectroscopic Results.—It is well known that C–H stretching frequencies in aromatic rings are in the 3000–3100 cm.$^{-1}$ region, while the corresponding C–D frequencies are found at 2200–2300 cm.$^{-1}$. The N–H stretching frequency in liquid pyrrole occurs at 3400 cm.$^{-1}$, and the N–D at 2530 cm.$^{-1}$. Thus the vibrational spectrum offers a good criterion for the isotopic purity of the products. Each of the deuteropyrroles has been studied by the Raman effect.[2] In every case valence frequencies were found only in the expected regions; even on long exposure there was no trace of lines due to an improper isotope. This is thought to mean that the isotopic purity was at least 99%. It also offers convincing proof that exchange between pyrrole and water at pH 1 involves all five of the pyrrole hydrogens, but that at pH 7 only the N-hydrogen is involved.

Acknowledgment is made for a grant-in-aid from the Hynson, Westcott and Dunning Fund. The author also wishes to thank the Chemical Foundation, Incorporated, for a fellowship for graduate study.

Summary

Simple and efficient methods of preparing pyrrole-N-*d*, *sym*-pyrrole-d_4, and pyrrole-d_5 are described. It is confirmed that exchange between pyrrole and water at pH 1 involves all five of the pyrrole hydrogens. In neutral solution only the N-hydrogen exchanges.

BALTIMORE, MARYLAND RECEIVED MARCH 20, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YENCHING UNIVERSITY]

Conductivity Studies.[1] III. The Limiting Equivalent Conductances of Potassium Chloride in Water at Temperatures between 15 and 40°

BY NORMAN C. C. LI[2] AND HSING FANG[3]

The determination of the electrical conductivity of electrolytes has been the subject of many investigations. A search of the recent extensive literature in this field shows that many investigators study conductivity as a function of concentration at some particular temperature or conductivity as a function of temperature at some particular concentrations, and only few study the variation of the limiting equivalent conductances with temperature.

Since aqueous solutions of potassium chloride have been used as standard solutions for determining cell constants, extensive conductivity studies on these are desirable. Recently Jones and Bradshaw[4] and Bremner and Thompson[5] studied the variation in conductance of "demal"

(1) Earlier papers in this series: Li and Fang, *J. Chinese Chem. Soc.*, **6**, 32–39, 44–50 (1938).

(2) Present address: Department of Chemistry, The Catholic University, Peiping, China.

(3) British Indemnity Research Assistant in Chemistry. This article is based on part of a thesis presented by H. Fang to the Faculty of the Graduate Yuan of Yenching University in partial fulllfiment for the degree of Master of Science, June, 1941.

(4) Jones and Bradshaw, THIS JOURNAL, **55**, 1780 (1933).

(5) Bremner and Thompson, *ibid.*, **59**, 2372 (1937).

potassium chloride solutions and Clews[6] applied the Debye–Hückel–Onsager equation to data on 0.1, 0.01 and 0.001 N potassium chloride solutions at different temperatures. Except at 18 and 25°, however, there are no precise values of the limiting equivalent conductance, Λ_0, of potassium chloride in water. It was the purpose of this investigation to study the electrical conductances of potassium chloride solutions over a wide range of concentrations and temperatures in order to determine the temperature coefficient of Λ_0. In the paper following this one, certain transference data will be used together with the conductance data reported in this paper to calculate the limiting equivalent conductances of several univalent ions at different temperatures.

Experimental

The Wheatstone bridge and accessory apparatus used in conductivity determinations have been described.[1] The temperatures investigated were 15, 20, 22, 25, 30 and 40°. For each temperature the bath was adjusted and the temperature variation observed by a Beckmann thermometer which had been compared against a standard thermometer. The temperature variation was 0.005°. The standard solutions for the determination of cell constants were the 0.1 and 0.01 demal solutions defined and measured by Jones and Bradshaw[4] at 0, 18 and 25°. The measured specific conductance was corrected in each case for the conductivity of the water used, amounting to about 1.2×10^{-6} at 25°. The potassium chloride was of Merck reagent quality and was further purified by repeated recrystallization from conductivity water, dried and fused. Solutions were prepared by direct weighing of both solute (or concentrated stock solution) and solvent, the balance used for weighing the dry salt being sensitive to 0.01 mg. with a 50-g. load and that for the solvent sensitive to 0.1 mg. The weights were carefully calibrated on each balance and all weighings were corrected to vacuum, taking the density of the air to be 0.0012 g./ml. and the density of potassium chloride to be 1.987.

Since the salt solutions were made up by weight and the concentrations used in the theory are on a volume basis (moles per liter, C), it was necessary to know the density of the solutions. It was found that the density of the aqueous solutions of potassium chloride was a linear function of the concentration up to the highest concentration used, and obeyed the equation

$$d = d_0 + bf_{KCl} \qquad (1)$$

where d is the density of a solution of f_{KCl} weight per cent. concentration in potassium chloride and d_0 is the density of pure water, both at the same temperature. The values of the density coefficients at 20, 22, 25, 30 and 40° were calculated from the density data in the "International Critical Tables." These were confirmed by the experimental determination of the density of the potassium chloride solutions at 25 and 30°. The density values for 15° are not given, but were calculated by the equation:

$$d = 1.00661 + 0.0000407\,t - 7.95 \times 10^{-6}t^2 + 4.83 \times 10^{-8}t^3$$

the equation obtained from an analysis of the data given in "I. C. T." for 1% potassium chloride solutions. The equations for density at different temperatures are listed

$$\begin{aligned} d_{15} &= 0.99913 + 0.00646f \\ d_{20} &= .99823 + .00640f \\ d_{22} &= .99780 + .00637f \\ d_{25} &= .99707 + .00635f \\ d_{30} &= .99567 + .00631f \\ d_{40} &= .99225 + .00622f \end{aligned}$$

The solutions were kept in seasoned and steamed Pyrex glass-stoppered bottles. In determining the resistance of a given solution, each cell was rinsed with four or five portions of the solution and allowed to stand, filled with the same solution, for fifteen to thirty minutes. The cell was then refilled with a fresh portion of the solution and immersed in the thermostat until temperature equilibrium was reached. The leads were placed in position and the bridge balanced. The leads were then shifted to the next cell and the bridge rebalanced.

Results

Table I gives the results of measurements on the potassium chloride solutions at different temperatures. The third column gives the equivalent conductances calculated from the Shedlovsky–Onsager equation

$$\Lambda_0 = \frac{\Lambda + \beta\sqrt{C}}{1 - \alpha\sqrt{C}} - BC$$

The fourth column lists the values of Λ_0'

$$\Lambda' = \frac{\Lambda + \beta\sqrt{C}}{1 - \alpha\sqrt{C}}$$

In order to calculate the theoretical coefficients α and β, we made use of the viscosity data given in "I. C. T." and the dielectric constant data of

(6) Clews, *Proc. Roy. Phys. Soc.* (London), **46**, 764 (1934).

Drake, Pierce and Dow[7] and substituted them in the equations[8]

$$\alpha = 8.147 \times 10^5/(DT)^{3/2} \quad \beta = 81.86/(DT)^{1/2}\eta \quad (2)$$

where D and η are the dielectric constant and viscosity of the medium at temperature T. These constants are collected in Table II for reference.

Graphs corresponding to the data in Table I for the various temperatures are shown in Fig. 1, where the values of Λ are plotted against $\sqrt{C}$ and Λ_0' plotted against C. The values of Λ_0 and B are obtained graphically from Fig. 1 and are listed in Table III.

TABLE I

EQUIVALENT CONDUCTANCES OF POTASSIUM CHLORIDE SOLUTIONS

$C \times 10^2$	$\Lambda_{obs.}$	$\Lambda_{calcd.}$	Λ_0'
	15°		
0.22312	117.43	117.58	120.89
.30737	117.09	117.04	121.16
.57183	115.82	115.76	121.38
.62728	115.70	115.54	121.53
.99925	114.29	114.29	121.64
1.1657	113.83	113.81	121.77
1.2696	113.64	113.55	121.94
2.3693	111.25	111.32	122.61
4.7486	108.36	108.31	124.54
5.0481	108.09	108.03	124.77
9.9195	104.79	104.76	128.45
9.9209	104.73	104.76	128.39
	20°		
0.07603	132.89	132.82	135.19
.15061	131.95	131.96	135.18
.15564	131.88	131.90	135.17
.28941	130.73	130.82	135.21
.30709	130.59	130.71	135.21
.31715	130.59	130.64	135.28
.58989	129.23	129.15	135.64
.64944	128.96	128.89	135.68
1.2035	126.93	126.92	136.09
1.2685	126.85	126.73	136.26
1.3220	126.66	126.59	136.27
2.4451	124.14	124.05	137.53
2.7090	123.74	123.67	137.54
9.9809	116.66	116.66	143.58
	22°		
0.07599	138.71	138.62	141.12
.13626	137.64	137.82	140.88
.15558	137.65	137.62	141.10
.27833	136.66	136.60	141.35
.31702	136.46	136.32	141.39
.56759	134.93	134.87	141.53
.64919	134.59	134.49	141.65
1.1627	132.45	132.54	141.88
1.3215	132.12	132.06	142.20
2.3789	129.50	129.53	143.06
4.8709	125.85	125.81	144.36
	25°		
0.03977	148.05	148.05	149.92
.06037	147.67	147.63	149.98
.08092	147.25	147.29	149.92
.12184	146.71	146.72	149.99
.16497	146.19	146.22	150.01
.33649	144.65	144.75	150.10
.49651	143.58	143.73	150.20
.68358	142.85	142.75	150.62
.99646	141.40	141.44	150.63
1.3802	140.01	140.14	151.06
1.3896	139.99	140.10	151.09
	30°		
0.16040	160.64	160.59	164.45
.19252	160.14	160.22	164.74
.31781	159.05	159.04	164.96
.38429	158.49	158.51	165.00
.63086	156.92	156.95	165.25
.68514	156.67	156.65	165.55
.76056	156.21	156.26	165.37
1.2504	154.21	154.17	165.97
1.5025	153.23	153.28	166.12
2.4956	150.69	150.60	167.33
4.9813	146.23	146.17	169.89
5.9252	144.92	144.96	170.77
	40°		
0.06189	191.10	191.08	194.29
.09635	190.31	190.33	194.28
.24763	188.14	188.11	194.51
.49164	185.79	185.80	194.77
.98778	182.65	182.64	195.40
1.9761	178.52	178.54	196.59
3.9341	173.50	173.43	199.12
7.7969	163.43	163.48	199.53

TABLE II

CONSTANTS PERTAINING TO EQUATION (2)

t, °C.	D_0	log η	η	α	β
15	82.32	−1.9413	0.011447	0.2231	46.44
20	80.41	−1.9962	.010087	.2252	52.86
22	79.67	−2.0174	.009608	.2260	55.57
25	78.57	−2.0482	.008949	.2273	59.77
30	76.79	−2.0967	.008004	.2294	67.04
40	73.41	−2.1847	.006536	.2338	82.61

TABLE III

LIMITING EQUIVALENT CONDUCTANCES AND SLOPES, B

t, °C.	Λ_0	B
15	120.88	75.9
18	129.4[9]	80[9]
20	135.06	85.3
22	140.96	89.4
25	149.84	94.9
30	164.62	104.5
40	194.18	123.7

The limiting conductance at 25° as obtained by Shedlovsky[9] and recalculated by Krieger and Kil-

(7) Drake, Pierce and Dow, *Phys. Rev.*, **35**, 613 (1930).

(8) MacInnes, "Principles of Electrochemistry," Reinhold Publishing Corp., New York, N. Y., 1939, Chapter 18.

(9) Data taken from Shedlovsky, THIS JOURNAL, **54**, 1410 (1932).

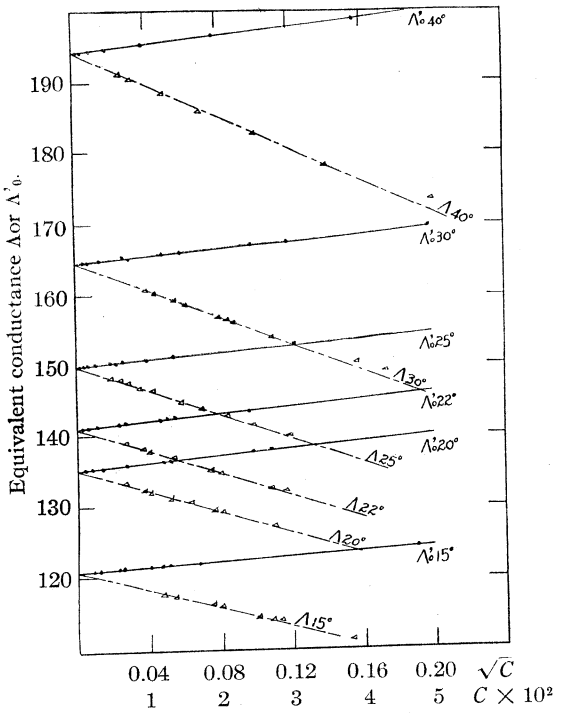


Fig. 1.—Variation of equivalent conductance with concentration.

patrick[10] is 149.86, with which our value of 149.84 is in good agreement. Figure 2 brings out the relationship between Λ_0 and temperature.

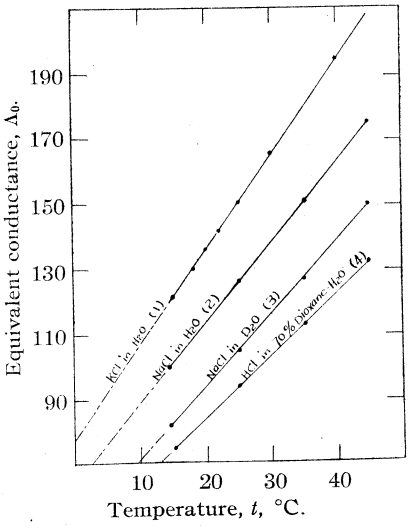


Fig. 2.—Variation of conductance at infinite dilution with temperature.

The relationship in Curve I can be expressed by the empirical equation $\Lambda_0 = 75.94 + 2.956\,t$. It is also interesting to note that the relationship between B and temperature is linear and can be expressed by the equation $B = 46.9 + 1.92\,t$.

Curves 2, 3 and 4 in Fig. 2 are plots taken from data by Brescia, LaMer and Nachod[11] and Owen and Waters[12] and the limiting conductances can be expressed by the equations

NaCl in H_2O	$\Lambda_0 = 64.08 + 2.462\,t$
NaCl in D_2O	$50 + 2.2\,t$
HCl in 70% dioxane	$45.9 + 1.91\,t$

It was shown by Owen and Waters[12] that viscosity and equivalent conductance in a given solvent at various temperatures are simply related by an equation $\Lambda_0\eta_0^s = r$. Figure 3 gives such a plot between log Λ_0 and log η_0 and the constants s and r are found to be 0.872 and 3.039, respectively.

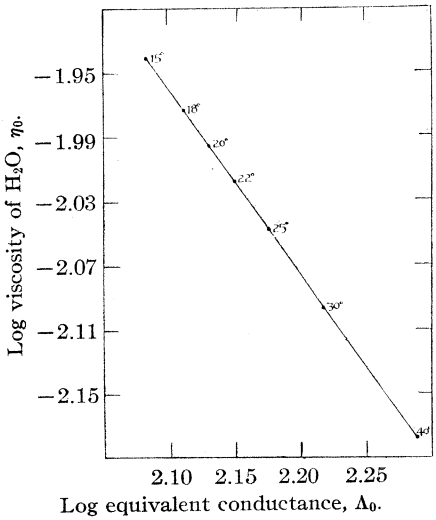


Fig. 3.—Variation of conductance at infinite dilution with viscosity of medium.

Summary

1. The equivalent conductances of potassium chloride solutions have been measured at 15, 20, 22, 25, 30 and 40° in the concentration range 0.0004 to 0.1 N. The experimental data follow closely the Onsager limiting slope at high dilutions. At other concentrations only one empirical constant B is needed.

2. The temperature dependence of the limiting conductance is linear between 15 and 40°. The variation with viscosity can be expressed by $\Lambda_0\eta_0^s = r$, s being less than 1.

PEIPING, CHINA RECEIVED APRIL 10, 1942

(10) Krieger and Kilpatrick, THIS JOURNAL, **59**, 1881 (1937).

(11) Brescia, LaMer and Nachod, *ibid.*, **62**, 615 (1940).

(12) Owen and Waters, *ibid.*, **60**, 2377 (1938).

[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

The Thermodynamic Theory of Electrocapillarity[1]

BY DAVID C. GRAHAME AND ROBERT B. WHITNEY

The Gibbs adsorption theorem (Gibbs' equation 508) is a relationship between the change in the interfacial tension between two phases, the change in chemical potential of the components of the phases, the change in the superficial density of entropy in the system and the amounts of the various independent components adsorbed at the interface.[1a] When some of the components of the system are electrically charged particles, as in an electrocapillary system, the Gibbs equation cannot be applied directly in its original form for reasons which will be pointed out below. In the study of electrocapillary phenomena it is desirable to have a thermodynamic equation analogous to the Gibbs adsorption theorem. The Lippmann equation[2] is a special case of such an equation.

Many discussions of this problem have focussed attention on the "potential-determining" ion, as though the causal agent producing the potential difference between the phases at equilibrium were the ions of the metal in the non-metallic phase (often present in amounts so small as to be meaningless except in a statistical sense) instead of the external apparatus by means of which the potential difference is fixed. The difficulties of this line of approach led Koenig[3] to give up the hope of extending the Gibbs equilibrium treatment and to regard the polarized electrode as a system in which equilibrium does not subsist between the phases. He assumed, instead, that n the interface there exists a barrier impermeable to charged particles. On this basis Koenig has derived a general equation of electrocapillarity for the ideal polarized electrode and has applied it to the deduction of equations referring to special experimental conditions which may be realized in the laboratory. It is the purpose of this paper to show that the equations developed by Koenig are not peculiar to the type of system which he postulates but may be derived for a polarized electrode *at equilibrium* with respect to the distribution of its charged components and *not* possessed of a barrier impermeable to charged particles. It appears to the present authors that real systems are best characterized in this manner and may be made to approach the postulated ideal condition of equilibrium as closely as the physical perfection of the experimental apparatus will permit. In addition, we shall show that the equations here developed have a wider scope and a slightly different significance from those of identical form given by Koenig.

Qualitative Considerations.—Consider a system composed of a metal in contact with an electrolytic solution and provided with some external means whereby the potential difference between the phases may be altered at will. It need not concern us that the absolute magnitude of the potential difference must remain unknown. We exclude from consideration all cases in which the system just postulated is not at equilibrium as regards ordinary chemical action or as regards the distribution of charged particles between the phases. In a system at equilibrium there will be no net transfer of charge from one phase to the other, and therefore there will be no current flowing through the external circuit by which the superimposed potential is applied. From a practical standpoint the systems we are considering form three classes of electrodes, ideal polarized electrodes, ideal non-polarizable electrodes and partially polarizable electrodes. We distinguish these three classes by the magnitude of the continuous current which flows through the external circuit when the potential difference between the phases is *altered* slightly from its value in the original (equilibrium) state. In an ideal polarized electrode no continuous current flows; in an ideal non-polarizable electrode a continuous current flows, limited only by the ohmic resistance of the system, whereas in a partially polarizable electrode a continuous current flows, but of magnitude less than that predicted by Ohm's law (if polarization e. m. f.'s are ignored). These distinctions are practical rather than thermodynamic criteria of polarizability, since Ohm's law and the concepts associated with that law are not a part of thermodynamics. Indeed, the distinction between ideal non-polarizable electrodes and partially polarizable electrodes appears to have no meaning

(1) Original manuscript received July 14, 1941.

(1a) J. W. Gibbs, "Collected Works," Vol. I, Longmans, Green and Co., New York, N. Y., 1928, pp. 219 *et seq.*

(2) G. Lippmann, *Pogg. Ann.*, **149**, 547 (1873); *Ann. chim. phys.*, [5] **5**, 494 (1875); **12**, 265 (1877); see also Gibbs' equation 690.

(3) F. O. Koenig, *J. Phys. Chem.*, **38**, 111, 339 (1934).

for thermodynamics, and the concept will not be used in the thermodynamic treatment which follows. The distinction between ideal polarized electrodes and the two types of electrodes just mentioned (regarded as a single class) may be made on the basis of the amounts of the charged components present in the two phases at equilibrium, as will presently appear.

When the potential difference across the phases of an electrode at equilibrium is altered slightly, there is a momentary surge of current through the external system as a result of a readjustment of the composition of the electrical double layer at the interface, but this readjustment takes place very quickly and in no way obscures the slow readjustment which may be observed as a continuous flow of current in a partially polarizable or non-polarizable electrode.

Although the two ideal types of electrode cannot be attained in practice, it is possible to prepare electrodes which approach ideal conditions almost as closely as desired. Thus a large reversible electrode is practically non-polarizable under favorable conditions, and a system composed of mercury in contact with aqueous potassium chloride is, to all intents and purposes, ideally polarized over a considerable range of superimposed potentials. The same system becomes partially polarizable when the potential difference between the phases is such that the concentration of mercurous ions in the aqueous phase is not negligible at equilibrium.

It will be recognized that *at equilibrium* the concentration of the so-called potential-determining ion in the non-metallic phase varies with the applied potential difference between the phases. In an ideal polarized electrode this concentration is necessarily extremely small in one of the two phases, for if it were not so, a change in the potential difference between the phases would result in a finite current flow during the relatively long period of time required for the system to attain a new state of equilibrium. Since any ion in the system might be regarded as a potential-determining ion, it follows that in an ideal polarized electrode the concentration of every charged species must be negligibly small in one of the two bulk phases. It is this circumstance which makes it unnecessary to postulate a barrier impermeable to charged particles in an ideal polarized electrode.

From the standpoint of thermodynamics it is desirable to *define* the ideal polarized electrode as one in which each charged species is present in appreciable amounts in only one of the two bulk phases. This definition is equivalent to the practical definition first given. An electrode at equilibrium and containing one or more charged components at finite concentrations in both phases would be classed as a non-polarized electrode. It should not be inferred from this nomenclature that the electrode is necessarily non-polarizable, however.

On the Application of the Gibbs' Adsorption Theorem to Systems in which Charged Substances Are Regarded as Independent Components.—The Gibbs' adsorption theorem, in its original form, applies to systems in which all components are regarded as neutral substances. (Any actual system may be so regarded, of course, provided the system as a whole remains electrically neutral.) It would appear reasonable to rewrite the equation, substituting electrochemical potentials for chemical potentials,[4] and to assume that the rewritten equation would apply to systems in which charged components are regarded as independent components. Such an assumption would not be strictly correct, however, as we now proceed to show.

The physical system treated by Gibbs is chosen as an internal part of a larger system of the same kind in order to eliminate from the discussion phase boundaries other than the one specifically under consideration. This is an important characteristic of the derivation not easily dispensed with if thermodynamic rigor is to be maintained. Such a system must remain electrically neutral as a result of the fact that any excess charge will accumulate on the external surfaces of the conducting system.[5] In a system constrained to remain electroneutral, the principal charged components[6] cannot be added or removed independently of one another. One of these components is not an independent component, yet the system cannot be regarded as formed from its independent

(4) For an uncharged component, the electrochemical potential may be regarded as identical with the chemical potential.

(5) It is debatable whether or not one may consider infinitesimal deviations from electrical neutrality in the interior of a conducting system. We avoid this question, and at the same time simplify our treatment, by restricting the allowable variations to those which can be carried out without destroying the electrical neutrality of the system as a whole. Since actual systems do remain electroneutral, the applicability of our final equations is not thereby impaired.

(6) By principal charged components we mean those substances which must be added to make up the system under consideration. Electrolytes which dissociate into two or more ionic species we regard as mixtures of these substances. Water is regarded as a single substance. Metals are regarded as mixtures of ions and electrons, each of which is a principal component.

components only. One of the principal charged components may be singled out and called a dependent component, yet its presence must be taken into account, either explicitly or implicitly, in any equation relating to the energy content of the system.

In the derivation of the adsorption theorem in its original form the chemical potentials enter as a substitution for the quantity $\partial E/\partial n_i$ where E is the energy of the system (regarded as a function of the entropy and the number of moles of the *independent* components) and n_i is the number of moles of the component X_i. In the particular kind of system we are now considering, it is not valid to write $\partial E/\partial n_i = \bar{\mu}_i$,[7] where $\bar{\mu}_i$ is the electrochemical potential, because the addition of a charged component necessitates the addition or removal of another charged component, regarded as a dependent component. It is this fact which makes it incorrect simply to write $\bar{\mu}_i$ for μ_i in the Gibbs' adsorption theorem.

Derivation of the General Equations of Electrocapillarity.—If we choose to regard the electrons of the metallic phase as the dependent component whose amount varies with the addition or removal of charged components in such a way that electrical neutrality is always preserved, we may write

$$\partial E/\partial n_i = \bar{\mu}_i + z_i\bar{\mu}_e \qquad (1)$$

where z_i is the "valence" (including sign) of X_i, and $\bar{\mu}_e$ is the electrochemical potential of the electrons in the system.

The derivation of the adsorption theorem can be carried through in the usual manner without substituting any new symbol for the quantity $\partial E/\partial n_i$. Then Gibbs' equation 508 becomes

$$\mathrm{d}\sigma + S_s\mathrm{d}T = -\sum^{c}\Gamma_i\mathrm{d}\left(\frac{\partial E}{\partial n_i}\right) \qquad (2)$$

In this equation σ is the interfacial tension of the interface under consideration, Γ_i is the excess of the component X_i, in moles per unit area, over that which would be present in the system if the density of X_i in each phase remained constant (at its value in the internal parts of the bulk phases) right up to a mathematical surface drawn parallel to, but not necessarily coincident with, the physical interface. The physical interface is assumed to be effectively plane, by which it is meant that its radius of curvature is very large relative to the thickness of the region of discontinuity at the interface. S_s is the superficial density of entropy (entropy per unit area) defined in a manner analogous to the Γ's. T is the (absolute) temperature. The summation is carried out over the *c independent* components. If charged substances are regarded as independent components, c will be less by one than the number of principal components.

Equation 2 is valid for any two-phase system at equilibrium, subject only to the usual limitations with regard to gravitational and electric fields, strains in solids, etc.[1a] If we agree to adopt the conventions appropriate to Eq. 1, we may write

$$\mathrm{d}\sigma + S_s\mathrm{d}T = -\sum^{c}\Gamma_i\mathrm{d}\bar{\mu}_i - \sum^{c}\Gamma_i z_i\mathrm{d}\bar{\mu}_e \qquad (3)$$

It may be noted in passing that this equation may be obtained somewhat more readily, if not so rigorously, by overlooking the requirement of electrical neutrality imposed upon the system by its physical arrangement. In that case the adsorption equation would be written

$$\mathrm{d}\sigma + S_s\mathrm{d}T = -\sum^{c+1}\Gamma_i\mathrm{d}\mu_i$$

where the $c + 1$ components include the electrons. Expanding this equation, and noting that *when* the system is electrically neutral $\sum^{c}\Gamma_i z_i = \Gamma_e$, we obtain

$$\begin{aligned}\mathrm{d}\sigma + S_s\mathrm{d}T &= -\sum^{c}\Gamma_i\mathrm{d}\bar{\mu}_i - \Gamma_e\mathrm{d}\bar{\mu}_e \\ &= -\sum^{c}\Gamma_i\mathrm{d}\bar{\mu}_i - \sum^{c}\Gamma_i z_i\mathrm{d}\bar{\mu}_e\end{aligned}$$

In these equations, as elsewhere, the subscript e refers to the electrons.

We may express electrochemical potentials in terms of chemical potentials and electrical potentials by the substitution[7]

$$\mathrm{d}\bar{\mu}_i = \mathrm{d}\mu_i + z_i F\mathrm{d}\varphi_i \qquad (4)$$

where F is the faraday and $\mathrm{d}\varphi_i$ is the change in the electrical potential of the phase in which the chemical potential, μ_i, is reckoned. Equation 4 is valid for electrons, as for ions. It is also valid for uncharged substances, since for these latter, $z_i = 0$. Substitution of Eq. 4 into Eq. 3 gives

$$\begin{aligned}\mathrm{d}\sigma + S_s\mathrm{d}T = &-\sum^{c}\Gamma_i\mathrm{d}\mu_i - \sum^{c}\Gamma_i z_i\mathrm{d}\mu_e - F\sum^{\alpha}\Gamma_i z_i\mathrm{d}\varphi^{\alpha} - \\ &F\sum^{\beta}\Gamma_i z_i\mathrm{d}\varphi^{\beta} + F\sum^{\alpha}\Gamma_i z_i\mathrm{d}\varphi^{\alpha} + F\sum^{\beta}\Gamma_i z_i\mathrm{d}\varphi^{\alpha} \qquad (5)\end{aligned}$$

$$= -\sum^{c}\Gamma_i\mathrm{d}\mu_i - F\sum^{\beta}\Gamma_i z_i\mathrm{d}(\varphi^{\beta} - \varphi^{\alpha}) - \sum^{c}\Gamma_i z_i\mathrm{d}\mu_e \qquad (6)$$

In these equations we have divided the summations containing φ's into two parts according to the phase in which the chemical potential of each

(7) E. A. Guggenheim, "Modern Thermodynamics," Methuen and Co., London, 1933, p. 133.

particular component has been reckoned. The symbols α and β over the signs of summation signify that the summation is to include those independent components whose chemical potentials have been reckoned in the metallic and non-metallic phases, respectively. φ^α and φ^β are the electrical potentials of these phases. It will be noted that in a system at equilibrium the electrochemical potential of every component is the same in the two phases, and it will therefore make no difference in which phase a component is reckoned. But it will usually be more convenient to measure the *chemical* potential in one phase rather than in the other, and this consideration will generally indicate the phase in which a given component may most conveniently be reckoned. Equations 5 and 6 have been written on the assumption that the electrons will be regarded as a component of the metallic phase. This is a matter of convenience rather than of thermodynamic necessity.

Equation 6 may be regarded as a general equation of electrocapillarity. It is applicable to polarized and non-polarized electrodes alike. In order to apply it more conveniently to ideal polarized electrodes we may define a quantity ϵ^β by the equation

$$\epsilon^\beta = F\sum^{\beta}\Gamma_i z_i \qquad (7)$$

Because of the electrical neutrality of the system as a whole we may write

$$\sum^{c}\Gamma_i z_i = \Gamma_e \qquad (8)$$

Substitution of Eqs. 7 and 8 into Eq. 6 yields the simplest form of the general equation, when this is to be used in connection with ideal polarized electrodes, as follows

$$d\sigma + S_s dT = -\epsilon^\beta d(\varphi^\beta - \varphi^\alpha) - \sum^{c+1}\Gamma_i d\mu_i \qquad (9)$$

Like Eq. 6, this equation applies to any electrode at equilibrium. It is restricted only by the requirement that the physical interface be essentially plane, as defined above. This restriction limits the possible variation of $\varphi^\beta - \varphi^\alpha$ and of the μ's to values such that the pressures within the two phases are (nearly) equal. Since this is also the requirement that the interfacial tension be measurable by the usual methods, the equations may be applied to any system for which the interfacial tension is measurable.[8]

(8) Our equations are valid for a system in which the interface is not essentially plane if the position of the dividing surface, with reference to which the Γ's are reckoned, is sensibly coincident with the physical interface. This point is discussed in detail by Gibbs, ref. 1a.

It is particularly to be noted that the position of the surface of reference, with respect to which S_s and the Γ's are reckoned, is not specified in the foregoing treatment but may be taken as any surface parallel to the (essentially plane) interface. This makes it possible to set any one of the Γ's equal to zero, whereby the position of the surface of reference is fixed. The component for which Γ is set equal to zero may be called the reference component. If it is desired to place the surface of reference as nearly coincident with the physical interface as possible, the reference component must be chosen as that component which may most reasonably be assumed not to undergo concentration or dilution at the physical interface. From the standpoint of thermodynamics alone, it is a matter of indifference which component is selected as a reference component except in certain very unusual cases discussed by Gibbs, ref. 1a, p. 234.

In an *ideal polarized electrode* the value of ϵ^β will be independent of the position of the surface of reference. This results from the fact that every charged component is to be found in only one of the bulk phases, and since the interior of each phase is electrically neutral, the *excess* of charge is uninfluenced by changes in the assumed volume of each such neutral phase.

For an ideal polarized electrode the quantity ϵ^β is nearly identical with what is commonly called the surface charge density, but it happens that the thermodynamically significant quantity is ϵ^β and not the surface charge density, as that term is commonly understood. For example, it is ϵ^β which is actually measured in experiments which purport to measure the surface charge density.[9,10] If physical interfaces are as sharply defined as is generally believed, the practical difference between these quantities is wholly negligible, but it is important from the standpoint of thermodynamics to realize that the quantities are not identical. The differential capacity of an ideal polarized electrode is identical with the quantity $\partial\epsilon^\beta/\partial(\varphi^\beta - \varphi^\alpha)$.[10] Thus it appears that the experimentally observable properties of an ideal polarized electrode form a self-consistent system independent of any concepts relating to the "true" surface charge density. It will be noted that the concept of a "true" surface charge density is analogous to the concept of a

(9) A. Frumkin, *Z. physik. Chem.*, **103**, 55 (1923); L. St. J. Philpot, *Phil. Mag.*, **13**, 775 (1932); I. M. Barclay and J. A. V. Butler, *Trans. Faraday Soc.*, **36**, 128 (1940).

(10) D. C. Grahame, THIS JOURNAL, **63**, 1207 (1941).

"true" degree of dissociation of an electrolyte.[11]

At constant temperature and composition, Eq. 9 reduces to the familiar Lippmann equation

$$d\sigma = -\epsilon^\beta d(\varphi^\beta - \varphi^\alpha) \qquad (10)$$

When the composition of the phases remains constant, $d(\varphi^\beta - \varphi^\alpha)$ is an experimentally observable quantity. At the potential of the electrocapillary maximum, $\epsilon^\beta = 0$.

Equation 9 gives rise to a number of other useful equations related to the electrocapillary properties of an ideal polarized electrode. These have been worked out in detail by Koenig[3] from an equation substantially identical with our Eq. 9. The only change in these further equations which our treatment requires is in the manner of interpreting ϵ^β and in the location of the surface of reference, which latter is arbitrary in our treatment. Since the form of the equations is not changed by these considerations, we have not thought it necessary to repeat the equations here. It should be pointed out to prospective users, however, that Koenig has defined his Γ's and μ's in terms of equivalents rather than in moles.

It is found experimentally that the Lippmann equation is sometimes obeyed with considerable accuracy even when the system under investigation is far removed from a state of equilibrium.[10] This circumstance is doubtless to be attributed to the fact that the properties of an interface are affected chiefly by the composition of the phases in the immediate neighborhood of the interface. Since this part of the system readily reaches a steady state only slightly different from an equilibrium state, it is understandable that the observable properties should be essentially those of a system at equilibrium.

Application of the General Equation to the Non-polarized Electrode.—At constant temperature, the only variation of a non-polarized electrode consistent with the condition of equilibrium is a simultaneous variation of composition and $\varphi^\beta - \varphi^\alpha$. The most important case of a system of this kind is the system formed by a pure metal in equilibrium with a solution of one of its simple salts (a salt which dissociates into two ionic species only). If we let the subscripts $_o$, $_+$ and $_-$ designate, respectively, quantities related to the solvent, the cation and the anion of the salt, then from Eq. 4, by equating $d\bar{\mu}_+^\alpha$ and $d\bar{\mu}_+^\beta$

$$z_+ F d(\varphi^\beta - \varphi^\alpha) = -d\mu_+^\beta \qquad (11)$$

The superscripts on the chemical and electrochemical potentials designate the phase in which the chemical potential of the component is to be reckoned. Substitution of Eq. 11 into Eq. 6 gives

$$d\sigma = -\Gamma_+ d\mu_+^\beta - \Gamma_- d\mu_-^\beta - \Gamma_o d\mu_o + \Gamma_+ d\mu_+^\beta + \frac{z_-}{z_+}\Gamma_- d\mu_+^\beta \qquad (12)$$

$$= -\frac{f}{z_+}\Gamma_- d\mu - \Gamma_o d\mu_o \qquad (13)$$

The symbol μ, without subscript, denotes the chemical potential of the salt, which is equal to $(z_+\mu_- - z_-\mu_+)/f$ where f is the largest common factor of z_+ and $-z_-$. In deriving Eq. 12 the cation was arbitrarily regarded as a component of the non-metallic phase. The same final result would have been obtained if it had been regarded as a component of the metallic phase. Equation 13 can also be derived very readily from the Gibbs adsorption theorem in its usual form by regarding the metal, the salt and the solvent as the three independent components of the system.

It has not been customary in the past to measure interfacial tensions of non-polarized systems under conditions suitable for the application of Eq. 13. However, there seems to be no reason why such measurements could not be carried out with mercury as the metallic phase and aqueous mercurous nitrate, for example, as the electrolyte. Taking the solvent as the reference component, one could readily calculate Γ_- at various concentrations of electrolyte, and also, by equation 8, $z_+\Gamma_+ - \Gamma_e$. It does not appear to be possible, however, to evaluate Γ_+ and Γ_e separately.

Summary

The thermodynamic equations of electrocapillarity have been derived with no assumptions other than that of equilibrium between the phases. It is shown that the interpretation of the equations so obtained is slightly different from what had previously been supposed. A general electrocapillary equation has been derived for a non-polarized electrode, and it is shown how this may be applied to experimentally obtainable data.

AMHERST, MASS. RECEIVED DECEMBER 6, 1941

(11) G. N. Lewis and M. Randall, "Thermodynamics," McGraw-Hill Book Co., Inc., New York, N. Y., 1923, pp. 317–325.

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

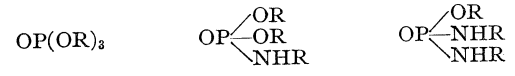
The Aquo Ammono Phosphoric Acids. III. The N-Substituted Derivatives of Phosphoryl and Thiophosphoryl Triamide as Hydrogen Bonding Agents

BY L. F. AUDRIETH AND A. D. F. TOY

Introduction

The alkyl and aryl esters of phosphoric acid have found extensive application as solvents, and as plasticizers for various polymeric substances. They are most effective for those polymeric materials which contain active acceptor atoms, such as the polyamides, the phenol-formaldehyde resins, the urea-formaldehyde resins, and the vinyl polymers. Hydrogen bonding is considered to play a very important role in this particular application, for it is assumed that the oxygen atoms in the phosphoric acid esters serve as the donor atoms in bonding to active hydrogen atoms. Copley, Zellhoefer and Marvel[1,2] have shown that the extraordinary solubility of CH_2Cl_2 in a series of phosphoric acid esters, such as $(C_2H_5O)_3PO$, $(C_3H_7O)_3PO$, $(C_4H_9O)_3PO$, $(C_6H_5O)_3PO$, $(o\text{-}C_6H_4O\text{-}CH_3)_3PO$, and $(CH_3OCH_2CH_2O)_3PO$, may be explained on the basis of hydrogen bond theory. The high heat of mixing of triethyl phosphate with chloroform also indicates that loose compound formation through a hydrogen bond occurs.[3]

The present investigation was undertaken in order to determine if the nitrogen analogs of phosphoric acid might not also be capable of acting as potential hydrogen bonding agents. The N-alkyl and N-aryl substituted derivatives of phosphoryl triamide, $OP(NH_2)_3$, may be looked upon as the nitrogen analogs of the esters of phosphoric acid. Compounds in which one or two of the -OR groups are replaced by an amine radical may be regarded as the mixed aquo ammono phosphoric acid esters. With this concept in mind, the close relationship between the aquo phosphoric acid esters and the N-substituted phosphoryl triamides should be evident.



Aquo ester — Mixed aquo ammono esters

$OP(NHR)_3$ or $OP(NR_2)_3$

Ammono esters[4]

Theoretically, the ammono phosphoric acid esters should be capable of acting as hydrogen bonding agents because of the presence of both oxygen and nitrogen atoms which may be capable of acting as donor atoms. Donor molecules (hydrogen bonding agents) have been found to exhibit extraordinarily high solubility in such solvents as chloroform, which contains an acceptor hydrogen atom. On the other hand, solubility of these same materials in solvents such as carbon tetrachloride is considerably less, despite the fact that the structures of chloroform and carbon tetrachloride are quite similar. This difference has been ascribed to the absence of an active hydrogen atom in carbon tetrachloride. This does not mean that such donor compounds are abnormally soluble in all hydrogen containing solvents. The hydrogen atom must possess some lability. Petroleum ether, for instance, exhibits no tendency to act as an acceptor solvent since the hydrogen atoms are non-labile. However, these considerations should not be taken as absolute criteria since a substance, because of its structure, may still exhibit considerable solubility or insolubility in typical non-polar solvents. Consequently the relation of structure to potential hydrogen bonding ability is a factor which should not be overlooked. It has already been shown by the authors[5] that phenyl di-(morpholido)-phosphate is extraordinarily soluble in many solvents, including water, while the diphenyl morpholido-phosphate is insoluble in water, but nevertheless very soluble in organic solvents. In order to determine the effect of structure upon hydrogen bonding ability, a series of N-substituted phosphoryl triamides were prepared and these together with related compounds were investigated for their solubility in chloroform and in carbon tetrachloride. A number of N-substituted thiophosphoryl triamides, derivatives of the thio ammono phosphoric acid, $SP(NH_2)_3$, were also prepared to determine specifically the effect of replacing oxygen by sulfur.

In the course of this work standard methods for the preparation of N-substituted phosphoryl

(1) Copley, Zellhoefer and Marvel, THIS JOURNAL, **60**, 2666 (1938).
(2) Copley, Zellhoefer and Marvel, *ibid.*, **60**, 2714 (1938).
(3) Marvel, Copley and Ginsberg, *ibid.*, **62**, 3109 (1940).
(4) Strictly speaking, the parent substance, $PO(NH_2)_3$, is still a mixed aquo ammono phosphoric acid from the Franklin point of view.
(5) Audrieth and Toy, THIS JOURNAL, **64**, 1337 (1942).

TABLE I

THE N-SUBSTITUTED PHOSPHORYL TRIAMIDES

Compound	Amine			$POCl_3$		C_5H_5N		Recrystallized from	G.	Yield, %	M. p., °C.	Ref.
		Grams	Moles	Grams	Moles	Grams	Moles					
$PO(NHC_6H_5)_3$	Aniline	111.7	1.2	30.78	0.2	47.4	0.6	75% EtOH	53	82	211–214; sl. dec. 250	8
$PO(NHC_6H_{11})_3$	Cyclohexylamine	118.8	1.2	30.78	.2	47.4	.6	High b. pet. ether	49	72	245–246 dec.	[a]
$PO(NHC_6H_4CH_3)_3$	*p*-Toluidine	64.3	0.6	15.4	.1	23.7	.3	95% EtOH	32	87.5	198–199; sl. dec. 250	11
$PO(NHC_6H_4CH_3)_3$	*o*-Toluidine	64.3	.6	15.4	.1	23.7	.3	75% EtOH	20	55	229–230 dec.	11
$PO(N_2H_2C_6H_5)_3$	Phenylhydrazine	64.8	.6	15.4	.1	23.7	.3	Abs. EtOH	31	84.3	185–187 dec.	12
$PO(NC_4H_8O)_3$	Morpholine	104.4	1.2	30.78	.2	94.8	1.2	CCl_4	41	67.8	191–192; dec. 250	[b]
$PO(NHC_6H_4OC_2H_5)_3$	*p*-Phenetidine	82.2	0.6	15.4	.1	23.7	0.3	75% EtOH	25.3	55.6	172–173; dec. 250	6
$PO(NHCH_2C_6H_5)_3$	Benzylamine	64.2	.6	15.4	.1	23.7	.3	65% EtOH	15	42.2	98–99; dec. 250	10

[a] Calcd. for $PO(NHC_6H_{11})_3$: C, 63.35; H, 10.63; N, 12.6. Found: C, 63.71; H, 10.79; N, 12.42.
[b] Calcd. for $PO(NC_4H_8O)_3$: C, 47.3; H, 7.87; N, 13.76. Found: C, 47.22; H, 7.95; N, 13.68.

triamides were investigated, but none found to be satisfactory. These compounds previously had been prepared from phosphoryl chloride and the corresponding amines, (a) in the presence of sodium hydroxide,[6] (b) by direct reaction in the cold and subsequent heating,[7,8] and (c) at higher temperatures under pressure in a closed tube,[9] or (d) in the presence of diluents.[10] The new and recommended procedure involves interaction of the phosphoryl chloride-pyridine complex with the amine in chloroform solution.

Experimental

A. Preparation of N-Substituted Phosphoryl Triamides.—To 15.4 g. (0.1 mole) of phosphoryl chloride dissolved in 200 cc. of chloroform in a 500-cc. 3-neck flask there was added slowly with stirring 23.7 g. (0.3 mole) of pyridine. The temperature of reaction was maintained at $0 \pm 1°$ by means of an ice–salt-bath. The addition of the first few cc. of pyridine had to be slow since a great deal of heat was generated. After this initial reaction the rest of the pyridine could be added rapidly (ten minutes). This solution was then transferred to a dropping funnel and added slowly (thirty to forty minutes) to 0.6 mole of amine dissolved in 200 cc. of chloroform in a 1-liter 3-neck flask cooled to $0 \pm 2°$ by an ice–salt-bath. The resulting product was heated on the steam-bath and refluxed for two hours to ensure complete reaction. If, upon cooling, a chloroform insoluble amine hydrochloride formed, it was removed by filtration and the residue was washed with chloroform. The combined filtrates were distilled over a steam-bath to remove most of the solvent, the last portions having been eliminated by heating over a very low free flame at a pressure of 3–4 mm. The residue was washed first with dilute hydrochloric acid and then with water until the washings gave no chloride test. The desired product was then recrystallized from a proper solvent. Any amine hydrochloride residue was also washed with water, for in this way an additional quantity of the water insoluble product was often recovered. Specific preparative details are given in Table I.

In the recommended procedure a ratio of $POCl_3$:Amine:C_5H_5N = 1:6:3 was used. In similar reactions pyridine acts not only to moderate the reaction, but also serves to take up the hydrogen chloride which is formed. If the latter function is also served in the present case, then the use of six moles amine to one of phosphoryl chloride represents a needless hundred per cent. excess of amine. An experiment was therefore carried out using a $POCl_3$:Amine:C_5H_5N ratio of 1:3:3. The other conditions of the reaction were kept identical with those given above. Specifically, 15.4 g. (0.1 mole) of phosphoryl chloride, 23.7 g. (0.3 mole) pyridine, and 28 g. (0.3 mole) of aniline were used. The yield of phosphoryl trianilide was 10.5 g. (32.3%) as compared to a yield of 82% when a $POCl_3$:$C_6H_5NH_2$:C_5H_5N ratio of 1:6:3 was used. This seems to indicate that the presence of pyridine serves largely to moderate the reaction and not react to take up the hydrogen chloride to form pyridine hydrochloride. It should also be pointed out that phosphoryl chloride actually forms pyridinium complexes[13] of the type $[POCl_2 \cdot Py]^+Cl^-$, and that these complexes undergo solvolysis much more smoothly than the acid chloride by itself or in some inert solvent.

B. Preparation of the N-Substituted Thiophosphoryl Triamides.—The method first employed by Michaelis and Steinkopf[14] was used for the preparation of the N-substituted thiophosphoryl triamides. The general procedure involved the addition of one mole of thiophosphoryl chloride to six moles of amine at $5 \pm 5°$. The resultant mixture was heated on a steam-bath for twelve hours. It was then cooled and washed free of amine hydrochloride with water. The water insoluble portion was recrystallized from a proper solvent. In the case of the thiophosphoryl trimorpholide which is slightly soluble in water, the reaction product was extracted with chloroform to separate the desired compound from morpholine hydrochloride.

(6) Autenrieth and Rudolph, *Ber.*, **33**, 2099 (1900).
(7) Schiff, *Ann.*, **101**, 299 (1857).
(8) Michaelis and Soden, *ibid.*, **229**, 334 (1885).
(9) Michaelis, *ibid.*, **326**, 256 (1903).
(10) Michaelis, *ibid.*, **326**, 177 (1903).
(11) Rudert, *Ber.*, **26**, 565 (1893).
(12) Michaelis and Oster, *Ann.*, **270**, 135 (1892).
(13) Boyd and Ladhams, *J. Chem. Soc.*, 215 (1928).
(14) Michaelis and Steinkopf, *Ann.*, **326**, 218 (1903).

TABLE II

THE N-SUBSTITUTED THIOPHOSPHORYL TRIAMIDES

Compound	Amine (0.6 mole)	Grams	$PSCl_3$ (0.1 mole) Grams	Recryst. from EtOH	Yield, Grams	%	M. p., °C.	Ref.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
$PS(NC_5H_{10})_3$	Piperidine	51	16.9	95%	28.5	90.5	121–122	14[a]						
$PS(NC_4H_8O)_3$	Morpholine	52.2	16.9	95%	28.5	89	145.5–146	[a]	44.85	44.85	7.54	7.46	13.07	13.08
$PS(NHC_6H_{11})_3$	Cyclohexylamine	59.4	16.9	Abs.	32	89.6	143.5–144.5	[b]	60.5	60.44	10.15	10.25	11.74	11.62

[a] Stable at 200°, darkens at 250°, but m. p. does not change. [b] Stable even at 250°.

TABLE III

SOLUBILITIES OF SOME MORPHOLINE DERIVATIVES AT 25°

Compound	Formula	G./100 g. H_2O	G./100 g. $CHCl_3$	G./100 g. CCl_4
Diphenyl morpholidophosphate	$(C_6H_5O)_2PO(NC_4H_8O)$	0.230	71.9	6.27
Phenyl di-(morpholido)-phosphate	$C_6H_5OPO(NC_4H_8O)_2$	336.0	138.0	20.80
Phosphoryl trimorpholide	$PO(NC_4H_8O)_3$	154.6	57.82	0.702
Thiophosphoryl trimorpholide	$PS(NC_4H_8O)_3$	0.322	47.20	1.341

TABLE IV

SOLUBILITIES OF SOME N-SUBSTITUTED PHOSPHORYL AND THIOPHOSPHORYL TRIAMIDES AT 25°

Compound	G./100 g. $CHCl_3$	G./100 g. CCl_4
$PO(NHC_6H_5)_3$	0.276	0.000
$PO(p\text{-}NHC_6H_4CH_3)_3$	1.10	.000
$PO(o\text{-}NHC_6H_4CH_3)_3$	1.87	.000
$PO(N_2H_2C_6H_5)_3$	0.064	.000
$PO(p\text{-}NHC_6H_4OC_2H_5)_3$	2.05	.000
$PO(NHC_6H_{11})_3$	68.10	6.05
$PO(NHCH_2C_6H_5)_3$	56.50	0.236
$PS(NHC_6H_{11})_3$	28.24	2.25
$PS(NC_5H_{10})_3$	99.50	32.97

The chloroform extract was then evaporated and the residue washed with a small quantity of ice-water to remove the last traces of morpholine hydrochloride. The N-substituted thiophosphoryl triamides are listed in Table II.

C. Solubility Determinations.—The solubilities of all compounds in chloroform and carbon tetrachloride at 25° were determined. Only in the case of the morpholine derivatives were quantitative solubilities in water also determined. The solubility data are given in Tables III and IV.

Discussion

The marked differences in the solubility of the N-substituted phosphoryl triamides in chloroform and in carbon tetrachloride may be ascribed to hydrogen bonding. This difference is especially striking in the case of the morpholine derivatives where not only are there oxygen atoms in peripheral positions in the ring, but also nitrogen atoms devoid of hydrogen atoms. While the derivatives of aniline and of amines of similar structure also are much more soluble in chloroform than in carbon tetrachloride, the solubility in chloroform is low in every case. This low solubility may be due to the fact that the nitrogen is located next to a phenyl ring which permits the pair of free electrons on the nitrogen to resonate with the electrons in the double bonds of the phenyl ring. The availability of the nitrogen as a donor atom is thus decreased. This hypothesis is substantiated by the observation that elimination of resonance (a) by reduction of the ring, as in the case of the cyclohexylamine derivatives, and (b) by separating the nitrogen from the phenyl group with a CH_2 group, as in the case of the benzylamine derivative, brings about a great increase in solubility in chloroform. The presence of an ether oxygen atom attached to the ring, as in the case of the *p*-phenetidine derivative, increases the solubility in chloroform presumably because the extra oxygen serves as another donor of electrons, that is, a point where hydrogen bonding may occur. However, this increase is not of the same order of magnitude as that observed in the case of the morpholine derivatives where the oxygen atom is in the ring. It may be that this difference is also due to the fact that the electrons in the oxygen next to the phenyl ring are in resonance with the electrons in the double bonds of the ring.

Our observations demonstrate clearly that the oxygen atom connected directly to the phosphorus atom also possesses some donor characteristics. The N-substituted thiophosphoryl triamides are in every case less soluble in chloroform than the corresponding phosphoryl compounds.

Summary

A number of phosphoryl and thiophosphoryl triamides have been prepared and their solubilities in chloroform, carbon tetrachloride, and water have been determined. The solubility data indicate that these substances are good hydrogen bonding agents and that the oxygen and the nitrogen atoms in these compounds are capable of acting as donor atoms in solvents such as chloroform which contains an active hydrogen atom.

URBANA, ILLINOIS RECEIVED APRIL 6, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

The Solubility of Propylene Vapor in Water as Affected by Typical Detergents

BY JAMES W. McBAIN AND A. M. SOLDATE

It has been shown[1,2] that potassium oleate added to water greatly increases the amount of hydrocarbon which can dissolve. The solubilized hydrocarbons are incorporated in or upon the colloidal particles or micelles of the soap, thus lowering the vapor pressure of the hydrocarbon and leaving the freezing point of the soap solution unaffected.

These observations are now extended to a series of typical detergents, surface active agents, and other substances in order to determine whether such solubilization always occurs with detergents, and to contrast it with the effects of salts and mixed solvents. The result is to show that all the detergents tested exhibit this property, whereas salts such as a carbonate, pyrophosphate, or a Calgon do not; and much larger quantities of an organic solvent must be added to produce a comparable effect.

Experimental

Propylene was used in all experiments following the procedure already described.[1] Although evacuation was carried out in each case for half an hour in a Cenco Hyvac pump, the evacuation was necessarily incomplete.[3] All data refer to solutions at 25°.

Since it was not always convenient to arrange for the same equilibrium pressure, it was assumed that Henry's law could be used within the range 500 to 700 mm. pressure. Hence all the data are expressed in terms of grams of propylene dissolved per gram of water per mm. pressure for this range.

The Data

The observations are collected in Table I, which gives the amount of detergent, salt, or other substance added expressed as per cent. (meaning, however, grams per 100 cc. of solvent), and the values of x/m, multiplied by 10^5, and a comment as to the effect noted.

Discussion

The chief result is to show that all the detergents exhibit solubilizing action for propylene in water, as well as for otherwise insoluble dye.

TABLE I

THE SOLUBILITY OF PROPYLENE IN AQUEOUS SOLUTIONS[a] AT 25° IN GRAMS × 10^{-5} OF PROPYLENE PER GRAM OF WATER PER MM. PRESSURE FOR THE RANGE 500–700 MM.

Solution		Mean	Effect
Water only	3.5, 3.4, 3.4, 3.3	3.4	standard
15% potassium oleate		18.7	great
12% potassium oleate	14.3, 15.6, 14.8	14.9	great
9% potassium oleate		12.5	great
1% potassium oleate	3.4, 3.3, 3.5, 3.9, 3.9	3.7	slight
15% pure Tergitol 4		13.6	great
1.5% Aerosol OT		7.5	fair
1% Aerosol OT	3.9, 3.0, 3.3, 3.2, 3.4	3.4	none
15% Aerosol MA	11.2, 10.8	11.0	good
15% Mixture; 1 pt. OT, 4 pts. MA	9.8, 10.4	10.1	good
15% Aerosol AY	7.7, 8.0, 10.9	8.9	good
1% Aerosol AY	2.8, 3.1	3.0	none?
15% Aerosol IB	5.5, 5.8	5.7	fair
10% Aerosol IB	4.9, 4.3	4.6	fair
15% Aerosol OS	7.0, 7.1	7.1	fair
15% sodium deoxycholate		6.1	fair
15% sodium dehydrocholate		0.8	salts out!
15% Aquasol AR (Turkey Red Oil)		14.4	great
15% Igepon A (thixotropic)	7.6, 7.8	7.7	fair
15% of 95% Triton NE		11.3	good
15% of 90% Alronal	11.5, 13.3	12.4	good
25% Triton K 60		32.6	great
15% potassium novenate		11.2	good
10% Nacconol NR		9.2	good
10% Sapamine KW		5.4	fair
15% diethylcarbitol		3.7	slight
0.4% Calgon	3.6, 3.6, 4.1	3.8	none?
2% Calgon		3.3	none
5% Calgon		3.8	none
12% KOl + 0.2% Calgon		14.6	Calgon none
12% KOl + 3% Calgon		15.2	Calgon none
5% K_2CO_3		3.0	negative
0.5% K_2CO_3		3.5	none?
12% KOl + 5% K_2CO_3		15.9	K_2CO_3 slight
12% KOl + 0.2% K_2CO_3		14.1	K_2CO_3 slight
12% KOl + 2% tetrasodium pyrophosphate		14.5	phosphate none
12% KOl + 5% tetrasodium pyrophosphate	15.0, 16.1	15.6	phosphate none

[a] For a description of the active agent in materials here designated only by trade names, see *Ind. Eng. Chem.*, **31**, 66 (1939); **33**, 16, 740 (1941).

This is strikingly emphasized by the contrasting behavior between the detergent, sodium deoxycholate, and the closely similar non-detergent, sodium dehydrocholate. Whereas the former doubled the solubility of propylene in water, the latter salts out three-quarters of what would otherwise dissolve in the water alone. Frazer, Stewart and Schulman have stated[4] that bile salts form no complexes with paraffin, but this is evidently not true in solution; therefore, the solubilized paraffin may be of some significance in experiments on digestive processes.

(1) J. W. McBain and J. J. O'Connor, THIS JOURNAL, **63**, 875 (1941).

(2) J. W. McBain and J. J. O'Connor, *ibid.*, **62**, 2855–59 (1940).

(3) J. W. McBain and M. Taylor, *Z. physik. Chem.*, **76**, 179 (1911).

(4) Frazer, Stewart and Schulman, *Nature*, **149**, 167 (1942).

Salts, as such, have a definite salting out effect, although the present method is usually too insensitive to show the influence of only a few per cent. of either salt or detergent. A small amount of electrolyte may have an enormous effect upon the viscosity of such a detergent as potassium oleate without altering its solubilizing power very noticeably. 15% detergent usually increases the solubility many fold, the highest value in Table I being 18.7 for potassium oleate. Even this is only a small fraction of the amount of propylene which would dissolve in equal weight of a similar pure organic solvent.

In contradistinction to the detergents, the addition of 15% of a good organic solvent has a comparatively negligible result. Thus 15% diethyl carbitol increases the solubility of propylene by only 10% of that of water alone. This again illustrates the difference between solubilizing by detergents which can be appreciable with only a few tenths of a per cent., whereas in hydrotropy with the addition of a good miscible solvent, very high concentrations are required to get a comparable result. The difference is that in the mixed solvent the added molecules are separate and are submerged in the excess of first solvent whereas with the detergent or colloidal electrolyte the solute is segregated in colloidal particles, which themselves incorporate the solubilized material.

Summary

A further study of the effect of added substances upon the solubility of propylene in water is to show that all the detergents tested greatly increase the amount of propylene dissolved, in spite of any salting out action which they may otherwise possess. This solubilizing effect is shown by anion active, cation active, and non-electrolytic detergents.

STANFORD UNIVERSITY, CALIF. RECEIVED MARCH 20, 1942

[CONTRIBUTION FROM THE POLYTECHNIC INSTITUTE OF BROOKLYN]

The Effect of Temperature and Solvent Type on the Intrinsic Viscosity of High Polymer Solutions

BY T. ALFREY, A. BARTOVICS AND H. MARK[1]

According to hydrodynamics, the specific viscosity of a Newtonian liquid containing a small amount of dissolved material should depend in first approximation only upon the volume concentration and the shapes of the suspended particles. By suitable application of such hydrodynamical considerations to solutions of long chain molecules, it is possible in a rough fashion to derive the Staudinger–Kraemer equation, denoting proportionality between specific or intrinsic viscosity and molecular weight. It is an experimental fact, however, that the proportionality constant, K_m, is dependent not only upon the type of polymer concerned, but also upon the temperature and the nature of the solvent. Even in the dilute range, where specific viscosity is linear with concentration, these variations are often quite considerable. This paper tries to treat such variations in a systematic fashion, and to advance for them an explanation which is based upon changes in the average geometrical shape of the particles. A relationship between intermolecular and intramolecular agglomeration tendency is presented.

(1) This paper was presented in October, 1941, at the meeting of the Society of Rheology in New York City.

Theoretical Considerations.—According to Burk,[1a] Eyring,[2] Flory,[3] Guth,[4] Huggins,[5] Kuhn,[6] Mark,[7] and Meyer,[8] a long chain hydrocarbon molecule in solution takes on a somewhat kinked or curled shape, intermediate between a tightly rolled up mass and the rigid linear configuration assumed by Staudinger.[9] Presumably all possible degrees of curling are represented, owing to the internal Brownian movement of the flexible chains, but the configurations of intermediate extension predominate statistically. The average or effec-

(1a) R. E. Burk and L. Laskowsky, *J. Chem. Phys.*, **7**, 465 (1939).

(2) H. Eyring, R. E. Powell and W. E. Roseveare, THIS JOURNAL, **60**, 3113 (1940); *Ind. Eng. Chem.*, **33**, 430 (1941).

(3) P. J. Flory, THIS JOURNAL, **61**, 3334 (1939); **62**, 1057 (1940).

(4) E. Guth and H. Mark, *Monatsh.*, **65**, 94 (1934); E. Guth and H. M. James, *Ind. Eng. Chem.*, **33**, 624 (1941).

(5) M. L. Huggins, *J. Phys. Chem.*, **42**, 911 (1938); **43**, 439 (1939); *J. Appl. Phys.*, **10**, 700 (1939).

(6) W. Kuhn, *Koll. Z.*, **68**, 2 (1934); **76**, 258 (1936); **87**, 3 (1939); *Z. physik. Chem.*, **A161**, 427 (1932).

(7) H. Mark and E. Valko, *Kautschuk*, **6**, 210 (1930); H. Mark, *Koll. Z.*, **53**, 32 (1930).

(8) K. H. Meyer, G. V. Susich and E. Valko, *ibid.*, **59**, 208 (1932); K. H. Meyer, *ibid.*, **95**, 70 (1941).

(9) H. Staudinger and collaborators, *Ber.*, **68**, 707 (1935); *ibid.*, **70**, 1565 (1937); *Melleand*, **18**, 681 (1937); **20**, 693 (1939).

tive value of any shape-dependent molecular property (such as hydrodynamical influences) may be obtained by summing this property over all configurational states, after each state has been given a proper weight factor. If the long chain molecule is surrounded by a continuous, energetically indifferent solvent, then the weight factor for a particular configuration is determined only by internal parameters—potential energy function for restricted rotation, prohibition of segment interpenetration, etc. The mean value of any molecular property in such ani ndifferent (and perhaps hypothetical) solvent might be called the "unbiased" statistical mean for the property.

If the solvent is energetically unfavorable, so that the dissolving of the high polymer is an endothermic process, then the polymer segments will attract each other in solution and squeeze out the solvent between them. The curling forces in such a case will be similar to those postulated in the Mack[10] theory of rubber elasticity. Those molecular configurations which involve many contacts of the molecule with itself will be weighted more heavily than in an indifferent solvent, and the mean value of any molecular property will represent a more curled and contracted shape than the unbiased mean. On the other hand, if a solvent is energetically more favorable than the indifferent solvent as previously defined, then in solution the long chain molecule will be surrounded by a solvated hull which tends to prevent polymer–polymer contacts. Uncurled configurations will be favored, and the mean value of any property will represent a more extended shape than the unbiased mean. Since an extended or uncurled configuration is associated with a high intrinsic viscosity, and *vice versa*, the first prediction as to effect of solvent type upon viscosity is the following.

Other conditions being equal, a given high polymeric material made up of flexible molecules will exhibit a high intrinsic viscosity in an energetically favorable solvent, and a low intrinsic viscosity in an energetically unfavorable solvent. This of course holds only for very diluted systems. At higher concentrations (around or above 5% by weight) an energetically unfavorable solvent will favor polymer–polymer contacts between different chains and hence lead to the danger of gelation, while an energetically favorable solvent will stand a higher concentration of the polymer and yet give a fluid, stable solution. Solvents are often classified as "good" or "bad" on the basis of the viscosity of concentrated solutions.

If a good solvent is mixed with a precipitating agent, the resulting mixture can be expected to be energetically less favorable to a long chain molecule than is the pure solvent. A dilute solution of high polymer in a solvent–non-solvent mixture should, therefore, exhibit a lower intrinsic viscosity than a solution of the same polymer in the pure solvent. It will be shown that a series of high polymer solutions of given polymer concentration, in mixtures of increasing non-solvent content, shows a regular decrease in specific viscosity until the precipitation point is reached.

We have interpreted variations in the intrinsic viscosity of a given high polymeric material as being due to changes in the degree of *intramolecular* agglomeration. If this interpretation is correct, there should be also a close connection between the intrinsic viscosity of a high polymer solution and the degree of *intermolecular* agglomeration. Exactly the same solvent characteristics which determine the mean geometrical properties of an isolated long chain molecule should also determine the amount of association of different solute molecules into aggregates. When a non-solvent is added to a high polymer solution, the point at which precipitation begins represents a certain definite agglomeration tendency for chain segments of different molecules. To a first approximation, therefore, it should represent a certain definite mean value for any shape-dependent *internal* property. That solvent composition which is critical from the standpoint of solubility should correspond to a certain intrinsic viscosity, no matter what the solvent and what the non-solvent. One would therefore conclude the following: The intrinsic viscosities of a series of solutions of a given polymer in solvent–non-solvent mixtures of increasing non-solvent content, should decrease to a final value at the limit of solubility. This final value should be in first approximation the same in all solvent–non-solvent systems.

All of these effects should be more pronounced for polymer molecules of high flexibility than for more rigid chains. A paraffin chain should exhibit greater shape changes than a cellulose derivative.

The effect of temperature upon intrinsic viscosity should depend strongly upon the nature of the solvent. In a poor solvent, the effective molecular shape is more compact and curled than the un-

(10) E. Mack, *J. Phys. Chem.*, **41**, 221 (1937).

biased statistical mean. An increase of temperature should increase the relative importance of entropy factors over energetic factors, and result in an uncurling of the molecule. In such a solvent, a temperature increase should result in an increase of intrinsic viscosity. In a very good solvent, the energetic weighting factors favor the more extended configurations; here a temperature increase should result in a downward approach to the unbiased statistical mean shape. In a very good solvent, therefore, a temperature increase should cause a decrease in intrinsic viscosity. There should be an intermediate case in which the intrinsic viscosity is independent of temperature over a limited range.

The above use of the "unbiased statistical mean" as the shape which is approached as the temperature increases is an oversimplification, since this value itself includes energetic weighting factors, arising from the internal potentials of the molecule. If we consider only the forces which depend upon the solvent, we can make the prediction: In a very good solvent, the intrinsic viscosity of a dilute solution of a flexible polymer should decrease with temperature; in a poor solvent, it should increase.

Experimental

Polystyrene, rubber, and cellulose acetate were used in this investigation. The polystyrene had a weight average molecular weight of 165,000, calculated from viscosity data and using a K_m value of 1.1×10^{-4}. The rubber was smoked crepe, with a weight average molecular weight of 223,000, based upon a K_m value of 2.7×10^{-4}. The cellulose acetate was a fraction with a molecular weight of 35,000, which had been obtained by Harris and Sookne from a sample of commercial cellulose acetate having a weight average molecular weight around 90,000.

Solutions of polystyrene at a concentration of 0.2% by volume in the following solvent–non-solvent systems were investigated: Methyl ethyl ketone–methanol, toluene–acetone, toluene–methanol, toluene–isoamyl alcohol. Figure 1 shows the variation of specific viscosity with non-solvent content. In each case, the specific viscosity decreases as the mixed solvent becomes less favorable until the coagulation point is reached. For all the solvent–non-solvent systems investigated, the specific viscosity at the solubility limit is in the same range.

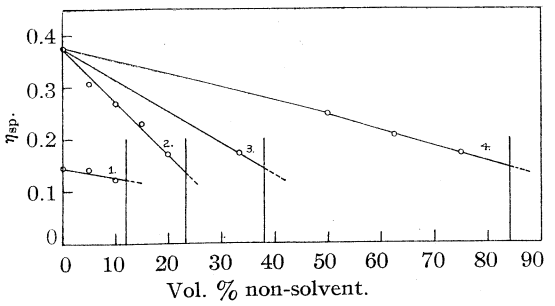


Fig. 1.—Variation of specific viscosity of 0.2% polystyrene solutions with non-solvent content: (1) methyl ethyl ketone–methanol; (2) toluene–methanol; (3) toluene–isoamyl alcohol; (4) toluene–acetone.

Solutions of rubber at a concentration of 0.0468% by volume in the following solvent–non-solvent systems were investigated: toluene–methanol, toluene–acetone, carbon tetrachloride–methanol, carbon tetrachloride–acetone. Figure 2 shows the variation of specific viscosity of these solutions with composition of the mixed solvent. Rubber behaves in the same general way as polystyrene.

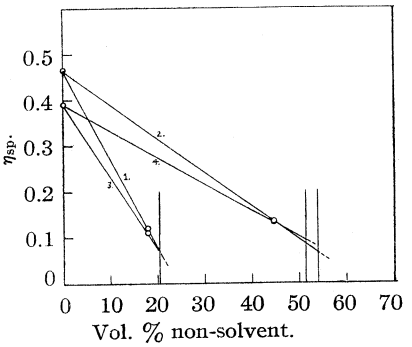


Fig. 2.—Variation of specific viscosity of 0.0468% rubber solutions with non-solvent content: (1) carbon tetrachloride–methanol; (2) carbon tetrachloride–acetone; (3) toluene–methanol; (4) toluene–acetone.

Solutions of cellulose acetate at 0.2% by volume in the following solvent–non-solvent systems were investigated: methylcellosolve–methanol, acetone–methanol, acetone–toluene. The specific viscosities of all solutions were about 0.33. The nature of the solvent medium apparently had no marked effect upon the shape of the cellulose acetate molecule in solution. It is to be expected that the cellulose chain is much less flexible than the rubber and polystyrene molecules.

Effect of Temperature.—Viscosities of many of the solutions were determined at two different temperatures, 25 and 60°. Table I shows the relation between the specific viscosity at 60°

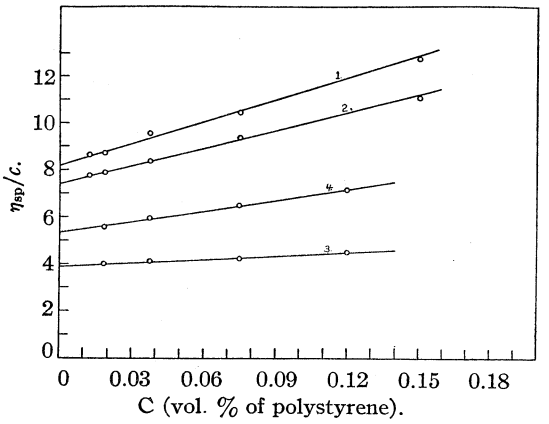


Fig. 3.—Relation between η_{sp}/c and c for polystyrene solutions: (1) toluene, 20°; (2) toluene, 80°; (3) 20% methanol, 80% toluene, 20°; (4) 20% methanol, 80% toluene, 60°.

and that at 25°, as a function of solvent composition, for several systems. In the pure solvents, specific viscosity decreases with temperature, while in the mixtures containing much non-solvent, specific viscosity increases with temperature.

TABLE I

η_{sp} AS A FUNCTION OF TEMPERATURE

Sample	Temperature, °C. 25	60
Rubber in		
Toluene	0.390	0.373
Carbon tetrachloride	.466	.430
Toluene–14% methanol	.205	.243
Polystyrene in		
Toluene	.370	.350
Toluene–10% methanol	.320	.317
Toluene–20% methanol	.160	.185
Toluene–10% amyl alcohol	.336	.340
Toluene–33% amyl alcohol	.170	.210

Effect of Concentration.—The effect of concentration on specific viscosity (in the dilute range) was investigated in both "good" and "poor" solvents, and at different temperatures. A sharp molecular weight fraction of polystyrene (mol. wt. 730,000) was used in this part of the investigation.

If η_{sp} is given by a power series in concentration, there will be a range in which all terms but the first can be neglected ($\eta_{sp} = ac$). Experimentally this range turns out to be very small in the case of a high molecular weight sample. Deviations from the simple linear relation are found at concentrations well below 0.05% by volume. For a somewhat wider range, the first two terms will serve to give the viscosity ($\eta_{sp} = ac + bc^2$). Experimentally, this range proves to be fairly wide, even for high molecular weight samples. When η_{sp}/c is plotted against c, the slope of the straight line gives the second coefficient, b, and the ordinate intercept gives the first coefficient, a. In Fig. 3, (η_{sp}/c) is plotted against c for polystyrene in toluene, and in a mixture of 80% toluene and 20% methanol. In this way is seen the effect of temperature and solvent type upon both virial coefficients. The presence of the non-solvent not only reduces the linear coefficient (which reflects the shape of individual molecules), but also reduces to an even greater degree the second coefficient (which is determined by the *degree of interaction* among different molecules).

An increase in temperature shifts the whole curve downward in the case of toluene, and upward in the case of the toluene–methanol mixture. In the toluene–methanol mixture, the interaction term, b, is least important at the lowest temperature.

It may be significant that Flory[11] has reported a similar situation in regard to the osmotic pressure–concentration relationship for high polymer solutions. The osmotic pressure is more nearly linear with concentration in "poor" solvents than in "good" solvents.

Summary

1. The specific viscosity of a dilute solution of polystyrene or rubber is strongly dependent upon the nature of the solvent; the specific viscosity is high in a good solvent, and low in a poor solvent or a solvent–non-solvent mixture. This has been interpreted as being due to changes in mean molecular shape. The specific viscosities of cellulose acetate solutions are not so sensitive to the nature of the solvent.

2. The extrapolated specific viscosity at the limit of solubility is in the same range for several different solvent–non-solvent systems.

3. The effect of a temperature increase is to lower the specific viscosity of rubber or polystyrene solutions in a good solvent, but to increase the specific viscosity in a mixture of solvent and non-solvent.

4. The specific viscosity of a dilute polystyrene solution is more nearly linear with concentration in a toluene–methanol mixture than in pure methanol. The quadratic term b in the equation ($\eta_{sp} = ac + bc^2$) is reduced relatively more than the linear term a by the presence of the non-solvent.

BROOKLYN, N. Y. RECEIVED APRIL 1, 1942

(11) P. J. Flory, *J. Chem. Phys.*, **10**, 51 (1942).

[COMMUNICATION NO. 847 FROM THE KODAK RESEARCH LABORATORIES]

Oxidation Processes. XIV.[1] The Effect of Silver on the Autoxidation of Some Photographic Developing Agents

BY A. WEISSBERGER AND D. S. THOMAS, JR.

The Ostwald-Abegg theory[2] of photographic development suggested that the developing agent reduces silver ions which are in solution. The silver ions may be added to the developer (physical development) or may come from the silver halide of the emulsion which dissolves as development proceeds (chemical development). The reduction comes to a standstill, for thermodynamic reasons, wherever a certain supersaturation of the silver atoms is reached in the emulsion. Silver specks, however, which are formed by the exposure of the silver halide to light act as crystallization nuclei. In their neighborhood the supersaturation is broken and the reduction continues. This theory obviously applies only to developers which form reversible oxidation–reduction systems and fails to explain the action of the common organic, sulfite-containing, developers. Piper[3] suggested a catalytic action of the latent image on the reduction process itself, and Sheppard,[4] and Volmer[5] explained the mechanism of this catalysis. Sheppard studied the effect of certain compounds on the induction period of development and suggested that the developing agent forms a complex with the silver halide which, in the presence of metallic silver, decomposes into silver and the oxidized developing agent. Volmer passed air through *N* carbonate alkaline solutions of a number of developing agents and found that the resulting discoloration was accelerated by the addition of colloidal silver. His results are shown in Table I. The figures state the number of seconds after which solutions without silver and solutions which contained 0.5 g. of colloidal silver in 5 ml. had about identical colors.

Taking the formation of color as a measure of the oxidation and drawing the analogy between oxidation by air and by silver ion, Volmer suggested that a similar catalysis is essential in photographic development. Such a catalysis would, like the quinone catalysis,[6,7,8] affect the reactivity of the developing agent directly. It would be unspecific with respect to the oxidizing agent, while the mechanism suggested by Sheppard[4] is specific for the reduction of metal salts. Likewise specific for metal ions is the mechanism suggested by James,[9] according to which the reduction of the silver ions is accelerated when the latter are deformed through adsorption to silver or because they are located at the interface of silver and silver halide. To complete this brief account[10] it may be mentioned that the unexposed grains are, according to Sheppard,[11] protected by an adsorption layer of gelatin which becomes permeable for the developing agents when silver nuclei are formed in the exposure. According to Schwarz and Urbach,[12] the protection of the unexposed grains of the common emulsions against reduction consists in an adsorbed electrical barrier. This is, according to James, the more effective the higher the charge of the active species of the developing agent, while it does not function against neutral molecules of the *p*-phenylenediamine type.

In view of their importance for the theory of development, Volmer's experiments were repeated with a volumetric control of the oxygen absorption. This appeared advisable because a change in the rapidity of discoloration of a developer through the addition of colloidal silver may or may not indicate that the silver affects the autoxidation itself, *i. e.*, the reaction of the developing agent with oxygen. The formation of the colored reaction products takes place in later phases of the reaction, and it may well be that the silver accelerates the discoloration without speeding up the autoxidation proper. Moreover, it may be questioned whether the effect recorded by Volmer is big enough to be significant for photographic

(1) Part XIII, James and Weissberger, THIS JOURNAL, **61**, 442 (1939).

(2) Ostwald, "Lehrbuch der allgemeinen Chemie," 2nd Ed., (1893), II, 1, p. 1078; Abegg, *Arch. für wiss. Phot.*, **1**, 15, 109 (1899).

(3) Piper, *Brit. J. of Phot.*, **55**, 195 (1908).

(4) Sheppard, *Phot. Journal*, **59**, 135 (1919); Sheppard and Meyer, THIS JOURNAL, **42**, 689 (1920).

(5) Volmer, *Z. wiss. Phot.*, **20**, 189 (1921); *Phot. Korr.*, **58**, 226 (1921).

(6) James and Weissberger, THIS JOURNAL, **60**, 98 (1938).

(7) James, Snell and Weissberger, *ibid.*, **60**, 2084 (1938).

(8) Kornfeld and Weissberger, *ibid.*, **61**, 360 (1939).

(9) James, *ibid.*, **62**, 536, 1649, 1654 (1940); *J. Phys. Chem.*, **43**, 701 (1939); *ibid.*, **45**, 223 (1941).

(10) For detailed information see C. E. K. Mees, "The Theory of the Photographic Process," The Macmillan Co., New York, N. Y.

(11) Sheppard, *Phot. Journal*, **69**, 330 (1929).

(12) Schwarz and Urbach, *Z. wiss. Phot.*, **31**, 77 (1932); Schwarz, *Phot. Korr.*, **69**, Suppl. No. 5, 27 (1933).

TABLE I

VOLMER'S RESULTS[a]

	Pyrocatechol	Metol	Hydroquinone	Glycine	*p*-Aminophenol	Amidol[b]	Eikonogen
With silver	60	30	40	30	20	30	30
Without silver	160	60	100	80	120	140	60

[a] Metol = N-methyl-*p*-aminophenol; Glycine = N-*p*-hydroxyphenylaminoacetic acid; Amidol = 3,4-Diaminophenol; Eikonogen = 1-Amino-2-hydroxynaphthalene-6-sulfonate.

[b] Aqueous solution without addition of carbonate.

development, unless the size of the observed catalysis was depressed by the experimental technique used.

Materials[12a] and Methods

Hydroquinone was recrystallized from water; catechol from benzene.

p-Aminophenol was sublimed in a high vacuum (0.003–0.004 mm.); m. p. 189°. *p*-Aminophenol oxalate was recrystallized twice from water, containing about 1% of oxalic acid, decolorizing with Nuchar. The filtered crystals were washed with water, alcohol, and ether; m. p. 224° dec. *p*-Methylaminophenol was precipitated from a concentrated aqueous solution of the sulfate by sodium carbonate, filtered and dried. It was then distilled *in vacuo* [140° (3 mm.)], recrystallized twice from benzene and washed with petroleum ether; m. p. 86–87°. *p*-Methylaminophenol sulfate was recrystallized from slightly acidulated water. No difference was found in the autoxidation between the free bases and the salts.

p-Hydroxyphenylaminoacetic acid (photographic glycin) was dissolved in aqueous carbonate, filtered from insoluble impurities, precipitated with acetic acid and washed with water and alcohol. *p*-Phenylenediamine was distilled *in vacuo* and kept as a solid cake, m. p. 140–141°, the surface of which was discarded in taking samples for measurements. *p*-Aminodimethylaniline sulfate was precipitated from an alcoholic solution of the freshly distilled free base with the theoretical amount of sulfuric acid, recrystallized from 50% methyl alcohol, and washed with methyl alcohol and ether. 2,4-Diaminophenol sulfate (amidol) was precipitated from an aqueous solution of the hydrochloride by sulfuric acid, recrystallized from water containing about 1% of sulfuric acid and washed with water, alcohol and ether.

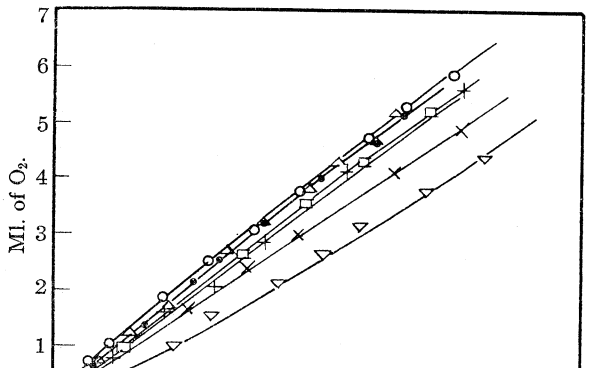


Fig. 1.—2 millimoles of hydroquinone in 50 ml. of 0.1 *N* barbital buffer, *p*H 8.06, with various shaking rates in oscillations per minute: O, 330 o.p.m.; Δ, 300; ●, 270; □, 240; +, 210; ×, 195; ▽, 180.

The silver was prepared by reduction of silver nitrate with formaldehyde as described by Volmer.[5]

The buffers were made up with potassium phosphate, carbonate, borate, diethyl barbiturate, or hydroxide. Twenty-five milliliters of 0.2 molar standard solutions was adjusted to the desired *p*H by addition of nitric acid or potassium hydroxide. The type of buffer and the *p*H are indicated with the experimental results. The hydrogen-ion concentrations were measured with a glass electrode. For solutions of a *p*H above 9 a special electrode[12b] was used to reduce errors caused by cations. These were further diminished by using potassium salts exclusively. The measurements were made on duplicates of the solutions actually oxidized.

The apparatus for measuring the reaction rates was that described in the preceding papers of this series.[13] The reactions were run at 20.0 ± 0.02°, the volumes given for the oxygen absorptions were measured over water at this temperature and reduced to 760 mm.; the G. M. V. for these conditions is 24.6 l. Before the start of the reaction, the buffer was in the bottom part of the reaction vessel, the developing agent in slightly acidulated solution in the top chamber. The silver was added to the buffer, and, in the experiments in presence of halogen ion, this was also added to the buffer. In the experiments with addition of permanganate, the vessel with two top chambers[6] was used.

Results and Discussions

A critical factor in autoxidations of high velocity is the supply of oxygen to the reaction mixtures. Unless this is fast enough to maintain a constant oxygen concentration in the solutions, it may become the limiting factor of the oxygen absorption. The capacity of an apparatus similar to the one used at present was tested by Weissberger, Mainz and Strasser[13] in the autoxidation of benzoin. With this reaction no observations were made in the very beginning of the absorption, and it appeared desirable to characterize the capacity of the present apparatus more completely. This is done in the experiments recorded in Fig. 1. At shaking rates of 270 oscillations per minute and

(12a) For the preparations we are indebted to Mr. E. C. Armstrong and Dr. John M. Snell†.

(12b) National Technical Laboratories, Berkeley, California.

(13) Weissberger, Mainz and Strasser, *Ber.*, **62**, 1942 (1929).

higher, and absorption rates of 1 ml. per minute and lower, equilibrium between the gaseous (oxygen) and liquid phases is established. The critical shaking rates are somewhat higher with the new than with the old apparatus. Most likely the difference is due to the fact that in the older apparatus vigorous splashing of the solutions occurred at lower rates than in the new one. For reactions of high rates, the shaking mechanisms should cause jerky, rather than smooth, movements. In the experiments described in this paper, shaking rates of 280 o. p. m. were maintained. Hence, it will demonstrate a catalytic effect if the addition of silver raises the rate of the oxygen absorption from values up to 1 ml./min. to higher values. Rates, however, which are higher than 1 ml. oxygen/min. will suffer a depression by a lack of saturation of the liquid phase which is the more serious the higher the rate.

An insufficient saturation of the liquid phase with oxygen appears to be responsible for results published recently by Green and Branch.[14] These authors claim that the rate of the autoxidation of hydroquinone is proportional to the *3/2 power* of the hydroxyl-ion concentration, and, on the basis of this result, draw conclusions about the mechanism of the reaction. The same rate law had been found by LaMer and Rideal,[15] while it is contradicted by the results of Euler and Brunius[16] and of Reinders and Dingemans,[17] who found that the autoxidation rate is proportional to the square of the hydroxyl-ion concentration. James, Snell and Weissberger[7] have confirmed this quadratic dependency. Green and Branch worked with solutions containing about 10 m. mole of hydroquinone and observed only the beginning of the autoxidation over a range where the uptake of oxygen per minute could be treated as constant. Plotting log (ml. O_2/min.) against *p*H, they obtained a straight line with the slope 3/2. James, Snell and Weissberger, using 0.5 m. mole of hydroquinone for each run, followed the course of the oxygen absorption until it had slowed down considerably. They calculated the rate constants according to the first-order law, using as final volume absorbed the theoretical one of the reaction

$$C_6H_4(OH)_2 + O_2 \longrightarrow C_6H_4O_2 + H_2O_2$$

When the logarithm of the rate constant was plotted against *p*H, a linear dependency was obtained with the slope 1.98. Following this procedure, with measurements made over a wider range of *p*H (6.95–8.21), the values of Fig. 2 marked by 0 were obtained. The straight line is drawn with a slope of 2.00, thus confirming the result of Euler and Brunius, Reinders and Dingemans, and James, Snell and Weissberger.

It might be contended that the use of the theoretical final volume in the calculation of the rate constants is arbitrary, although ample reasons exist for the validity of the above equation.[6,7] To avoid this contention, the values of ml. O_2/min. for each measured point of a number of experiments were plotted against the time, and the initial rates in ml. O_2/min. were determined by extrapolation to time = 0. When these initial rates were plotted against *p*H, the values marked by X in Fig. 2 were obtained, which confirm that *the autoxidation rate of hydroquinone increases with the square of the hydroxyl-ion concentration.* The latter method of evaluation of the results is free from any assumption about the final volume and corresponds to that used by Green and Branch. The difference in the determination of the initial rates is necessitated by the fact that only 1/20 of the amount of hydroquinone used by Green and Branch was used in the present experiments in order to keep well within the limits of capacity of the apparatus.

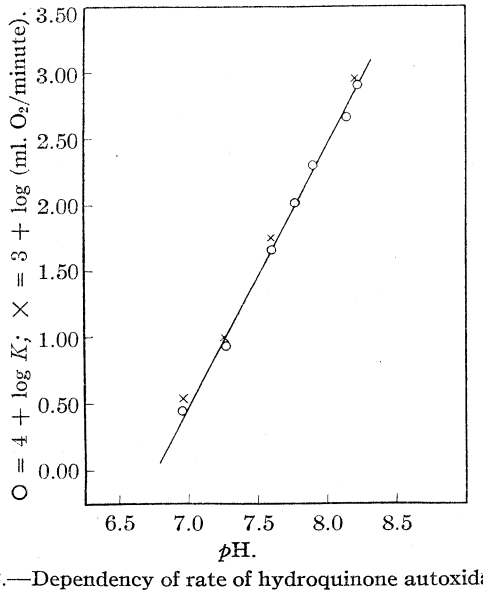


Fig. 2.—Dependency of rate of hydroquinone autoxidation on *p*H.

Experiments in the absence of silver with the concentrations and alkalinity used by Volmer proceeded at rates which were too high to maintain

(14) Green and Branch, THIS JOURNAL, **63**, 3441 (1941).
(15) LaMer and Rideal, *ibid.*, **46**, 223 (1924).
(16) Euler and Brunius, *Z. physik. Chemie*, **139**, 615 (1928).
(17) Reinders and Dingemans, *Rec. trav. chim.*, **53**, 209 (1934).

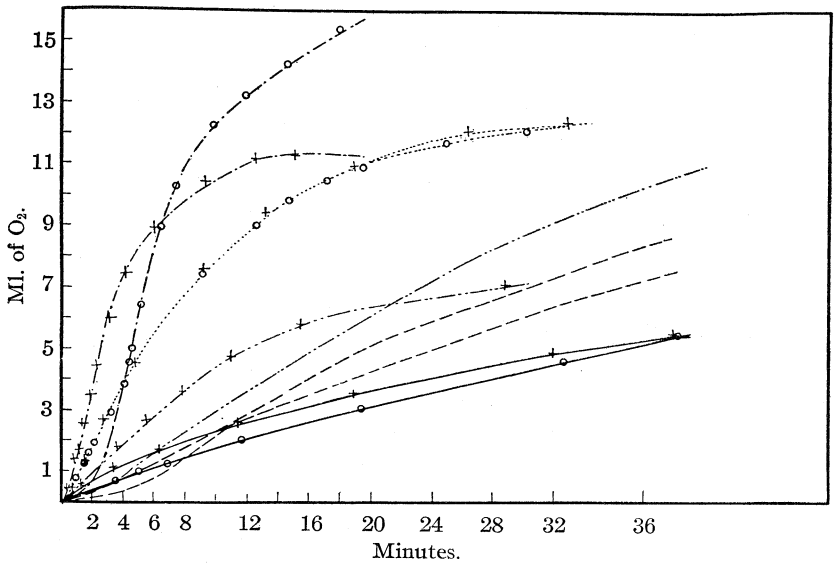


Fig. 3.—Reactions without silver, experimental points marked O; reactions with silver, experimental points marked +.

	Compound	*p*H	Buffer
———	Hydroquinone	7.98	Barbital
. . . . .	Amidol	5.57	Phthalate
– – – – –	Glycine	7.50	Phosphate
– · – · – ·	Glycine	9.18	Carbonate
– ·· – ·· –	*p*-Aminophenol	8.57	Borate

constant oxygen concentrations in the solutions. It may be mentioned, however, that in such experiments with catechol, metol, amidol and glycine no great increase in the rate of the oxygen absorption could be observed when silver was added. If it was the capacity of the apparatus which limited the effect in our experiments, the same might apply to Volmer's because the oxygen supply in our experiments was probably not less efficient than in those of this author. In order to obtain more exact data, buffered solutions containing 0.5 m. mole of the developing agents in 50 ml. were used. The *p*H's were so chosen that the absorption rates kept within the limits given above, and oxygen was used instead of air to keep the gas phase constant throughout the reactions. With each compound two experiments were made at the same *p*H, one of them with and the other without the addition of silver in a large excess (1.8 g. for each run).

When silver is added to the reaction mixtures containing hydroquinone (Figs. 3 and 4), the absorption of oxygen is accelerated only little in spite of the large excess of the metal and only in the beginning of the reactions. After an uptake of about 0.4 mole of oxygen per mole of hydroquinone, the absorption of the silver-containing solutions sinks below those of the corresponding silver-free systems, and the curves show that the silver decreases the total amount of absorbed oxygen. One might suspect that this deficit is caused by the presence of silver oxide which oxidizes part of the developing agent. However, analyses, for which we thank Mr. Ballard of these Laboratories, showed that the silver contained less than 0.4% of oxide. This can account for an oxidation of not more than 10% of the develop-

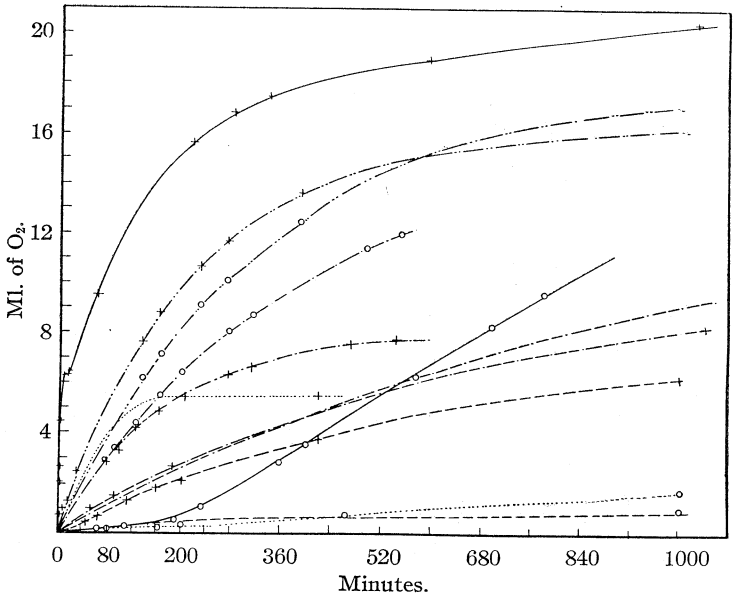


Fig. 4.—Reactions without silver, experimental points marked O; reactions with silver, experimental points marked +.

	Compound	*p*H	Buffer
———	*p*-Phenylenediamine	13.05	Potassium hydroxide
. . . . .	*p*-Phenylenediamine	9.08	Borate
– – – – –	*p*-Phenylenediamine	7.57	Phthalate
– . – . – .	Metol	6.20	Phosphate
– .. – .. –	Catechol	8.40	Barbital
– – . – – .	Hydroquinone	7.41	Phosphate

ing agent. The total absorption of oxygen by hydroquinone, however, may upon addition of silver drop as much as 25%, and that by other developing agents, *e. g.*, metol and *p*-aminophenol, even more than 50%.

A silver-catalyzed evolution of oxygen from peroxide (formed according to the above equation), is likely to contribute to the deficit. The catalytic action of silver on the decomposition of peroxide is well known.[18] Table II illustrates the extent of this catalysis under the conditions of our experiments. It gives the times at which one half of the total oxygen evolution had taken place when solutions of 1 m.mole of hydrogen peroxide in 50 ml. of the various buffers were shaken at 20.0° with and without addition of 1.8 g. of silver. It is evident that hydrogen peroxide formed in the autoxidation will, in the presence of silver, decompose rapidly, and the liberation of oxygen contributes toward the deficit in the observed oxygen absorption.

TABLE II

*p*H	Times in minutes Without silver	With silver
11.8	70	
11.7		0.1
7.9		1.4
7.6	21×10^3	

Moreover, the reaction of hydrogen peroxide with the developing agent itself is catalyzed by silver. This is shown by the following experiments. One m.mole of hydrogen peroxide and 0.5 m.mole of hydroquinone in 50 ml. of 0.1 molar dipotassium phosphate of *p*H 7.5 were kept under nitrogen for twenty minutes. During this time, the volume of the gas phase did not change measurably. Then 20 ml. of 0.25 molar permanganate solution was added, and an evolution of 19.2 ml. of oxygen indicated that 78% of the peroxide was still present. In two corresponding experiments, but with addition of 2 g. of silver, the gas phase increased during the keeping period of twenty minutes by 0.6 and 1.2 ml., respectively, by the silver-catalyzed decomposition of the peroxide. In the absence of hydroquinone under otherwise identical conditions, this decomposition yields 5.5 ml. of oxygen. The reduction in the evolution of oxygen in the presence of hydroquinone is caused by a reaction of the hydroquinone with the hydrogen peroxide, which is catalyzed by the silver; when permanganate solution was added to the solutions which had evolved 0.6 and 1.2 ml., no further evolution occurred, showing that the peroxide had been used up completely. The observation that the deficit in the total oxygen absorption of the developing agents, which is caused by the presence of silver, varies with the different developing agents shows that the silver-catalyzed reaction between peroxide and developing agent takes place to a considerable degree. In the absence of silver, most of the peroxide appears to react with the quinonoid oxidation products of the developing agents.[6,7]

Oxidation by silver oxide contaminating the silver will produce oxidation products of the developing agents and thus accelerate the autoxidation of those compounds which are subject to quinone catalysis.[6,7] This acceleration is, however, not caused by a catalytic action of the silver. On the other hand, the consumption of developing agent by the silver oxide and by the silver-catalyzed reaction with hydrogen peroxide diminishes the amount of autoxidizable material, and, therefore, the rate of the oxygen absorption. This apparent rate of autoxidation is likewise diminished by the liberation of oxygen in the silver-catalyzed decomposition of hydrogen peroxide.

In Figs. 3–5, the absorption of oxygen is plotted against the time for pairs of experiments with

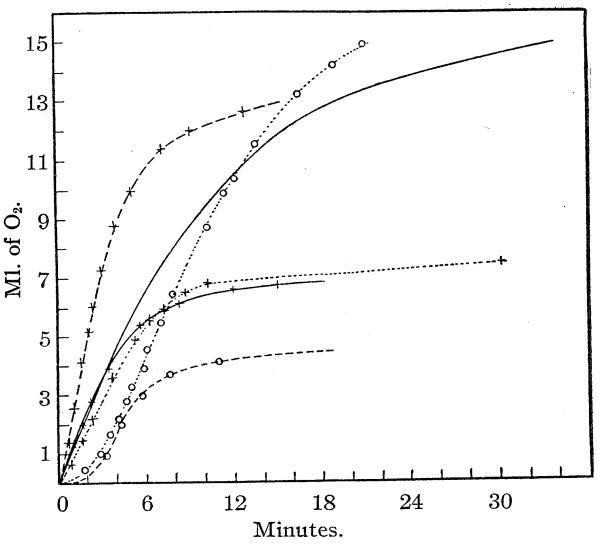


Fig. 5.—Reactions without silver, experimental points marked O; reactions with silver, experimental points marked +.

	Compound	*p*H	Buffer
———	Metol	7.66	Phosphate
. . . .	*p*-Aminophenol	9.23	Borate
– – – –	*p*-Aminodimethylaniline	13.2	Potassium hydroxide

(18) McIntosh, *J. Phys. Chem.*, **6**, 15 (1902); Wiegel, *Z. physik. Chem.*, **A143**, 81 (1929).

and without silver. In view of the badly defined end-points of many of the reactions, the calculation of rate constants does not afford an advantage for the interpretation of these data. The discussion will, therefore, be based upon an inspection of the curves themselves. The figures show that the silver accelerates the initial oxygen absorption of hydroquinone, catechol, *p*-aminophenol and glycine. The absence of an observable induction period with hydroquinone[7] and catechol[19] makes it unlikely that with these compounds the acceleration can be attributed to the elimination of an induction period. The latter effect is unmistakable in the cases of *p*-aminophenol and glycine, where it causes at least part of the observed speeding-up of the oxygen absorption. With metol and amidol no absolute acceleration of the oxygen absorption was observed on addition of silver. However, considering the above-mentioned simultaneous reactions as they are evidenced by the deficit in the total oxygen absorption, silver may cause some acceleration in the autoxidation of metol, while hardly any influence of the silver can be observed with amidol at *p*H 5.57. The total absence of an effect with amidol may be due to the low *p*H of the measurement. With all the other systems, the silver causes some small acceleration. It has not been studied whether the effect is limited to silver or whether it can likewise be caused by other metals. The latter is rather probable,[6] but the effect is not general for fine powders as such, because the addition of purified diatomaceous earth had no effect at all.

The *p*H of our experiments with catechol, *p*-aminophenol, glycine and amidol included regions in which these developing agents can be used in practical development. With hydroquinone and metol the *p*H for the measurements had to be lower in order to keep the rates within the capacity of our apparatus. However, observations at different *p*H leave little doubt that at higher *p*H the influence of the silver would not show a significant increase. Hence, *no silver catalysis which is likely to be of importance for photographic development is observed in the autoxidation of the above-mentioned developing agents.* The acceleration of the rate of the darkening of these developing agents beyond that of their autoxidation in the presence of silver must be caused by an effect of the metal on other reactions than the autoxidation proper. The colored compounds are formed by polymerization of the oxidized developing agents, and the silver-catalyzed oxidation of the developing agents by hydrogen peroxide may explain a certain amount of the darkening in Volmer's experiments. Moreover, the reaction of the hydrogen peroxide with quinonoid oxidation products of the developing agents in the absence of silver may be responsible for a decreased formation of dark products if the metal is not present.

Volmer did not include in his investigation *p*-phenylenediamine or its derivatives. It is these compounds, however, which show a marked effect of silver on their autoxidation. This is demonstrated in Figs. 4 and 5. With *p*-phenylenediamine the acceleration is about 10^2 fold; with *p*-aminodimethylaniline it is less, but still pronounced. The curve of the silver-catalyzed autoxidation of *p*-phenylenediamine at *p*H 13.05 has a marked and reproducible inflection after an absorption of about $^1/_2$ equivalent of oxygen. In the beginning of the reaction, the concentration of hydrogen peroxide builds up, while that of the oxidized compound sinks, and conditions can be reached where the liberation of oxygen from peroxide just compensates for the absorption of oxygen by the developing agent. In certain other cases even a temporary increase in the oxygen volume was observed. The fact that a considerable catalytic action of the silver is limited to a certain type of the developing agents shows that neither an adsorption of oxygen to the silver nor the intermediary formation of silver oxide[20] gives a sufficient explanation for this catalysis. Such a mechanism might, however, be considered in connection with the small acceleration of the oxygen uptake by the developing agents of the types of hydroquinone and aminophenol. The lack of a silver catalysis with hydroquinone agrees with the results of Perry, Ballard and Sheppard[21] who, disproving observations of Rabinowitsch,[22] showed that this compound is not adsorbed to silver to any measurable extent. It would be interesting to see whether *p*-phenylenediamine is adsorbed to a higher degree.

The systems described above differ from developing emulsions by the absence of halogen ion. Addition of chloride ion depressed the effect of the

(19) Joslyn and Branch, THIS JOURNAL, **57**, 1779 (1935).

(20) Benton and Drake, *ibid.*, **56**, 255 (1934); Benton and Bell, *ibid.*, **56**, 501 (1934).

(21) Perry, Ballard and Sheppard, *ibid.*, **63**, 2357 (1941).

(22) Rabinowitsch and Peissachowitsch, *Z. wiss. Phot.*, **33**, 94 (1934).

silver on *p*-phenylenediamine. With the other developing agents it eliminated the effect of the silver on the total oxygen absorption, showing that the halogen ion interferes with the silver catalysis of the decomposition of hydrogen peroxide and of the oxidation of the developing agents by hydrogen peroxide. The effect of halogen ion on the shortening of the induction period, *e. g.*, of metol, is much less pronounced.

According to the present results, a catalytic effect of silver in photographic development of the type suggested by Volmer, *i. e.*, a catalysis which directly affects the reactivity of the developing agents is most unlikely with developing agents of the types of dioxybenzene and aminophenol. It may possibly play some role in development with *p*-phenylenediamine and its derivatives. For the discrimination between exposed and unexposed grains in general, however, the other mechanisms indicated in the introductory remarks should be responsible.

Summary

1. The oxygen absorption of hydroquinone at various rates of shaking was investigated to check the conditions under which the concentration of oxygen in the liquid phase remains constant.

2. In agreement with results in earlier papers of this series and in disagreement with Green and Branch, it was shown that the rate of autoxidation of hydroquinone between *p*H 7 and 8.2 increases with the square of the hydroxyl-ion concentration.

3. Silver accelerates the autoxidation of hydroquinone, catechol, *p*-aminophenol, and glycine only to a very small degree. With these developing agents, therefore, the catalysis suggested by Volmer is most unlikely to be of significance for photographic development.

4. The autoxidation of *p*-phenylenediamine and *p*-dimethylaminoaniline shows a more considerable catalysis by silver.

5. The addition of silver strongly diminishes the total amount of oxygen which is absorbed by the developing agents in alkaline solutions. This is chiefly caused by a catalytic effect of the silver on reactions of peroxide formed in the autoxidation.

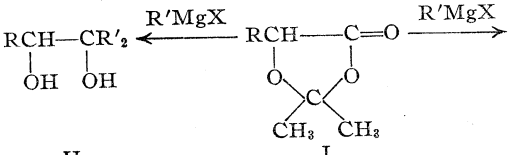
ROCHESTER, N. Y. RECEIVED MARCH 10, 1942

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

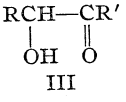
Reductive Cleavage of Dioxolones by the Grignard Reagent

BY REYNOLD C. FUSON AND A. I. RACHLIN

Dioxolones, acetone derivatives of α-hydroxy acids (I), are known to react with the Grignard reagent to form glycols (II).[1] It seemed probable that if the reagent had a very highly branched radical, acyloins (III) might be produced.

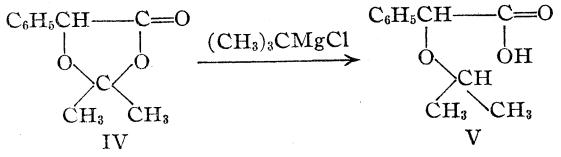


II I



III

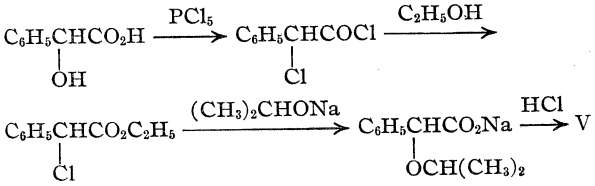
In an attempt to obtain the latter type of compound, the acetone derivative of mandelic acid (IV) was treated with *t*-butylmagnesium chloride. The product was not the acyloin, however, but α-isopropoxymandelic acid (V). Isobutylene was evolved.



IV V

The reaction is a hydrogenolysis of the dioxolone ring and appears to be new in type. Moreover, it has no parallel among the reactions between the Grignard reagent and esters or lactones.

The structure of the product was established by synthesis. The following series of reactions was employed



V

It has been found that the reaction is general for acetone derivatives of α-hydroxy acids. The iso-

(1) Freudenberg, Todd and Seidler, *Ann.*, **501**, 210 (1933).

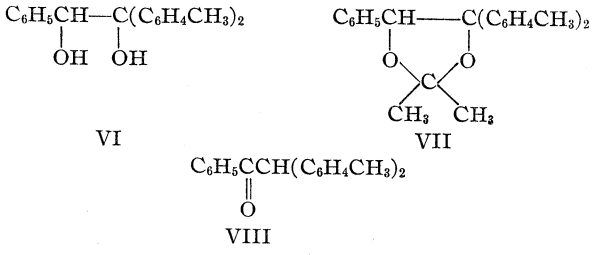
propyl ethers of mandelic, *p*-methylmandelic, *p*-bromomandelic, α-mesitylglycolic, lactic and α-hydroxyisobutyric acids have been prepared by this method in yields of 57, 66, 71, 80, 20 and 50%, respectively. All these acids are new compounds.

Unsuccessful attempts were made to produce the cleavage with the binary mixture (Mg + MgI_2),[2] aluminum isopropoxide, the zinc–copper couple and hydrogen in the presence of platinum. Hydrogen with copper chromite has been reported[3] to convert dioxolones into a mixture of compounds none of which is analogous to the product described here.

Attempts to effect the reduction of the acetone derivative of mandelic acid by use of other alkyl Grignard reagents were unsuccessful, indicating that the reaction may be peculiar to *t*-butylmagnesium halides.

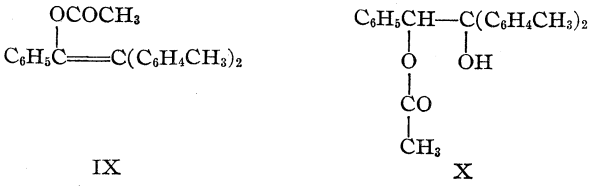
No evidence of reduction was observed in reactions involving aryl Grignard reagents. Normal addition was the principal reaction, with steric hindrance playing an interesting role. For example, phenylmagnesium bromide gave a 66% yield of triphenylethylene glycol as reported by Freudenberg, Todd and Seidler.[1]

Mesitylmagnesium bromide produced an intractable oil. On the other hand, *o*-tolylmagnesium bromide converted the dioxolone into the glycol (VI). Small amounts of the corresponding dioxolane (VII) and the ketone (VIII), formed from the glycol by dehydration, were also isolated.



VI VII VIII

The glycol (VI) was transformed readily into the ketone (VIII) by acids. Treatment of the glycol with acetic anhydride in the presence of a mineral acid produced an acetate (IX) obtained by similar treatment of the ketone (VIII). On the other hand, acetic anhydride in pyridine produced a different acetate (X), which was readily dehydrated to the other acetate (IX) by acetyl chloride. The glycol had two active hydrogen atoms.

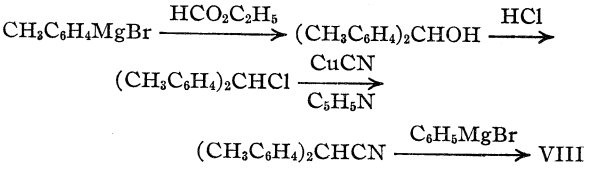


IX X

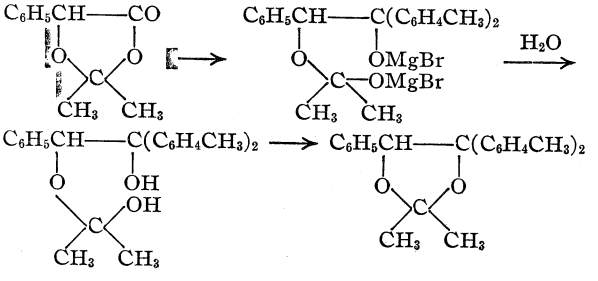
An attempt to synthesize the glycol by treating methyl mandelate with *o*-tolylmagnesium bromide resulted in the formation of an oil. A similar experience was reported by Roger and McKay[4] who used the ethyl ester.

The structure of the dioxolane (VII), an acetal, is based on the analysis, the transformation to the ketone (VIII) in the presence of acid and the synthesis by condensing the glycol (VI) with acetone. The dioxolane had no active hydrogen atom. When it was treated with acetic anhydride and acid, the acetate (IX) was formed.

The ketone (VIII) was synthesized in the following manner.



The formation of the dioxolane may be explained by assuming that the behavior of the original dioxolone toward *o*-tolylmagnesium bromide resembles that of lactones. The transformation may be represented as



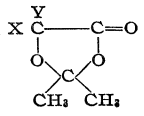
Experimental

The dioxolones were made by condensing acetone with the appropriate α-hydroxy acids by means of concentrated sulfuric acid. The method, essentially that of Audrieth and Sveda,[5] was modified in order to give a pure product. The following directions for making acetonemandelic acid illustrate the general procedure.

A solution of 304 g. of mandelic acid in 880 cc. of dry acetone was cooled to −10° in an ice–salt-bath. The solution was stirred vigorously while 196 g. of concentrated sulfuric acid was added. The addition was made over a period of one hour and the unused acid was neutralized by

(2) Gomberg and Bachmann, THIS JOURNAL, **49**, 237 (1927).
(3) Oeda, *Bull. chem. soc. Japan*, **10**, 531 (1935).
(4) Roger and McKay, *J. Chem. Soc.*, 2232 (1931).
(5) Audrieth and Sveda, "Organic Syntheses," **20**, 62 (1940).

TABLE I

Compound, with substituents at X and Y in the formula		M. p. or b. p., °C.	Yield (%)	Analyses, %[6] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
C_6H_5	H	45[a]	77	...	...	..	..
$CH_3C_6H_4$	H	56–57	32	69.55	69.92	7.29	7.07
BrC_6H_4	H	65–66	35	48.75	49.01	4.06	4.26
Mes[b]	H	92	72	71.76	71.70	7.74	7.89
CH_3	H	58–60 (18 mm.)[c,d]	30	...	...	..	..
CH_3	CH_3	71 (42 mm.)[e]	35	58.31	58.76	8.39	8.69

[a] Described by Audrieth and Sveda.[5] [b] "Mes" is used to represent mesityl. [c] Described by Oeda.[3] [d] The reaction mixture was poured into benzene. The benzene layer was treated with diethylamine to neutralize the acid, dried over magnesium sulfate and distilled. [e] $n^{20}D$ 1.4065.

pouring the reaction mixture into an ice-cold solution of 400 g. of anhydrous sodium carbonate in 3500 cc. of water. The curdy white product was collected on a suction filter and sucked dry. Purification was effected by washing the solid with four 250-cc. portions of ether. The ether solution was dried over calcium chloride and the solvent was removed by distillation. Removal of the last traces of ether *in vacuo* caused the acetone compound to solidify in a white mass. The hard cake was pulverized and used without further purification.

The physical constants, yields and analytical data for this and similar compounds are given in Table I.

The Action of *t*-Butylmagnesium Chloride on Dioxolones.—The procedure, illustrated for the reaction of *t*-butylmagnesium chloride on acetone-mandelic acid, was the same in all cases.

t-Butylmagnesium chloride was made by adding 55.8 g. of *t*-butyl chloride to a mixture of 14.4 g. of magnesium and 150 cc. of ether. To this well-stirred solution was added 38.4 g. of acetone-mandelic acid dissolved in 100 cc. of ether. The time of addition was one-half hour. The solution was stirred and refluxed for an additional hour before decomposition with 200 cc. of concentrated hydrochloric acid and 1000 g. of ice. After separation of the layers, the aqueous part was extracted with 200 cc. of ether. The combined ethereal solution was extracted repeatedly with 10% potassium bicarbonate. Acidification of the alkaline solution with hydrochloric acid caused the α-isopropoxymandelic acid to precipitate as an oil. The oil solidified when the mixture was allowed to stand for a few hours; yield, 22 g., 57% of theoretical.

One experiment was devoted to the examination of the gaseous by-product. By means of a stream of nitrogen the gas was forced through a series of wash bottles containing the following solutions in order: 64 g. of bromine in 200 cc. of carbon tetrachloride (0°); 10 g. of bromine in 100 cc. of carbon tetrachloride (0°); 25 cc. of sodium sulfite in 300 cc. of water; an empty trap at dry-ice temperature. The reaction was carried out as described above, using the Grignard reagent made from 24 g. of magnesium, 92 g. of *t*-butyl chloride, 250 cc. of ether and a solution of 76.8 g. of acetone-mandelic acid in 200 cc. of ether. The solution was refluxed a total of two hours, after the addition of the acetone compound. No other effort was made to drive the gas out of the ether. The carbon tetrachloride solutions were combined, washed with sodium sulfite solution, water and distilled. There was produced 20 g. (24%) of pure dibromoisobutane; b. p. 146–147°; $n^{20}D$ 1.508. The absence of a condensate in the dry-ice trap indicated that no saturated hydrocarbon was formed. The reaction mixture was worked up as described above and yielded 34 g. (45%) of isopropoxymandelic acid; m. p. 57–58°.

The physical constants, yields and analyses of the isopropoxy acid and their *p*-phenylphenacyl esters are given in Table II.

Synthesis of α-Isopropoxymandelic Acid.—Phenylchloroacetyl chloride was made, according to the directions of Bischoff and Walden,[7] by heating mandelic acid with phosphorus pentachloride at 140°. This compound was converted to ethyl phenylchloroacetate, reported by Findlay and Turner,[8] by heating it with absolute ethanol. A sodium isopropoxide solution, prepared by dissolving 8 g. of sodium in 120 cc. of dry isopropyl alcohol, was refluxed on a steam-bath while 30 g. of phenyl chloroacetate was added. The mixture was heated for four hours, cooled and filtered. The solid was dissolved in water and the solution acidified with hydrochloric acid. The oily product was isolated by extraction with ether, drying the ethereal extract with calcium chloride and removing the solvent by distillation. Treatment of the residual oil with low-boiling petroleum ether caused the separation of 14 g. of white acid; m. p. 41–55°. Several recrystallizations from low-boiling petroleum ether resulted in a pure product melting at 58–59°—alone or when mixed with the compound obtained by the other method.

The Reaction of *o*-Tolylmagnesium Bromide with Acetone-mandelic Acid.—To an *o*-tolylmagnesium bromide solution, prepared from 342 g. of *o*-bromotoluene and 48 g. of magnesium in 500 cc. of ether, was added, with vigorous stirring over a period of one hour, a solution of 96 g. of acetone-mandelic acid in 300 cc. of ether. The solution was stirred and refluxed for an additional three hours after which it was cooled and decomposed with 400 cc. of concentrated hydrochloric acid and 1500 cc. of ice. The ether was distilled from the organic layer and the residue was subjected to steam distillation in order to remove the toluene. The residue was dissolved in ether and repeatedly extracted with 10% potassium bicarbonate

(6) The microanalyses reported in this paper were carried out by Miss Mary S. Kreger, Miss Margaret McCarthy, Miss Theta Spoor and Mr. L. G. Fauble.

(7) Bischoff and Walden, *Ann.*, **279**, 122 (1894).

(8) Findlay and Turner, *J. Chem. Soc.*, **87**, 756 (1905).

TABLE II

ACIDS AND *p*-PHENYLPHENACYL ESTERS[a]

Compound, with substituents at X and Y in the formula	Y X—CCOOH OR[b]	Yield, %	M. p. or b. p., °C.	Neutral equivalent Calcd.	Neutral equivalent Found	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
C_6H_5	H	57	58–59	194	191	68.02	68.29	7.27	7.33
Ester		..	114–115	..	..	77.29	77.53	6.23	6.28
$CH_3C_6H_4$	H[c]	66	...	..	..	...	...	..	..
Ester		..	93–94	..	..	77.58	77.55	6.51	6.45
BrC_6H_4	H[c]	71	...	..	..	...	...	..	..
Ester		..	90–91	..	..	63.24	63.46	4.96	4.93
Mes	H[d]	80	83–84	236	242	71.15	71.52	8.53	8.69
CH_3	H[c]	20	72–75 (2 mm.)	132	134	54.53	54.62	9.15	8.80
CH_3	CH_3[f]	50	102–103 (15 mm.)	146	146	57.51	57.18	9.65	9.72
Ester		..	88	..	..	74.15	73.96	7.06	7.33

[a] The *p*-phenylphenacyl esters were made from *p*-phenylphenacyl bromide according to the method described in Shriner and Fuson, "Identification of Organic Compounds," 2nd Edition, John Wiley and Sons, New York, N. Y., 1940, p. 132. [b] R is used to represent isopropyl. [c] The product was a clear uncrystallizable oil. [d] "Mes" is used to represent mesityl. [e] $n^{20}D$ 1.4158. [f] $n^{20}D$ 1.4196.

solution. Acidification of the alkaline solution with hydrochloric acid produced 3 g. of mandelic acid.

The ether was distilled from the organic layer after it was washed with water and dried over calcium chloride. The residue was treated with 150 cc. of methanol and cooled in an ice-bath. A solid product (39 g.) melting at 118–132° was removed by filtration. Concentration of the mother liquor followed by cooling and filtration produced 3 g. of a solid (VIII), m. p. 100–102°. The pure compound, recrystallized from methanol, melted at 104–106°.

Anal. Calcd. for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C. 88.25; H, 6.88.

The crude solid melting at 118–132° was washed with 200 cc. of low-boiling petroleum ether. The insoluble residue (VI) weighed 30.5 g. and melted at 139–141°. After recrystallization from methanol, it melted at 146°.

Anal. Calcd. for $C_{22}H_{22}O_2$: C, 82.99; H, 6.99. Found: C, 83.23; H, 7.19.

A Zerewitinoff determination showed the presence of two active hydrogen atoms in the molecule.

The wash solution was evaporated to an oily residue. Treatment of the oil with methanol produced 8.5 g. of a solid (VII), melting at 104–106°. The dioxolane, recrystallized from methanol, melted at 108–109°.

Anal. Calcd. for $C_{25}H_{26}O_2$: C, 83.76; H, 7.31. Found: C, 83.97; H, 7.69.

A Zerewitinoff determination showed the absence of active hydrogen.

The Condensation of 1-Phenyl-2,2-di-*o*-tolylethylene Glycol (VI) with Acetone.—To a solution of 0.6 g. of the glycol in 10 cc. of anhydrous acetone was added 0.4 cc. of concentrated sulfuric acid and 1 g. of anhydrous sodium sulfate. The reaction flask was allowed to stand with occasional shaking for twenty-four hours. The solution was filtered and the solvent was removed by a stream of air. The residue, dissolved in ether, was washed with 10% potassium bicarbonate solution and water, dried over calcium chloride and evaporated to an oil. Treatment of the oil with methanol caused the separation of a solid; m. p. 104–106°. The compound was recrystallized from methanol and melted at 108–109° alone or mixed with other samples of the dioxolane. The yield of pure product was 0.4 g.

Reaction of 1-Phenyl-2,2-di-*o*-tolylethylene Glycol with Acetic Anhydride and Pyridine.—Five grams of the glycol was dissolved in 50 cc. of a 20% solution of acetic anhydride in pyridine. The solution was heated on a steam-bath for twelve hours. About 35 cc. of the solvent was removed by distillation and the residue was added to 100 cc. of water. The solution was digested for fifteen minutes, cooled and extracted with ether. The ethereal solution was dried over calcium chloride and concentrated to an oil. Treatment with methanol produced 4 g. of a solid (X), which melted at 153–155°. The acetate, recrystallized from methanol, melted at 158–160°.

Anal. Calcd. for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 80.01; H, 6.81.

The compound had one active hydrogen atom.

Reaction of 1-Phenyl-2,2-di-*o*-tolyl Ethylene Glycol with Acetic Anhydride and Hydrochloric Acid.—Three grams of the glycol was refluxed for eighteen hours with 30 cc. of acetic anhydride and 3 drops of concentrated hydrochloric acid. The reaction mixture was poured into 100 cc. of water and digested for fifteen minutes, cooled and extracted with ether. The ethereal solution was dried over calcium chloride and evaporated to an oil. Treatment of the oil with methanol produced 2.5 g. of a white solid (IX) which melted at 133–135°. The acetate, recrystallized from methanol, melted at 138.5–140°.

Anal. Calcd. for $C_{24}H_{22}O_2$: C, 84.20; H, 6.48. Found: C, 84.09; H, 6.53.

The Reaction of Acetyl Chloride with the Acetate (X).—Two grams of the acetate (X) was heated at the refluxing temperature for four hours with 20 cc. of acetyl chloride. The reaction mixture was poured on ice and allowed to come to room temperature. The organic matter was extracted with ether. The ethereal solution was washed with 10% potassium bicarbonate solution and water and then dried over calcium chloride. The solvent was removed and the residue was taken up in hot methanol. Cooling caused the precipitation of 1.2 g. of a compound

melting at 135–136°. Recrystallized from methanol, it melted at 138.5–140° alone or mixed with the acetate (IX).

Reaction of the Dioxolane (VII) with Acetic Anhydride and *p*-Toluenesulfonic Acid.—Two grams of the dioxolane was heated at the refluxing temperature for four hours with 20 cc. of acetic anhydride and a few crystals of *p*-toluenesulfonic acid. The reaction mixture was worked up in the usual manner; yield, 1.5 g. of a white compound melting at 129–132°. Recrystallization from methanol gave a melting point of 138.5–140° alone or mixed with other samples of the acetate (IX).

Transformation of 1-Phenyl-2,2-di-*o*-tolylethylene Glycol and the Dioxolane in Acid Solution.—One gram of the compound was dissolved in 4 cc. of methanol and three drops of concentrated hydrochloric acid. The solution was refluxed for twelve hours and the solvent was removed by distillation. The residue was 0.75 g. of a solid identified as ω,ω-di-*o*-tolylacetophenone (VIII).

Treatment of the dioxolane (VII) with hydriodic acid, 30% sulfuric acid, phosphoric acid or *p*-toluenesulfonic acid gave practically quantitative conversion to ω,ω-di-*o*-tolylacetophenone. Treatment of the 1-phenyl-2,2-di-*o*-tolylethylene glycol with hydrochloric acid or *p*-toluenesulfonic acid gave similar results.

Reaction of ω,ω-Di-*o*-tolylacetophenone with Acetic Anhydride and Pyridine.—Two grams of the compound was heated at the refluxing temperature for twelve hours with 4 cc. of pyridine and 16 cc. of acetic anhydride. The reaction mixture was worked in the usual fashion; yield, 1.5 g. of the acetate (IX); m. p. 133–135°; the pure compound melted at 138.5–140°.

Synthesis of Di-*o*-tolylcarbinol.—A solution of *o*-tolylmagnesium bromide was prepared from 171 g. of *o*-bromotoluene, 24 g. of magnesium and 250 cc. of ether. To this solution was added 33.4 g. of ethyl formate. The solution was refluxed and stirred for seven hours before it was cooled and decomposed with hydrochloric acid and ice. It was necessary to add 250 cc. of benzene to the mixture in order to dissolve all the organic matter. The organic layer was separated, dried over calcium chloride and evaporated; yield, 70 g. (73%); m. p. 115–119°[9].

Synthesis of Di-*o*-tolylchloromethane.—The di-*o*-tolylcarbinol was converted, without further purification, into di-*o*-tolylchloromethane by the method of Reid[10]; yield, 94%.

Synthesis of Di-*o*-tolylacetonitrile.—A mixture of 23.1 g. of di-*o*-tolylchloromethane, 10.7 g. of cuprous cyanide and 20 cc. of dry pyridine was heated for twenty-four hours at 200–215°. Ground glass equipment, protected from moisture by a calcium chloride tube, was used. The dark mass was cooled and poured into dilute aqueous ammonia. The organic matter was extracted with ether. It was necessary to remove some dark solid material by filtration. The ethereal solution was washed successively with dilute ammonia, water, dilute hydrochloric acid and finally with water. The solution was dried with calcium chloride and evaporated to dryness. The residue was recrystallized from 95% ethanol; m. p. 107–109°; yield, 12 g. (54%). The pure compound, recrystallized from 95% ethanol, melted at 114–115°.

Anal. Calcd. for $C_{16}H_{15}N$: C, 86.83; H, 6.83. Found: C, 87.17; H, 6.91.

Synthesis of ω,ω-Di-*o*-tolylacetophenone.—A solution of phenylmagnesium bromide, made from 14.1 g. of bromobenzene, 1.94 g. of magnesium and 35 cc. of ether, was added to a well-stirred solution of 4.5 g. of di-*o*-tolylacetonitrile in 75 cc. of ether. The solution was stirred and refluxed for twenty-four hours, after which it was cooled and decomposed with hydrochloric acid and ice. The organic layer was separated and discarded. The aqueous layer was digested on a steam-bath for two hours. Cooling to room temperature produced an oil which soon solidified; yield, 4 g.; m. p. 100–102°. Recrystallized from methanol, the product melted at 104–106° alone or mixed with other samples of (VIII).

Summary

Dioxolones, acetone derivatives of α-hydroxy acids, react with *t*-butylmagnesium chloride to yield the corresponding α-isopropoxy acids. The reaction is a hydrogenolysis of the dioxolane ring and appears to be new in type.

URBANA, ILLINOIS RECEIVED FEBRUARY 2, 1942

(9) Boyd and Hatt, *J. Chem. Soc.*, 898 (1927).

(10) Reid, THIS JOURNAL, **61**, 3238 (1939).

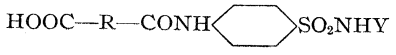
[CONTRIBUTION FROM THE MEDICAL-RESEARCH DIVISION, SHARP AND DOHME]

Dicarboxylic Acid Derivatives of Sulfonamides[1]

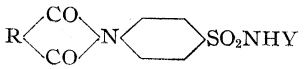
BY MAURICE L. MOORE AND CHARLES S. MILLER

In continuing our studies of the possible chemotherapeutic activity of sulfonamide compounds,[2] it was found that certain of the derivatives from dicarboxylic acids possessed interesting activity as intestinal antiseptics. We undertook to prepare a large series of these compounds, some of which have been studied as intestinal antiseptics.[3] One of these, succinylsulfathiazole,[4,5] has shown unusually marked activity for this purpose. In this paper we describe the preparation and properties of these compounds and discuss some of the results obtained from the reactions involved in their preparation.

The condensation of succinic, maleic and phthalic anhydrides with the various sulfonamides, using anhydrous alcohol or dioxane as a solvent according to the method previously described for the sulfanilamide and sulfanilhydroxamide derivatives,[2b,c] occurred in the ratio of 1:1, giving monobasic acids of the general formula I. Condensa-



I



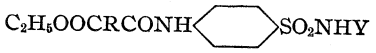
II

tion of succinic anhydride with sulfanilamide in the presence of pyridine had been found to give the anil II.[2c] Recently, Shapiro and Bergmann[6] have found that in the condensation of sulfapyridine with succinic and phthalic anhydrides temperatures below 100° give acid amides I while temperatures above 100° give the anils II. They found that with maleic anhydride the acid amide was the sole reaction product, even at 190°. However, neither Shapiro and Bergmann nor we had obtained any of the diamides III in condensations with anhydrides.



III

The oxalic and malonic acid derivatives of sulfathiazole, sulfadiazine and sulfaguanidine were made by refluxing the sulfonamide with an excess of the ethyl ester of the appropriate acid and hydrolyzing the ester amides IV thus formed with



IV

alkali to give the corresponding acid amides. The ester amides were obtained in yields above 80%, although, in most cases there was isolated a small quantity of by-product which appeared to be the diamide. Esters of higher acids, such as ethyl glutarate and sebacate, did not condense with sulfathiazole even when heated at 160–170° for two hours.

The higher acid derivatives, *i. e.*, from glutaric, adipic and sebacic acids, were made by heating the sulfonamide with the acid itself at a temperature between 150–170° for one to two hours. Succinylsulfathiazole (compound no. 8) was also prepared in this manner and the reaction studied in some detail. It appears that with an equimolar mixture of the components, or with as much as 5 or 10% excess of the acid, the reaction proceeded with the formation of the anil and about 5–7% of the diamide. Hydrolysis of the anil with 5–10% sodium hydroxide solution gave the acid amide which was removed from the diamide by solubility in cold bicarbonate solution. Similar results have been obtained by carrying out the condensation in refluxing "Carbitol."

Condensation of adipic acid with sulfapyridine, sulfathiazole and sulfaguanidine, followed by treatment with alkali, led to the isolation of the acid amides and the diamides, with a larger portion of the product being the diamides. However, with glutaric and sebacic acids, the diamides were the principal product from the condensation with sulfathiazole.

Attempts to condense *p*-succinimidobenzenesulfonyl chloride with 2-aminothiazole led to some interesting observations. With two equivalents of 2-aminothiazole, in pyridine or acetone as a sol-

(1) This paper was presented before the Division of Medicinal Chemistry of the American Chemical Society in Memphis, April, 1942.

(2) (a) Moore and Miller, THIS JOURNAL, **63**, 2781 (1941); (b) Moore, Miller and Miller, *ibid.*, **62**, 2097 (1940); (c) Miller, Rock and Moore, *ibid.*, **61**, 1198 (1939).

(3) Poth and Knotts, *Arch. Surg.*, **44**, 187 (1942).

(4) To this compound Sharp and Dohme has applied its trademark "Sulfasuxidine."

(5) (a) Poth and Knotts, *Proc. Soc. Exp. Biol. and Med.*, **48**, 129 (1941); (b) Poth and Knotts, *Arch. Surg.*, **44**, 208 (1942).

(6) Shapiro and Bergmann, *J. Org. Chem.*, **6**, 774 (1941).

vent, the acid amide was obtained in about a 1:1 ratio with an unidentified product. Similar results were obtained with 1 equivalent of 2-aminothiazole in sodium carbonate solution.

Experimental

1. Anhydride Condensations.—Five hundred grams (1.96 moles) of sulfathiazole was added to 5000 cc. of anhydrous alcohol and heated to refluxing with mechanical stirring. When refluxing occurred, 250 g. (2.5 moles, 25% excess) of succinic anhydride was added and the mixture refluxed for forty-five minutes. During this period, all of the materials had gone into solution and toward the end of the reaction a solid began to crystallize out, which after standing overnight was obtained in a yield of 90%. Yields equally as good were obtained by using only 5 or 10% excess of succinic anhydride. Purification was effected by recrystallizing 104 g. of the crude material from a refluxing solution of 400 cc. of alcohol and 300 cc. of water. The yield was 89 g. (77%), melting at 192–195°, with decomposition.

Dioxane was used as the solvent for the condensation of succinic anhydride with 2-sulfanilamido-5-ethyl-4-thiazolone, sulfadiazine and sulfanilylsulfathiazole.

2. Ester Condensations.—Twenty grams (0.078 mole) of sulfathiazole was added to 60 g. (0.375 mole) of ethyl malonate and heated under reflux at a temperature of 130–150° for two hours. After cooling the reaction mixture to room temperature, the solid product was filtered and washed thoroughly with dilute hydrochloric acid and water. A yield of 24.7 g. (85%) of the ester amide IV, compound no. 6, was obtained and after purification by recrystallizing from dilute alcohol, it melted at 193–194.5° with decomposition.

A similar yield was obtained when only two equivalents of the ethyl malonate was used under the same experimental conditions. However, in this experiment, a small quantity of material was obtained which was insoluble in dilute alcohol. On crystallization from methyl "Cellosolve" and water, this product melted at 233–236° with decomposition. A mixed melting point with acetylsulfathiazole, m. p. 256–257°, was 225–226° followed by decomposition. Reactions and analysis suggest that the product was the diamide, **malonamide-4,4′-bis-(2-benzenesulfonamidothiazole)**.

Anal. Calcd. for $C_{21}H_{18}O_6N_6S_4$: N, 14.53. Found: N, 14.00.

An 86% yield of ester amide was obtained by condensing sulfathiazole with two equivalents of ethyl oxalate under the above conditions and no diamide was isolated.

Hydrolysis of the ethyl malonylsulfathiazole to the acid amide was accomplished by heating 14 g. of the material in 150 cc. of 2.5% sodium hydroxide solution at 85–95° for one-half hour. The solution was decolorized with charcoal (Darco) and the product precipitated from the solution by neutralization with dilute hydrochloric acid. A yield of 10 g. (77%) was obtained and after several recrystallizations from dilute alcohol the malonylsulfathiazole decomposed in the range of 240–250°, without definitely melting.

3. Acid Condensations.—(A) Ten grams (0.0392 mole) of sulfathiazole and 4.6 g. (0.0392 mole) of succinic acid were mixed in a flask and heated in a sand-bath to a temperature of 150–160° for one hour, with occasional stirring. At the end of the hour, the reaction melt began to solidify, while stirring, as a granular solid. The material was treated with a boiling solution of 90% acetic acid and an insoluble product filtered. The yield was 0.9 g. and melted at 277–279° with decomposition after purification by dissolving in dilute ammonia and precipitating with dilute hydrochloric acid. The product was soluble in dilute ammonia and alkali but insoluble in cold sodium bicarbonate solution. This corresponded to the diamide III, **succinamido-4,4′-bis-(2-benzenesulfonamidothiazole)**.

Anal. Calcd. for $C_{22}H_{20}O_6N_6S_4$: N, 14.19. Found: N, 14.13.

The hot acetic acid filtrate from the above was allowed to cool overnight and a white crystalline solid was obtained. The yield of the product was 5.6 g. and it melted at 266–267° after recrystallization from anhydrous methyl "Cellosolve." It was soluble in dilute ammonia and alkali but insoluble in cold sodium bicarbonate solution. This corresponded to the anil II, **2-(4′-succinimidobenzenesulfonamido)-thiazole.**

Anal. Calcd. for $C_9H_{11}O_4N_3S_2$: N, 12.46. Found: N, 12.30.

A sample of the anil was converted into the acid amide, succinylsulfathiazole, by dissolving in a warm 2.5% sodium hydroxide solution and precipitating with dilute hydrochloric acid. The product was readily soluble in cold sodium bicarbonate solution with the evolution of carbon dioxide and it melted at 140° with decomposition. After several crystallizations from dilute alcohol the product melted at 185–187° with decomposition.

A sample of the diamide was dissolved in 5% sodium hydroxide solution, refluxed for a few minutes and after cooling to room temperature the solution was carefully neutralized with dilute hydrochloric acid giving sulfathiazole; m. p. 196°. A mixed sample with authentic sulfathiazole, m. p. 199–200°, melted at 199–200°.

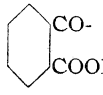
(B) Ten grams of sulfathiazole and 4.6 g. of succinic acid were heated together under the same conditions as described above. The solid obtained from the reaction mixture was dissolved in dilute ammonia, the solution decolorized with charcoal (Darco), and precipitated by the careful addition of a slight excess of dilute hydrochloric acid. A yield of 9.9 g. of an unidentified product (A) was obtained which melted at 194.5–195.5° after four recrystallizations from methyl "Cellosolve" and water. It was insoluble in cold bicarbonate solution. *Anal.* Found: N, 14.63. The identity of this compound is being investigated.

Four grams of the above compound was dissolved in 50 cc. of 5% sodium hydroxide solution and heated at about 90° for ten minutes. The acid amide, succinylsulfathiazole, melting at 129–133° with decomposition, was isolated by precipitation with dilute hydrochloric acid and after several recrystallizations from dilute alcohol melted at 185–187°.

(C) Sulfathiazole, 100 g. (0.392 mole), and 48.8 g. (0.411 mole) of succinic acid were mixed in a liter flask and heated

TABLE I

N^4-ACYL-N^1-SUBSTITUTED SULFANILAMIDES

N^4-Acyl	N^1-Substituent	Method of preparation	Yield, %	M. p., °C.[a] (uncor.)	Formula	Nitrogen analyses, %[b,c] Calcd.	Found
$HOOC(CH_2)_2CO$-	2-Pyridyl	1	81	135–140[d,e]	$C_{15}H_{15}O_5N_3S$	12.01	11.99
HOOCCH=CHCO-[f]	2-Pyridyl	1	..	193–194[d]	$C_{15}H_{13}O_5N_3S$	12.08	12.11
$HOOC(CH_2)_4CO$-[g]	2-Pyridyl	3E	11	184–185°	$C_{17}H_{19}O_5N_3S$	11.12	11.07
C_2H_5OOCCO-	2-Thiazolyl	2	88	233–234	$C_{13}H_{13}O_5N_3S_2$	11.83	11.95
HOOCCO-[g,h]	2-Thiazolyl	2	82	207–208	$C_{11}H_9O_5N_3S_2$	12.84	12.70
$C_2H_5OOCCH_2CO$-	2-Thiazolyl	2	85	193–194.5	$C_{14}H_{15}O_5N_3S_2$	11.38	11.31
$HOOCCH_2CO$-	2-Thiazolyl	2	76	240–250's	$C_{12}H_{11}O_5N_3S_2$	12.31	12.14
$HOOC(CH_2)_2CO$-	2-Thiazolyl	1, 3A, 3B, 3C, 3D	90	192–195[i]	$C_{13}H_{13}O_5N_3S_2$	11.83[j]	11.66
HOOCCH=CHCO-[k]	2-Thiazolyl	1	..	215–216	$C_{13}H_{11}O_5N_3S_2$	11.90	11.79
$HOOC(CH_2)_3CO$-	2-Thiazolyl	3E	56	196–197	$C_{14}H_{15}O_5N_3S_2$	11.38	11.32
$HOOC(CH_2)_4CO$-[f]	2-Thiazolyl	3E	47	196–197°	$C_{15}H_{17}O_5N_3S_2$	10.96	10.82
$HOOC(CH_2)_8CO$-	2-Thiazolyl	3F	..	171–172°	$C_{19}H_{25}O_5N_3S_2$	9.56	9.43
	2-Thiazolyl	1	72	260's[u]	$C_{13}H_{13}O_5N_3S_2$	10.42	10.43
$HOOC(CH_2)_2CO$-[l]	2-(5-ethyl-4-thiazolonyl)	1	82	161–162	$C_{15}H_{17}O_6N_3S_2$	10.52	10.45
HOOCCH=CHCO-		1	..	179–181	$C_{15}H_{15}O_6N_3S_2$	10.58	10.78
$HOOC(CH_2)_2CO$-	2-(5,5-diethyl-4-thiazolonyl)	1	82	208–209	$C_{17}H_{21}O_6N_3S_2$	9.83	9.70
$C_2H_5OOCCH_2CO$-	Guanyl	2	80	225–226	$C_{12}H_{16}O_5N_4S$	17.07	17.33
$HOOCCH_2CO$-[f]	Guanyl	2	53	172–175[m]	$C_{10}H_{12}O_5N_4S$	18.66	18.71
$HOOC(CH_2)_2CO$-	Guanyl	1	60	214–215	$C_{11}H_{14}O_5N_4S$	17.83	17.89
HOOCCH=CHCO-	Guanyl	1	78	201–202	$C_{11}H_{12}O_5N_4S$	17.94[n]	18.00
$HOOC(CH_2)_4CO$-	Guanyl	3E	18	132–133°	$C_{13}H_{18}O_5N_4S$	16.37	16.26
	Guanyl	1	78	266–267°	$C_{15}H_{14}O_5N_4S$	15.47	15.44
C_2H_5OOCCO-[p]	2-Pyrimidyl	2	61	230–235	$C_{14}H_{16}O_5N_4S$	15.99	15.87
HOOCCO-	2-Pyrimidyl	2	96	250's[u]	$C_{12}H_{10}O_5N_4S$	17.39	17.70
$C_2H_5OOCCH_2CO$-[p]	2-Pyrimidyl	2	84	198–199°	$C_{15}H_{16}O_5N_4S$	15.38	15.43
$HOOCCH_2CO$-	2-Pyrimidyl	2	87	215–216°	$C_{13}H_{12}O_5N_4S$	16.66	16.91
$HOOC(CH_2)_2CO$-[q,l]	2-Pyrimidyl	1	91	212–213	$C_{14}H_{14}O_5N_4S$	15.99	16.14
$HOOC(CH_2)_4CO$-	2-Pyrimidyl	3C	..	188	$C_{16}H_{18}O_5N_4S$	14.81	14.95
$HOOC(CH_2)_2CO$-[f]	2-(4-Methyl-pyrimidyl)	1	49	201–202[q]	$C_{15}H_{16}O_5N_4S$	15.38	15.27
$HOOC(CH_2)_2CO$-[r,s]	4-Sulfamylphenyl	1	95	234	$C_{16}H_{17}O_7N_3S_2$	9.83	9.85
$HOOC(CH_2)_2CO$-[r,l,t]	4-(2-Thiazolylsulf-amyl)-phenyl	1	81	237	$C_{19}H_{18}O_7N_4S_2$	10.98	10.99

[a] Most of these compounds actually decomposed with effervescence instead of melting. In some cases these decomposition ranges were difficult to recheck. [b] The analyses were carried out in these laboratories by Mr. John R. Taylor. [c] All samples were dried in the Abderhalden dryer for at least one hour before analyzing. [d] Shapiro and Bergmann [*J. Org. Chem.*, **6**, 774 (1941)] reported a melting point of 145° for the succinyl derivative and 208° for the maleyl derivative without mentioning their decomposition. [e] A sample of this compound decomposed at 191–194° after standing for seven months. *Anal.* Found: N, 11.94. [f] Recrystallized from water. [g] Purified by dissolving in dilute ammonia and precipitating with dilute hydrochloric acid. [h] Hygroscopic; takes up water during weighing. [i] The first samples of this compound decomposed at 184–186°. *Anal.* Found: N, 11.60. After standing for six months the same samples decomposed at 192–195°. All subsequent samples prepared by the anhydride condensation have decomposed at the higher range. [j] *Anal.* before drying. Calcd. for $C_{13}H_{13}O_5N_3S_2 \cdot H_2O$: N, 11.26. Found: N, 11.21. [k] This compound is unstable in solution and is subject to hydrolysis. [l] The anhydride condensation was carried out in dioxane as the solvent. [m] A sample of this compound was heated at the melting point until no further decomposition occurred. After recrystallizing from water it melted at 260–261°. Mixed with an authentic sample of N^4-acetylsulfanilylguanidine, m. p. 266–267°, it melted at 260–262°. [n] *Anal.* before drying. Calcd. for $C_{11}H_{12}O_5N_4S \cdot H_2O$: N, 16.97. Found: N, 17.00. [o] Melted to a clear liquid. [p] Recrystallized from methyl "Cellosolve" and water. [q] Solidified after melting at this temperature and remelted at 270°. [r] We are indebted to Dr. T. M. Immediata for the preparation of these compounds. [s] Recrystallized from acetone and water. [t] Recrystallized from dioxane and water. [u] Charred instead of melting.

in an oil-bath to approximately 165° for one hour with stirring. At the end of this time, the reaction melt had begun to solidify and the flame was removed from the oil-bath. With the flask still in the oil-bath, 380 cc. of 10% sodium hydroxide solution was cautiously added and after stirring for about fifteen minutes all of the solid had dissolved. After cooling to room temperature, the alkali solution was poured into a mixture of 88 cc. of concentrated hydrochloric acid and 960 cc. of water giving 130 g. of crude product (melting at 129–135° with decomposition), which was removed by filtration and purified by dissolving in a solution of 1000 cc. of ethanol and 200 cc. of water, decolorizing with charcoal (16 g. of Norite) and filtering with the aid of 16 g. of Filter-cel. Crystallization was completed by the addition of 504 cc. of water and 40 cc. of concentrated hydrochloric acid. The yield of succinylsulfathiazole was 87.5 g., which after further crystallization from dilute alcohol melted at 138–140°.

The diamide formed was removed by the Norite and Filter-cel and was isolated by treating with dilute alkali, filtering and precipitating with dilute hydrochloric acid. A yield of 6–9 g. was obtained.

(D) One hundred grams of sulfathiazole and 48.8 g. of succinic acid were heated together in 100 cc. of diethyl "Carbitol" under the same conditions as described in (C) above, for two hours. During the heating all of the materials went into solution and at the end of one and one-half hours a solid began to precipitate. After standing overnight, the product was filtered, dissolved in 400 cc. of 10% sodium hydroxide and precipitated with dilute hydrochloric acid. A yield of 81.9 g. (59%) of succinylsulfathiazole was obtained after recrystallization from dilute alcohol. Eight grams of crude diamide was recovered from the Norite and Filter-cel.

(E) Ten grams (0.0467 mole) of sulfaguanidine was mixed with 6.7 g. (0.0467 mole) of adipic acid and heated at 140–150° for one hour. After standing overnight, the solid was treated with 60 cc. of 10% sodium carbonate solution and the insoluble product filtered. A yield of 8 g. was obtained, melting at 234–240° with decomposition. After having been washed with dilute ammonia, hydrochloric acid and water and recrystallized from methyl "Cellosolve," the product melted at 268–269° with decomposition. It corresponded to the diamide, **adipamido-4,4′-bis-(benzenesulfonylguanidine)**.

Anal. Calcd. for $C_{20}H_{26}O_6N_8S_2$: N, 20.82. Found: N, 20.51.

The carbonate soluble filtrate was neutralized with dilute hydrochloric acid and a yield of 2.8 g. of adipoylsulfaguanidine was obtained, melting at 132–133° after recrystallization from dilute alcohol.

Similar results were obtained by the condensation of adipic acid with sulfapyridine and sulfathiazole.

(F) Ten grams (0.0392 mole) of sulfathiazole was mixed with 7.9 g. (0.0392 mole) of sebacic acid and heated to 150–170° for one and one-half hours. The cooled solid reaction mixture was treated with 200 cc. of 5% sodium hydroxide solution, decolorized with charcoal (Darco) and precipitated with dilute hydrochloric acid. The crude product (14 g.) was extracted thoroughly with saturated sodium bicarbonate solution, leaving 7.5 g. of insoluble material which was thoroughly washed with dilute hydrochloric acid and water and crystallized from dilute methyl "Cellosolve" containing a small amount of sodium bicarbonate. Purification by further crystallization from dilute methyl "Cellosolve" gave the diamide, **sebacamido-4,4′-bis-(2-benzenesulfonamidothiazole)**, melting at 245–246°.

Anal. Calcd. for $C_{28}H_{32}O_6N_6S_4$: N, 12.42. Found: N, 12.31.

Acidification of the sodium bicarbonate solution gave unreacted sebacic acid, m. p. 133°.

Glutaramido-4,4′-bis-(2-benzenesulfonamidothiazole), melting at 251–254° with decomposition after crystallization from dilute methyl "Cellosolve," was obtained in the same manner from glutaric acid and sulfathiazole.

Anal. Calcd. for $C_{23}H_{22}O_6N_6S_4$: N, 13.84. Found: N, 13.56.

Succinimidobenzenesulfonyl chloride was prepared by the method reported by Adams, Long and Jeanes.[7] However, the compound was purified by two recrystallizations from acetone and water, melting at 189–195° with decomposition.

Anal. Calcd. for $C_{10}H_8O_4NSCl$: N, 5.12. Found: N, 5.10.

Condensation of Succinimidobenzenesulfonyl Chloride with 2-Aminothiazole.—Twenty grams (0.2 mole) of 2-aminothiazole was dissolved in 75 cc. of anhydrous pyridine and 27.4 g. (0.1 mole) of succinimidobenzenesulfonyl chloride was added slowly with stirring. After the addition, the solution was heated on the steam-bath for one-half hour and the pyridine was then removed by distillation under reduced pressure. The residue was triturated with 50 cc. of cold water and the brown insoluble solid (4 g.) was filtered. After purification by several recrystallizations from dioxane and water the solid melted at 250.5–251.5° with decomposition. It was insoluble in cold sodium bicarbonate solution.

Anal. Found: N, 14.85.

The aqueous filtrate from above was acidified with concentrated hydrochloric acid and after chilling for several days 6.8 g. of succinylsulfathiazole was obtained, melting at 180–184°. It was soluble in cold sodium bicarbonate solution with evolution of carbon dioxide.

Condensations with two equivalents of 2-aminothiazole in acetone or one equivalent of 2-aminothiazole in sodium carbonate solution gave similar results.

Summary

A series of dicarboxylic acid derivatives of sulfonamides has been prepared for study as intestinal antiseptics.

Succinic, maleic and phthalic anhydrides condensed with the sulfonamides to give the monobasic acid amides I. Ethyl oxalate and ethyl malonate condensed with sulfathiazole, sulfadiazine and sulfaguanidine to give the ester amides IV, which were easily hydrolyzed by alkali to give the acid amides I, and a small amount of the diamides III. Esters of higher acids, such as ethyl glutarate, adipate and sebacate did not con-

(7) Adams, Long and Jeanes, THIS JOURNAL, **61**, 2316 (1939).

dense with sulfathiazole even when heated at 160–170° for two hours.

Succinic acid condensed with the sulfonamides, when heated at a temperature of 150–170° for one to two hours, to give the anils II and 5–7% of the diamides IV. Hydrolysis of the anils II with 5–10% alkali gave the corresponding acid amides I. Condensation of glutaric, adipic and sebacic acids with the sulfonamides led to the isolation of the acid amides I and diamides III, in varying proportions.

p-Succinimidobenzenesulfonyl chloride condensed with 2-aminothiazole, under varying conditions, to give N^4-succinylsulfathiazole and an unidentified product.

GLENOLDEN, PA. RECEIVED MARCH 27, 1942

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

The Condensation of Some Secondary Aliphatic Alcohols with Benzene in the Presence of Aluminum Chloride

BY R. C. HUSTON AND I. A. KAYE[1]

Previous work in this Laboratory has shown that *t*-aliphatic alcohols condense with benzene and phenol in the presence of aluminum chloride to give the expected *t*-alkylbenzenes.[1a-3] Secondary aliphatic alcohols have been condensed with benzene too, but the nature of the products was not determined.[1a] The purpose of the present investigation was to extend the study of the condensation of secondary aliphatic alcohols with benzene, using aluminum chloride as catalyst, and to determine the nature of the products obtained.

s-Propyl, butyl, amyl, hexyl and nine of the *s*-heptyl alcohols were condensed with benzene. That isopropyl and *s*-butyl alcohols gave the expected hydrocarbons, cumene and *s*-butylbenzene, was shown by their monoacetamino derivatives whose melting points agreed with those in the literature.[4] The other monoalkylbenzenes were nitrated yielding the *p*-nitro derivatives which were then reduced to the amines. Phenols were prepared from the latter through the diazonium salts. The α-naphthylurethans of the phenols were then prepared. By comparison with the melting points of the α-naphthyl-urethans of known *t*-alkylphenols[2,3] and by mixed melting point determinations with these compounds, it was established that 2-methylbutanol-3, 2-methylpentanol-3, 2-methyl-hexanol-3 and 3-methylhexanol-4 gave the *t*-alkylbenzenes, 2-methyl-2-phenylbutane, 2-methyl-2-phenylpentane, 2-methyl-2-phenylhexane and 3-methyl-3-phenylhexane.

The *p*-hydroxy derivatives and their α-naphthylurethans of 2-phenylpentane, 3-phenylpentane, 2-phenylhexane, 3-phenylhexane, 3-methyl-2-phenylpentane, 2-methyl-4-phenylpentane, 2,2-dimethyl-3-phenylbutane, 2-phenylheptane, 3-phenylheptane, 4-phenylheptane, 2-methyl-4-phenylhexane, 2-methyl-5-phenylhexane, 3-methyl-2-phenylhexane, and 2,2-dimethyl-3-phenylpentane were synthesized. The condensation of pinacolyl alcohol with benzene gave an alkylbenzene which was converted into a phenol identical with synthesized 2,2-dimethyl-3-*p*-hydroxyphenylbutane. The other alcohols, pentanol-2, pentanol-3, hexanol-2, hexanol-3, 3-methylpentanol-2, 2-methylpentanol-4, heptanol-2, heptanol-3, heptanol-4,2-methylhexanol-4, 2-methylhexanol-5, 3-methylhexanol-2 and 2,2-dimethylpentanol-3 undoubtedly gave mixtures of monoalkylbenzenes such as might be formed by the splitting out of water and the condensation of the resulting olefin in either of the two possible positions. This formation of mixtures in the condensation of the *s*-amyl alcohols with benzene and phenol and in the condensation of the secondary hexylphenols has been observed by others[5,6,7] and it is quite possible that the same phenomenon occurs with the higher homologs. The formation of tertiary products in the condensation of *s*-aliphatic alcohols with methyl groups adjacent to the carbinol group has also been reported.[5,6,7]

(1) From a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(1a) Huston and Hsieh, THIS JOURNAL, **58**, 439 (1936).

(2) Huston and Hedrick, *ibid.*, **59**, 2001 (1937).

(3) Huston and Guile, *ibid.*, **61**, 69 (1939).

(4) Ipatieff and Schmerling, *ibid.*, **59**, 1056 (1937).

(5) Ipatieff, Pines and Schmerling, *J. Org. Chem.*, **5**, 253 (1941).

(6) Huston and Esterdahl, Master's Thesis, Michigan State College (1940).

(7) Huston and Curtis, *ibid.* (1941).

TABLE I

MONOALKYLBENZENES FROM s-ALIPHATIC ALCOHOLS

s-Aliphatic alcohol condensed with benzene	% Yield of mono-alkylbenzene	B. p., °C.	Mm.	d^{25}_4	$n^{25}D$	Surface tension drop weight	Surface tension Du Nouy	%C	%H
Propanol-2	71	151	759	0.8600	1.4858	27.78	29.28		
Butanol-2	81	171	759	.8597	1.4878	28.20	29.40		
Pentanol-2	83	190	759	.8599	1.4864	28.49	29.72	88.89	10.98
						Calcd. for $C_{11}H_{16}$		89.12	10.88
Pentanol-3	65	189–190.5	757	.8605	1.4877	28.51	29.65	88.97	10.83
2-Methyl-butanol-3	54	188.5–190	760	.8684	1.4908	28.60	29.97	89.23	10.79
Hexanol-2	72	208–210	760	.8608	1.4866	28.79	30.16	88.86	11.06
						Calcd. for $C_{12}H_{18}$		88.82	11.18
2-Methyl-pentanol-4	50	205–206	760	.8754	1.4932	28.79	29.84	88.53	11.31
Hexanol-3	65	209–211	760	.8580	1.4845	28.93	29.84	88.67	11.11
3-Methyl-pentanol-2	56	207–211	760	.8760	1.4951	29.28	30.55	89.17	10.94
2-Methyl-pentanol-3	66	208–209	760	.8702	1.4900	28.96	29.78	89.00	11.04
2,2-Dimethyl-butanol-3	62	205–207	760	.8763	1.4942	28.92	30.16	88.96	10.99
Heptanol-2	72	226–227	760	.8585	1.4837	28.94	29.72	88.47	11.40
						Calcd. for $C_{13}H_{20}$		88.56	11.49
Heptanol-3	67	227–228	762	.8569	1.4828	28.73	30.03	88.55	11.59
2-Methyl-hexanol-3	62	225–226	762	.8688	1.4893	29.08	30.09	88.19	11.56
3-Methyl-hexanol-4	60	224–226	762	.8727	1.4913	29.88	30.91	88.27	11.63
2-Methyl-hexanol-4	54	224–225	762	.8654	1.4873	28.74	29.84	88.13	11.40
2-Methyl-hexanol-5	44	223–226	760	.8777	1.4929	29.06	29.97	88.43	11.31
3-Methyl-hexanol-2	56	224–225.5	762	.8767	1.4939	29.14	30.09	88.99	11.52
2,2-Dimethyl-pentanol-3	58	221–223	762	.8720	1.4912	28.67	29.65	88.63	11.30
Heptanol-4	63	226–229	760	.8613	1.4847	29.03	29.78	88.29	11.62

Alcohols listed in Table I were prepared by the Grignard method. Some of their physical constants were redetermined. Other alcohols used showed constants which agreed with those in the literature.

Condensation of the Secondary Aliphatic Alcohols with Benzene.—All condensations were carried out in the same manner. One-half mole of the alcohol, dissolved in 50 ml. of benzene, was added dropwise and with vigorous stirring to a suspension of 50 g. of anhydrous aluminum chloride in 400 ml. of ice-cold anhydrous, thiophene-free benzene. Dry hydrogen chloride gas was bubbled through the reaction mixture at the same time at a rate such that the bubbles could just be counted. The reaction mixture was stirred one hour after the addition of the alcohol and then permitted to stand eight hours at room temperature.

In the case of the straight-chain alcohols, refluxing the reaction mixture eight hours longer, while bubbling in hydrogen chloride gas, was found to improve the yields. This practice was omitted in the condensation of the branched alcohols, since poorer yields were obtained.

The reaction mixture was then poured on ice; hydrochloric acid was added, and the benzene layer was separated and washed once with water, twice with a dilute sodium bicarbonate solution and once more with water. After drying over anhydrous sodium sulfate, the benzene was removed *in vacuo*. The residual liquid was distilled at atmospheric pressure using a ten-inch Vigreux column.

Derivatives of the Monoalkylbenzenes.—Acetamino derivatives were prepared by the method of Ipatieff and Schmerling.[4] The *p*-nitroalkylbenzenes, *p*-aminoalkylbenzenes and *p*-hydroxyalkylbenzenes were prepared by the methods given in Fisher's test.[8] α-Naphthylurethans were prepared by the method of French and Wirtel.[9]

Synthesis of the s-Alkylbenzenes.—These compounds were prepared by a modification of the method of Klages.[10] The alkyl Grignard reagent was treated with acetophenone or its homologs. The tertiary alcohol formed was not isolated but converted directly into an olefin by refluxing, using a Dean–Stark moisture trap[11] to collect the water which was eliminated. The product was then distilled and

(8) Fisher, "Laboratory Manual of Organic Chemistry," 4th ed., 1938, John Wiley and Sons, Inc., New York, N. Y.

(9) French and Wirtel, THIS JOURNAL, **48**, 1736 (1926).

(10) Klages, *Ber.*, **36**, 622 (1903).

(11) Dean and Stark, *Ind. Eng. Chem.*, **12**, 486 (1920).

TABLE II

DERIVATIVES OF THE MONOALKYLBENZENES

Secondary alcohols	*p*-Nitro B. p., °C.	*P*, mm.	*p*-Amino B. p., °C.	*P*, mm.	*p*-Hydroxy B. p., °C.	*P*, mm.	α-Naphthylurethan M. p., °C.	Nitrogen, % Calcd.	Found
Pentanol-2	112–114	2	101–102	2	100–104	2	99–99.5	4.12	4.13
Pentanol-3	111–117	2	103–105.5	2	100–101	2	97.5–98.5	4.12	4.18
2-Methylbutanol-3	113–118	2	99–103	2	110–114	3	125–126.5	4.12	4.17
					m. p. 89–90				
Hexanol-2	133–141	3	111–114	2	108–113	2	95–96.5	4.03	3.99
2-Methylpentanol-4	134–138	3	124–125	3	115–119	3	108–112	4.03	3.97
Hexanol-3	122.5–124	2	121.5–122	3	117–119	3	95–96	4.03	4.03
3-Methylpentanol-2	124–127	2	112–113	2	117–121	3	103–105.5	4.03	3.99
2-Methylpentanol-3	123.5–127	2	111–113	2	116–119	3	123.5–125	4.03	4.00
2,2-Dimethylbutanol-3	117–123[a]	2	115–118[b]	2	115–118[c]	3	109–110	4.03	3.98
					m. p. 122				
Heptanol-2	154–156	3	124–127	2	120–122	2	94.5–96.5	3.87	3.82
Heptanol-3	143–149	3	124–126	2	125–127	2	95.5–97.5	3.87	3.86
Heptanol-4	146–150	3	129–130	2	117–121	2	93.5–94	3.87	3.82
2-Methylhexanol-3	140–146	3	127–129	2	123–127	3	125–126	3.87	3.83
3-Methylhexanol-4	143–148	3	124–126	2	128–131	3	101–103	3.87	3.87
2-Methylhexanol-4	136–143	3	120–124	2	122–129	3	119–121	3.87	3.79
2-Methylhexanol-5	139–142	3	123–127	2	123–126	3	119–121	3.87	3.86
3-Methylhexanol-2	135–139	3	120–125	2	121–125	3	106–108	3.87	3.83
2,2-Dimethylpentanol-3	139–141	3	120–126	2	131–133	3	114–115	3.87	3.79

[a] Calcd. for $C_{12}H_{17}O_2N$: N, 6.73. Found: N, 6.68. [b] Calcd. for $C_{12}H_{19}N$: N, 7.87. Found: N, 7.74. [c] Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.63; H, 10.35.

TABLE III

SYNTHESIZED *s*-ALKYLBENZENES AND DERIVATIVES

Alkylbenzenes Name	B. p., °C.	*P*, mm.	*p*-Nitro B. p., °C. (2 mm.)	Nitrogen, % Calcd.	Found	*p*-Amino B. p., °C. (2 mm.)	Nitrogen, % Calcd.	Found	*p*-Hydroxy- B. p., °C. (2 mm.)	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
3-Phenylpentane	189–191	741	110–115	7.25	7.18	107–116[a]	8.58	8.43	108–117[b]	...	...	...	...
2-Phenylpentane	191–193	762	112–118	7.25	7.21	101–104	8.58	8.49	101–103	81.19	80.83	10.48	10.33
2-Phenylhexane	210–211	737	120–128	6.72	6.62	112–116	7.87	7.78	110–112	...	...	...	...
4-Phenylheptane	221–224	760	140–143	6.33	6.29	128–13[illegible]	7.32	7.25	121–123	81.19	80.78	10.48	10.27
2-Methyl-4-phenylpentane	197–198	735	132–133	6.73	6.66	113–115	7.87	7.83	109–110	80.85	80.37	10.18	10.01

[a] 3 mm. [b] M. p. 75.5°.

TABLE IV

SYNTHESIS OF *p*-HYDROXYPHENYLALKANES

Secondary *p*-hydroxyphenylalkane	B. p., °C.	*P*, mm.	Analyses, % Found C	H	Calculated C	H	Starting materials
3-*p*-Hydroxyphenylhexane	133	4	80.67	10.11	80.85	10.18	*n*-Propyl bromide and *p*-methoxypropiophenone
3-*p*-Hydroxyphenylheptane	117	2	81.07	10.31	81.19	10.48	*n*-Butyl bromide and *p*-methoxypropiophenone
2,2-Dimethyl-3-*p*-hydroxyphenylpentane	108	2	80.87	10.64	81.19	10.48	*t*-Butyl chloride and *p*-methoxypropiophenone
2-Methyl-4-*p*-hydroxyphenylhexane	111	2	81.49	10.29	81.19	10.48	Isobutyl bromide and *p*-methoxypropiophenone
3-Methyl-2-*p*-hydroxyphenylpentane	120–123.5	3	80.71	9.99	80.85	10.18	*s*-Butyl bromide and *p*-methoxyacetophenone
2-*p*-Hydroxyphenylheptane	140	4	80.78	10.52	81.19	10.48	*n*-Amyl bromide and *p*-methoxyacetophenone
2-Methyl-5-*p*-hydroxyphenylhexane	123.5	2	80.79	10.20	81.19	10.48	Isoamyl bromide and *p*-methoxyacetophenone
3-Methyl-2-*p*-hydroxyphenylhexane	123–125	2	80.77	10.37	81.19	10.48	*s*-Amyl chloride and *p*-methoxyacetophenone
2,2-Dimethyl-3-*p*-hydroxyphenylbutane[a]	123	4	80.94	10.64	81.19	10.48	*t*-Butyl chloride and *p*-methoxyacetophenone

[a] M. p. 120–121°.

reduced to the hydrocarbon by dissolving 0.25 mole in 375 ml. of absolute ethanol. Forty grams of sodium was added to the boiling solution in small portions over a period of time. Water was added when all the sodium had dissolved and the mixture was extracted three times with ether. The combined ether extracts were washed free of alcohol, dried over anhydrous sodium sulfate and the ether removed by distillation. The residue was shaken thoroughly with a saturated aqueous potassium permanganate solution and the excess permanganate reduced by the addition of solid sodium bisulfite. The alkylbenzene was then extracted with ether and distilled at atmospheric pressure after drying and removing the ether. The product was then converted into the *p*-hydroxyphenylalkane (see Table III, C) through the *p*-nitro and amino derivatives. The α-naphthylurethan of the phenol was then prepared.

TABLE V

α-NAPHTHYLURETHANS OF THE SYNTHESIZED *p*-HYDROXYPHENYLALKANES

Parent compound	α-Naphthylurethan, m. p., °C.	Nitrogen, % Calculated	Found
2-*p*-Hydroxyphenylpentane	100–101	4.12	4.09
3-*p*-Hydroxyphenylpentane	114	4.12	4.07
2-*p*-Hydroxyphenylhexane	108–109	4.03	3.98
2-Methyl-4-*p*-hydroxyphenylpentane	107	4.03	3.96
3-*p*-Hydroxyphenylhexane	95–95.5	4.03	3.99
3-Methyl-2-*p*-hydroxyphenylpentane	100–101	4.03	3.95
2-*p*-Hydroxyphenylheptane	115–116	3.87	3.85
3-*p*-Hydroxyphenylheptane	100	3.87	3.79
4-*p*-Hydroxyphenylheptane	104–105	3.87	3.88
2-Methyl-4-*p*-hydroxyphenylhexane	117–117.5	3.87	3.81
2-Methyl-5-*p*-hydroxyphenylhexane	125	3.87	3.81
3-Methyl-2-*p*-hydroxyphenylhexane	110–111	3.87	3.82
2,2-Dimethyl-3-*p*-hydroxyphenylpentane	118–119	3.87	3.82

TABLE VI

MONOALKYLBENZENES FROM *s*-ALCOHOLS WITHOUT REARRANGEMENT

Alcohol condensed with benzene	M. p. of derivatives, °C. Monoacetamino	Diacetamino	Pure compound alkylbenzene	M. p. of derivatives, °C. Monoacetamino	Diacetamino
Isopropyl	105	213–214	Cumene	106[5]	216[5]
s-Butyl	126	...	2-Phenylbutane	126[5]	...

	p-Hydroxyphenol	Phenol	M. p. of Phenol
Pinacolyl	122[a]	2,2-Dimethyl-3-*p*-hydroxyphenylbutane	120–121[b]

[a,b] Melting point of mixture of *a* and *b* showed no depression.

Table VI indicates definitely that propanol-2 condenses with benzene to form only cumene, and butanol-2 forms only 2-phenylbutane. The only other case of apparent simple replacement of the hydroxyl with phenyl was found in the condensation of 2,2-dimethylbutanol-3 with benzene. The alkylbenzene gave, upon nitration, reduction and diazotization, a phenol which was proved by mixed melting point and melting points of derivatives to be identical with 2,2-dimethyl-3-*p*-hydroxyphenylbutane. This is especially noteworthy in view of the fact that it has been found in this Laboratory[7] that pinacolyl alcohol reacts with phenol in the presence of aluminum chloride at 50° to give 2,3-dimethyl-2-*p*-hydroxyphenylbutane.

Of the remaining alcohols listed (Table II), none showed simple replacement of the hydroxyl with the phenol group. The α-naphthylurethan from the condensation of 3-methylpentanol-2 gave a melting point (not sharp) intermediate between that of the α-naphthylurethan of 3-methyl-2-*p*-hydroxyphenylpentane (Table V) and of 3-methyl-3-*p*-hydroxyphenylpentane, while the α-naphthylurethan from 3-methylhexanol-2 melted between that of 3-methyl-2-*p*-hydroxyphenylhexane and of 3-methyl-3-*p*-hydroxyphenylhexane.[2]

The other four alcohols in which the hydroxyl is on a carbon adjacent to one carrying tertiary hydrogen gave products identical with those obtained from tertiary alcohols. 2-Methylbutanol-3 gave an alkylbenzene which was converted into 2-methyl-2-*p*-hydroxyphenylbutane.[1a] 2-Methylhexanol-3 gave 2-methyl-2-*p*-hydroxyphenylhexane,[2] and 3-methylhexanol-4 gave 3-methyl-3-*p*-hydroxyphenylhexane.[2] Identification was accomplished by mixed melting points of the α-naphthylurethans.[12] Probability of the admixture of some secondary alkylbenzene in the condensation products was indicated by the repeated crystallizations which were necessary in order to obtain the α-naphthylurethans in the pure state.

All straight chained alcohols and those in which branching occurs on carbons not adjacent to the alcoholic group give mixtures of condensation products which may be accounted for by assuming the elimination of water and the reaction of the mixture of alkenes with benzene. Both 2-methylhexanol-4 and 2-methylhexanol-5 gave urethan mixtures melting at 119–121°. This is between

(12) The earlier publication reported a m. p. of 110–111° for the α-naphthylurethan of 2-methyl-2-*p*-hydroxyphenylhexane and 82.3° for the α-naphthylurethan of 3-methyl-3-*p*-hydroxyphenylhexane. The melting points of these derivatives, as prepared by the authors from the phenols prepared by Huston and Hedrick, were found to be 125° and 101°, respectively.

the melting points of the α-naphthylurethans of 2-methyl-5-*p*-hydroxyphenylhexane and of 2-methyl-4-*p*-hydroxyphenylhexane.

Unlike 2,2-dimethylbutanol-3, 2,2-dimethylpentanol-3 apparently forms a mixture of condensation products. The melting point of the α-naphthylurethan mixture is 114–115°. This is well below that of the α-naphthylurethan of 2,3-dimethyl-3-*p*-hydroxyphenylpentane[2] (124–125°) or of 2,3-dimethyl-2-*p*-hydroxyphenylpentane[2] (122–123°) but is quite near that of 2,2-dimethyl-3-*p*-hydroxyphenylpentane. This leads to the suggestion that the mixture is the result of the reaction of 2,2-dimethylpentene-3 with benzene and not of methyl migration.

Summary

1. The *s*-propyl, butyl, amyl, hexyl and nine of the *s*-heptyl alcohols were condensed with benzene in the presence of aluminum chloride.

2. The alkylbenzenes obtained in the condensations were converted to the corresponding *p*-hydroxy compounds through the *p*-nitro and *p*-amino derivatives. α-Naphthylurethans of the *p*-hydroxy compounds were also prepared as well as acetamino derivatives of some of the alkylbenzenes.

3. A number of pure *s*-alkylbenzenes and *s*-alkylphenols were synthesized and their α-naphthylurethans prepared.

4. By comparison of the melting points of the acetamino derivatives of the alkylbenzenes with those in the literature and of the melting points of the phenols and of the α-naphthylurethans with those synthesized and with those of *t*-alkylphenols, the following facts have been established: (a) Isopropyl, *s*-butyl and pinacolyl alcohols gave the corresponding *s*-alkylbenzenes in pure form. (b) 2-Methylbutanol-3, 2-methylpentanol-3, 2-methylhexanol-3 and 3-methylhexanol-4 gave tert-alkylbenzenes. (c) The straight chain alcohols, those having a branched methyl group remote from the carbinol group, and 2,2-dimethylpentanol-3 gave mixtures of monoalkylbenzenes. (d) 3-Methylpentanol-2 and 3-methylhexanol-2 also gave mixtures consisting, probably, of the *s* and *t*-alkylbenzenes.

EAST LANSING, MICHIGAN RECEIVED MARCH 9, 1942

[CONTRIBUTION FROM THE CHEMICAL DIVISION OF THE WOBURN DEGREASING COMPANY OF N. J.]

Solid 10,12-Octadecadienoic Acid-1. A New Conjugated Linoleic Acid Melting at 57°

BY J. D. VON MIKUSCH

When linoleic and linolenic acids or their glycerides are treated with an excess of alcoholic potash for prolonged periods of time, a rearrangement of the double bonds into the conjugated position has been found to take place.[1] In the case of linolenic acid, a solid isomer, pseudoeleostearic acid, is formed, which was identified by Kass and Burr[2] as 10,12,14-octadecatrienoic acid-1. Linoleic acid, on the other hand, was found by Moore[1] (pp. 145, 147) to give rise "to a product which remains liquid at room temperature." On alcoholic-potash isomerization of maize oil containing linoleic but no linolenic acid, "no solid acids were formed" (ref. 1, p. 143).

Burr and collaborators, however, disclose an isomerization of linoleic acid to crystalline forms as a result of treatment with sodium butylate,[3] and give absorption spectrum, diene number and extinction coefficient for a solid 10,12-linoleic acid.[4] They also describe a solid 10,12-linoleyl alcohol.[5]

As a result of extensive studies in this Laboratory[6] a commercial conjugating process has been developed in which oils and fatty acids are isomerized with caustic soda in aqueous medium (patents pending). When oils containing a large proportion of linolenic acid, for instance linseed oil, are subjected to this process, the melting point or titer of their free fatty acids rises, indicating the formation of solid products. The fatty acids of oils containing little or no linolenic acid but a large proportion of linoleic acid experience a drop in titer.[7] From this it appears that linoleic acid does not yield solid isomerization products to any appreciable extent under the conditions

(1) Moore, *Biochem. J.*, **31**, 138–154 (1938).
(2) Kass and Burr, THIS JOURNAL, **61**, 3294 (1939).
(3) Kass, Miller and Burr, *ibid.*, **61**, 482 (1939).
(4) Miller and Burr, *Chem. Reviews*, **29**, 419 (1941).
(5) Kass and Burr, THIS JOURNAL, **62**, 1796 (1940).
(6) Woburn Bulletins No. 121 and 123, Woburn Degreasing Company of N. J., Harrison, N. J.
(7) Titer of linseed fatty acids: 18° before, 23.1° after isomerization; of soybean fatty acids: 22° before, 12.5° after isomerization.

of the commercial process. In order to verify this, the fatty acids of walnut oil were freed from the bulk of their solid constituents by storing and pressing at 0–3°. When the resulting liquid fraction was isomerized, the conjugated fatty acid product was liquid at room temperature and remained liquid on renewed cold storage at 0–3°.

In contrast herewith, it was found that a sample of dehydrated castor oil ("isoline"), the fatty acids of which remain liquid at 3°, produces a fatty acid mixture upon isomerization which sets to a semi-solid mass at 3°, and from which a considerable quantity of a solid acid separates even at room temperatures. The fatty acids of dehydrated castor oil have previously been found to contain 26% or less of 9,11-linoleic acid, the remainder being largely non-conjugated, *i. e.*, 9,12-linoleic acid.[8]

The diene value of dehydrated castor oil increases considerably during the caustic treatment, and the solid fatty acid formed, m. p. 57°, methyl ester m. p. 25°, is conjugated as shown by its analysis. It is found to be not identical with Mangold's[9] solid 9,11-linoleic acid. Another solid conjugated linoleic acid, m. p. 56°, which was obtained by Smit[10] by the debromination of tetrabromostearic acid, m. p. 124° and believed to be also a 9,11-isomer, was not available; but no bromide melting at 124° was formed by the new acid.

Oxidation with permanganate, both in alkaline and neutral solution, served to characterize the new acid as 10,12-octadecadienoic acid-1 and it may, therefore, be concluded that it resulted from the isomerization of the 9,12-linoleic acid present in dehydrated castor oil. Since other oils containing 9,12-linoleic acid, such as soybean or walnut, do not yield a solid fatty acid under similar treatment, it may be further concluded that the linoleic acid present in dehydrated castor oil, or at least a portion of it, is not identical with ordinary linoleic acid but a stereoisomer thereof.

Only one of the four theoretically possible 10,12-linoleic acids has in the past been identified. It was found by Böeseken and collaborators[11,12] in the products of partial hydrogenation of both alpha- and beta-eleostearic acids and their esters and had a melting point of 28.5°. The melting point of the 10,12-linoleic acid referred to by Burr, *et al.*,[2–5] has not been reported.

(8) Priest and von Mikusch, *Ind. Eng. Chem.*, **32**, 1314 (1940); Priest and von Mikusch, Chapter on dehydrated castor oil in "Protective and Decorative Coatings, etc.," J. J. Mattiello, Editor, 1st ed. vol. 1, page 128, John Wiley and Sons, New York, N. Y., 1941.

(9) Mangold, *Monatsh.*, **15**, 309 (1894).

(10) Smit, *Rec. trav. chim.*, **49**, 539 (1930).

(11) Böeseken, Smit, Hoogland and van der Broek, *ibid.*, **46**, 623 (1927).

(12) Böeseken and van Krimpen, *Koninkl. Akad. Wetensch. Amsterdam, wisk. natk. Afd.*, **37**, 66–8; *Chem. Zentr.*, **99**, I, 2704 (1928); Böeseken, van Krimpen and Blanken, *Rec. trav. chim.*, **49**, 247 (1930).

Experimental

The fatty acid product obtained from the commercial isomerization of dehydrated castor oil ("Isoline") with caustic soda in an aqueous medium was refrigerated at 3° for forty-eight hours. Repeated filtration and pressing on a suction funnel yielded a dry cake weighing more than 20% of the original total fatty acids.

Two recrystallizations from petroleum ether gave snow-white crystals, m. p. 55–56°, which, with Wijs solution, showed the color of free iodine characteristic for conjugated double bonds,[13] Wijs I. V., 130; diene value, −88.5 (Ellis–Jones).

Two recrystallizations of the purified product from ether, in which it is less soluble at low temperatures than stearic acid, and two from 95% alcohol yielded crystals melting at 56.3–57.7° (cor.), which became tacky when left exposed to air, showing sensitivity to oxidation. The final crop formed a clear solution in a little warm petroleum ether but, in ample excess, this solvent precipitated a white cloud indicating the presence of oxidized fatty acids. The dilute solution was, therefore, filtered with charcoal and cold stored. Before each of the following determinations, a sample of the resulting acid suspension in petroleum ether was removed, filtered, and dried under carbon dioxide; properties, melting point 55.7–57.5° (cor.); partial iodine value (modified Wijs, 2 min. on ice)[14] 89.91, 89.80 (calcd. 90.52); total iodine value (Woburn Method, 0.32 *N* iodine bromide solution, 1 hr., 20°)[15] 186.7 (calcd. 181.0); acid value 199.6 (calcd., 200.06); from this: mol. wt. 281.1 (calcd. 280.436); refractive index, $n^{60}D$ 1.4689; $n^{70}D$ 1.4656[16]; density by pycnometer, d^{70}_4 0.86857; molar refraction (Lorenz–Lorentz) 89.36,[16] calcd. (acc. to Eisenlohr) 85.93, exaltation, +3.43.[17]

The white lead soap, precipitated quantitatively from the hot aqueous potassium soap solution, was practically insoluble in cold benzene (6°), but 100 ml. of boiling benzene dissolved approximately 3 g. After one crystalliza-

(13) Böeseken and Gelber, *ibid.*, **46**, 162 (1927).

(14) von Mikusch, *Oil and Soap*, **15**, 186 (1938).

(15) von Mikusch and Frazier, *Ind. Eng. Chem., Anal. Ed.*, **13**, 782 (1941). Data on the determination of total and partial iodine values and diene values, by difference of the two, are being prepared for publication by von Mikusch and Frazier.

(16) The author is indebted to H. E. Riley for determining the refractive indices listed, and suggesting improvements in the preparation of the manuscript. Mr. Riley also points out in a private communication that the specific refraction of the new acid is 0.31853, compared to a value of 0.31772 for 9,11-linoleic acid calculated from the data cited by Smit and Böeseken.

(17) Böeseken, *et al.*,[11] report a molar refraction of 88.9 for 9,11-linoleic acid, m. p. 52.2°, but from this value incorrectly derive an exaltation of +3.4, although Smit (ref. 10, p. 545) correctly states the calculated molar refraction to be 85.9, showing an exaltation of +3.0. If the values for $n^{77}D$ 1.4624 and sp. gr. at 77° 0.8659 as reported identically by Böeseken, *et al.*, and Smit[10] are used together with the calculated molecular weight for octadecadienoic acid using 1941 atomic weights, m. wt. 280.4, a molar refraction of 89.1 results giving an exaltation of +3.2. This is seen to be close to the present value for the 10,12-isomer.

tion from boiling benzene, the lead soap melted indistinctly at 115°.

Mangold's acid was prepared in the usual manner by the dry distillation of ricinelaidic acid.[3,11] The yield after one recrystallization from 95% alcohol was 17.4%, m. p. 52°. A mixture of this with the new acid melted at 48 to 51°, or lower than either acid alone.

Methyl Ester.—Twenty-four grams of a sample of the new acid which had been recrystallized only once from petroleum ether was refluxed with twice its weight of anhydrous methyl alcohol for three and one-half hours while passing hydrogen chloride gas into the solution. Recrystallization of the product from methyl alcohol gave 12.2 g. of white scales melting at 25°; the remaining brown oil was not further investigated; (9,11-linoleic methyl ester, m. p. 29.8°, according to Böeseken, *et al.*[11]). The bulk of the dried scales distilled at 207–208° (uncor.) at 9 mm. The distillate solidified sharply at 23–23.5°; total iodine value (Woburn, 1 hr. 20°)[15] 173.4; 173.4 (calcd. 172.4); partial iodine value (mod. Wijs, 2 min., ice)[14] 86.6; 86.1 (calcd. 86.2); Woburn diene value (by diff.) compare[15] 87.0 (calcd. 86.2).

Bromination of the new acid in cold petroleum ether with one mole of bromine and storing of the solution at 3° for forty-eight hours did not lead to solid products. After adding a second mole of bromine and allowing to stand in diffuse daylight at room temperature for two days, the color of free bromine had disappeared and a white solid had settled out, m. p. 104–113°. Extensive fractional crystallizations from 95% alcohol resulted in two portions, melting at 149.5–150.5° and 104–105° (cor.), respectively; acid values 95.8 and 94.7 resp. (calcd. 93.5 for tetrabromide).

Mild oxidation with alkaline potassium permanganate of 15 g. of the once recrystallized acid yielded a cake of hydroxy acids from which 0.1 g. of soluble substance was extracted with petroleum ether. Extraction of the remaining cake with warm ether yielded 4.8 g. of a viscous, almost water-white liquid which did not solidify after several days at 3°; acid value 178.6 (calcd. for dihydroxystearic acid, 178.4).

The remaining hydroxy acids were extracted successively with hot chloroform and boiling alcohol. These extracts on cooling yielded 0.3 and 0.9 g., respectively, of white precipitates, identical although of different purity, melting at 177–182° and 186–189°, recrystallized, 187–188.5° (cor.); acid value 159.9 and 156.6 (calcd. for tetrahydroxy stearic acid 161.0).

Ether extraction of the aqueous solution remaining after the separation of the hydroxy acids yielded 2.5 g. of an oil which on extraction with boiling water yielded crystals, melting after one recrystallization at 127–129.5°. They showed no depression with sebacic acid; acid value 580 (calcd. for sebacic acid 554.8). Other oxidation products, in evidence, were not further investigated.

Destructive Oxidation of Methyl Ester.—Following in general the procedure of Armstrong and Hilditch,[18] 8 g. of the recrystallized and distilled methyl ester was oxidized with 75 g. of powdered potassium permanganate in 250 ml. of boiling acetone. The ether-soluble oxidation products were dry-distilled at atmospheric pressure. When the distillate, which had the odor of caproic acid, was redistilled, the two main fractions collected passed over at 193–201° and 201–205.5°, respectively, and had equivalent weights by titration of 106.1 and 110.3 (caproic acid, mol. wt., 116.2; b. p. 202°).

The residue was boiled with alcoholic potassium hydroxide, acidified with dilute sulfuric acid, and the acidified solution extracted three times with ether. After evaporation, a white solid, contaminated with a yellow oil, remained. The solid was soluble in boiling water, which on cooling yielded 1.4 g. of white crystals, m. p. after four recrystallizations from boiling water 130.5–132.5°, acid value 542, which gave no depression with genuine sebacic acid.

Summary

A new solid conjugated isomer of linoleic acid, melting at 57°, was isolated from the isomerization products obtained from dehydrated castor oil in a commercial conjugating process using aqueous alkali. It is identified as 10,12-octadecadienoic acid-1 by its oxidation products.

The exaltation of the new acid compares with that of 9,11-octadecadienoic acid-1, which has been recalculated from data listed in the literature.

Properties of the acid and some of its derivatives are given.

Since other oils containing linoleic acid do not yield the new solid isomer upon identical treatment, it is concluded that it is formed from a stereoisomer of 9,12-linoleic acid in dehydrated castor oil which is not identical with ordinary linoleic acid.

HARRISON, N. J. RECEIVED FEBRUARY 5, 1942

(18) Armstrong and Hilditch, *J. Soc. Chim. Ind.*, **44**, 43T (1925)

[CONTRIBUTION FROM THE CHARLES EDWARD COATES LABORATORY OF CHEMISTRY AT LOUISIANA STATE UNIVERSITY]

Furfuryl Formate

BY W. R. EDWARDS, JR., AND LESLIE H. REEVES[1]

Furfuryl formate does not appear to have been prepared previously. Tobie[2] attempted this by mixing furfuryl alcohol with formic acid, whereupon the mixture became hot and a violent explosion resulted. The present authors succeeded in preparing it by employing the reaction of furfuryl alcohol with acetyl formate[3] at a moderate temperature: after unsuccessful attempts (1) by treatment of furfuryl alcohol with formic acid at temperatures from 0 to 25°, (2) by refluxing these materials in low-boiling organic solvents, (3) by treatment of furfuryl chloride with sodium formate, (4) by alcoholysis, using *n*-heptyl formate and furfuryl alcohol, distilling slowly at atmospheric pressure, and (5) by treatment of furfuryl alcohol with formamide at 100 to 120°.

Preparation of Acetyl Formate.—Following Béhal,[4] three moles of formic acid and four moles of acetic anhydride were mixed and heated at 50° for one hour. Because of the difficulty of protecting a vacuum pump from the quantity of corrosive fumes evolved, Béhal's method of separation of the product was modified conveniently by employing an aspirator, distilling at 45 mm., and collecting distillates at 43–46° and 42–43.5°, respectively, before and after washing with petroleum ether.

Furfuryl Formate.—To a mixture of 2.5 moles of furfuryl alcohol[5] and 0.75 mole of sodium formate in a flask with a mercury-seal stirrer, 3.4 moles of acetyl formate was added dropwise. The flask was cooled with tap water during the addition, and then immersed in a water-bath at 60° for five hours. Stirring was continuous during addition and subsequent heating. The resultant mixture was separated by addition of water, in which the ester was nearly insoluble. The ester layer was withdrawn, shaken with saturated aqueous sodium bicarbonate, separated again, and dried over anhydrous sodium sulfate. It was then distilled four times at 16 mm., using a 45-cm. Widmer column; yield 138 g. (44%) of an almost constant-boiling product.

With another batch, a second water washing was employed after the first distillation; only one additional distillation was then required. The product appeared to be equal in quality to the first batch, but the yield was lower.

Anal. Calcd. for $C_6H_6O_3$: C, 57.12; H, 4.80; mol. wt., 126.0. Found: C, 57.41; H, 5.07; mol. wt. (Cottrell), 127.4.

Saponification of the ester with aqueous sodium hydroxide yielded furfuryl alcohol (identified by the melting point of its α-naphthyl urethan) and the salt of formic acid (identified by Duclaux constant determinations).

The high carbon content, and the fact that the boiling point was higher than might have been predicted from a study of the data on other furfuryl esters, suggest some contamination of the product by furfuryl alcohol, a difficult substance to eliminate completely. It may be observed, however, that Zanetti[6] has suggested that the accepted boiling point of furfuryl acetate may be several degrees too low. If this is true, the boiling point of the formate occupies a more nearly regular position in the series.

Furfuryl formate is a colorless liquid with a pleasant odor; b. p. 66.2–66.5° (16 mm.), 166.3° (with some coloration) (760 mm.); d^{25}_4 1.1584; d^0_4 1.1830; $n^{25}D$ 1.4662. The sample obtained as described did not crystallize at −68°. Sealed in a glass tube, it turned faintly yellow on standing two months; exposed to air, it darkened rapidly. One hundred grams of water at 25° dissolved 1.31 g. of the ester. It was infinitely soluble in ether, benzene and ethanol. It dissolved 34% of its own weight of nitrocellulose (viscosity, 1/2 second), forming a viscous, greenish paste; and 25% of its own weight of cellulose acetate (Celanese satin), forming a viscous, transparent, colorless paste.

Attempted Oxidation.—The oxidation of furfuryl formate should be of interest, since the formyl group might be expected to undergo elimination during the process, simultaneously influencing the nature of the reaction of the remainder of the molecule. In an initial attempt to investigate this, furfuryl formate (0.45 mole) was added dropwise to 1.35 moles of hydrogen peroxide (30% aqueous solution) containing a trace of ferrous sulfate. The mixture was stirred vigorously for one hour at room temperature, and then for two hours at 50°; at the end of this time, no odor of the ester could be detected. Formic acid (36% of the theoretical) and furfural (18% of the theoretical) were identified among the diverse products of the reaction; identification of other products was incomplete.

Preparation and Properties of a Resin.—Recent work[7] on the use of synthetic resins for the removal of chlorides and sulfates from aqueous solutions included the observation that several resins prepared from either furfural or furfuryl alcohol, usually by condensation with a diamine, possessed widely varying efficiencies. The present authors prepared, washed, dried and sub-divided a resin by an essentially similar procedure, using furfuryl formate, *m*-phenylenediamine, and hydrochloric acid. The initial reaction was vigorous but not violent. The resultant resin was black and very hard. One gram of it was shaken for three hours at 31° with 250 cc. of water containing 500 p. p. m. of sulfuric acid. There was no decrease in the sulfate ion concentration of the solution.

(1) From a thesis submitted by Leslie H. Reeves in partial fulfillment of the requirements for the degree of Master of Science.

(2) Tobie, *Ind. Eng. Chem., News Ed.*, **19**, 72 (1940).

(3) The mixed anhydride of formic and acetic acids.

(4) Béhal, *Compt. rend.*, **128**, 1460 (1899).

(5) The authors wish to thank Dr. F. N. Peters and the Quaker Oats Company for a gift of the furfuryl alcohol used in these experiments.

(6) Zanetti, THIS JOURNAL, **47**, 535 (1925).

(7) Schwartz, Edwards and Boudreaux, *Ind. Eng. Chem.*, **32**, 1462 (1940).

Growth-promoting Action.—Initial tests by Dr. C. F. Moreland on tomato leaves showed furfuryl formate to be ineffective in giving an epinastic response. On this tentative basis, it appears probable that the formate does not possess the growth-promoting power which Traub[8] reported as a conspicuous characteristic of furfuryl acetate and a number of other furan derivatives.

Attempted Preparation of Furfuryl Oxalate.—(1) Oxalic acid and furfuryl alcohol were mixed, ether was added, and the mixture was refluxed with stirring for eight hours; there was no reaction. (2) Furfuryl acetate (0.75 mole) and oxalic acid (0.67 mole) were heated together at 70°, with stirring, for five hours; there was no apparent reaction. The temperature was then raised. At about 85–90° there was an explosion which scattered a black tarry material over a circle of ten feet radius.

(8) Traub, *Proc. Am. Soc. Hort. Sci.*, **35**, 438 (1937).

Summary

Furfuryl formate has been prepared in fair yield by the reaction between furfuryl alcohol and acetyl formate at 60°. Its properties have been ascertained and some of its reactions have received preliminary study. Attempts to prepare furfuryl oxalate were unsuccessful.

BATON ROUGE, LOUISIANA RECEIVED MARCH 16, 1942

[CONTRIBUTION NO. 71 FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF UTAH]

Organoboron–Nitrogen Compounds. II. The Reaction of Boron Chloride with *p*-Toluidine

BY CORLISS R. KINNEY AND MARTIN J. KOLBEZEN

In an earlier paper the results of a study of the salt of aniline and boron chloride ($C_6H_5NH_2BCl_3$) were described[1] which indicated that several types of organoboron–nitrogen compounds could be made from such salts or addition compounds by the elimination of the halogen acid. In order to determine the extensiveness of these reactions the behavior of *p*-toluidine and boron chloride was studied and is described in the experimental part.

Experimental Part

The Salt of *p*-Toluidine and Boron Chloride, $CH_3C_6H_4NH_2BCl_3$.—A 500-ml. two-necked flask equipped with a mercury-sealed stirrer and a dropping funnel was used. Into the flask, 114 g. of sodium dried benzene was introduced and 13.9 g. (0.118 mole) of boron chloride was distilled into the benzene. The flask was cooled with snow and 9.7 g. (0.0906 mole) of *p*-toluidine dissolved in 127 g. of dry benzene was dropped in slowly and with stirring. With the dilute solutions used the precipitate redissolved immediately but, toward the end, 180 g. more benzene was added and the cooling bath removed in order that the product be kept in solution. When more concentrated solutions were used, the addition compound separated as a white powder which could not be purified readily.

When all of the *p*-toluidine had been added, the stirrer and dropping funnel were removed and the clear solution vacuum distilled. The pressure was about 370 mm. A fine stream of dry carbon dioxide was admitted to minimize bumping. When about one-half of the benzene had been removed, the distillation was stopped and the crystals which had formed filtered out. The filtrate was concentrated to about 50 ml. and a second crop of crystals obtained. The product weighed 19.4 g., a yield of 95.4%. Considering the material left in the 50 ml. of mother liquor, the reaction must proceed quantitatively.

The product was decomposed rapidly by the moisture in the air. Filtrations were made using a Büchner funnel into which was fitted a rubber stopper carrying a tube connected with a source of dry air. The melting point was 159–160° with evolution of hydrogen chloride. Also, when dissolved in dry boiling benzene, hydrogen chloride was evolved and the product obtained on cooling had a melting point of 147–149°. The salt is quite insoluble in cold benzene or other anhydrous solvent and further attempts at recrystallization were unsuccessful. The solubility was determined to be 0.896 g. per 100 ml. of dry benzene at 27°.

Anal.[1] Calcd. for $CH_3C_6H_4NH_2BCl_3$: B, 4.83; Cl, 47.48. Found: B, 4.87, 4.81, 4.83; Cl, 47.32, 47.32, 47.14.

On heating the salt to its melting point or in boiling benzene, hydrogen chloride was evolved with no evidence of boron chloride. The number of equivalents of hydrogen chloride was determined by heating 0.0059 mole with boiling benzene. A current of dry carbon dioxide was used to remove the hydrogen chloride which on titration required 0.0124 equivalent of base. The chloride ion was determined gravimetrically and 0.0120 mole was found, which demonstrated that the acid was entirely hydrogen chloride within a small error because, if boron trichloride had been liberated, three equivalents of hydrogen chloride and one of boric acid would have been produced. Similar quantitative results were obtained when the salt was heated dry.

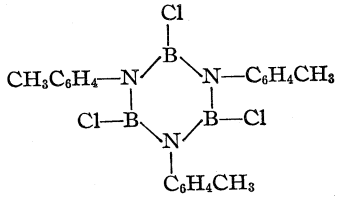
Tri-*p*-tolyltrichlorotriboron–nitride $(CH_3C_6H_4NBCl)_3$.—The clear colorless benzene solution obtained by refluxing the addition compound until no more hydrogen chloride was evolved was concentrated and allowed to cool. From the solution a colorless compound slowly crystallized,

(1) Jones and Kinney, THIS JOURNAL, **61**, 1378 (1939).

usually taking two or three days for complete crystallization. The crystals were proved to contain benzene of crystallization by removing the benzene and making the dinitro derivative. On standing in air the crystals became opaque and eventually fell to a powder. The melting point was 308–309° with slight softening at 304°. The substance darkened on melting and if heated for some time turned black, indicating extensive decomposition.

Anal. Calcd. for $(CH_3C_6H_4NBCl)_3 \cdot C_6H_6$: B, 6.10; Cl, 20.00; C_6H_6, 14.66; mol. wt., 532. Found: B, 6.15, 6.02, 6.10; Cl, 20.09, 19.81, 20.07; C_6H_6, 15.55; mol. wt. in freezing benzene, 505–492, 526–556, 512–524.

This is clearly the benzene addition product of the trimer which may be assigned the cyclic structure



The compound decomposes slowly in air giving off hydrogen chloride fumes, but appears to be quite stable when kept under dry benzene. It is quite insoluble in cold anhydrous solvents such as benzene, carbon tetrachloride, ethyl acetate or ether. It reacts slowly with cold water and rapidly with hot forming *p*-toluidine hydrochloride and presumably boric acid. With 95% alcohol or moist ether the compound dissolves rapidly and heat is liberated. In an attempt to hydrolyze the compound to a trihydroxy derivative corresponding to that obtained with the phenyl homolog,[1] a dry benzene solution was mixed with moist benzene. However, only *p*-toluidine hydrochloride and boric acid could be isolated.

Boric Tri-*p*-toluidide $(CH_3C_6H_4NH)_3B$.—To 8.9 g. of boron chloride dissolved in 85 g. of dry benzene and cooled in a freezing mixture, 41.7 g. of *p*-toluidine dissolved in 83 g. of benzene was added slowly while the mixture was stirred constantly. The amount of toluidine was 2.5 g. less than the calculated to account for the loss of boron chloride in the early stages of the reaction. When the addition was complete, the cooling bath was replaced by an oil-bath and the reaction mixture refluxed with constant stirring for three hours. The temperature of the oil-bath was 110°.

The mixture was filtered hot using suction. The precipitate of toluidine hydrochloride was returned to the reaction flask and extracted with 200 ml. of boiling benzene for ten minutes. The benzene was filtered and combined with the first filtrate. The residue gave no test for boron, but did give tests for nitrogen and chlorine. The melting point was 240.5° and was not lowered by admixture with *p*-toluidine hydrochloride (m. p. 241°).

The combined filtrates were distilled to a volume of 40 ml. On cooling fine colorless needles formed which were filtered, washed with dry benzene, and dried in a current of dry air; the yield was 35%. More of the product was obtained from the mother liquor, but this was impure and was not easily purified.

The substance was recrystallized readily from dry benzene, crystallization occurring suddenly. The melting point was 165–166°. On cooling and remelting, the melting point was not lowered, indicating that no decomposition had occurred.

Anal. Calcd. for $(CH_3C_6H_4NH)_3B$: B, 3.29. Found: B, 3.28, 3.29.

The compound was hydrolyzed easily and was not stable in air. Even in a desiccator over calcium chloride, the odor of toluidine soon became apparent. However, the compound could be kept apparently indefinitely when covered with dry benzene.

The compound reacted readily with dry hydrogen chloride in a benzene solution, forming a solid product. No boron chloride or other boron compound was carried out in sufficient quantities to give the characteristic green flame of boron when ignited. The solid product, in part, reacted violently with water and part dissolved more slowly. No method was found for purifying the product. However, when it was heated with boiling benzene, hydrogen chloride was evolved, the boron containing material passed into solution, and the solid remaining was identified as *p*-toluidine hydrochloride melting at 241°. From the benzene extract, the trimer, tri-*p*-tolyltrichlorotriboron-nitride, was obtained. All of these observations indicate that the product was a mixture of the addition compound, $CH_3C_6H_4NH_2BCl_3$, and *p*-toluidine hydrochloride.

Summary

The reactions of *p*-toluidine with boron trichloride have been investigated. The addition salt $CH_3C_6H_4NH_2BCl_3$ was prepared. Upon heating it evolved hydrogen chloride and formed a trimer which was named tri-*p*-tolyltrichlorotriboron-nitride and was assigned a cyclic structure. By heating the salt with an excess of *p*-toluidine, boric tri-*p*-toluidide $(CH_3C_6H_4NH)_3B$ was obtained. By treating boric tri-*p*-toluidide with excess dry hydrogen chloride the reaction was reversed.

SALT LAKE CITY, UTAH RECEIVED FEBRUARY 24, 1942

[CONTRIBUTION FROM THE INSTITUTE OF EXPERIMENTAL BIOLOGY, UNIVERSITY OF CALIFORNIA]

Electrophoresis of Crotoxin*

BY CHOH HAO LI AND H. FRAENKEL-CONRAT

The crystalline protein (crotoxin), isolated by Slotta and Fraenkel-Conrat[1] from rattlesnake venom, has been shown to behave as a homogeneous substance in ultracentrifuge and diffusion studies.[2] The electrophoretic behavior of this beautifully crystalline substance will now be reported.

Experimental

Approximately 150 mg. of crystalline crotoxin was prepared from the crude venom[2a] and crystallized twice according to the method described previously.[1] The electrophoretic experiments were carried out in the Tiselius apparatus[3] at 1.5°.

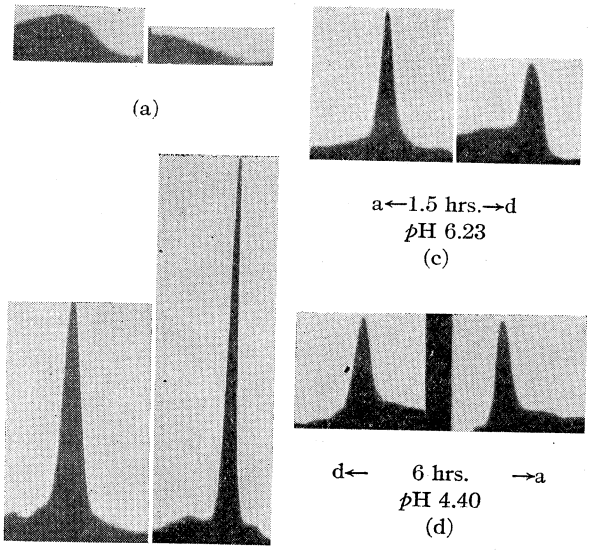


Fig. 1.—Electrophoretic patterns of crotoxin solutions in buffers of different *p*H and ionic strength 0.10 at 1.5° after the current has been put on for 2.0, 1.5 or 6 hours: (a) is the base line for the electrophoretic patterns.

The electrophoretic patterns were recorded by the method described by Longsworth.[4] Buffers were prepared according to Clark[5] and brought to ionic strength 0.10 by the addition of sodium chloride. The *p*H of the solution was obtained with the aid of a glass electrode–vacuum tube assembly at room temperature. No corrections were made for 1.5°. The conductance was measured with the usual Wheatstone bridge type of circuit and a Washburn conductivity cell at 1.5°. The mobility was calculated from the descending boundary as recommended by Longsworth and MacInnes[6] and was determined in the manner described in a previous paper.[7]

Results

The first experiment was conducted in a phosphate buffer of *p*H 7.20 with 1.0% crotoxin solution. The boundaries appeared very sharp and there was no indication of the appearance of other components after the current had been on for two hours in a field gradient of 6.40 volts per cm. (see Fig. 1b). Studies in solutions of other *p*H also indicate that the crystalline crotoxin is an electrophoretically homogeneous protein. Fig. 1[8] presents a few typical patterns obtained in *p*H 7.20, 7.00, 6.23 and 4.40 buffer solutions. Each experiment was made in a field gradient approximately 6 volts per cm.

It is to be noted that here, as in the case of other proteins, the ascending boundary is always sharper than the descending one. This anomaly is currently attributed to variations of the electric field strength in the boundary.[9] When the current is reversed and the descending boundary becomes a rising one, this boundary should gradually become sharper. This is the case for the crotoxin solutions. Figure 2A shows a series of photographs taken after electrolysis for one and two hours at 6.26 volts per cm. with a 0.5% crotoxin solution

* Aided by grants from the Board of Research of the University of California, the Rockefeller Foundation and Parke, Davis and Company.

(1) Slotta and Fraenkel-Conrat, *Ber.*, **71**, 1076 (1938); *Nature*, **142**, 213 (1938).

(2) Gralen and Svedberg, *Biochem. J.*, **32**, 1375 (1938).

(2a) We are greatly indebted to Professor K. H. Slotta for his interest in this investigation as well as for his coöperation in drying and preserving the crude rattlesnake venom kindly put at our disposal by Dr. Cavalcanti of the Instituto Butantan, São Paulo. Our thanks are also due to Professor H. M. Evans for enabling us to undertake this investigation.

(3) Tiselius, *Trans. Faraday Soc.*, **33**, 524 (1937).

(4) Longsworth, THIS JOURNAL, **61**, 529 (1939).

(5) Clark, "The Determination of Hydrogen Ions," Williams and Wilkins Co., Baltimore, Md., 1922.

(6) Longsworth and MacInnes, THIS JOURNAL, **62**, 705 (1940).

(7) Li, Lyons and Evans, *J. Gen. Physiol.*, **23**, 433 (1940).

(8) It may be noted that the base lines of these patterns are very irregular. This is generally the case using a poor Schlieren lens. For the interpretation of these patterns, the distorted base line is given in Fig. 1.

(9) Longsworth and MacInnes, THIS JOURNAL, **62**, 705 (1940).

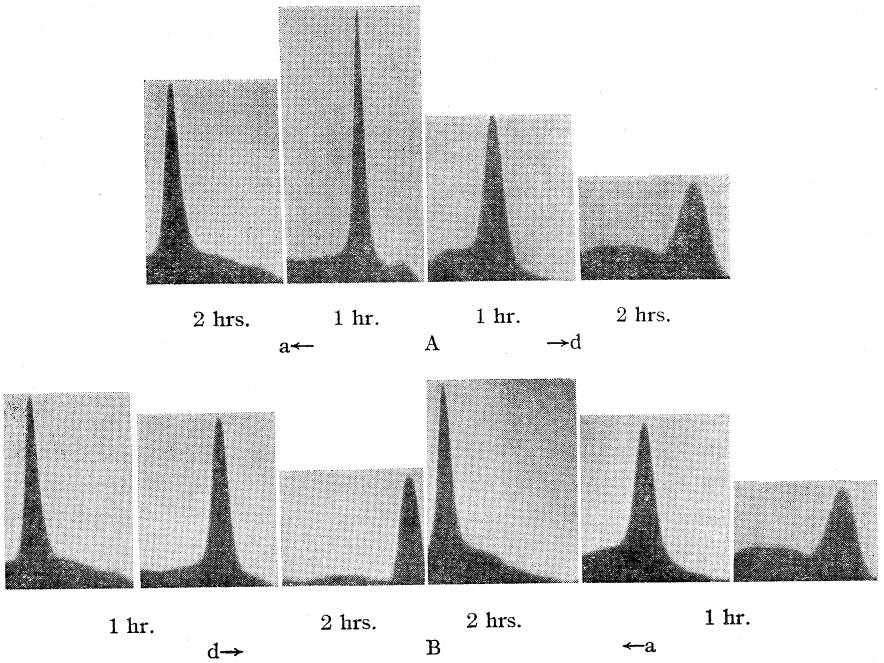


Fig. 2.—Electrophoretic patterns of a crotoxin solution illustrating no "reversible boundary spreading" phenomena in *p*H 7.00 phosphate buffer of ionic strength 0.10 at 1.5°.

in a *p*H 7.00 phosphate buffer of ionic strength 0.10. After the current was reversed, the descending pattern became much sharper while the rising one showed spreading as indicated in Fig. 2B. These observations are particularly interesting, for certain proteins always give rise to a phenomenon of "reversible boundary spreading" which, as first discovered by Tiselius and Horsfall,[10] indicates that "an initial sharp boundary will become diffuse as the electrolysis proceeds but if the direction of the amount is reversed will progressively recover most of its initial sharpness."[11] Some authors[11] believe that this phenomenon is due to the inhomogeneity of the protein and others[12] express the view that it is a property of pure proteins. Here, we have a case which does not show the phenomenon of "reversible boundary spreading" as illustrated in Fig. 2, nor was it observed in any other experiment with crotoxin.

Table I summarizes the mobility determinations in different *p*H solutions of ionic strength 0.10. A plot of *p*H against mobility is found in Fig. 3. The isoelectric point is located from the straight line which is drawn through the points made in acetate buffers of *p*H 3.91, 4.23, 4.40 and 4.90. This seems to be justified, for phosphate ions have been shown[13] to alter the electrophoretic mobility of a protein as compared with that made in a monovalent salt buffer. Thus, the isoelectric point of crotoxin is found to be 4.71 and the $d\mu/dpH_0$ value is 4.65×10^{-5} in a solution of ionic strength 0.10.

TABLE I

ELECTROPHORETIC MOBILITY OF CROTOXIN IN DIFFERENT *p*H OF IONIC STRENGTH 0.10 AT 1.5°

*p*H	Buffer salt	Protein concn.	μ_d (10^5)
7.20	Phosphate	1.0	−4.97
7.00	Phosphate	0.4	−4.51
6.23	Phosphate	.5	−2.80
4.90	Acetate	.3	−0.57
4.40	Acetate	.4	+1.19
4.23	Acetate	.3	+2.28
3.91	Acetate	.5	+3.71

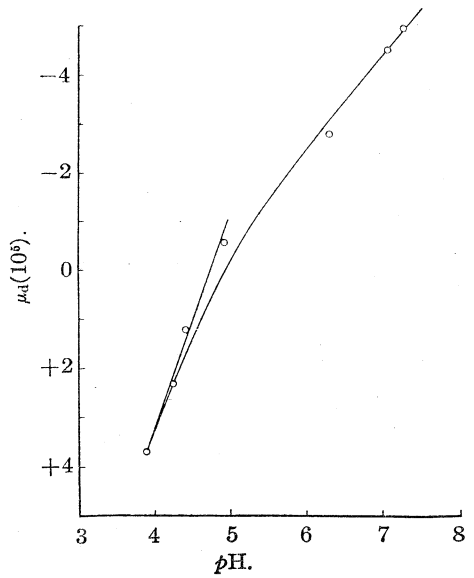


Fig. 3.—The electrophoretic mobility of crotoxin as a function of the *p*H.

(10) Tiselius and Horsfall, *Ark. Kemi. Mineral Geol.*, **13A**, No. 18 (1939).

(11) Longsworth, Cannan and MacInnes, THIS JOURNAL, **62**, 2586 (1940).

(12) Shedlovsky, *et al.*, *Science*, **92**, 198 (1940).

(13) Longsworth, *Ann. N. Y. Acad. Sci.*, **XLI**, 267 (1941).

Summary[14]

1. Crotoxin, the crystalline neurotoxin isolated from rattlesnake venom, has been shown to be a homogeneous substance in electrophoresis experiments.

2. Crotoxin solutions do not exhibit the phenomenon of "reversible boundary spreading" to a detectable extent, in contradistinction to all other proteins studied.

3. The isoelectric point of crotoxin has been determined and the $d\mu/dpH_0$ value.

(14) The authors are indebted to Dr. L. G. Longsworth for his suggestions during the preparation of the manuscript.

BERKELEY, CALIFORNIA RECEIVED JANUARY 19, 1942

[CONTRIBUTION FROM THE WESTINGHOUSE RESEARCH LABORATORIES]

Ionization and Dissociation by Electron Impact: Normal Butane, Isobutane, and Ethane

BY D. P. STEVENSON[1] AND J. A. HIPPLE, JR.

Introduction

Mass spectrometer studies of the dissociation products resulting from electron bombardment of gases at low pressures have provided many interesting and instructive results. In particular, the work on the lower hydrocarbons, methane,[2] ethane,[3] ethylene,[4,5] propane,[6] propylene[6] and allene[6] has yielded considerable data on energies and unimolecular reactions of the ions CH_4^+, $C_2H_6^+$, etc., not obtainable in any other way. It was felt that the extension of such studies to one of the simplest isomeric pairs, *n*- and *i*-butane, would be helpful in deciding or at least defining questions of interpretation raised by the work on the simpler molecules. Furthermore, the continually growing interest in the application of the mass spectrometer to problems in the analysis of hydrocarbon mixtures makes necessary a knowledge of the complete mass spectra, so that the limitations of this analytical tool can be discussed. With this latter point in mind we have extended the results of the previously published investigation of ethane.[3]

Experimental

Inasmuch as the apparatus is to be described in detail by one of the authors (J. A. H.) in a separate publication, we will give but a cursory discussion of the pertinent details here.

The 180° tube (~16 cm. radius) and accessories are supported within a water-cooled spherical solenoid. The strength of the magnetic field used throughout this investigation was ~1000 Oersteds, corresponding to 130 volts accelerating potential to bring $m/e = 100$ into focus. The positive ion accelerating voltage is supplied by a 1200 volt electronic power source. The electrons are obtained from an oxide coated platinum cathode, their accelerating potential being controlled by means of a wire wound drum potentiometer. An electrometer tube amplifier and sensitive galvanometer are used to measure the positive ion current. The resolving power of the tube with the wide slits used is 1:150 as indicated by the extent to which the mercury isotopes are resolved.

The gases are admitted to the ionization chamber through a glass capillary leak. A separate pumping lead to the arm of the tube containing the cathode chamber assures the complete removal of any pyrolysis products formed on the filament.

The samples of the two butanes were obtained from the Gulf Research Laboratories, while the ethane was taken from a sample given to us by the Standard Oil Co. of Indiana.

Preliminary examinations of the mass spectra of the butanes were made using an automatic recorder. The peaks corresponding to the various masses were all quite symmetrical, and were spaced in exact accord with the inverse relationship between m/e and accelerating voltage. No satellites or shoulders were observed for any of the masses. The measurements reported in this paper were all manually recorded. The symmetry of the peaks indicated that the current at the top of the maxima could be taken as a measure of the total current due to the corresponding ion. The linear variations of the positive ion current with the density of the electron beam and with the pressure in the ionization chamber indicate that only the products of primary reactions were observed. The total electron emission from the cathode ran from 5 to 15 μ amp., while the intensity of the bombarding beams lay between 0.1 and 3 μ amp.

Results

The results of this investigation may be divided, for convenience, into two parts: (A) the variation of the mass spectra of the molecules with the electron energy, V^-, for V^- large with respect to the critical potentials; and (B) the determination

(1) Westinghouse Research Fellow.
(2) L. G. Smith, *Phys. Rev.*, **51**, 263 (1937).
(3) J. A. Hipple, *ibid.*, **53**, 530 (1938).
(4) P. Kusch, A. Hustrulid and J. T. Tate, *ibid.*, **52**, 843 (1937).
(5) J. Delfosse and J. A. Hipple, *ibid.*, **54**, 1060 (1938).
(6) J. Delfosse and W. Bleakney, *ibid.*, **56**, 256 (1939).

of the critical potentials for the more abundant ions in the mass spectra.

A. The relative abundances of some of the principal ions in the spectrum of ethane are given for round values of V^- in Table I. The dots in this and subsequent tables indicate no measurements were made. The data of Hipple[3] for 100 volt electrons are included for comparison. Since the earlier work was carried out with a tube whose focusing properties are independent of the initial velocity of the ions[7] in contrast to our tube in which the initial velocities of the ions enter into the focusing, the agreement is very satisfactory.

Tables II and III summarize the behavior of the spectra of the butanes. No corrections were made for the presence of C^{13} in its natural abundance, 1.1%. Thus the spectra as given correspond to the mass numbers (m/e), rather than to the formulas. Since the correction is small and the relative currents due to the masses are of analytical interest, the uncorrected values have been tabulated.

Careful comparison of the ratios of the currents due to masses 44 and 43 and masses 30 and 29 showed that the butane samples were free of propane and ethane. The exact correspondence of the ratio 44/43 to that calculated for

$$\left(\frac{C^{13}C_2^{12}H_7^+}{C_3^{12}H_7^+}\right) \text{ and of } \frac{30}{29} \text{ to } \left(\frac{C^{13}C^{12}H_5^+}{C_2^{12}H_5^+}\right)$$

TABLE I

MASS SPECTRUM OF ETHANE

m/e = V^-, e. v.	30 $C_2H_6^+$	29 $C_2H_5^+$	28 $C_2H_4^+$	27 $C_2H_3^+$	26 $C_2H_2^+$	25 C_2H^+	15 CH_3^+
30	100	72	347	70	29.5	..	7.3
60	132	101	462	147	99	..	11.8
100	135	106	488	153	101	16	15.5
100[a]	(135)[b]	103	486	142	84	16	12
175	126	99	452	140	88	..	12.5

[a] Ref. 3 of the text. [b] This value assumed to fit our scale.

TABLE II

MASS SPECTRUM OF *n*-BUTANE

m/e = V^-	58 $C_4H_{10}^+$	57 $C_4H_9^+$	56 $C_4H_8^+$	55 $C_4H_7^+$	54 $C_4H_6^+$	53 $C_4H_5^+$	52 $C_4H_4^+$	51 $C_4H_3^+$	50 $C_4H_2^+$	49 C_4H^+	48 C_4^+
30	100	13.5	3.4	3.5	...	...	...	...	...	...	...
50	119	15.3	4.4	5.6	1.1	4.2	1.2	3.9	3.3	0.4	<0.1
100	125	16.0	4.4	5.6	1.1	4.1	1.4	5.3	7.3	2.5	...

m/e = V^-	43 $C_3H_7^+$	42 $C_3H_6^+$	41 $C_3H_5^+$	40 $C_3H_4^+$	39 $C_3H_3^+$	38 $C_3H_2^+$	37 C_3H^+	36 C_3^+
30	462	68	105	...	12.1	...	...	...
50	530	79	140	7.3	52	5.7	2.0	<0.1
75	555	82	149	...	53	7.4	3.9	0.4
100	580	83	153	7.9	52	8.1	4.6	0.7

m/e = V^-	29 $C_2H_5^+$	28 $C_2H_4^+$	27.5 $C_4H_7^{++}$	27 $C_2H_3^+$	26.5 $C_4H_5^{++}$	26 $C_2H_2^+$	25.5 $C_4H_3^{++}$	25 C_2H^+	15 CH_3^+
30	162	125	..	71	..	..	...	...	1.2
50	222	164	..	172	..	..	...	...	12.8
70	236	...	0.15	...	0.27	27	1.9	1.7	..
100	240	179	..	184	..	31	...	...	..

TABLE III

MASS SPECTRUM OF *i*-BUTANE

m/e = V^-	58 $C_4H_{10}^+$	57 $C_4H_9^+$	56 $C_4H_8^+$	55 $C_4H_7^+$	54 $C_4H_6^+$	53 $C_4H_5^+$	52 $C_4H_4^+$	51 $C_4H_3^+$	50 $C_4H_2^+$	49 C_4H^+	48 C_4^+
30	100	32	...	...	...	...	...	...	...	...	..
50	117	37	7.5	6.8	1.4	6.4	1.5	5.9	4.9	0.7	0.15
100	123	39	7.7	6.9	0.9	5.5	1.5	7.6	9.7	3.2	0.79

m/e = V^-	43 $C_3H_7^+$	42 $C_3H_6^+$	41 $C_3H_5^+$	40 $C_3H_4^+$	39 $C_3H_3^+$	38 $C_3H_2^+$	37 C_3H^+	36 C_3^+
30	877	292	248	..	29	..	..	..
50	1020	344	352	18.7	120	13.7	4.8	0.26
75	1070	354	370	19.2	128	16.7	10.1	0.74
100	1070	361	377	18.6	120	20.2	11.4	1.30

m/e = V^-	29 $C_2H_5^+$	28 $C_2H_4^+$	27 $C_3H_3^+$	26 $C_2H_2^+$	25.5 $C_4H_3^{++}$	25 C_2H^+	15 CH_3^+
30	128	80	126	..	...	...	2.0
50	188	112	279	21	...	...	29
100	196	122	296	32	2.8	2.7	37

(7) W. Bleakney and J. A. Hipple, *Phys. Rev.*, **53**, 521 (1938).

indicated that neither of the butanes gives the ions $C_3H_8^+$ or $C_2H_6^+$. This point will be returned to later.

The currents of masses 29^+ and 28^+ could conceivably be due in part to $C_4H_{10}^{++}$ and $C_4H_8^{++}$. We searched very carefully, but were unable to find currents due to masses 29.5 or 28.5 ($C^{13}C_3^{12}H_{10}^{++}$ or $C^{13}C_3^{12}H_8^{++}$), hence concluded that the ions $C_4H_{10}^{++}$, $C_4H_9^{++}$ and $C_4H_8^{++}$ are absent from the butane spectra.

B. The method used to derive the critical or appearance potential, $A(X^+)$, from the initial portions of the ionization efficiency curves has been discussed by Smith[2] (see below). Argon was used to correct the voltage scale for the contact potential of the cathode. Its ionization potential, $I^Z(A) = 15.69$ e. v. was taken from the tables of Bacher and Goudsmit.[8]

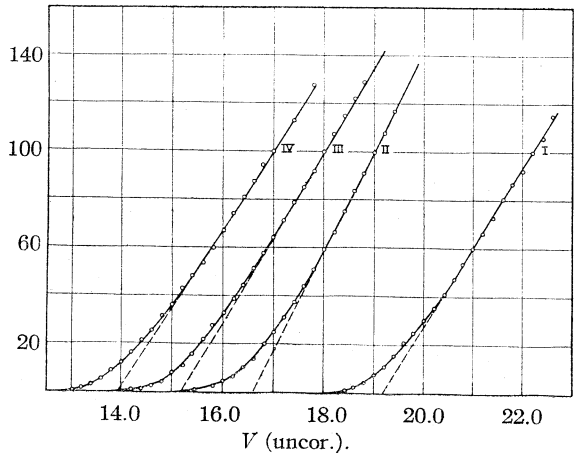


Fig. 1.—Ionization efficiency curves for the processes I, $A \rightarrow A^+$; II, $C_2H_6 \rightarrow C_2H_5^+$; III, $C_2H_6 \rightarrow C_2H_6^+$ and IV, i-$C_4H_{10} \rightarrow C_4H_{10}^+$. Vertical scale is arbitrary and different for each curve.

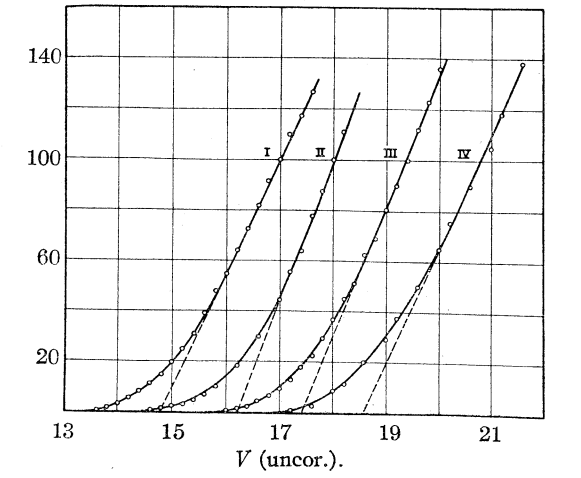


Fig. 2.—Ionization efficiency curves for the processes I, i-$C_4H_{10} \rightarrow C_3H_7^+$; II, n-$C_4H_{10} \rightarrow C_2H_5^+$; III, i-$C_4H_{10} \rightarrow C_3H_5^+$ and IV, n-$C_4H_{10} \rightarrow C_2H_3^+$. Vertical scale is arbitrary and different for each curve.

In Table IV the results of our investigation of ethane are compared with the earlier results of Hipple.[3] The agreement between the results given by such very different instruments is excellent.[8a]

TABLE IV

Ion	A (ion) [This Research], e. v.	A (ion) [Hipple[3]], e. v.
$C_2H_6^+$	11.59 ± 0.1	11.6 ± 0.1
$C_2H_5^+$	12.84 ± 0.1	12.7 ± 0.2
$C_2H_4^+$	12.09 ± 0.1	12.1 ± 0.1
$C_2H_3^+$	15.1 ± 0.2	15.2 ± 0.3

The appearance potentials of those ions in the spectra of the butanes, which were investigated, are given in Table V. Typical examples of the ionization efficiency curves from which the appearance potentials were determined are given in Figs. 1 and 2.

TABLE V

APPEARANCE POTENTIALS FOR n- AND i-BUTANE (ELECTRON VOLTS)

ion = R^+	$A_6(R^+)$ n-C_4H_{10}	$A_6(R^+)$ i-C_4H_{10}	Probable process
$C_4H_{10}^+$	10.34 ± 0.1	10.34 ± 0.1	$C_4H_{10}^+ + \epsilon^-$
$C_4H_9^+$	12.0 ± 0.3	11.5 ± 0.3	$^z C_4H_9^+ + H + \epsilon^-$
$C_3H_7^+$	11.14 ± 0.1	10.94 ± 0.1	$C_3H_7^+ + CH_3 + \epsilon^-$
$C_3H_6^+$	10.94 ± 0.1	10.74 ± 0.1	$^z C_3H_6 + CH_4 + \epsilon^-$
$C_3H_5^+$	13.09 ± 0.1	13.54 ± 0.1	$^z C_3H_5^+ +$ { $CH_4 + H$ / $CH_3 + H_2 + \epsilon^-$
$C_2H_5^+$	12.04 ± 0.1	12.7 ± 0.2	$C_2H_5^+ + C_2H_5 + \epsilon^-$
$C_2H_4^+$	11.49 ± 0.1	12.0 ± 0.2	$^z C_2H_4^+ + C_2H_6 + \epsilon^-$
$C_2H_3^+$	14.1 ± 0.3	14.6 ± 0.3	$^z C_2H_3^+ + ? + \epsilon^-$
CH_3^+	>20	20 ± 2	$CH_3^+ + C_3H_7^+ + 2\epsilon^-$

[z] Ambiguity with respect to the structure of the positive ion; see text.

The method employed in determining the critical potentials given in Tables IV and V is not completely satisfactory. Considerable personal factors may be involved in the choice of the initial break (V_B^-) of the ionization efficiency curve, $I^+(V^-)$. Furthermore, greatest weight is given to measurements of least accuracy, that is, those near the appearance potential. For these reasons

(8) R. F. Bacher and S. Goudsmit, "Atomic Energy States," McGraw-Hill Book Co., New York, N. Y., 1932.

(8a) The reason that our value of $A(C_2H_5^+)$ is higher than Hipple's lies in the fact that we corrected our ionization efficiency curve for mass 29 for the contribution by the ion $C^{13}C^{12}H_4^+$. This correction was suggested by Dr. O. Beeck and Mr. Eltenton of the Shell Development Co. in a letter to one of the authors. The value of $A(29^+)$ derived from the uncorrected ionization efficiency curve is in exact agreement with Hipple's value. It may be noted that the correction is entirely insignificant for similar processes in the butanes.

we examined the curves, $I^+(V^-)$, for various processes in ethane, the butanes, argon and neon very carefully in the hope that some other characteristic, subject to a more objective determination, could be used in estimating the appearance potentials.

The observation that all the ionization efficiency curves, $I^+(V^-)$, are linear over the range $\sim 7\%$ to $\sim 65\%$ of their maximum values, suggested that the intercept of the extrapolated linear portion with the V^- axis ($I^+ = 0$), V_L^-, might be used in making estimates of the appearance potentials. It was found that for the process, $R \rightarrow R^+ + \epsilon^-$, in eight atoms or molecules[9] $V_L^- - V_B^- = 1.06_5$ volts. The mean deviation was $\pm$ 0.06 volt and the maximum deviation was 0.12 volt from the average, which are well within the uncertainty of the individual measurements. Thus the linear intercepts, V_L^-, can be used in place of the initial breaks, V_B^-, in determining the appearance potentials of the parent ions.

For more complex processes, such as those involving the rupture of a C–C or a C–H bond, the difference $V_L^- - V_B^-$ is also constant but greater than for simple ionization. Eleven reactions of the types, $R—CH_3 \rightarrow R^+ + CH_3$ or $R—H \rightarrow R^+ + H$, have $V_L^- - V_B^- = 1.54 \pm 0.09$ volts. In a recent article one of the authors[10] applied differences between the V_B^-'s for such reactions to the estimation of C–H and C–C bond strengths. The use of V_L^-'s gives the same results. If one wishes to compare the appearance potentials of the reactions $R_1—R_2 \rightarrow R_1—R_2^+ + \epsilon$ and $R_1—R_2 \rightarrow R_1^+ + R_2 + \epsilon^-$, the apparent difference given by the V_L^-'s is ~ 0.5 volt greater than that given by the V_B^-'s.

The still more complex processes, such as the formation of $C_2H_3^+$ from ethane, normal or isobutane, have $V_L^- - V_B^- = 2.3 \pm 0.2$ volts. The various phenomena discussed here are illustrated in Figs. 1 and 2.

Discussion

Ignoring the questions concerning the suitability of the method used to correct the voltage scale, we may associate the appearance potentials of the parent ions, $C_2H_6^+$, i-$C_4H_{10}^+$ and n-$C_4H_{10}^+$ with their vertical ionization potentials.[11] It has been pointed out by Mulliken[12] that the lowest ionization potential in ethane is probably that of removing an electron from the C–C bonding orbital $[\sigma + \sigma]$ and that I_{vert} $[\sigma + \sigma]$ is undoubtedly greater than $I_{adiabatic}$ $[\sigma + \sigma]$. The reason for the inequality $I_{vert} > I_{ad}$ lies in the fact that the removal of a bonding electron will cause an increase in the equilibrium separations of the atoms. In ethylene a comparison of the appearance potential of $C_2H_4^+$ (10.8 e. v.)[-1] with the spectroscopic ionization potential $I_{ad}(C_2H_4) = 10.41$ e. v.[13] suggests that in ethane the inequality is at least 0.4 e. v. Thus, one might estimate $I_{ad}(C_2H_6) \leq 11.6 - 0.4 = 11.2$ e. v. The electron removed in ionizing a butane probably comes from the same type of orbital as in ethane. Since the electron deficiency is much less in the ions $C_4H_{10}^+$ than in $C_2H_6^+$ it is likely that $I_{vert} \sim I_{ad}$, and thus from Table V, $I_{ad}(C_4H_{10}) \leq 10.34 \pm 0.1$ e. v.

If we take the strength of the first C–H bond in ethane as 4.2 e. v.[10] and the appearance potential, $A(C_2H_5^+) = 12.7$ e. v. given in Table IV as the heat of the reaction $C_2H_6 \rightarrow C_2H_5^+ + H$, we find $I_{ad}(C_2H_5) = 8.5$ e. v. If the linear intercepts discussed above were used to estimate the appearance potentials, this value would be increased by 0.5 e. v. to $I_{ad}(C_2H_5) = 9.0$ e. v. It is clear that a reliable direct measurement of $I_{ad}(C_2H_5)$ would be extremely valuable in determining the relative merits of the two possible modes of calibrating the voltage scale.

The relative reactivities of C–H bonds are in the order primary < secondary < tertiary. The lower value of $A(C_4H_9^+)$ in isobutane than in n-butane is probably due in part to this. The greater number of C–C acceptor bonds for hyper conjugation[14] in the t-$C_4H_9^+$ ion (3) than in the s-$C_4H_9^+$ ion (2) probably results in greater stability for the former. Thus one might expect $I_{ad}(t\text{-}C_4H_9) < I_{ad}(s\text{-}C_4H_9)$. If one guesses that the inequality signs in the reactivity sequence correspond to ~ 0.1 e. v.[15] and that the strength of a primary C–H bond is 4.2 e. v.,[10] we get

$$D[s\text{-}C_4H_9\text{-}H] = 4.2 - 0.1 = 4.1 \text{ e. v.}$$
$$D[t\text{-}C_4H_9\text{-}H] = 4.2 - 0.2 = 4.0 \text{ e. v.}$$

Combining these estimates with the corresponding appearance potentials from Table V, we find

(9) Neon, argon, ethane, n- and i-butane, propane, propylene and isobutene.

(10) D. P. Stevenson, *J. Chem. Phys.*, submitted for publication.

(11) By "vertical transition" we are to understand the transitions favored by the Frank–Condon principle. We will use "adiabatic" to indicate transition from $v' = 0$ to $v'' = 0$, where v is the vibrational quantum no.

(12) R. S. Mulliken, *J. Chem. Phys.*, **3**, 517 (1935).

(13) W. C. Price, *Phys. Rev.*, **47**, 444 (1935).

(14) R. S. Mulliken, C. A. Rieke and W. G. Brown, THIS JOURNAL, **63**, 41 (1941).

(15) J. O. Smith and H. S. Taylor, *J. Chem. Phys.*, **7**, 39 (1939).

$I_{ad}(s\text{-}C_4H_9) = 7.9$ e. v. and $I_{ad}(t\text{-}C_4H_9) = 7.5$ e. v. Due to the low precision of the appearance potentials of $C_4H_9^+$ from the butanes great weight cannot be given to these estimates of $I_{ad}(C_4H_9)$.

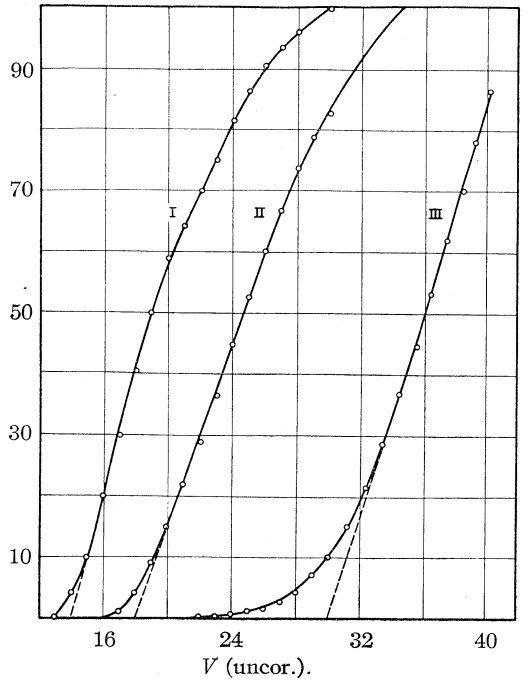


Fig. 3.—Ionization efficiency curves for I, $i\text{-}C_4H_{10} \rightarrow i\text{-}C_4H_{10}^+$; II, $i\text{-}C_4H_{10} \rightarrow C_3H_5^+$; and III, $i\text{-}C_4H_{10} \rightarrow CH_3^+$. Vertical scale is different for each curve. Maximum values are I, 121; II, 123; and III, 180. Compare with Table III.

It seems reasonable to assume that no molecular rearrangement accompanies the formation of $C_3H_7^+$ from either butane. Then, since isobutane is 0.07 e. v.[16] more stable than normal butane one concludes from the values of $A(C_3H_7^+)$ given in Table V that $s\text{-}C_3H_7^+$ is 0.3 e. v. lower in energy than $n\text{-}C_3H_7^+$. If a secondary C–H bond is 0.1 e. v. weaker than a primary C–H bond, we can write, $I_{ad}(s\text{-}C_3H_7) + 0.2$ e. v. $= I_{ad}(n\text{-}C_3H_7)$.

The high value of the appearance potential of CH_3^+ in both butanes is probably to be attributed to the simultaneous formation of $C_3H_7^+$. If the vertical ionization of C_4H_{10} to $C_4H_{10}^{++}$ results in the doubly charged ion being formed in a state above the dissociation limit this result is explained. Our failure to observe any $C^{13}C_3^{12}H_{10}^{++}$ ions is in accord with this explanation. The marked second break in $I^+(V-)$ for the CH_3^+ at ~28 volts indicates that a second state of $C_4H_{10}^{++}$ is involved. Since the maxima corresponding to the ions CH_3^+ and $C_3H_7^+$ in the mass spectra are quite symmetrical there is no indication that a fraction of these ions is formed with excessive kinetic energy. We may thus conclude that the second reaction giving rise to CH_3^+ involves electronic excitation and not simply an antibonding state of C_3H_7—CH_3^{++}. The ionization efficiency curve for CH_3^+ is compared with those of $i\text{-}C_4H_{10}^+$ and $s\text{-}C_3H_5^+$ in Fig. 3.

From its structure, one would not expect isobutane to give rise to the ion $C_2H_5^+$. The fact that $C_2H_5^+$ is observed indicates that rearrangements can occur in the ions $C_nH_{2n+2}^+$ in the short time between their formation and dissociation. The value of $A(C_2H_5^+) = 12.0$ e. v. in isobutane indicates that C_2H_5 is the accompanying product, since any other products would require at least 2 volts more energy. The ~0.7 e. v. difference between $A(C_2H_5^+)$ from isobutane and normal butane can probably be associated with the activation energy of the isomerization $i\text{-}C_4H_{10}^+ \rightarrow n\text{-}C_4H_{10}^+$.

The magnitude of the appearance potentials of the ions $C_2H_4^+$ and $C_3H_6^+$ in the spectra of ethane and the butanes indicates that the formation of these ions is accompanied by the formation of stable molecules.[3,6] Two mechanisms are possible for these reactions. The one suggested by Delfosse and Bleakney[6] involves the assumption that the atoms or groups which form the stable un-ionized accompanying product are originally bound to the same carbon atom. This suggests an ethylidine structure for the ions $C_2H_4^+$ and $C_3H_6^+$. The other possible mechanism would involve the groups forming the stable un-ionized molecule coming from adjacent carbon atoms, and suggests that the ions $C_2H_4^+$ and $C_3H_6^+$ are olefinic molecular ions.

One might expect the resonance between the equivalent structures

$$H_2C\text{—}C^+H_2 \qquad H_2C^+\text{—}CH_2$$

in the olefinic molecular ions to stabilize them with respect to the isomeric ethylidene ions by at least 0.5 e. v. If this is true, the appearance potentials given in Tables IV and V for $C_2H_4^+$ and $C_3H_6^+$ indicate that the second mechanism is the more probable one.

From Rossini's review article[16] we can write

$$C_2H_6 = C_2H_4 + H_2 \qquad \Delta H^0_{298.1} = 1.42 \text{ e. v.} \quad (1)$$

$$n\text{-}C_4H_{10} = C_2H_4 + C_2H_6 \qquad \Delta H^0_{298.1} = 0.96 \text{ e. v.} \quad (2)$$

$$i\text{-}C_4H_{10} = C_3H_6 + CH_4 \qquad \Delta H^0_{298.1} = 0.80 \text{ e. v.} \quad (3)$$

$$n\text{-}C_4H_{10} = C_3H_6 + CH_4 \qquad \Delta H^0_{298.1} = 0.73 \text{ e. v.} \quad (4)$$

(16) F. D. Rossini, *Chem. Rev.*, **27**, 1 (1940) (1 kcal. = 0.04338 e. v.).

Treating the appearance potentials, $A(C_2H_4^+)$ and $A(C_3H_6^+)$ as heats of reaction, we find

C_2H_6: $I_{ad}(C_2H_4) = 12.09 - 1.42 = 10.67$ e. v. (1′)
n-C_4H_{10}: $I_{ad}(C_2H_4) = 11.49 - 0.96 = 10.53$ e. v. (2′)
i-C_4H_{10}: $I_{ad}(C_3H_6) = 10.74 - 0.80 = 9.94$ e. v. (3′)
n-C_4H_{10}: $I_{ad}(C_3H_6) = 10.94 - 0.73 = 10.21$ e. v. (4′)

Equations (1′) and (2′) compare very favorably with Price's[13] directly measured $I_{ad}(C_2H_4) = 10.41$ e. v. Delfosse and Bleakney[6] found C_3H_6; $A(C_3H_6^+) = 10.0$ e. v.[17] with which Eqs. (3′) and (4′) are to be compared. The essential agreement between the directly observed $I_{ad}(C_2H_4)$ and $I_{ad}(C_3H_6)$ with the indirect calculations (1′ to 4′) suggests that olefinic molecular ions rather than ethylidinic ions are formed in these reactions.

The mechanism suggested by Delfosse and Bleakney was suggested by the observations of Delfosse and Hipple[5] that in the reactions $C_2H_4 \rightarrow H_2^+ + \ldots$ the hydrogens forming the H_2^+ are originally attached to the same carbon atom. Kusch, Hustrulid and Tate[4] have shown that this reaction of ethylene is considerably more complex than the reactions like $C_2H_6 \rightarrow C_2H_4^+ + H_2$. In this connection it will be noted that the reactions $C_4H_{10} \rightarrow C_3H_8^+$ or $C_2H_6^+$ do not occur.

The ~0.7 e. v. difference between $A(C_2H_4^+)$ in normal butane and in isobutane may be attributed to an activation energy of isomerization as was done in the discussion of the formation of $C_2H_5^+$ from isobutane. On the other hand, it might be that the "same atom mechanism" operates in the dissociation of isobutane and the 0.7 e. v. is the difference in energy between the ethylene and the ethylidene ions.

Attempts to interpret the appearance potentials of the ions $C_3H_5^+$ and $C_2H_3^+$ from the butanes are impeded not only by the ambiguity with respect to the structures of these ions but also by the fact that several sets of un-ionized products of roughly the same energy are possible. The magnitudes of the appearance potentials are indicative of a minimum decrease in the number of bonds.

If we combine Eq. 2 given above with $A(C_2H_3^+)$ in ethane, Table IV, we get

$$n\text{-}C_4H_{10} = C_2H_3^+ + C_2H_4 + H_2 + H \quad A \sim 16.1 \text{ e. v.} \quad (5)$$

Kusch, Hustrulid and Tate[4] found $A(C_2H_3^+)$ in ethylene to be 14.1 e. v., thus we can write

$$n\text{-}C_4H_{10} = C_2H_6 + C_2H_3^+ + H \quad A \sim 15.1 \text{ e. v.} \quad (5')$$

These values are considerably greater than our observed n-C_4H_{10}; $A(C_2H_3^+) = 14.1$ e. v. Similar difficulties exist in attempted interpretations of the observed values of $A(C_3H_5^+)$.

The ionization efficiency curves for the ion $C_2H_3^+$ from both butanes indicate a second break ~4–4.5 e. v. above the initial break. Since this is just the order of the strength of C–C and C–H bonds, one can infer that the accompanying un-ionized products are more dissociated for electron energies greater than 18 e. v. than for electrons with energies between 14–18 e. v.

An examination of the distribution of the ions in the mass spectra of the two butanes (Tables II and III) immediately reveals certain limitations to the applicability of the mass spectrometer to hydrocarbon analysis. The excessively large fragmentation to ions in the C_3 and C_2 mass regions will reduce considerably the accuracy with which C_3 and C_2 hydrocarbons can be determined in the presence of butanes. Although this is particularly true with respect to C_3 and C_2 unsaturates, it is also true for propane and ethane. The large relative abundances of the ions $C_3H_7^+$ and $C_2H_5^+$ give rise to considerable quantities of masses 44 and 30 through the ions $C^{13}C_2^{12}H_7^+$ and $C^{13}C^{12}H_5^+$. Since the natural abundance of C^{13} is 1.1%, the relative current of mass 44 will be ~3.3% of mass 43 and of mass 30 will be 2.2% of mass 29. For concentrations of propane and ethane of the order of 2–3% or less, the corrections will be of the order of the quantity to be measured which is always unsatisfactory. In contrast to this less pleasant aspect it should be noted that extremely small traces of the butanes can be determined with ease in the presence of large concentrations of lower hydrocarbons. This is possible because at the low pressures involved there is no building up of heavier ions by recombination.

The relatively small abundances of the ions $C_4H_8^+$—C_4^+ to which the butanes give rise, will make possible the determination of C_4 unsaturates with reasonable precision.

It is interesting to note that a definite similarity exists between the unimolecular dissociation reactions of the ions $C_nH_{2n+2}^+$ and the thermal reactions of the hydrocarbons. The carbon–carbon bond in the ethane ion shows but little tendency to break; less than 10% of its spectrum lies in the C_1 region. The butanes on the other hand have only ~10% of their spectra in the parent C_4 region. A direct comparison of the ions in the mass spectra with the pyrolysis products

(17) One of the authors (D. P. S.) has found, C_3H_6; $A(C_3H_6^+) = 9.7$ e. v.

of hydrocarbons or hydrocarbon free radicals[18] cannot be made because none of the ions in the mass spectra result from collisions after the initial ionization. Thus the characteristic chain reactions are absent.

Summary

The variation of the relative abundances of the ionic dissociation products formed by electron impact in ethane, normal and isobutane are reported as a function of the energy of the bombarding electrons. The critical potentials of a number of the processes have been measured, and their significance is discussed. Certain limitations of the mass spectrometer as an analytical tool are also discussed.

(18) F. O. Rice and K. K. Rice, "The Aliphatic Free Radicals," The Johns Hopkins Press, Baltimore, Md., 1935.

PITTSBURGH, PENNA. RECEIVED MARCH 20, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICAL CHEMISTRY, THE HEBREW UNIVERSITY]

The Mechanism of the Catalytic Conversion of Para-hydrogen on Nickel, Platinum and Palladium

BY A. FARKAS AND L. FARKAS

The catalytic conversion of para-hydrogen on metals was explained by the dissociation of the hydrogen molecules on the surface of the catalyst.[1] This mechanism was later extended to the ortho–para conversion of deuterium and to the reaction $H_2 + D_2 = 2HD$.[2]

It seemed to receive confirmation when it was found that the rate of ortho–para conversion on palladium was very nearly equal to the rate of the diffusion of hydrogen through palladium.[3] From these experiments the conclusion was drawn that in the conversion and in the diffusion process the rate determining step is the dissociation of the hydrogen molecules on the surface of the catalyst.

Roberts questioned the correctness of the suggested mechanism[4] on the basis of his own experiments.[5] In these he was able to show that a clean tungsten surface will take up hydrogen molecules with great speed, that the molecules will be dissociated and that the atoms form a very stable layer on the surface of the tungsten. As this layer will give off atoms or molecules only at a very high temperature it was suggested that it is more reasonable to assume that the ortho–para conversion of hydrogen involves a reaction between the atomic layer and the molecules adsorbed or impinging on this layer. A direct proof for this view was brought forward by Eley and Rideal,[6] who showed that on an evaporated tungsten layer which has been in contact with hydrogen, the rate of the para-hydrogen conversion and the rate of exchange of atoms between molecular deuterium and the hydrogen in the tungsten layer are about equal.

The object of the present paper was the examination of the mechanism of the para-hydrogen conversion on typical hydrogenation catalysts such as nickel, palladium and platinum.

Experimental

The reaction vessel was either a bulb or a cylindrical vessel having a volume of 700 to 1100 cc. The pressure in the reaction system was measured by a Pirani gage. The entrance of vapors of grease or mercury into the reaction vessel or into the Pirani gage was prevented by traps cooled by liquid air. The gases were introduced into the reaction vessel by means of locks having a volume of 0.1 to 0.2 cc.

The reaction vessel was equipped with an electrically heated wire. The catalyst was prepared by heating the wire to a temperature at which the evaporation of the metal begins and thus an invisible layer of high activity is formed on the inner surface of the reaction vessel. The active layer thus prepared was, on the average, not more than one or two atoms deep, since the whole of the wire when completely evaporated would have formed a layer about one hundred atoms deep and actually only a small fraction of the wire, certainly not more than one per cent., was evaporated.

The concentration of para-hydrogen and of deuterium was determined according to the micro-thermal conductivity method.[2,7]

Nickel.—In the first series of experiments a reaction vessel of 730 cc. volume and having an inner surface of 390 sq. cm. was used. This vessel was provided with a nickel wire 11 cm. long, 0.1 mm. in diameter.

Table I shows the dependence of the half-life time of the para-hydrogen conversion on pressure in the presence of an evaporated nickel film.

(1) Bonhoeffer and Farkas, *Z. physik. Chem.*, **B12**, 231 (1935); Bonhoeffer, Farkas and Rummel, *ibid.*, **B21**, 225 (1933).

(2) Farkas and Farkas, *Proc. Roy. Soc.* (London), **A144**, 467 (1934).

(3) Farkas, *Trans. Faraday Soc.*, **32**, 1667 (1936).

(4) Roberts, *ibid.*, **35**, 941, 944 (1939).

(5) Roberts, *Proc. Roy. Soc.* (London), **A152**, 452 (1935).

(6) Eley and Rideal, *Nature*, **146**, 401 (1940); Eley, *Proc. Roy. Soc.* (London), **A178**, 452 (1941).

(7) Farkas, *Z. physik. Chem.*, **B22**, 344 (1933).

TABLE I

EXPT. 1, TEMPERATURE 20°

Pressure × 10^3 in mm.	Half-life time in minutes
5.2	1.6
10	2.6
26	3.2
76	4.2
26	2.9
Apparent order of reaction.	0.65

In two other series (Expts. 2 and 3), on the same catalyst, but in a less active stage, the order of 0.7 was found in the pressure region 3.4×10^{-3} to 3.4×10^{-2} mm.

In Expt. 4, on a fresh catalyst the para-hydrogen conversion was found to be complete in five minutes. Then (Expt. 5) a sample of pure deuterium was admitted into the reaction vessel at a pressure of 0.013 mm. and the deuterium content of the sample was determined after a four-minute contact with the catalyst. Then after evacuation with a mercury diffusion pump to a pressure of 10^{-6} mm., fresh deuterium was admitted and analyzed and this procedure repeated twice more with deuterium and four times with hydrogen (Expt. 6). In the experiments with hydrogen the pressure was 0.0095 mm. The results obtained are given in Table II. It will be seen that there

TABLE II

Expt.		Change in D-content in %
5	First sample	−26
	Second sample	−8.5
	Third sample	−6.3
	Fourth sample	−4.2
6	First sample	20
	Second sample	14
	Third sample	13
	Fourth sample[a]	10

[a] Time of contact nine minutes.

is reversible exchange between the hydrogen adsorbed on the catalyst and the molecular deuterium; *i. e.*, the deuterium introduced by exchange into the catalyst can be recovered by exchange with hydrogen. Furthermore, the extent of the exchange observed indicates that the amount of hydrogen in the catalyst is comparable to the amount of hydrogen (or deuterium) present in the gaseous phase.

By heating the reaction vessel the catalyst was deactivated and neither the conversion of para-hydrogen nor the exchange reaction took place.

The amount of exchangeable hydrogen in the catalyst can be determined by adding up the amount of exchanged hydrogen in a number of consecutive experiments.

Before Expts. 10 and 11 were performed, a fresh deuterium layer was produced on the catalyst by exchange with a great excess of deuterium. In Expt. 10 the catalyst was brought into contact five times with fresh hydrogen samples each time, at a pressure of 0.006 mm. for five minutes, after which period the deuterium content of the gas was determined. In Expt. 11 the pressure was 0.0057 mm., the contact time two minutes and the exchange was repeated six times. The results are given in Table III.

TABLE III

TEMPERATURE 20°

	Expt. 10 %D in sample	Expt. 11 %D in sample
First sample	33	16.4
Second sample	18	12
Third sample	11	8.4
Fourth sample	7	5.9
Fifth sample	4	5.3
Sixth sample		3.7

Taking the amount of gas present in each experiment in the reaction vessel as unity, the sum of exchanged hydrogen, a, is 0.73 in Expt. 10 and 0.52 in Expt. 11. If the amount of exchangeable deuterium is allowed for that which remains in the catalyst layer after the first five or six exchanges, the above figures can be corrected to 0.8 and 0.6, respectively.

Assuming that in equilibrium the concentration of deuterium is equal in the gas and in the catalyst layer the half-life time of the exchange calculated for Expts. 10 and 11 is 2.4 minutes.

Immediately after Expt. 11 the rate of the para-hydrogen conversion was measured at a pressure of 0.006 mm. and a half-life time of two minutes was found. Thus on the nickel catalyst the conversion of para-hydrogen and the exchange reaction proceed at practically identical rates in agreement with the findings of Eley and Rideal on a tungsten catalyst.

In a second series of experiments a Pyrex reaction vessel of cylindrical form (volume 750 cc., surface 550 sq. cm.) was used, equipped with a 34-cm. long nickel wire 0.1 mm. in diameter. This reaction vessel was placed in an electric oven so that it could be baked out at higher temperatures and maintained at any desired temperature.

The first experiments in this reaction were carried out at 64° and again it was found that at pressures of $7–10 \times 10^{-3}$ mm., the para-hydrogen conversion and the exchange reaction proceeded at similar speed, the half-life times being 2.5 and four minutes, respectively. The amount of exchangeable hydrogen was 0.82 if the gas present in the reaction vessel at 0.01 mm. and 64° was taken as unity (Expts. 39 and 40).

As it is known that hydrogen atoms are exchanged between molecular hydrogen and ethylene in the presence of a catalyst,[8] it was tested whether such an exchange reaction takes place between ethylene and the hydrogen layer. This test was performed by bringing hydrogen into contact with a layer containing about 50% deuterium before and after it had been in contact with ethylene or by saturating the layer with deuterium and continuing the saturation after having exposed the layer to ethylene.

The results of this test (Expts. 41 to 44 at 64°, and Expts. 56 to 59 at 30°) are summarized in Table IV. In Expt. 41 a catalyst layer containing 48% deuterium produced a deuterium content of 17.6% in a hydrogen sample which had been in contact with the catalyst for four minutes. After this experiment a new layer with 49% deuterium was exposed to ethylene and then to a sample of hydrogen. In Expts. 56–57 a hydrogen layer was treated four times with fresh samples of deuterium. After each treatment the loss in the deuterium content of the samples was smaller, showing that the deuterium content of the catalyst layer was increasing. When, however, ethylene

(8) Farkas, Farkas and Rideal, *Proc. Roy. Soc.* (London), **A146**, 630 (1934); Farkas and Farkas, THIS JOURNAL, **60**, 22 (1938).

TABLE IV

Expt.	Pressure in mm.	Gas	Time in min.	D content of sample in %
41	0.0059	H_2	4	17.6
43	.012	C_2H_4	10	..
44	.0059	H_2	4	2.5
56	.0094	D_2	3	20
	.0094	D_2	3	50
	.0094	D_2	3	67
	.0094	D_2	3	79
57	.028	D_2	5	89
58	.014	C_2H_4	10	..
59	.0093	D_2	3	39
	.0093	D_2	3	54

was brought into contact with the deuterated catalyst, the loss in the deuterium content of the deuterium applied subsequently was nearly as large as the loss in the very first treatment in Expt. 56.

Both series of experiments show clearly that fresh exchangeable hydrogen appears on the catalyst layer after the contact with ethylene, indicating that either the hydrogen layer is capable of exchanging with ethylene or that the ethylene is taken up and retained by the catalyst in a form which can subsequently exchange with molecular deuterium. This point requires further investigation but it was proved by special experiments that no measurable amounts of hydrogen are displaced from the catalyst and evolved when the hydrogen layer is brought into contact with ethylene.

Palladium.—In the next series of experiments a reaction vessel having a volume of 1150 cc. and an inner surface of 520 sq. cm., equipped with a palladium wire 10 cm. long, 0.1 mm. in diameter, was used.

The results of Expts. 14 and 15, which were carried out in the same manner as Expts. 5 and 6, are given in Table V. In Expt. 14 deuterium samples and in Expt. 15 hydrogen samples were brought into contact with the catalyst, the pressure being 0.0073 and 0.0082 mm., respectively. Before and after these experiments, the half-life time of the para-hydrogen conversion was found to be fifteen seconds at the reaction temperature of 25°.

TABLE V

Reaction time in min.	Change in D-content in %	Reaction time in min.	Change in D-content in %
	Expt. 14		Expt. 15
1	−53	2	33.7
2	−31.5	2	19.6
2	−21.8	2	9.8
2	−13.0	2	6.5
2	− 9.8	10	5.4
2	− 8.7	20	5.8
90	−16.3	1	2.5
		1	1.4

If the exchange reaction had proceeded at the same speed as the para-hydrogen conversion, equilibrium would have been established in about two minutes. It will be noted, however, that, in the last run, after a reaction time of ninety minutes, the amount of exchange was higher than in the previous run after a reaction time of two minutes. This shows that there is a certain amount of slowly exchangeable hydrogen on the catalyst. The half-life time calculated with $a = 1.5$ varies between twenty and sixty seconds for the first four runs in Expt. 14, while for the first four runs in Expt. 15 half-life times of fifty-five to one hundred and twenty-five seconds are obtained. In Expt. 15, $a = 1$.

The results of all experiments with palladium layers are summarized in Table VI and it will be seen that the para-hydrogen conversion is up to fifteen times faster than the exchange reaction and that the amount of exchangeable hydrogen is in no direct relation to the rate of the conversion reaction.

TABLE VI

PALLADIUM, TEMPERATURE 20°

Expt.	Gas	a corrected for 0.01 mm.	Half-life time in seconds
13[a]	p-H_2	..	20
14	D_2	1.09	20–60
15	D_2	0.82	55–125
16	p-H_2	..	15
21[a]	p-H_2	..	15
22	D_2	0.9	120
23	p-H_2	..	8
25[a]	p-H_2	..	2
26	D_2	.27	8
29	p-H_2	..	4
30	D_2	.22	24

[a] Indicates fresh catalyst.

Platinum.—In this series the reaction vessel was a bulb having a volume of 800 cc. and an inner surface of 410 sq. cm., and equipped with a 12 cm. long platinum wire 0.1 mm. in diameter. As shown by the results summarized in Table VII, the conversion of para-hydrogen is five to six times faster on an evaporated layer of platinum than the exchange reaction.

TABLE VII

PLATINUM, TEMPERATURE 20°

Expt.	Pressure in mm.	Gas	a	Half-life time in seconds
31	0.0057	p-H_2	..	15
32	.0068	D_2	0.20	45
37	.0057	p-H_2	..	10
38	.0068	D_2	.18	60

Discussion

The described experiments with nickel, palladium and platinum catalysts indicate, in accordance with Roberts' conclusions and Eley and Rideal's findings on tungsten, the following points:

1. There is a hydrogen layer on these metals which is not removed by pumping at room temperature and which can exchange atoms readily with molecular hydrogen, and in the case of nickel with ethylene as well.

2. The rate of this exchange reaction with molecular hydrogen is on nickel equal to the rate of the conversion of para-hydrogen, but it is smaller on palladium and on platinum than that of the para-hydrogen conversion.

The explanation of the findings on nickel is that either the mechanisms of the exchange and conversion reactions are the same or the rate determining steps in these two reactions are the same.

Before discussing the various possible reaction mechanisms, the number of exchangeable hydrogen atoms in the stable hydrogen layer will be calculated. This number will be of some importance as it can be taken as the number of the active centers and will indicate that fraction of the catalyst's area which is active.

The difference between the number of exchangeable hydrogen atoms and the number of the hydrogen atoms in the layer on the catalyst is significant. While it is possible to determine the amount of hydrogen in the layer by adsorption measurements, all of these "chemisorbed" hydrogen atoms are not necessarily exchangeable and the whole surface covered by chemisorbed hydrogen is not necessarily catalytically active.

In Expt. 10 the volume of the reaction vessel was 730 cc., its surface 390 sq. cm., the hydrogen pressure 0.006 mm., $a = 0.77$ and the temperature 20°. From these data the number of the hydrogen atoms in the reaction vessel is 2.90×10^{17} and the number of the exchangeable atoms in the layer is 2.22×10^{17}.

If each hydrogen atom is attached to a different nickel atom, 2.22×10^{17} is the number of active centers on the nickel catalyst. The total area of the active catalytic layer is obtained by multiplying the number of active centers by the area covered by each nickel atom. For an unoriented nickel layer the area covered by one nickel atom can be taken as 6.7×10^{-16} sq. cm., being the arithmetic mean of the areas 5.32, 6.15 and 8.7×10^{-16} sq. cm., in the (111), (100) and (110) planes, respectively[9]; thus the total area of 148 sq. cm. As the apparent area of the glass vessel was 390 sq. cm. and the catalyst layer was on the average not deeper than a few atoms it follows that at least one-tenth of the nickel atoms evaporated was catalytically active.

The figure of 2.22×10^{17} corresponds to 5.7×10^{14} active centers per sq. cm. of apparent catalytic area. In other experiments values of the same order were obtained ranging from 1.6 to 16×10^{14} per sq. cm.

These results have significance if considered together with recent experiments of Beeck, Smith and Wheeler.[9] These authors have found that oriented nickel films of definite crystal structure and reproducible activity for the hydrogenation of ethylene can be prepared by evaporation in an indifferent gas atmosphere at a few millimeters pressure, and that the active regions of the catalyst coincide with a homogeneous, definite crystal lattice, rather than with extra-lattice atoms and related atomic combinations. They have also measured the adsorption of hydrogen on fresh nickel layers up to a thickness of several thousand atoms and have found that an instantaneous, irreversible adsorption, "chemisorption," takes place in agreement with Roberts' results on tungsten.[5] The chemisorption observed in this case is probably closely related to the chemisorption type A described by Brunauer and Emmett[10] on iron.

There are two different types of reactions which might be operative in the exchange and conversion reactions:

1. Reaction between the stable layer of hydrogen on the catalyst and gas molecules impinging thereon.

2. Reaction between the stable layer of hydrogen on the catalyst and hydrogen adsorbed on places adjacent to those occupied by the stable layer.

According to Roberts and Beeck, Wheeler and Smith, and also to Brunauer and Emmett, the stable layer consists of chemisorbed atoms, but we have no definite information about the hydrogen in the second layer. The hydrogen may be present in the second layer either in the form of more or less deformed molecules or in the form of atoms which can recombine and leave the catalyst in contradistinction to chemisorbed atoms.

The apparent order of a reaction of the first type should be one since the concentration of the hydrogen in the stable layer is independent of the pressure and the number of molecules impinging is proportional to the pressure. Furthermore, one would expect that the collision efficiency of a reaction of this type such as

$$p\text{-}H_2 + H_{ads} = o\text{-}H_2 + H_{ads} \qquad (1)$$

would be much smaller than that of the homogenous reaction

$$p\text{-}H_2 + H = o\text{-}H_2 + H \qquad (2)$$

(9) Beeck, Smith and Wheeler, *Proc. Roy. Soc.* (London), **A177**, 62 (1940).

(10) Brunauer and Emmett, THIS JOURNAL, **62**, 1752 (1940); **59**, 1553 (1937); **57**, 1631 (1935).

because in the latter case the hydrogen atom is free and the molecule can approach the atom in the direction of the line joining the nuclei and thus encounter the least energy of activation.[11]

Actually, the observed order of reaction (Table I) is definitely below unity and the calculated collision efficiencies for reaction 1 are of the same order as, and in some cases ten to twenty times higher than, the collision efficiencies for reaction 2. For these reasons one might rule out the reaction of type 1 as highly improbable.

On the other hand, it is not possible to decide between the two alternatives of reaction type 2; *i. e.*, whether the reaction with the stable layer involves adsorbed molecules or adsorbed atoms. A close investigation of the conversion of para-hydrogen and of the exchange reaction on palladium and platinum might help to decide between the two mechanisms if it would be possible to ascertain whether the difference in the rates of conversion and exchange is real and not only apparent owing to the existence of centers of various catalytic activity. A renewed comparison of the para-hydrogen conversion on palladium with the diffusion of hydrogen into the metal may also contribute to the solution of the above problem.

In case it is definitely proved that the exchange and para-hydrogen conversion involve adsorbed molecules rather than adsorbed atoms, all conclusions drawn from the assumption that the rate of the para-hydrogen conversion is governed by the rate of dissociation of the molecules, will need revision.

For example, the repeatedly observed parallelism between the rate of the para-hydrogen conversion and the rate of the hydrogenation of ethylene on the same catalyst[12] was explained by the assumption that the dissociation of the hydrogen molecules is the rate determining step in both processes. In case the participation of atoms other than those in the stable layer in the exchange and conversion must be ruled out, another explanation will be needed. The following might be possible. In the exchange reaction between the stable layer and the adsorbed molecules the rate determining step is the adsorption and deformation of the molecules preceding the actual exchange of atoms. In fact this mechanism would not disagree with the general picture of catalytic hydrogenation according to which both hydrogen atoms of the same molecule are added simultaneously in the act of hydrogenation.[13]

If the dissociation of the hydrogen molecules takes place only in the chemisorbed layer and the recombination of the atoms in this layer is too slow to cause conversion or exchange it is not probable that a dissociation of hydrocarbons into hydrogen atoms and hydrocarbon radicals will contribute to the catalytic exchange of hydrogen atoms between hydrocarbons and molecular hydrogen as postulated by the dissociative theory.[8,14]

The exchange of hydrogen atoms between hydrocarbons and the stable hydrogen layer is possible according to the experimental results given in Table V. This possibility must be taken into account especially when dealing with exchange of hydrogen atoms between hydrocarbons.[15]

Finally, the bearing of the present experiments on two catalytic isomerization reactions will be referred to. Twigg[16] observed that in the catalytic interaction of butene-1 and deuterium the double bond migration was faster than the exchange reaction, while the isomerization was very slow in the absence of hydrogen or deuterium. A similar observation was made by Baxendale and Warhurst[17] in the catalytic hydrogenation of methyl oleate with deuterium when a considerable amount of "light" elaidic ester was formed, indicating that the *cis–trans* conversion proceeded faster than the exchange reaction. Again the isomerization was slow and soon stopped completely when no hydrogen was present.

Both observations can be explained by assuming that the isomerization is caused by an interaction with the stable layer of hydrogen. The effect of hydrogen or deuterium in accelerating the isomerization might be due to the circumstance that the hydrogen in the stable layer is gradually removed by addition to the unsaturated hydrocarbon and gaseous hydrogen is needed for replacing the used-up layer. Since each hydrogen or deuterium atom will cause a number of isomerization processes before it is removed the isomerization will appear to be faster than the exchange.

Summary

The catalytic conversion of para-hydrogen was

(11) Pelzer and Wigner, *Z. physik. Chem.*, **B15**, 445 (1932).
(12) Farkas, *Trans. Faraday Soc.*, **35**, 909 (1939).
(13) Farkas and Farkas, *ibid.*, **33**, 837 (1937).
(14) Farkas and Farkas, *ibid.*, **33**, 678, 827 (1937); **35**, 917 (1939); **36**, 522 (1940).
(15) J. Aman, Thesis, 1941, The Hebrew University, Jerusalem.
(16) Twigg, *Proc. Roy. Soc.* (London), **A178**, 106 (1941).
(17) Baxendale and Warhurst, *Trans. Faraday Soc.*, **36**, 1161 (1940).

investigated at room temperature and a pressure of about 0.01 mm. on evaporated layers of nickel, palladium and platinum. It was found that there is a stable layer of hydrogen on the catalysts which is not removed by pumping at room temperature and which exchanges readily with molecular hydrogen or deuterium. The rate of this exchange is equal to the rate of the para-hydrogen conversion on nickel, but is smaller on palladium and platinum. It is shown that the amount of exchangeable hydrogen in the stable layer can be taken as an indication of the number of active centers on the catalyst. This number is 10^{14} to 10^{15} cm.$^{-2}$ and shows that a great fraction of the apparent catalytic surface is active. The various possible mechanisms for the conversion of para-hydrogen and the exchange are discussed and their bearing on other exchange, hydrogenation and isomerization reactions considered.

JERUSALEM, PALESTINE RECEIVED JANUARY 26, 1942

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

Fluorochlorobromomethane

BY KENNETH L. BERRY[1,2] AND JULIAN M. STURTEVANT

In connection with recent theories of optical activity,[3] an optically active pentatomic molecule would be of considerable interest. Attempts have therefore been made to resolve fluorochlorobromoethane, perhaps the most readily obtainable of the few such substances having potential optical activity. During this work several physical properties of this substance have been determined.

Swarts[4] attempted to resolve this substance by fractional crystallization of the complex it forms with salicylide, but without success. He was also unsuccessful[5] in attempts to decarboxylate optically active fluorochlorobromoacetic acid to yield the active substituted methane.

Preparation and Purification.—Ethyl chloroacetal was prepared by the addition of chlorine to vinyl acetate in alcohol solution according to the method of Filachione.[6] Bromination[7] of the chloroacetal, followed by hydrolysis, yielded chlorodibromomethane. This latter halide on treatment with antimony trifluoride and bromine gave fluorochlorobromomethane[4] in fair yield, though contaminated with considerable amounts of higher and lower boiling halides. The crude product was washed at 0° with very dilute alkali followed by water, dried over calcium chloride, and fractionated from phosphorus pentoxide through a 48-cm. vacuum-jacketed column packed with glass helices. The main fraction was collected between 36.3 and 36.8°, and was stored in sealed ampoules in the dark. Over-all yields of approximately 25% were obtained.

Anal. 0.2097 g. gave 0.4693 g. AgCl + AgBr; calcd. 0.4711 g. AgCl + AgBr.

One hundred and forty grams of material boiling at 36.3–36.8° was refractionated, and the middle cut of 65 g. was again fractionated to give a 37 g. fraction boiling at 36.11–36.18° (cor.) (756.0–756.2 mm.). This sample was used for the determination of physical properties. It remained perfectly colorless when sealed in an ampoule and stored in the dark.

Physical Properties.—The fusion curve of fluorochlorobromomethane, which was observed in an apparatus similar to that described by Skau,[8] showed the 36.11–36.18° fraction to be quite pure. The melting point was found to be −115° (cor.).

The density was determined dilatometrically from 0 to 25°, and can be represented in this range by the equation (t = °C.)

$$d_t = 1.9771 - 2.51 \times 10^{-3}t - 2.03 \times 10^{-5}t^2 + 3.3 \times 10^{-7}t^3 \quad (1)$$

A Pulfrich refractometer was employed to determine the refractive dispersion of fluorochlorobromomethane in the visible spectrum at 0.5, 10.0 and 20.0°. The data were fitted to an equation of the form recommended by Tilton[9] (λ = wave length in microns)

$$n^2 = a^2 - k\lambda^2 + \frac{m}{\lambda^2 - l^2} \quad (2)$$

(1) The material in this communication constitutes part of a dissertation submitted by Kenneth L. Berry to Yale University in partial fulfillment of the requirements for the Ph.D. degree, June, 1940.

(2) Present address: Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware.

(3) Kuhn, *Z. physik. Chem.*, **B31**, 23 (1936); Kirkwood, *J. Chem. Phys.*, **5**, 479 (1937); Condon, Altar and Eyring, *ibid.*, **5**, 753 (1937).

(4) Swarts, *Bull. acad. roy. Belg.*, [3] **26**, 102 (1893).

(5) Swarts, *ibid.*, [3] **31**, 28 (1896); *ibid.*, Memoirs Couronnes, **54**, 54 (1896).

(6) Filachione, THIS JOURNAL, **61**, 1705 (1939).

(7) Jacobsen and Neumeister, *Ber.*, **15**, 601 (1882).

(8) Skau, *Proc. Am. Acad. Arts Sci.*, **67**, 551 (1933).

(9) Tilton, *Bur. Standards J. Research*, **17**, 646 (1936).

The constants for this equation listed in Table I reproduce the data within the experimental accuracy from λ 0.7065 to λ 0.4047.

TABLE I

THE CONSTANTS OF EQUATION (2)

Temp., °C.	a^2	k	m	l^2
0.5	2.0083	0.00432	0.01175	0.01832
10.0	2.0041	.01828	.00873	.03954
20.0	1.9778	.00610	.01082	.02256

The Lorenz–Lorentz molecular refractivities for the sodium D line are $R_{0.5} = 19.24$, $R_{10} = 19.26$, $R_{20} = 19.31$. Using the atomic refractivities[10] of carbon, hydrogen, chlorine and bromine, one finds the atomic refractivity of fluorine at λ 0.5893 and 20° to be 0.956.

Attempted Resolution.—Three types of procedure for accomplishing the resolution of fluorochlorobromomethane suggest themselves: (a) formation of solid addition compounds with optically active substances; (b) utilization of vapor pressure differences in asymmetric solvents; and (c) selective adsorption on optically active adsorbents. Limitations of time have not permitted an extensive investigation of these procedures, though indications of positive results were obtained with the first method.

It was found that digitonin[11,12] forms an insoluble digitonide with fluorochlorobromomethane. This digitonide cannot be dried and characterized since it very readily loses its volatile component. The halide was added to an aqueous alcoholic solution of digitonin at 0°; after vigorous shaking the mixture was centrifuged, and the precipitate was then warmed to 55° under a slow stream of air to sweep the vaporized halide into a dry-ice-cooled receiver. The distillates thus obtained had rotations varying from zero to +0.15° (1-decimeter tube). The irreproductibility of the results, and the poor recovery of the very expensive digitonin make further experiments along this line seem unpromising.

(10) "Organic Chemistry, An Advanced Treatise," edited by H. Gilman, John Wiley and Sons, Inc., New York, N. Y., 1938, p. 1739.

Summary

Fluorochlorobromomethane was prepared in pure form, and its boiling point, melting point, density and refractive dispersion determined. Inconclusive results were obtained in attempts to resolve the substance through its insoluble digitonide.

(11) Windaus and Weinhold, *Z. physiol. Chem.*, **126**, 299 (1923).
(12) Windaus, Klänhardt and Weinhold, *ibid.*, **126**, 308 (1923).

NEW HAVEN, CONNECTICUT RECEIVED FEBRUARY 5, 1942

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

The Pressure–Area–Temperature and Energy Relations of Monolayers of Octadecanenitrile

BY L. E. COPELAND AND WILLIAM D. HARKINS

1. Introduction

Until recently only three liquid phases have been known to exist in monolayers. These are (1) the liquid expanded or L_1 phase, (2) the intermediate or I phase, and (3) the liquid condensed or L_2 phase. Any one of these may exist at low pressures, and therefore may be designated as a low pressure liquid phase. Recently a new liquid LS[1,2] phase has been discovered, but is found to exist only at high film pressures, since it is formed by a transition from the liquid condensed (L_2) phase when the pressure is raised to a sufficiently high value. Except at the lowest temperatures at which this new phase is formed, the transition is of the second order, so at the transition point the molecular area is the same in the high pressure LS phase as in the low pressure L_2 phase. However, by increase of pressure the area for the LS phase may be reduced below any possible area, for the given temperature, at which the L_2 phase may exist. This new high pressure phase has been found to form in monolayers of the normal long chain paraffin alcohols, but its lower limiting molecular area is 19.98 sq. Å., since below this it transforms into the "solid" or S phase.

At the highest pressure at which a low pressure liquid alcohol monolayer is stable, its molecular area may be below that possible for the stable existence of the high pressure liquid phase. Thus at 2.85° and 14 dyne cm.$^{-1}$ the molecular area for octadecanol is 19.8 sq. Å., the lowest area

(1) W. D. Harkins and L. E. Copeland, *J. Chem. Physics*, **10**, 272 (1942).
(2) L. E. Copeland, W. D. Harkins and G. E. Boyd, *ibid.*, **10**, June (1942).

thus found for any liquid phase. The area at 0° as obtained by extrapolation would be about 19.7 sq. Å.

Reliable measurements of the molecular areas of the normal long paraffin chain acids have not been made at such low temperatures but even at 25° the L_2 film of nonadecanoic acid has a minimum value of 20.2 sq. Å., while the minimum for octadecanol is 20.53 sq. Å. Thus the data seem to indicate that at 25° the minimum area for the acid is lower than that for the alcohol. The molecular areas obtained at 25° by extrapolation to zero pressure are 22.41 sq. Å. for the alcohol and 24.41 for the acid when the molecule of each contains 18 carbon atoms. The larger area for the acid at low pressure and the nearly equal areas at high pressure are explained by the higher mean compressibility of the monolayer of the acid as compared with that of the alcohol.

The fact that the minimum molecular area for the acid is lower than that of the alcohol may be misleading if the pressure of the transformation of liquid (L_2) into the high pressure phase is not taken into account, since the transition pressure is much higher (24 dyne cm.$^{-1}$) than for the alcohol (14 dyne cm.$^{-1}$). At this latter pressure the areas are 20.53 sq. Å. for the alcohol, but 21.7 for nonadecanoic, and 21.9 for stearic, acid, so at equal pressures the acid has the higher area.

2. The Liquid Condensed Monolayer of Octadecanenitrile

Since in monolayers of the long chain alcohols and acids the polar groups are oriented toward the water, they are also brought close together, if the film is condensed. With either of these substances there is a possibility that there may be hydrogen bonding either in (1) the film itself, or (2) between polar groups in the film and molecules of water.

It is, therefore, of interest to learn the effect, upon the molecular area, which is produced by the elimination of the first possibility, that is, of hydrogen bonding in the film. This may be eliminated by the use of a long chain nitrile.

The pressure–area–temperature relations obtained with monolayers of octadecanenitrile are exhibited in Fig. 1. From this figure it is evident that the —C≡N group gives a much higher area (with a minimum of 25.82 sq. Å. at 15.1°) in the monolayer than either —CO·OH or —OH. Adam[3] explains the relations on the basis of the assumption that the nitrile group is the largest, and the hydroxyl group the smallest of the three. However, it does not seem possible that the nitrile group, with its two atoms and a carbon–nitrogen distance of only 1.15 Å., can be larger than the carbonyl group with its content of four atoms, even though one (H) of the latter is small. Therefore it seems necessary to reject Adam's hypothesis, and to seek another cause for the high area in the nitrile monolayers. Obviously if there is intramonolayer hydrogen bonding in the case of the acids and alcohols, its absence in the nitrile films would give a sufficient explanation of their higher areas. Unfortunately the existence of this type of bonding in the film itself has not been demonstrated, even in the case of the alcohols and acids.

Some investigators assume, without solving the statistical mechanics of the problem, that the dipoles in monolayers of this type always repel each other. If this were assumed the higher dipole moment of the nitriles (3.56×10^{-18}) as compared with those of the acids (1.4×10^{-18}) and the alcohols (1.7×10^{-18}) would give a sufficient cause for the higher areas exhibited by the nitriles. This problem will be considered in a later paper which considers other relations of the nitrile mono-layers.

3. The Intermediate Phase

The interesting feature revealed by Fig. 1, as related to the intermediate phase of octadecanenitrile, is that the pressure (π)–area (σ) curves are very much steeper than those exhibited by the normal long chain paraffin acids. Thus the compressibilities of the nitriles, in this phase, are very much smaller. In contrast the esters give much larger compressibilities than the acids.

At 25.8° the intermediate phase of the nitrile has a compressibility of 0.06 at areas close to that at which this phase is formed by a transition, on increase of pressure, from the liquid expanded state. As the area is reduced the compressibility falls to about 0.015. Adam and Harding[4] have obtained a maximum compressibility of the order of 0.45 for the intermediate phase of margaric nitrile, but their value is very much higher than any obtained by us at any temperature with the 18 carbon atom nitrile.

4. The Liquid Expanded Phase

The compressibilities exhibited by the liquid expanded phase of the nitriles are of the same order

(3) N. K. Adam, "The Physics and Chemistry of Surfaces," Oxford, Clarendon Press, 1938, p. 53.

(4) N. K. Adam and J. B. Harding, *Proc. Roy. Soc.* (London), **A143**, 104 (1934).

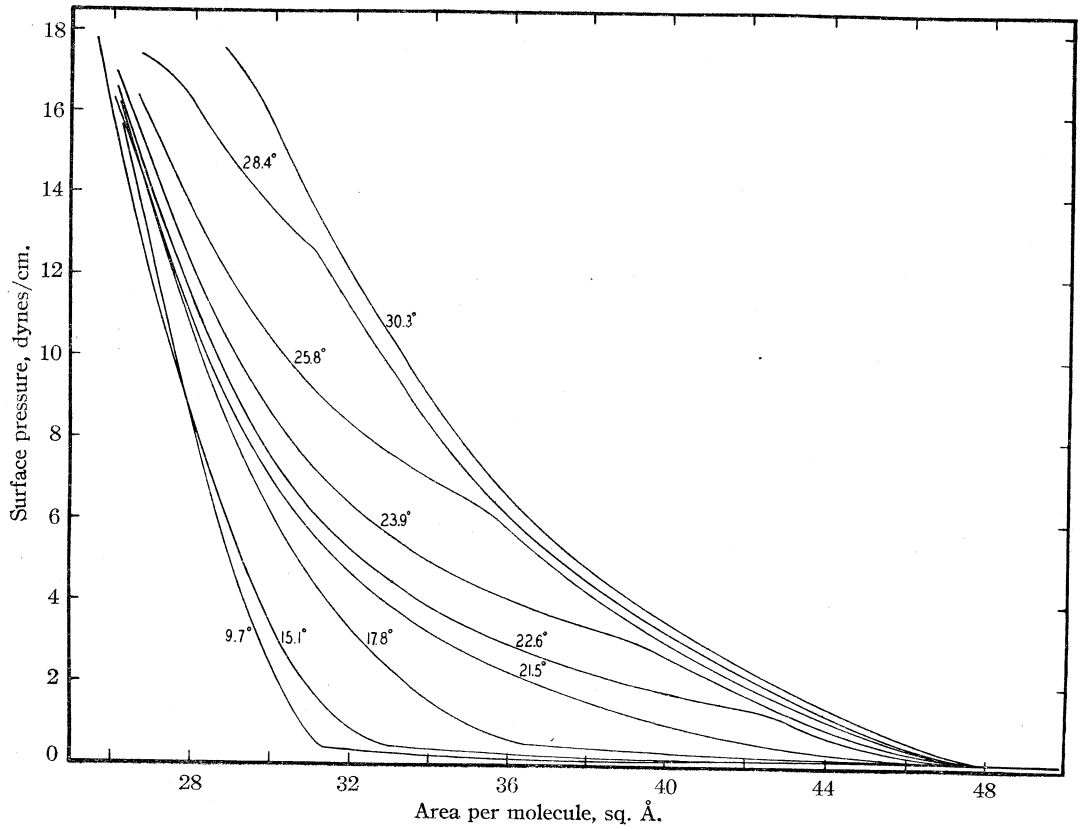


Fig. 1.—Pressure–area–temperature relations of monolayers of octadecane nitrile on water.

of magnitude as those of the acids. That the phase is of the liquid rather than of the vapor type is indicated by the areas at which the film pressures become small, and which are of the order of those to be expected when a liquid expanded film begins to vaporize. At 22.6° and 30.3° the areas are 46 and 48 sq. Å., while with pentadecylic acid, known to be in the liquid expanded state, the areas are 44 and 49 sq. Å. at 17.9 and 35.2°. In the case of myristic acid the transition occurs at 42 and 46 sq. Å. at 4° and 25°.

5. Energy of Spreading and Extension

The values of the energies of extension of the surface of clean water, which are the same as the energies of surface formation, are given in the first row of Table I. The energies of extension of the water covered by the nitrile monolayer are all higher (than those of water), except for the free energies which are lower. Any energy of spreading may be obtained from the corresponding energy of extension by subtracting the value for water. As usual there is a decrease of free energy but an increase of total energy, and of entropy, and of absorption of heat when the monolayer spreads.

TABLE I

THE ENERGIES OF THE MONOLAYER OF OCTADECANE-NITRILE IN THE VARIOUS STATES AT 20°

Energy in erg cm.$^{-2}$ and entropy in erg cm.$^{-2}$ deg.$^{-1}$

Phase	Area	Process	f	h	q	s
Clean water			72.75	116	43.2	0.148
L_1	40.0	extension	72.25	155	82.2	.282
		spreading	−0.49	38.8	39.3	.134
I	32.0	extension	69.00	170	201	.685
		spreading	−3.75	154	158	.537
L_2	28.0	extension	66.38	124	57.5	.197
		spreading	−6.37	7.9	14.3	.049

The effect of pressure and temperature upon the energy values for the monolayers, as obtained at various constant areas, are given in Table II. The values are not extremely high, as in the case of the alcohols,[1,2] but are of somewhat the same order of magnitude as those for pentadecylic acid. As is usual they are very much higher for the intermediate phase than for the expanded and condensed liquid phases.

This publication was made possible by funds granted by the Carnegie Corporation of New York. That Corporation is not, however, the author, owner-publisher or proprietor of this publication, and is not to be understood as approving

TABLE II

THE EFFECT OF PRESSURE ON A MONOLAYER OF OCTADECANENITRILE AT VARIOUS AREAS

Phase		t, °C.	s_s	q_s	h_s
		28 sq. Å./molecule			
L_2	6.3	19.60	0.00	00	0
	6.5	21.05	.203	60	54
I	7.0	22.64	.442	131	124
	8.0	24.60	.600	179	171
	9.0	25.85	1.12	322	313
	10.0	26.80	0.917	275	265
L_1	11.0	28.30	.00	0	0
		32 sq. Å./molecule			
I	3.0	18.40	0.337	98	95
	4.0	20.46	.564	166	162
	5.0	22.00	.770	217	212
	6.0	23.31	.770	230	224
	7.0	24.51	.902	268	261
	8.0	25.60	.972	290	282
L_1	9.0	27.35	.104	31	22
		40 sq. Å./molecule			
I	1.0	18.85	0.203	59	58
	2.0	20.96	.815	240	238
	3.0	22.05	.797	235	232
	4.0	23.52	.541	160	156

by its grant any of the statements made or views expressed therein.

Summary

1. The lowest area thus far found, in accurate work, for any n-long chain paraffin derivative in its monolayer on water is 19.57 sq. Å. This was obtained with n-octadecanol in the S-phase at 2.85°. At lower temperatures somewhat lower areas could be obtained. In solid three dimensional crystals the area of the hydrocarbon chain is 18.5 sq. Å. Nonadecanoic acid in its monolayer at 25° has been compressed to 20.2 sq. Å. At 25° the extrapolated area at zero pressure is, for the liquid condensed phase, 22.41 sq. Å. for octadecanol and 24.41 sq. Å. for stearic acid.

2. In monolayers of the alcohols and acids there is the possibility of hydrogen bonding between the polar groups in the film itself as well as with water. In monolayers of n-octadecane nitrile hydrogen bonding in the film itself is no longer possible, and it was found that the minimum area obtained at any temperature and pressure employed was 25.8 sq. Å. at 15.1° and 18 dyne cm.$^{-1}$, while the lowest area found by extrapolation at zero pressure was 30 sq. Å. Thus the —C≡N end group gives much less condensed films than either the —COOH or the —OH groups. Unfortunately the dipole moment of the nitrile is much higher (3.56×10^{-18}) than that of the alcohol or the acid, so there is a possibility that this produces a repulsion which accounts for the greater area. The decision as to which factor is responsible for the high area, is left to later work.

3. The hypothesis that the larger area of the nitrile is due to a large size of the —C≡N group, with its interatomic distance of only 1.15 Å., as compared with the —COOH group, is rejected.

4. The pressure–area curves for the intermediate phase are much steeper than those for the long chain acids. Thus in this phase the nitriles exhibit a much smaller compressibility.

5. The pressure–area curves for the expanded phase fall to low pressures at just those areas characteristic of the liquid expanded state, so these films are not gaseous. Thus at 22.6° and 30.3° these areas are 46 and 48 sq. Å., while with pentadecylic acid at 17.9° and 35.2° the corresponding areas are 44 and 49 sq. Å.

CHICAGO, ILLINOIS RECEIVED APRIL 23, 1942

[CONTRIBUTION FROM RESEARCH LABORATORIES OF INSTITUTUM DIVI THOMAE AND SIENA HEIGHTS COLLEGE]

Ultraviolet Absorption Spectra of Nitrogenous Heterocycles. IV. Effect of *p*H and Irradiation on the Spectra of Isoguanine and 2-Hydroxy-6,8-diaminopurine

BY SR. MIRIAM MICHAEL STIMSON, O. P.

The introduction of a hydroxy group on the second carbon atom of adenine to give isoguanine and the same relative positions of the hydroxy and amino groups on the pyrimidine ring of 2-hydroxy-6,8-diaminopurine permits a study of the combination effect of tautomerism of the imidine type[1] and of the amide-imidole type.[2]

Although the spectrum of guanine was found by Holiday[3] and by Heyroth and Loofbourow[4] to be greatly affected by *p*H change, the position of the amino group on carbon 2 rather than 6 introduces the possibility that some of the variation may be positional[5] rather than a modification of the spectrum of adenine by introduction of a hydroxy group.

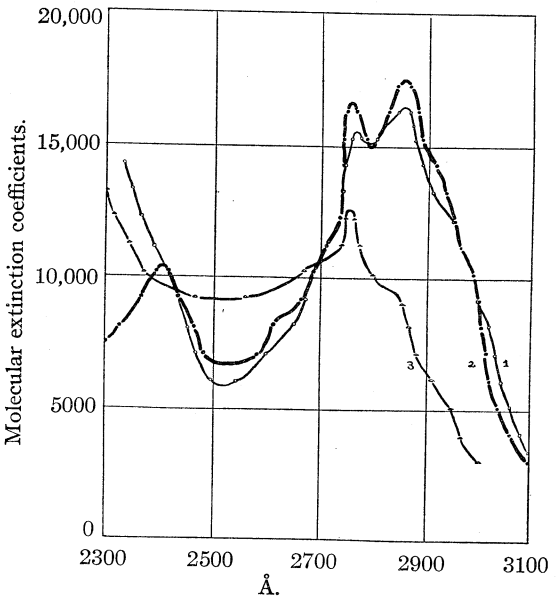


Fig. 1.—Isoguanine: 1, *p*H 3.0; 2, *p*H 7.0; 3, *p*H 11.0.

Experimental

Materials.—The isoguanine and 2-hydroxy-6,8-diaminopurine were kindly furnished by Mr. Joseph R. Spies, Bureau of Chemistry and Soils, U. S. Department of Agriculture.

(1) Loofbourow and Stimson, *J. Chem. Soc.*, 844 (1940); Stimson and Loofbourow, THIS JOURNAL, **63**, 1827 (1941).
(2) Loofbourow and Stimson, *J. Chem. Soc.*, 1275 (1940).
(3) Holiday, *Biochem. J.*, **24**, 619 (1930).
(4) Heyroth and Loofbourow, THIS JOURNAL, **56**, 1728 (1934).
(5) Unpublished laboratory results of Loofbourow and Stimson.

Method.—The details of the techniques employed were given in Part I of this series.

Results and Discussion

Figure 1 shows the spectra of isoguanine at *p*H 3, 7, 11. The $\epsilon_{max.}$ is greatest for *p*H 7 and is considerably lower for *p*H 11.0 than for *p*H 3.0. In 6-aminopyrimidine[6] and 6-aminopurine[1] $\epsilon_{max.}$ for neutral solution is less than that for acid reaction. On the other hand, unpublished findings of Loofbourow and Stimson indicate $\epsilon_{max.}$ for cytosine to be greatest at *p*H 7.0. From this it may be concluded that the downward trend of the amino (on C 6) $\epsilon_{max.}$ with change from acid to alkaline conditions is over balanced by the high absorption of the hydroxyl group at *p*H 7.0.[2] The effect of the hydroxyl in position 6 is weaker than in 2, however, since the work of Williams, *et al.*,[6] shows 5-methyl-6-hydroxypyrimidine to absorb less at the long wave maximum in neutral solution than in either acid or alkaline reaction. Unpublished findings of Stimson and Loofbourow for hypoxanthine also show the influence of the hydroxyl on C 6 to be insufficient to raise $\epsilon_{max.}$ for neutral solutions above that for acid or alkaline solutions. Although $\lambda_{max.}$ for 6-aminopyrimidine and 6-aminopurine shifts progressively to longer wave lengths with increase in *p*H, the reverse condition is true for the compounds with the 2-hydroxy-6-amino arrangement. The introduction of the second amino group in position 8 shows in 2-hydroxy-6,8-diaminopurine, the shift of $\lambda_{max.}$ to be in the same direction as the other two 2-hydroxy-6 amino compounds although the degree is considerably less (Fig. 2). However $\epsilon_{max.}$ here again takes on the characteristics of purely amino substituted compounds, which may be attributed to overbalancing the hydroxyl absorption. The short wave maximum found by Williams, *et al.*, for 6-amino- and 6-hydroxy compounds, by Stimson and Loofbourow for 2-chloro-6-aminopyrimidine and by Uber and Winters[7] is indicated only at *p*H 7 for isoguanine and did not appear in the photographic ultraviolet for 2-hydroxy-6,8-di-

(6) Williams, Ruehle and Finkelstein, THIS JOURNAL, **59**, 526 (1937).
(7) Uber and Winters, *ibid.*, **63**, 137 (1941).

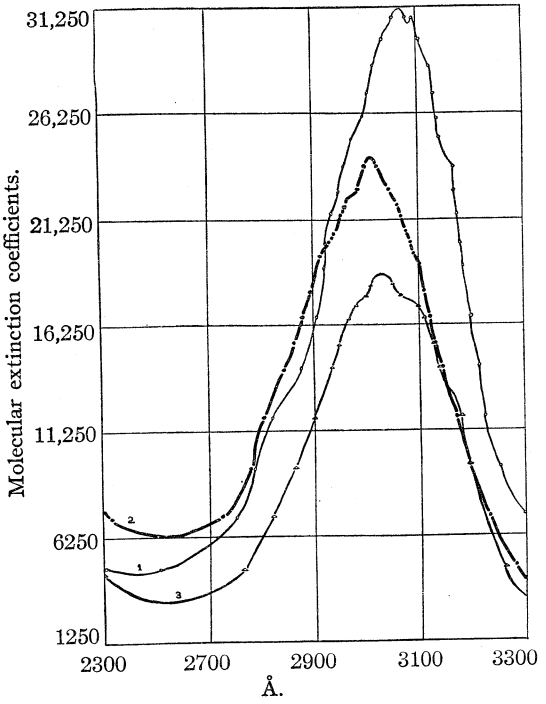


Fig. 2.—2-Hydroxy-6,8-diaminopurine: 1, *p*H 3.0; 2, *p*H 7.0; 3, *p*H 11.0.

aminopurine. In the case of isoguanine the inability to photograph the peak in acid and in alkaline solution may be due to the absorption of the buffers in the short wave end of the spectrum. This, in conjunction with any shift which might occur, could readily prevent it from being recognized under the experimental conditions.[8]

Figure 3 shows the effect of irradiation on isoguanine for as long as four hours. Unlike adenine, which is markedly stable to ultraviolet radiation isoguanine shows response of the type shown by barbituric acid.[4]

Summary

1. A comparison of 2-hydroxy-6-amino-pyrimidine and purine with 6-amino-pyrimidine and purine shows that the substitution of the hydroxyl group causes $\lambda_{max.}$ to shift to shorter wave lengths with increase in *p*H and $\epsilon_{max.}$ to rise at *p*H 7 and then to fall so that the value at *p*H 11.0 is lower than that at *p*H 3.

2. Location of the hydroxy group on C 6 in these compounds tend to increase $\epsilon_{max.}$ at neutral *p*H above that in acid or alkaline *p*H, whereas certain 2-hydroxy purines and pyrimidines have a reduced $\epsilon_{max.}$ at *p*H 7.0.

3. An additional amino group in the case of 2-hydroxy-6,8-diaminopurine shows the same general *p*H effect on $\lambda_{max.}$ but to a lesser degree, however $\epsilon_{max.}$ follows the amino substitutes.

4. Whereas adenine showed only negligible change on irradiation, isoguanine showed a decided change in extinction.

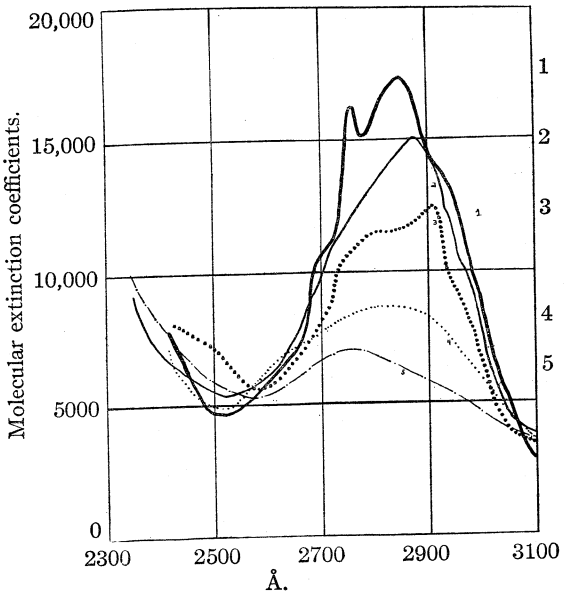


Fig. 3.—Effect of irradiation on isoguanine: 1, 15 min.; 2, 1 hr.; 3, 2 hr.; 4, 3 hr.; 5, 4 hr.

CINCINNATI, OHIO
ADRIAN, MICHIGAN

RECEIVED APRIL 16, 1942

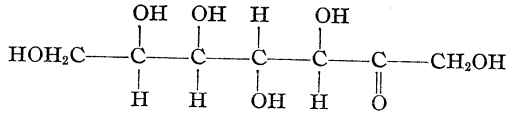
(8) Smakula, *Z. physiol. Chem.*, **230**, 231 (1934).

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

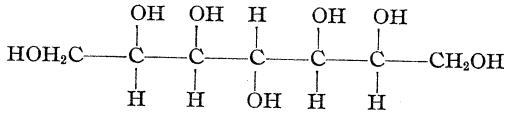
Some Studies on L-Glucoheptulose

BY W. DAYTON MACLAY, RAYMOND M. HANN AND C. S. HUDSON

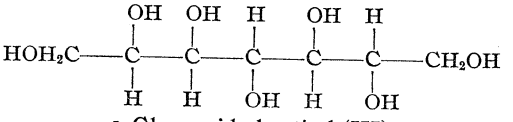
The biochemical oxidation of a number of polyatomic alcohols to ketoses by *Acetobacter suboxydans* has been reported[1] in previous publications from this Laboratory. The present article describes the preparation of L-glucoheptulose through the biochemical oxidation of D-gluco-D-gulo-heptitol[2] (α-glucoheptitol) by the procedure previously found to be successful for the oxidation of D-manno-D-gala-heptitol (perseitol) to L-galaheptulose. The L-glucoheptulose was obtained in a yield of 88%; the pure ketose melted at 172–173° (cor.) and exhibited a specific rotation $[\alpha]^{20}D$ of $-67.8°$ in water without mutarotation; these constants agree with those reported (m. p. 173.5°; $[\alpha]^{20}D$ $-67.1°$) by Bertrand and Nitzberg[3] for the "α-glucoheptulose" which they obtained by the biochemical oxidation of D-gluco-D-gulo-heptitol with *Bacterium xylinum* (syn. *Acetobacter xylinum*). Austin[4] has shown that "α-glucoheptulose" is L-glucoheptulose since it is the enantiomorph of D-glucoheptulose (m. p. 171–174°; $[\alpha]^{20}D$ $+67.7°$) prepared by the Lobry de Bruyn rearrangement of D-gluco-D-gulo-heptose (D-α-glucoheptose). He prepared the D-glucoheptose phenylosazone that is common to D-gluco-D-gulo-heptose and D-glucoheptulose and showed that it mutarotates in absolute alcohol–pyridine solution from $-5.3°$ to $+35.0°$; he pointed out that the phenylosazone of "α-glucoheptulose," which had been described by Bertrand and Nitzberg as identical with D-glucoheptose phenylosazone, must in reality have been the enantiomorphous L-glucoheptose phenylosazone. Bertrand and Nitzberg did not report its rotation; Austin did not have the L-form of glucoheptulose available for the repreparation of its phenylosazone. We have now confirmed the observation of Austin on the rotation of D-glucoheptose phenylosazone; we have also prepared the enantiomorphous L-glucoheptose phenylosazone from L-glucoheptulose and find that it mutarotates from $+6.0°$ to $-35.3°$ in absolute alcohol–pyridine solution, proving that the phenylosazones are enantiomorphs, as was concluded by Austin. Confirmation of the configuration of L-glucoheptulose (I) was obtained also through its reduction with hydrogen and Raney nickel to form a mixture of the inactive L-gluco-L-gulo-heptitol (syn. D-gluco-D-gulo-heptitol, α-glucoheptitol) (II) and the active L-gluco-L-ido-heptitol (syn. L-β-glucoheptitol) (III).



L-Glucoheptulose (I)



L-Gluco-L-gulo-heptitol (II)
(syn. D-Gluco-D-gulo-heptitol, α-Glucoheptitol)



L-Gluco-L-ido-heptitol (III)
(syn. L-Ido-D-gulo-heptitol, L-β-Glucoheptitol)

The alcohols were separated by conversion into their respective heptaacetates, that of L-gluco-L-gulo-heptitol crystallizing readily while that of L-gluco-L-ido-heptitol remained dissolved in the acetylating solution. The L-gluco-L-gulo-heptitol heptaacetate was optically inactive, melted at 118–119° (cor.) and gave a quantitative yield of the inactive L-gluco-L-gulo-heptitol upon deacetylation. The L-gluco-L-ido-heptitol heptaacetate was obtained as a sirup, which upon deacetylation yielded crystalline L-gluco-L-ido-heptitol, melting at 129–130° (cor.) and exhibiting a specific rotation $[\alpha]^{20}D$ of $-0.8°$ in water. The recorded values[5] of these constants for the enantiomorphous D-gluco-D-ido-heptitol are 130–131° and $+0.8°$, respectively, and we also have observed a melting point of 129–130° (cor.) and a specific rotation $[\alpha]^{20}D$ of $+0.7°$ in water on a sample of D-gluco-D-ido-heptitol prepared by the catalytic reduction of D-gluco-D-ido-heptose with hydrogen and Raney nickel. The L-gluco-L-ido-

(1) Hann, Tilden and Hudson, THIS JOURNAL, **60**, 1201 (1938); Hann and Hudson, *ibid.*, **61**, 336 (1939); Tilden, *J. Bact.*, **37**, 629 (1939).

(2) Concerning this nomenclature, see Hudson, THIS JOURNAL, **60**, 1537 (1938).

(3) Bertrand and Nitzberg, *Compt. rend.*, **186**, 925, 1172 (1928).

(4) Austin, THIS JOURNAL, **52**, 2106 (1930).

(5) Phillipe, *Compt. rend.*, **147**, 1481 (1908).

heptitol was further characterized by conversion to its crystalline heptabenzoate and this compound was found to have the same melting point, namely, 181–182° (cor.) as authentic D-gluco-D-ido-heptitol heptabenzoate; the specific rotation of the heptabenzoate in chloroform solution (−25.3°) was equal in magnitude, but opposite in sign, to that of the D-isomer. The data from the reduction therefore confirm the accepted configuration of L-glucoheptulose (I). They are also in agreement with the results obtained by Khouvine,[6] who has shown that D-glucoheptulose is reduced by hydrogen and Raney nickel to form D-gluco-D-gulo-heptitol and D-gluco-D-ido-heptitol, although reduction with sodium amalgam yielded D-gluco-D-gulo-heptitol and a substance designated as α-D-glucoheptulitol, which Humoller, Kuman and Snyder[7] regard as mixed crystals of D-gluco-D-gulo-heptitol and a small amount of an optically active impurity of undetermined identity.

We express our appreciation to Mr. L. B. Lockwood, Dr. Evelyn B. Tilden and Dr. W. T. Haskins for assistance in parts of this work.

Experimental

L-Glucoheptulose (I) from D-Gluco-D-gulo-heptitol.—A medium for inoculating the solution employed in the biochemical oxidation was prepared as follows: a solution of 10 g. of D-gluco-D-gulo-heptitol, 1.0 g. of Difco yeast extract, 0.6 g. of potassium acid phosphate and 0.1 g. of glucose in 200 cc. of water was placed in a 500-cc. Jena glass gas-washing bottle; following sterilization, a bacterial suspension of *Acetobacter suboxydans* was added, and the bottle was placed in a 30° constant temperature room and sterile air was passed through the suspension at a rate of 200 cc. per minute; after twenty-four hours the oxidation of the alcohol to ketose was complete and the inoculum was ready for use. A solution of 400 g. of D-gluco-D-gulo-heptitol, 20 g. of Difco yeast extract, 12 g. of potassium acid phosphate, 2 g. of glucose and 0.5 g. of octadecyl alcohol in 4000 cc. of water was sterilized in a 10-liter Pyrex bottle suitably equipped with an air intake and dispersion unit. After introduction of the previously described inoculum the bottle was placed in a 30° constant temperature room and sterile air was passed through the culture at a rate of 12 liters per minute. Subsamples were analyzed for reducing value at the expiration of 24, 48, 96, 120 and 144 hours and the analyses indicated that the oxidation was 9, 28, 80, 93 and 100% complete at these periods. The solution was clarified by filtration and successive treatments with lead acetate and hydrogen sulfide, and the final filtrate was concentrated *in vacuo* at 60° to a volume of 400 cc.; the sirup was diluted with 700 cc. of warm alcohol and as the solution cooled it deposited the crystalline ketose in a yield of 349 g. (m. p. 166–167°). A second crop of 6 g. was obtained by concentrating the filtrate to a volume of 55 cc. and adding 285 cc. of warm alcohol, and the final mother liquor, upon treatment with *p*-bromophenylhydrazine, gave a yield of L-glucoheptose *p*-bromophenylosazone equivalent to 12 g. of ketose. The yield of crystalline ketose was therefore 355 g. or 88%, and the over-all yield was 367 g. or 91%. The compound was recrystallized by solution in 1 part of water and addition of 5 parts of alcohol; it formed large rhombs which melted at 172–173° (cor.) and showed a specific rotation of −67.8° (*c*, 2.5; *l*, 4) in water, without detectable mutarotation. Bertrand and Nitzberg[3] reported a melting point of 173.5° and a specific rotation of −67.1° in water for "α-glucoheptulose" and Austin[4] reported a melting point of 171–174° and a specific rotation of +67.7° in water for D-glucoheptulose.

Mr. G. L. Keenan, of the Food and Drug Administration of the Federal Security Agency, has examined the L-glucoheptulose and finds its optical-crystallographic properties to be identical with those of authentic D-glucoheptulose, as would be expected. *In ordinary light*, the powdered L-glucoheptulose consists of angular fragments, showing by the immersion method in oily organic liquids refractive indices, $n_\alpha = 1.545$, n_β indeterminate and $n_\gamma = 1.560$, both ±0.002; *in parallel polarized light* (*crossed nicols*) the birefringence is moderate and the fragments extinguished sharply with crossed nicols, only an occasional fragment being found which remains bright; *in convergent polarized light* (*crossed nicols*), a partial biaxial interference figure is only rarely observed.

A mixture of 1.0 g. each of pure L- and D-glucoheptulose was recrystallized from 15 parts of warm alcohol. The crystals which were deposited as the solution cooled melted at 150–152° (cor.) and this melting point was unchanged by further recrystallization. This D,L-glucoheptulose showed no optical rotation in aqueous solution. An optical-crystallographic examination by Mr. Keenan disclosed that the indices of refraction of the crystals were identical with those of the optically active forms of the ketose; the crystals form therefore a mixture of the D- and L-modifications rather than a true racemate.

L-Glucoheptose Phenylosazone.—A solution of 10.0 g. of L-glucoheptulose in a mixture of 25 cc. of phenylhydrazine 12.5 cc. of acetic acid and 100 cc. of water was heated on the steam-bath for two hours. The osazone, which separated as an oil as the reaction progressed, crystallized readily as the suspension was cooled. The yield was 18.1 g. (98%). The compound was recrystallized from 25 parts

TABLE I

MUTAROTATION OF D- AND L-GLUCOHEPTOSE PHENYLOSAZONES

Concentration 1.6 g. in 100 cc.; tube length 1 dm.; temp. 20 ± 0.5°.

Time after making soln., hr.	D-Form	L-Form
0.25	− 5.6°	+ 6.0°
3	+ 9.0	− 9.6
6	+15.5	−15.7
24	+30.2	−31.0
48	+32.7	−34.2
96	+34.9	−35.3
120 (final)	+34.9	−35.3

(6) Khouvine, *Compt. rend.*, **204**, 983 (1937).

(7) Humoller, Kuman and Snyder, THIS JOURNAL, **61**, 3370 (1939).

of boiling alcohol in the form of yellow needles which melted with decomposition at 181–182° (cor.). The specific rotation was determined in a mixture of 2 parts of pyridine and 3 parts of absolute alcohol and, as shown in the following summary, it was equal in magnitude, but opposite in sign to that of a sample of authentic D-gluco-heptose phenylosazone.

A mixture of 1.0 g. of each of the enantiomorphous osazones was dissolved by refluxing in 250 cc. of alcohol and, upon cooling, the solution deposited yellow needles which melted at 176–177° (cor.). This melting point was not changed by recrystallization from alcohol and a pyridine–alcohol solution of the recrystallized product showed no rotation. Since the melting point of the compound is lower than that of its components it may be designated at the present time only as D,L-glucoheptose phenylosazone.

Anal. Calcd. for $C_{19}H_{24}O_5N_4$: C, 58.75; H, 6.23. Found: (for L-form) C, 58.78; H, 6.14; (for D,L-form) C, 58.13; H, 6.18.

Reduction of L-Glucoheptulose.—A solution of 50.0 g. of L-glucoheptulose in 250 cc. of water was heated for six hours at 100° under a pressure of 2500 pounds (167 atm.) of hydrogen in the presence of 10.0 g. of Raney nickel. Following removal of the catalyst, the solution was concentrated *in vacuo* at 60° to a thick sirup, which was thinned with 25 cc. of water and then mixed with 300 cc. of warm alcohol. As the solution cooled it deposited 47.5 g. of a mixture of plates and needles (m. p. 116–119°) and an additional 2.6 g. of crystalline material (m. p. 116°) was obtained from the mother liquor. The total yield was therefore 50.1 g. (99%). It was found impractical to separate the mixture of crystalline heptitols by fractional crystallization, and accordingly, 45.0 g. of the mixed alcohols was acetylated by heating for two hours on the steam-bath with 180 cc. of acetic anhydride and 11.3 g. of fused sodium acetate. The acetylation mixture was poured upon crushed ice and the precipitated L-gluco-L-gulo-heptitol heptaacetate (41 g., 38%) was removed by filtration. The acetate, after recrystallization from 4 parts of alcohol, melted at 118–119° (cor.) and this melting point was not depressed upon admixture with authentic L-gluco-L-gulo-heptitol heptaacetate. A chloroform solution of the substance showed no optical activity. Upon deacetylation the heptaacetate gave a quantitative yield of L-gluco-L-gulo-heptitol.

Anal. Calcd. for $C_{21}H_{30}O_{14}$: C, 49.79; H, 5.97; CH_3CO, 59.5. Found: C, 49.68; H, 5.89; CH_3CO, 59.2.

The dilute acetic acid mother liquor remaining, after removal of the crystalline L-gluco-L-gulo-heptitol heptaacetate, was neutralized with sodium bicarbonate and extracted with chloroform. The washed extract was concentrated to a dry sirup (59.5 g., 55%) which was dissolved in 500 cc. of absolute methanol and deacetylated with barium methylate in the usual manner. The solution was freed of barium ion by balancing out with sulfuric acid, and after concentration to a sirup was dissolved in 100 cc. of boiling methanol. The alcoholic solution upon cooling deposited L-gluco-L-ido-heptitol in a yield of 21.8 g. (48%). The substance was recrystallized by solution in 0.5 part of water and the addition of 10 parts of warm methanol; it formed plates which melted at 129–130° (cor.) and showed a specific rotation $[\alpha]^{20}D$ of −0.8° (*c*, 4.0; *l*, 4) in water. Pure D-gluco-D-ido-heptitol, prepared by the catalytic reduction of D-gluco-D-ido-heptose, melted at 129–130° (cor.) and showed a specific rotation $[\alpha]^{20}D$ of +0.7° in water in agreement with the recorded value[5] (m. p. 130–131°; $[\alpha]^{20}D$ +0.8°) of Phillipe. An examination by Mr. G. L. Keenan showed that the L- and D-forms of the alcohol possessed identical optical crystallographic properties. *In ordinary light* they consist of thin quadratic plates showing refractive indices, $n_\alpha = 1.552$, n_β indeterminate and $n_\gamma = 1.561$, both ±0.002; *in parallel polarized light* (*crossed nicols*) the birefringence is weak and low order polarization colors are invariably shown; no interference figures were observed *in convergent polarized light* (*crossed nicols*).

Anal. Calcd. for $C_7H_{16}O_7$: C, 39.60; H, 7.60. Found: C, 39.66; H, 7.54.

L-Gluco-L-ido-heptitol Heptabenzoate (L-β-Glucoheptitol Heptabenzoate).—A mixture of 1.0 g. of L-gluco-L-ido-heptitol, 5 cc. of pyridine, and 6 cc. (10.5 molecular equivalents) of benzoyl chloride was heated in a boiling water-bath for two hours. The solid reaction products were dissolved in a mixture of chloroform and water and the chloroform layer was separated, washed, dried over anhydrous sodium sulfate and concentrated to a sirup; the sirup was dissolved in 475 cc. of boiling alcohol and as the solution cooled it deposited the heptabenzoate in a yield of 3.2 g. (72%). The compound was recrystallized from 150 parts of boiling alcohol and was obtained in the form of needles which melted at 181–182° (cor.) and exhibited a specific rotation $[\alpha]^{20}D$ of −25.3° (*c*, 2.0; *l*, 4) in chloroform. D-Gluco-D-ido-heptitol heptabenzoate, prepared from D-gluco-D-ido-heptitol, obtained by the catalytic reduction of D-gluco-D-ido-heptose, showed the same melting point and its rotation, +25.1°, was the same in magnitude, but opposite in sign. Phillipe[5] recorded the melting point of D-gluco-D-ido-heptitol heptabenzoate as 182°, but did not measure its rotation.

Anal. Calcd. for $C_{56}H_{44}O_{14}$: C, 71.48; H, 4.71; C_6H_5CO, 78.2. Found: C, 71.55; H, 4.65; C_6H_5CO, 77.7.

Racemic Gluco-ido-heptitol Heptabenzoate (Racemic β-Glucoheptitol Heptabenzoate).—A mixture of 0.4 g. each of D-gluco-D-ido- and L-gluco-L-ido-heptitol heptabenzoates was dissolved in 640 cc. of boiling 95% alcohol and as the solution cooled it deposited the racemate in the form of small needles. The pure compound may be recrystallized from 750 parts of alcohol; it was devoid of optical activity in chloroform solution. Its melting point of 193–194° (cor.) is considerably higher than that of its components, which shows that it is a true racemate.

Anal. Calcd. for $C_{56}H_{44}O_{14}$: C, 71.48; H, 4.71; C_6H_5CO, 78.2. Found: C, 71.54; H, 4.63; C_6H_5CO, 78.0.

Racemic Gluco-ido-heptitol (Racemic β-Glucoheptitol).—A mixture of 1.0 g. each of pure D-gluco-D-ido-heptitol and L-gluco-L-ido-heptitol was dissolved in 1 cc. of water and the aqueous solution diluted with 50 cc. of hot absolute methanol. As the solution cooled, racemic gluco-ido-heptitol was deposited in a yield of 1.85 g. (92%). The substance was recrystallized by solution in 1 part of water and the addition of 30 parts of methanol and formed small plates which melted at 114–115° (cor.) and showed no ro-

tation in an aqueous solution. An optical-crystallographic examination of the compound by Mr. Keenan showed that *in ordinary light* the refractive indices were $n_\alpha = 1.552$, n_β indeterminate and $n_\gamma = 1.555$, both ± 0.002; *in parallel polarized light* (*crossed nicols*) the birefringence is weak and low order polarization colors are usually seen; no interference figures were observed *in convergent polarized light*. The differences in these optical-crystallographic properties from those of L-gluco-L-ido-heptitol indicate that the substance which is here described is a true racemate.

Anal. Calcd. for $C_7H_{16}O_7$: C, 39.60; H, 7.60. Found: C, 39.66; H, 7.72.

Summary

L-Glucoheptulose has been prepared in high yield through the biochemical oxidation of α-glucoheptitol with *Acetobacter suboxydans*. The phenylosazone of the ketose has been shown to possess a specific rotation equal in magnitude, but opposite in sign, to that of D-glucoheptose phenylosazone. Catalytic reduction of L-glucoheptulose by hydrogen and Raney nickel produces L-gluco-L-gulo-heptitol and L-gluco-L-ido-heptitol and thus provides supporting evidence for the accepted configuration of the ketose. New substances which have been described are D,L-glucoheptulose, L-gluco-L-ido-heptitol (L-β-glucoheptitol), L-gluco-L-ido-heptitol heptabenzoate, racemic gluco-ido-heptitol heptabenzoate, and racemic gluco-ido-heptitol.

BETHESDA, MD. RECEIVED APRIL 13, 1942

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

The Oxidative Degradation of L-Glucoheptulose

BY NELSON K. RICHTMYER AND C. S. HUDSON

In an earlier communication from this Laboratory[1] we reported the isolation of potassium L-galactonate in a 45% yield from the degradation of perseulose (L-galaheptulose) in alkaline solution by oxygen, according to the procedure developed by Spengler and Pfannenstiel.[2] Having available a considerable amount of L-glucoheptulose from another research,[3] we had planned to degrade it in similar fashion to potassium L-gluconate, and thus to obtain, by reduction of the lactone, the difficultly accessible L-glucose.[4] Unfortunately for our purpose the oxidation could not be controlled sufficiently to yield L-gluconic acid as the principal degradation product. Instead there was formed one of those complex mixtures of acids such as have been obtained, by a succession of enolizations and cleavages, from the oxidation of other sugars in alkaline solution by air.[5]

When the oxidation of L-glucoheptulose was carried out in the manner described previously for L-galaheptulose, the first product to be isolated was the readily crystallized potassium L-arabonate, in a yield of 31%. It was identified by its rotation[6] of +5.2° in water as compared to −5.0° for potassium D-arabonate, and by conversion to the benzimidazole derivative described by Moore and Link.[7] The remainder of the oxidation products was converted to a mixture of brucine salts. Crystallized from water, the least soluble fraction, about 14% of the theoretical yield, consisted of approximately equal amounts of the brucine salts of L-gluconic and L-erythronic acids. Brucine L-gluconate was identified by comparison of its constants with those recorded in the literature, by conversion to potassium L-gluconate rotating −11.3° in water as compared to +11.3° for potassium D-gluconate, and by conversion to 2-[L-*gluco*-pentahydroxyamyl]-benzimidazole. This last-named compound has the same melting point as the D-derivative described by Moore and Link,[8] while the rotation, −9.0° in citric acid solution, is about equal in magnitude but is opposite in sign to that recorded for its better-known antipode.

Brucine L-erythronate was identified by analy-

(1) Richtmyer, Hann and Hudson, THIS JOURNAL, **61**, 340 (1939).

(2) Spengler and Pfannenstiel, *Z. Wirtschaftsgruppe Zuckerind.*, **85**, Tech. Tl. 547 (1935).

(3) Maclay, Hann and Hudson, THIS JOURNAL, **64**, 1606 (1942).

(4) Fischer, *Ber.*, **23**, 2618 (1890); for the crystalline L-gluconolactone, see Kiliani, *ibid.*, **58**, 2349 (1925); Upson, Sands and Whitnah, THIS JOURNAL, **50**, 519 (1928). Although L-glucose has been reported to occur in *Grindelia robusta* [Power and Tutin, *Pub. Wellcome Chem. Research Lab.*, **57**, 1 (1905)], in capsularin, a glycoside from jute (*Corchorus capsularis*) [Saha and Choudhury, *J. Chem. Soc.*, **121**, 1044 (1922)], and collagen [Beek, THIS JOURNAL, **63**, 1483 (1941); *J. Research Natl. Bur. Standards*, **27**, 507 (1941)], the evidence is not conclusive in any case.

(5) See, for example, the degradation of D-glucose [Power and Upson, THIS JOURNAL, **48**, 195 (1926)].

(6) Throughout the article the rotations are specific rotations at 20° for sodium light; *c* designates concentration in grams per 100 cc. of solution, and *l* the length of the tube in decimeters.

(7) Moore and Link, *J. Biol. Chem.*, **133**, 300 (1940).

(8) Moore and Link, ref. 7; see also Haskins and Hudson, THIS JOURNAL, **61**, 1267 (1939).

sis, melting point and rotation, and by conversion to the known, crystalline L-erythronolactone. The latter was characterized further by preparing from it 2-[L-*erythro*-trihydroxypropyl]-benzimidazole, which has the same melting point as 2-[D-*erythro*-trihydroxypropyl]-benzimidazole prepared from D-erythronolactone; the rotations are similar in magnitude, but are opposite in sign.

The more soluble fractions of the brucine salts contained some additional brucine L-gluconate, but carbon and hydrogen analyses indicated that the rest of the material consisted chiefly of the brucine salts of hydroxy acids containing only two or three carbon atoms.

While the oxidative degradation of L-galaheptulose to L-galactonic acid had been satisfactory in regard to yield, the degradation of L-glucoheptulose was disappointing because the principal product isolated was L-arabonic acid. However, such a two-carbon atom degradation would be very useful if the oxidation of sedoheptulose should be found to produce D-ribonic acid in considerable amount in addition to the small yield of D-altronic acid already reported.[9]

The degradation of L-glucoheptulose to L-gluconic acid derivatives, as reported above, completes a series of reactions by which D-glucose has been transformed to its mirror-image, L-glucose, as follows: D-glucose → D-gluco-D-gulo-heptose (= D-α-glucoheptose)[10] → D-gluco-D-gulo-heptitol (= L-gluco-L-gulo-heptitol = α-glucoheptitol)[10] → L-glucoheptulose[11] → L-gluconic acid → L-glucose.[12]

Experimental Part

Oxidation of L-Glucoheptulose; Isolation of Potassium L-Arabonate.—A solution of 21 g. of L-glucoheptulose (0.1 mole) in 100 cc. of water was added to 150 cc. of 2 *N* aqueous potassium hydroxide (0.3 mole) and the mixture was shaken vigorously with oxygen at 20–25°. After twenty-four hours the oxygen consumption had ceased at about 3000 cc., measured at room temperature. A product was isolated, as in the oxidation of perseulose, by concentration, precipitation with methyl alcohol, and crystallization from water by the addition of methyl alcohol. It was identified as potassium L-arabonate,[13] and was obtained in a 31% yield (average).

Anal. Calcd. for $C_5H_9O_6K$: K, 19.15. Found: K, 19.20.

A thrice recrystallized sample rotated[6] +5.2 ± 0.1° in water (*c*, 5; *l*, 4). For comparison, a specimen of potassium D-arabonate was crystallized to constant rotation and showed −5.0 ± 0.1° in water (*c*, 5; *l*, 4). Both D- and L-salts melted about 220° with decomposition. The potassium L-arabonate was characterized further by conversion to 2-[L-*arabo*-tetrahydroxybutyl]-benzimidazole by the procedure of Moore and Link.[7] This derivative melted at 235° (decomp.) and rotated +49.7 ± 0.2° in 5% citric acid solution (*c*, 2), in good agreement with the data reported by those authors.

Isolation of L-Gluconic Acid Derivatives.—After 145 g. of potassium L-arabonate had been separated from the products obtained by the oxidation of 478 g. of L-glucoheptulose, the mother liquor was acidified with hydrochloric acid until all the organic acids had been liberated. The solution was concentrated *in vacuo* to a thin sirup which was diluted with methyl alcohol and most of the potassium chloride was removed by filtration. The filtrate was concentrated to a thick sirup which was heated *in vacuo* for two hours at 70°, and the lactones and acids were extracted from the remainder of the potassium chloride with hot absolute alcohol. The alcohol was removed by distillation, and the residue was heated for several hours with 1500 cc. of water and 60 g. of calcium carbonate. Excess carbonate and any calcium oxalate were removed by filtration. Inasmuch as no crystalline calcium salt could be obtained by concentrating the aqueous solution, the calcium ions were removed by the addition of an equivalent amount of oxalic acid, as determined by analysis of an aliquot portion, and the organic acids were then converted to brucine salts in the usual manner. Upon concentration of the aqueous solution of the brucine salts, there were obtained several crops of crystals, totaling 181 g. An attempt to purify this material showed that it consisted of about equal amounts of the brucine salts of L-gluconic and L-erythronic acids which could be separated, partially, by a series of extractions and crystallizations with methyl alcohol. In this way we were able to isolate **brucine L-gluconate** in clusters of elongated, more or less rectangular, plates which were solvent-free after being dried in the air at room temperature. The rotation, −28.6° in water (*c*, 4), is higher than −25.4° in water (*c*, 4), the only value recorded previously, by Upson, Sands and Whitnah.[14] The melting point, 180° with evolution of gas, is in agreement with that of those authors, but is higher than the value 167–168° reported by Kiliani.[14]

Anal. Calcd. for $C_{29}H_{38}N_2O_{11}$: C, 58.97; H, 6.49. Found: C, 59.36; H, 6.59.

A portion of the brucine L-gluconate was converted to barium L-gluconate by treatment with barium hydroxide in the usual manner. Although barium L-gluconate has been obtained in crystalline form by Kiliani,[14] our product was amorphous. By reacting with an equivalent amount of potassium sulfate, the barium salt was converted to a crystalline potassium salt. **Potassium L-gluconate,** twice recrystallized from water by the addition of methyl alcohol, separated in clusters of flattened, acicular prisms. It melted about 185° with decomposition, and rotated −11.3 ± 0.2° in water (*c*, 4; *l*, 4).

Anal. Calcd. for $C_6H_{11}O_7K$: K, 16.69. Found: K, 16.82, 16.62.

(9) Richtmyer, Hann and Hudson, THIS JOURNAL, **61**, 343 (1939).
(10) Fischer, *Ann.*, **270**, 64 (1892).
(11) Bertrand and Nitzberg, *Compt. rend.*, **186**, 925 (1928).
(12) Fischer, ref. 4.
(13) First prepared by Kiliani, *Ber.*, **21**, 3009 (1888); neither m. p. nor rotation was reported.
(14) Upson, Sands and Whitnah, THIS JOURNAL, **50**, 519 (1928). *cf.* Kiliani, *Ber.*, **55**, 100 (1922); **58**, 2349 (1925).

Potassium D-gluconate, prepared for comparison and thrice recrystallized as similar acicular prisms, melted at 185° (decomp.), and rotated +11.3 ± 0.2° in water (*c*, 4; *l*, 4). This value is higher than the value +10.3° reported by May, Weisberg and Herrick[15] but lower than the +13.0° reported by Nilkantum.[16]

Final identification of L-gluconic acid was obtained by converting it to **2-[L-*gluco*-pentahydroxyamyl]-benzimidazole** by the procedure of Moore and Link.[7] This compound, after four recrystallizations as colorless needles from water, melted about 215° with decomposition, and rotated −9.0 ± 0.2° in 5% citric acid solution (*c*, 2; *l*, 4). Although optical enantiomorphs should have equal and opposite rotations, according to the classical views of stereochemistry,[17] this rotation is slightly lower in magnitude than the value +9.6° reported by Moore and Link, and +9.5 ± 0.2° as confirmed by our own measurements for the D-antipode; this is due perhaps to the presence of a very small amount of the dextrorotatory (+49.7°), rather insoluble L-*arabo*-benzimidazole which might accompany the L-*gluco* derivative as an impurity.

Anal. Calcd. for $C_{12}H_{16}N_2O_5$: C, 53.72; H, 6.02. Found: C, 53.72; H, 6.04.

Isolation of L-Erythronic Acid Derivatives.—Besides brucine L-gluconate we were able to isolate, from the less soluble brucine salts, **brucine L-erythronate.** This salt crystallized from methyl alcohol as small, colorless prisms with many faces. The air-dried product contained about 0.9% of water which it lost in a desiccator but regained upon subsequent exposure to the air. It melted about 210° with vigorous decomposition. The rotation, on a solvent-free basis, was −31.6° in water (*c*, 4), or slightly higher than the value −28.4° in water (*c*, 4) reported by Ruff.[18]

Anal. Calcd. for $C_{27}H_{34}N_2O_9$: C, 61.12; H, 6.46. Found, on sample dried at 100° *in vacuo:* C, 61.08; H, 6.42.

The conversion of brucine L-erythronate to **L-erythronolactone** was accomplished by standard procedures. The lactone crystallized from ethyl acetate as elongated, flattened prisms, which appeared to consist of bundles of tough, flexible needles. The m. p. 102–103° and the rotation +73.0° in water (*c*, 4) are in agreement with the data of Glattfeld and Forbrich.[19]

Benzimidazole derivatives were prepared from both D- and L-erythronolactones by the procedure of Moore and Link.[7] The compounds were recrystallized from 12 parts of hot water, as colorless, prismatic needles melting at 177–178°. A thrice-recrystallized sample of **2-[D-*erythro*-trihydroxypropyl]-benzimidazole** rotated +9.0 ± 0.2° in 5% citric acid solution (*c*, 2; *l*, 4), and the twice recrystallized **2-[L-*erythro*-trihydroxypropyl]-benzimidazole** rotated −8.3 ± 0.2° under identical conditions. The L-form may be contaminated with a very small amount of the L-*arabo*-benzimidazole which would lower the rotation.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81. Found: (D-form) C, 57.73; H, 5.76; (L-form) C, 57.58; H, 5.78.

One of the authors (N. K. R.) desires to thank the Chemical Foundation of New York for a Research Associateship. The authors express their indebtedness to Dr. W. Dayton Maclay and Dr. Raymond M. Hann for their generous gift of L-glucoheptulose, and to Dr. Arthur T. Ness for carrying out the micro-analyses.

Summary

1. L-Glucoheptulose has been degraded in alkaline solution by oxygen to potassium L-arabonate in a 31% yield. Smaller amounts of L-gluconic and L-erythronic acids were isolated and identified by means of their salts and other derivatives.

2. The D- and L-forms of 2-[*erythro*-trihydroxypropyl]-benzimidazole have been described.

3. The transformation of D-glucose to L-glucose has now been completed by the step involving the degradation of L-glucoheptulose to L-gluconic acid.

BETHESDA, MD. RECEIVED APRIL 13, 1942

(15) May, Weisberg and Herrick, *J. Wash. Acad. Sci.*, **19**, 443 (1929).

(16) Nilkantum, *J. Sci. Tech.* (India), **2**, 39 (1936); *C. A.*, **32**, 1402 (1938).

(17) This has been verified in the case of the *arabo* and *galacto* pairs of benzimidazoles; see Richtmyer and Hudson, THIS JOURNAL, **64**, 1612 (1942).

(18) Ruff, *Ber.*, **34**, 1369 (1901); see also Nef, Hedenburg and Glattfeld, THIS JOURNAL, **39**, 1638 (1917).

(19) Glattfeld and Forbrich, *ibid.*, **56**, 1209 (1934); *cf.* Ruff, ref. 18.

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

A Benzimidazole Rule for the Determination of Configuration of the Aldonic Acids and Related Compounds

BY NELSON K. RICHTMYER AND C. S. HUDSON

During the course of a recent investigation[1] in which several 2-[*aldo*-polyhydroxyalkyl]-benzimidazoles were prepared for the identification of aldonic acids, as recommended by Moore and Link,[2] a certain correlation was noticed between the sign of rotation and the configuration of the compound. This correlation may be stated in the form of a "benzimidazole rule" as follows: *whenever the hydroxyl group on the second (or alpha) carbon atom of an aldonic acid is written on the right in the conventional projection formula, the rotation of the derived benzimidazole is positive, and conversely, when the hydroxyl group is written on the left, the rotation of the benzimidazole derivative is negative.*

In Table I are recorded the specific and molecular rotations in either aqueous citric or hydrochloric acid, or both, of the known benzimidazoles derived from the optically active aldonic acids. Of these, the D-*ribo*, the D-*glucomethylo*, the L-*galacto*, and the D-*gluco*-L-*gala*-*octo* derivatives are described for the first time; the D-*arabo*, the D-*galacto* and the D-*gluco* derivatives have been prepared and recrystallized to constant rotation the better to compare the D- and L-forms of these substances. All twenty-three compounds, or all nineteen if we include only one member of a D and L pair, are in agreement with the rule stated above. From the laws of probability we should expect this rule to hold for other benzimidazoles of this class which may be prepared in the future.[2a] Consequently, this benzimidazole rule, like the well-known phenylhydrazide[3] and amide[4] rules, may be used to determine the configuration of the hydroxyl group on the carbon atom adjacent to the carboxyl group of an aldonic acid.

If the benzimidazole derivatives listed in Table I are arranged according to the configurations of the hydroxyl groups on the second and third carbon atoms, certain additional correlations will be noted. When these hydroxyl groups are in a *cis* relationship, as in compounds 1, 2, 5, 6, 9, 15, 17, 18, 19 and 20, the molecular rotations are of relatively low magnitude, the highest being +7350 in the case of the L-*mannomethylo* derivative. When the hydroxyl groups in question are in a *trans* relationship, the compounds may be separated further into two classes. The members of the one class, with the hydroxyl groups on the second, third and fourth carbon atoms in a + − − or − + + sequence (arabonic configuration), as in compounds 3, 4, 10, 11, 12, 22 and 23, have relatively high molecular rotations, between 11,750 and 14,750. The members of the other class, with the same three hydroxyl groups in a + − + or − + − sequence (xylonic configuration), seem to show no regularity in their molecular rotations, the values ranging from +1900 for the D-*glucomethylo* to +15,450 for the D-*xylo* derivative. As new benzimidazoles are prepared in the future for characterization and determination of configuration of other aldonic acids, additional regularities or irregularities in their rotations may become evident.

One of the authors (N. K. R.) desires to thank the Chemical Foundation of New York for a Research Associateship. The authors also express their indebtedness to Dr. Arthur T. Ness for carrying out the microanalyses.

Summary

1. The "benzimidazole rule" may be stated as follows: whenever the hydroxyl group on the second (or alpha) carbon atom of an aldonic acid is written on the right in the conventional projection formula, the rotation of the derived benzimidazole is positive and, conversely, when the hydroxyl group is written on the left, the rotation of

(1) Richtmyer and Hudson, THIS JOURNAL, **64**, 1609 (1942).

(2) Moore and Link, *J. Biol. Chem.*, **133**, 300 (1940); *J. Org. Chem.*, **5**, 637 (1940).

(2a) Note added June 10, 1942.—Dimler and Link [*J. Biol. Chem.*, **143**, 557 (1942)] have reported the rotation of the benzimidazole derivative of L-lactic acid ("sarco" lactic acid, with the configuration $CH_3-\underset{H}{\overset{OH}{C}}-COOH$) to be −33.4° in ethyl alcohol, and the rotation of the D-antipode to be +33.4° in the same solvent. Inasmuch as the L-derivative has a rotation of −14.7° in 5% aqueous citric acid [Moore, Dimler and Link, *Ind. Eng. Chem., Anal. Ed.*, **13**, 160 (1941)] the data for these derivatives of the simplest optically active α-hydroxy acid are in accord with the benzimidazole rule.

(3) Levene, *J. Biol. Chem.*, **23**, 145 (1915); Hudson, THIS JOURNAL, **39**, 462 (1917).

(4) Hudson, THIS JOURNAL, **40**, 813 (1918).

TABLE I

ROTATIONS OF 2-[*aldo*-POLYHYDROXYALKYL]-BENZIMIDAZOLES

No.	Substituent group	Configuration of the second carbon atom[a]	Rotation in 5% aqueous citric acid[b] $[\alpha]^{20}D$	$[M]^{20}D$	Rotation in *N* HCl[b] $[\alpha]^{20}D$	$[M]^{20}D$
1	D-Erythro	+	+ 9.0°[c]	+ 1,850		
2	L-Erythro	−	− 8.3[c,d]	− 1,750		
3	D-Arabo[e]	−	−49.4	−11,750	−49.7	−11,850
4	L-Arabo	+	+49.7[c,f]	+11,850	+49.8[g]	+11,850
5	D-Lyxo	−	−12.8[h]	− 3,050		
6	D-Ribo[i]	+	+21.6	+ 5,150		
7	D-Xylo	+	+64.8[h]	+15,450		
8	D-Glucomethylo[j]	+	+ 7.6	+ 1,900		
9	L-Mannomethylo[k]	+	+27.4[h]	+ 6,900	+29.1[l]	+ 7,350
10	D-Altro	−			−48.1[l]	−12,900
11	D-Galacto	+	+44.5[m]	+11,950	+45.1[n]	+12,100
12	L-Galacto[o]	−	−44.1	−11,850	−45.0	−12,050
13	D-Gluco	+	+ 9.5[p]	+ 2,550	+ 8.7[q]	+ 2,350
14	L-Gluco	−	− 9.0[c,d]	− 2,400	− 8.3[d]	− 2,250
15	D-Gulo	+			+16.7[l]	+ 4,500
16	D-Ido	−			−19.2[l]	− 5,150
17	D-Manno	−	−22.0[h]	− 5,900	−23.7[l]	− 6,350
18	D-Talo	−			−23.0[l]	− 6,150
19	D-Gala-L-manno-hepto[r]	+			+18.5[l]	+ 5,500
20	D-Gluco-D-gulo-hepto[r]	+			+14.3[l]	+ 4,250
21	D-Gluco-D-ido-hepto[r]	−			−27.6[l]	− 8,250
22	D-Manno-D-gala-hepto[r]	+			+49.5[l]	+14,750
23	D-Gluco-L-gala-octo[r,s]	−			−44.7	−14,700

[a] A plus sign indicates that the hydroxyl group on the second carbon atom is on the right, and a minus sign indicates that the hydroxyl group is on the left, when the aldonic acid is written in the usual vertical projection formula. [b] The specific rotations reported by the present authors, either here or in a preceding paper (ref. *c*), were measured in a 4-dm. tube; the values are considered accurate to ±0.2°. Concentrations were 2 g. per 100 cc. of solution unless otherwise noted. The rotations reported by Moore and Link (ref. *h*) were observed at 25°. [c] Richtmyer and Hudson, THIS JOURNAL, **64,** 1609 (1942). [d] The rotations observed in the cases of the L-*erythro* and L-*gluco* benzimidazoles were slightly lower than the corresponding values in the D-series; this is due, probably, to the presence of a trace of a high dextrorotating, less soluble impurity (see ref. *c*). [e] This compound was prepared first by Moore and Link (ref. *h*, p. 307). The rotation was reported as −51°; no analysis was given. *Anal.* Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92. Found: C, 55.31; H, 5.88. [f] Reported as +49.2° by Moore and Link, ref. *h*. [g] Reported as +51.96° in 5 *N* HCl (*c*, 1.6) by Ohle, *Ber.*, **67,** 162 (1934). [h] Moore and Link, *J. Biol. Chem.*, **133,** 301 (1940). [i] **2-[D-*Ribo*-tetrahydroxybutyl]-benzimidazole** was prepared from D-ribonolactone which was obtained in turn from cadmium D-ribonate, furnished through the courtesy of Dr. C. R. Addinall of the Merck Research Laboratories. The product was recrystallized from hot water, in which it is readily soluble, as prismatic needles melting about 190° (decomp.). *Anal.* Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92. Found: C, 55.48; H, 5.81. [j] Also known as D-*isorhamno* (see ref. *r*). The **2-[D-*glucomethylo*-tetrahydroxyamyl]-benzimidazole** was recrystallized from hot water, in which it is readily soluble, as needles melting about 190° (decomp.). *Anal.* Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39. Found: C, 57.28; H, 6.25. [k] Also known as L-*rhamno* (see ref. *r*). [l] Haskins and Hudson, THIS JOURNAL, **61,** 1267 (1939). [m] Reported as +43.3° by Moore and Link, ref. *h*. [n] Reported as +44.4° by Haskins and Hudson, ref. *l*, and also by Moore and Link, ref. *h*, p. 309. [o] **2-[L-*Galacto*-pentahydroxyamyl]-benzimidazole** was prepared from the γ-L-galactonolactone described by Richtmyer, Hann and Hudson, THIS JOURNAL, **61,** 342 (1939). The product was recrystallized four times from 50% aqueous alcohol as fine needles melting about 250° (decomp.). *Anal.* Calcd. for $C_{12}H_{16}N_2O_5$: C, 53.72; H, 6.02. Found: C, 53.82; H, 6.18. [p] Reported as +9.6° by Moore and Link, ref. *h*. [q] Reported as +8.9° by Haskins and Hudson, ref. *l*, and +9.4° by Moore and Link, ref. *h*, p. 309. [r] For the nomenclature of the methylpentoses, heptoses and octoses, see Hudson, THIS JOURNAL, **60,** 1537 (1938). [s] The **2-[D-*gluco*-L-*gala*-*octo*-heptahydroxyheptyl]-benzimidazole** was prepared in this Laboratory by Dr. Alice T. Merrill and Dr. Raymond M. Hann, to whom we are indebted for permission to publish their data. The compound was thrice recrystallized from water as fine needles melting at 246–247° with decomposition. The rotation was observed at a concentration of 1 g. per 100 cc., in a 4-dm. tube. *Anal.* Calcd. for $C_{14}H_{20}N_2O_7$: C, 51.21; H, 6.14; N, 8.53. Found: C, 51.05; H, 5.96; N, 8.69.

the benzimidazole derivative is negative. No exceptions have been noted.

2. D-*Ribo*, D-*glucomethylo*, L-*galacto* and D-*gluco*-L-*gala*-*octo* benzimidazoles have been described.

BETHESDA, MD. RECEIVED APRIL 13, 1942

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

The Structure of Di-*o*-nitrobenzylidene-dulcitol (1,3:4,6-Di-*o*-nitrobenzylidene-dulcitol)

BY RAYMOND M. HANN, W. T. HASKINS AND C. S. HUDSON

Tanasescu and Macovski[1] have assigned the structure of a 1,2:5,6-di-*o*-nitrobenzylidene-dulcitol to a substance which they obtained by condensing *o*-nitrobenzaldehyde and dulcitol through the agency of 75% sulfuric acid. They stated that the behavior exhibited by dulcitol in forming this supposed 1,2:5,6-diacetal was a general property of this hexitol and in their communication they assigned 1,2:5,6-diacetal structures to the dimethylene-dulcitol of Weber and Tollens[2] and the dibenzylidene-dulcitol of Emil Fischer,[3] although the original investigators did not designate 1,2:5,6 or any other structure for the diacetals which were described by them. No evidence justifying the assignment of a definitive structure to any of these diacetals appears in the experimental work reported by Tanasescu and Macovski. Recently it has been established that Fischer's dibenzylidene-dulcitol is 1,3:4,6-dibenzylidene-dulcitol[4] and that the dimethylene-dulcitol of Weber and Tollens is 1,3:4,6-dimethylene-dulcitol.[5] In the present paper we present conclusive evidence that the di-*o*-nitrobenzylidene-dulcitol of Tanasescu and Macovski possesses an analogous structure and is therefore 1,3:4,6-di-*o*-nitrobenzylidene-dulcitol and not 1,2:5,6-di-*o*-nitrobenzylidene-dulcitol as was assumed by its discoverers.

The di-*o*-nitrobenzylidene-dulcitol which was employed in the investigation was prepared by the method of Tanasescu and Macovski and melted at 261–262° (cor.) in substantial agreement with the melting point of 256–258° (presumably uncor.) reported by them. It formed a dibenzoate which melted at 320–321° (cor.); the melting point recorded for the dibenzoate by them was 310° (presumably uncor.). The diacetal was tested for the presence of contiguous hydroxyl groups by oxidation with lead tetraacetate in glacial acetic acid. It was concluded that they were absent, because of the slight consumption of oxidant (only 0.043 of a molecular equivalent in twenty-two hours); thus hydrolysis of the diacetal appears to be necessary before oxidation can proceed. If the compound possessed the structure proposed by Tanasescu and Macovski it would contain a glycol grouping at positions 3 and 4 and it should consume one molecular equivalent of lead tetraacetate upon oxidation. The acetal linkages therefore cannot be at positions 1,2 and 5,6 of the hexitol. Definitive proof of their location at positions 1,3 and 4,6 was obtained when it was found that dibenzoyl-di-*o*-nitrobenzylidene-dulcitol, upon simultaneous hydrolysis and acetylation in a 2% sulfuric acid acetylating mixture, formed the known 2,5-dibenzoyl-1,3,4,6-tetraacetyl-dulcitol. Previous experience has indicated that this reaction proceeds with the substitution of acetyl groups on those hydroxyl groups which are concerned in the acetal formation as evidenced by the formation of 2,5-dibenzoyl-1,3,4,6-tetraacetyl-dulcitol from 2,5-dibenzoyl-1,3:4,6-dibenzylidene-dulcitol[4] and of 1,6-dibenzoyl-2,3,4,5-tetraacetyl-dulcitol from 1,6-dibenzoyl-2,3,4,5-dibenzylidene-dulcitol.[6] Acyl migration of benzoyl groups has not been observed in the transformation of a dibenzoylated hexitol diacetal into a dibenzoyltetraacetyl-hexitol by this reagent. The isolation of the same dibenzoyl-tetraacetyl-dulcitol from the dibenzoate of di-*o*-nitrobenzylidene-dulcitol and from 2,5-dibenzoyl-1,3:4,6-dibenzylidene-dulcitol may thus be accepted as strong evidence that the acetal linkages in di-*o*-nitrobenzylidene-dulcitol are at positions 1,3 and 4,6 of the dulcitol moiety.

We express our appreciation to the Atlas Powder Company for furnishing a supply of dulcitol.

Experimental

1,3:4,6-Di-*o*-nitrobenzylidene-dulcitol.—This compound was prepared from dulcitol and *o*-nitrobenzaldehyde by the procedure described by Tanasescu and Macovski.[1] It was recrystallized from 40 parts of acetic acid or dioxane and formed yellow needles which melted at 261–262° (cor.). Tanasescu and Macovski recorded a melting point of 256–258°. The yield of product from 5 g. of dulcitol was 12.0 g. (98%).

Anal. Calcd. for $C_{20}H_{20}O_{10}N_2$: C, 53.57; H, 4.50; N, 6.25. Found: C, 53.51; H, 4.47; N, 6.17.

(1) Tanasescu and Macovski, *Bull. soc. chim.*, [4] **53**, 1097 (1933).
(2) Weber and Tollens, *Ann.*, **299**, 316 (1898).
(3) Fischer, *Ber.*, **27**, 1534 (1894).
(4) Haskins, Hann and Hudson, THIS JOURNAL, **64**, 132 (1942).
(5) Hann, Haskins and Hudson, *ibid.*, **64**, 986 (1942).
(6) Haskins, Hann and Hudson, *ibid.*, **64**, 137, 139 (1942).

Failure of Lead Tetraacetate to Oxidize 1,3:4,6-Di-*o*-nitrobenzylidene-dulcitol.—To a solution of 0.1605 g. of the di-*o*-nitrobenzylidene-dulcitol in 80 cc. of glacial acetic acid, 12 cc. of 0.09108 *N* lead tetraacetate-glacial acetic acid solution (3.05 molecular equivalents) was added and the volume was adjusted to 100 cc. with glacial acetic acid. Analysis of 5-cc. aliquots at the expiration of fifteen minutes, one hour, and twenty-two hours, at 20°, showed that 0.016, 0.016 and 0.043 molecular equivalents of oxidant had been consumed; this slight reducing action was presumably due to a slow hydrolysis of the diacetal. A 1,2:5,6-di-*o*-nitrobenzylidene-dulcitol should reduce one molecular equivalent of lead tetraacetate; the failure of the substance to reduce lead tetraacetate indicated that it does not contain a glycol grouping, and therefore cannot possess the 1,2:5,6-diacetal structure proposed by Tanasescu and Macovski.

2,5-Dibenzoyl-1,3:4,6-di-*o*-nitrozylidene-dulcitol.—A solution of 1.0 g. of the di-*o*-nitrobenzylidene-dulcitol in 20 cc. of pyridine was cooled in an ice-bath and after the addition of 5.0 g. of benzoyl chloride, the reaction mixture was allowed to stand at room temperature (25°) for seventy-two hours. The dibenzoate, which precipitated in quantitative yield from the mixture upon the addition of water, was recrystallized from 15 parts of pyridine; it formed yellow prisms which were devoid of optical activity in pyridine solution and melted at 320–321° (cor.) on an electrically heated microscope stage. Tanasescu and Macovski recorded a melting point of 310° for the compound.

Anal. Calcd. for $C_{34}H_{28}O_{12}N_2$: C, 62.19; H, 4.30. Found: C, 62.16; H, 4.19.

2,5-Diacetyl-1,3:4,6-di-*o*-nitrobenzylidene-dulcitol.—The diacetate was obtained in quantitative yield by the acetylation of the di-*o*-nitrobenzylidene-dulcitol in pyridine solution with acetic anhydride. The substance was practically insoluble in boiling alcohol or chloroform, but could be recrystallized from 200 parts of acetic anhydride; it formed small needles which melted at 320–321° (cor.) on an electrically heated microscope stage.

Anal. Calcd. for $C_{24}H_{24}O_{12}N_2$: C, 54.13; H, 4.54; CH_3CO, 16.2. Found: C, 54.00; H, 4.66; CH_3CO, 16.0.

2,5-Ditosyl-1,3:4,6-di-*o*-nitrobenzylidene-dulcitol.—A solution of 1.0 g. of the di-*o*-nitrobenzylidene-dulcitol and 1.5 g. of *p*-toluenesulfonyl chloride in 25 cc. of pyridine was refluxed for two hours; the 1.0 g. of precipitate which formed on cooling the solution was separated by filtration and recrystallized from 50 parts of acetic anhydride to constant physical properties. The ditosylate formed light yellow needles which decomposed at 221–222° (cor.) and were optically inactive in pyridine.

Anal. Calcd. for $C_{34}H_{32}O_{14}S_2N_2$: C, 53.96; H, 4.26; S, 8.47. Found: C, 54.15; H, 4.31; S, 8.32.

2,5-Dibenzoyl-1,3,4,6-tetraacetyl-dulcitol from 2,5-Dibenzoyl-1,3:4,6-di-*o*-nitrobenzylidene-dulcitol.—A suspension of 2.0 g. of the dibenzoyl-di-*o*-nitrobenzylidene-dulcitol in 50 cc. of an acid acetylating solution, prepared by adding 1 cc. of concentrated sulfuric acid dropwise to an ice-cold mixture of 35 cc. of acetic anhydride and 15 cc. of acetic acid, was agitated until the suspended solid dissolved completely (two and one-half hours) and the solution was allowed to stand at 20° overnight. The mixture was then poured into 300 cc. of ice-cold water and the crystalline precipitate (1.0 g., 59%) which formed was separated by filtration and recrystallized twice from 25 parts of alcohol. It then showed a melting point of 157–158° (cor.), and a mixed melting point with authentic 2,5-dibenzoyl-1,3,4,6-tetraacetyl-dulcitol[4] showed no depression. The conversion of the dibenzoate of the di-*o*-nitrobenzylidene-dulcitol of Tanasescu and Macovski to 2,5-dibenzoyl-1,3,4,6-tetraacetyl-dulcitol is a definitive proof that the acetal linkages in the former compound are at positions 1,3 and 4,6 of the dulcitol molecule and not at the 1,2 and 5,6 positions as assumed by these investigators.

Anal. Calcd. for $C_{28}H_{30}O_{12}$: C, 60.21; H, 5.41. Found: C, 60.32; H, 5.49.

Summary

The di-*o*-nitrobenzylidene-dulcitol described by Tanasescu and Macovski is not oxidized by lead tetraacetate in glacial acetic acid and therefore cannot possess the structure of 1,2:5,6-di-*o*-nitrobenzylidene-dulcitol arbitrarily assigned to it by its discoverers. Its crystalline dibenzoate is converted to the known 2,5-dibenzoyl-1,3,4,6-tetraacetyl-dulcitol by treatment with an acid acetylating mixture, a fact which proves that the acetal linkages are at positions 1,3 and 4,6 of the dulcitol molecule. The compound of Tanasescu and Macovski is therefore 1,3:4,6-di-*o*-nitrobenzylidene-dulcitol and its structure is analogous to that of the diacetals which dulcitol forms with benzaldehyde and formaldehyde.

BETHESDA, MD. RECEIVED APRIL 21, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Isolation of a Copper Bearing Protein from Cow's Milk

BY WILLIAM L. DILLS AND J. M. NELSON

The presence of traces of copper in plant and animal tissues is attracting more and more attention. Not only is it being recognized as essential for the formation of hemin iron in animals[1] but it also has been found to play a role in the form of copper proteins as oxidases in plants.[2] Recently Saha and Guha[3] report the presence in animal tissues of a non-hemin iron associated with copper in the form of a copper–iron nucleoprotein complex.

Cow's milk contains from 0.09 to 0.17 mg. of inherent copper per liter.[4] Since the copper in milk appears not to be combined with the fat, it has been suggested that it probably occurs combined with the protein.[5] In the present study, a protein has been isolated from milk containing around 15% nitrogen and 0.19% copper. Dialysis experiments showed the copper in this protein to be non-ionic in form. Due to lack of sufficient material it was not possible to establish definitely that the protein isolated was absolutely pure, although comparing its copper content with those of other copper bearing proteins listed below suggests that it might have been mainly a single chemical substance. No attempt was made in the present study to see whether the milk copper protein was related in any way to the haemocuprein in blood.

Copper protein	Source	Copper, %
Laccase[6]	Juice of the lac-tree	0.15
Ascorbic acid oxidase[7]	Crook-neck squash	.15
Tyrosinase[8]	Lactarius piperatus	.23
Tyrosinase[2]	Common mushroom	.30
Tyrosinase[10]	Potato	.20
Haemocyanins[11]	Certain invertebrates	0.19–0.26
Haemocuprein[9]	Blood	0.34

No reactions were found in which the milk copper protein showed enzymatic activity. The authors are inclined to the opinion that this non-enzymatic activity cannot be attributed to denaturation during its isolation, although no definite proof for this conclusion can be offered. Other enzymes present in the milk, such as peroxidase, continued to accompany, in the active form, the milk copper-protein during several steps in the isolation process, without being inactivated. This conclusion is also favored by the fact that the process of isolating the milk protein was quite similar to those employed in the isolation of other copper proteins in their native condition. The isolation of tyrosinase from mushrooms and from potatoes, and ascorbic acid oxidase from squash, may be mentioned as examples.

It has been reported that milk shows a loss of antiscorbutic activity on standing.[12] Since ascorbic acid oxidase is a copper protein,[7] it was deemed worth while to test the milk copper protein for ascorbic acid oxidase activity. The result, however, proved to be negative. Likewise the milk copper protein showed no polyphenolase activity.

Experimental

Raw (unpasteurized) skimmed milk was used for the isolation of the copper bearing protein. Twenty-four to thirty-six hours had elapsed from the time the milk had been taken from the cow up to the time it was used. Forty liters of this milk contained before treatment about 1200 g. of solids, and this quantity of solid matter contained 4 mg. of copper.

The 40 liters of milk was made 0.3 saturated with ammonium sulfate by adding the salt gradually with stirring. The resulting mixture was allowed to stand overnight in a cool place. The clear supernatant liquid, formed on standing, was siphoned off and the remaining wet solids suspended in muslin bags and allowed to drain overnight. The liquid thus obtained, together with that obtained by siphoning, amounted to 33 liters (solution A), and contained 200 g. of solids (dry weight basis) exclusive of salts. The *p*H of the liquid was 6.6 and the 200 g. of solids contained 2 mg. of copper.

Solution A was made 0.7 saturated with ammonium sulfate, permitted to stand overnight, filtered and the filtrate discarded. The precipitate was dissolved in 4 liters of 0.1 *M* Na_2HPO_4, *p*H 8, yielding a clear reddish-yellow solution B. Solution B was next subjected to successive fractional precipitations with 0.2, 0.3, 0.4, 0.5 and 0.7 saturation with ammonium sulfate, dissolving the precipitates, formed in each precipitation, in 0.1 *M* Na_2HPO_4.

(1) C. A. Elvehjem, *Physiol. Rev.*, **15**, 471 (1935).
(2) D. Keilin and T. Mann, *Proc. Roy. Soc.* (London), **125B**, 187 (1938); F. Kubowitz, *Biochem. Z.*, **299**, 32 (1938).
(3) Saha and Guha, *Nature*, **148**, 595 (1941).
(4) Elvehjem, Steenbock and Hart, *J. Biol. Chem.*, **83**, 27 (1929); Sylvester and Lampitt, *Anal.*, **60**, 376 (1935).
(5) R. J. McIlray, *New Zealand J. Sci. Tech.*, **17**, 710 (1936).
(6) Keilin and Mann, *Nature*, **143**, 23 (1939).
(7) Lovett-Janison and Nelson, THIS JOURNAL, **62**, 1409 (1940).
(8) Dalton and Nelson, *ibid.*, **61**, 2946 (1939).
(9) Keilin and Mann, *Proc. Roy. Soc.*, (London) **126B**, 303 (1938).
(10) Kubowitz, *Biochem. Z.*, **299**, 32 (1938).
(11) Redfield, *Biol. Rev.*, **9**, 175 (1934).
(12) Tauber, *Proc. Soc. Exptl. Biol. Med.*, **35**, 422 (1931).

In this way solutions C, D, E, F, and G, described in Table I, were obtained.

TABLE I

Soln.	Satn. amt. of $(NH_4)_2SO_4$ used	Vol., cc.	Color	Solids exclusive of salts, g.	Mg Cu	% Cu
C	0.2	295	Tan, turbid	17.0	0.12	0.0007
D	.3	370	Tan, turbid	56.2	.37	.0007
E	.4	520	Clear deep red	28.2	.24	.0008
F	.5	1340	Clear light red	73.0	1.00	.0014
G	.7	425	Colorless	17.0	0.10	.0006

Solution F, containing the highest percentage of copper, was selected for obtaining the copper protein in still higher state of purity. It was subjected to more fractional precipitation by means of varying concentrations of ammonium sulfate, following much the same procedure as that followed in obtaining the solutions described in Table I. The solutions thus obtained are described in Table II.

TABLE II

Soln.	Satn. amt. of $(NH_4)_2SO_4$ used	Vol., cc.	Color	Solids exclusive of salts, g.	Mg Cu	% Cu
H	0.6	1365	Deep red	68.60	0.64	0.0013
I	.7	510	Light red	3.10	.18	.0056
J	Saturated	320	Colorless	0.84	.10	.0120

Solution J, containing the highest percentage of copper, was selected for further purification of the copper protein. For this purpose 3 cc. of a 2.5% basic lead acetate solution was added to the 320 cc. of solution J. This operation was followed immediately by the addition of 30 cc. of cold acetone (cooled with solid carbon dioxide). The precipitate formed was removed by centrifugation and discarded since it contained no copper. To the remaining liquid 3 cc. more of the basic lead acetate solution was added followed by the addition of 30 cc. of cold acetone, the resulting precipitate removed by centrifugation and discarded. To the clear supernatant liquid, 30 cc. more of cold acetone was added and the precipitate M which was formed was separated by means of the centrifuge. Precipitate M, containing most of the copper, was suspended in 50 cc. of 0.1 *M* disodium phosphate, and allowed to stand for an hour, with intermittent stirring. Lead phosphate separated, was removed in the centrifuge, and the clear liquid thus obtained was dialyzed until free of phosphate. This dialyzed solution, M1, contained 0.23 g. of solids having 0.07 mg. or 0.03% of copper.

Further purification of the material contained in solution M1 was accomplished by adsorption to alumina at *p*H 6.8, followed by elution with 0.1 *M* disodium phosphate. After elution with 0.1 *M* disodium phosphate and dialysis, the resulting solution (solution O) was found to contain 0.14 g. of solids containing 0.06 mg. or 0.043% of copper.

Solution O was then treated dropwise with 2.5% basic lead acetate solution (about 2 cc.) at *p*H 7.5 until no further precipitate formed. The precipitate (P) was removed by centrifugation, and the clear supernatant liquid, containing no copper, discarded. The precipitate P was then suspended in 40 cc. of 0.1 *M* disodium phosphate and allowed to stand for three hours with intermittent stirring. The lead phosphate which had formed was removed in the centrifuge and the clear liquid dialyzed, yielding solution P1. The latter contained 0.04 g. of solids, containing 0.034 mg. or 0.085% of copper.

The contents of solution P1 were then subjected to adsorption to alumina followed by elution by means of 0.1 *M* disodium phosphate. The clear solution thus obtained was then dialyzed for four days at 0° yielding a solution Q, which contained 0.0088 g. of solids (dry basis). This solid matter, on analysis, was found to contain 0.017 mg. or 0.19% of copper and 15% of nitrogen.

Determination of Copper.—The method used for the copper determinations was that of Warburg as modified by Warburg and Krebs.[13]

Determination of Nitrogen.—Two samples from solution Q, one equivalent to 2 and the other to 2.8 mg. of solids, were analyzed for nitrogen by the micro-Kjeldahl method. Both determinations gave values for nitrogen content equal to 15%.

To ensure no contamination by extraneous copper, all the samples used for copper determinations were dialyzed against distilled water which had been redistilled in glass vessels.

Dry weights of the solids were determined by the method described by Lutz and Nelson.[14]

The Copper in the Protein Is Non-ionic.—A freshly prepared milk protein fraction, containing in solution 540 mg. of solids (dry basis), which in turn had a copper content of 0.0185%, was divided into two equal portions, (I) and (II). To one aliquot, (I), was added 0.05 mg. of copper ion($CuSO_4$) thereby bringing the copper in its solid matter (the latter determined by evaporating a given amount of the solution) up to 0.037%. The two solutions, (I) and (II), were dialyzed separately at 0° for six days, at *p*H 6.5. At the end of each of the first three days, the solutions were removed from the dialyzing bags, and samples taken for copper determinations. The remaining solutions were again placed in fresh bags[15] and the dialysis

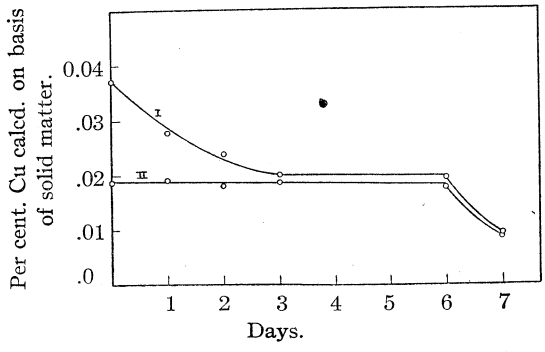


Fig. 1.

continued. As shown in Fig. 1, at the end of the three days of dialysis, the copper content of the solids in solution (I) had dropped to practically the same value (0.018%) as that of solution (II). On the other hand, the copper content of the solids in (II) remained at the original value (0.018%). In other words, the added ionic copper in solution (I) was lost in the dialysis while the copper belonging to the milk protein was not. From the end of the

(13) Warburg and Krebs, *Biochem. Z.*, **190**, 143 (1927).

(14) Lutz and Nelson, *J. Biol. Chem.*, **107**, 169 (1934).

(15) Visking sausage casing, made by the Visking Corporation, Chicago, was used in all dialyses.

third day up to the end of the sixth day of the dialysis, both solutions (I) and (II) lost no copper. Since most copper proteins lose copper in dilute acid solutions,[16] at the end of the sixth day both solutions were made *p*H 3.5 with hydrochloric acid, and under these conditions the copper belonging to the milk protein was lost in the dialysis.

The authors wish to express their thanks to the Borden Company for their generous supply of milk which made this study possible.

(16) Kubowitz, *Biochem. Z.*, **299**, 32 (1938).

Summary

A procedure is described for isolation of a copper bearing protein from cow's milk.

The copper in the protein is non-ionic and cannot be removed by dialysis at *p*H 6.5.

Up to the present, no chemical reactions have been found which are catalyzed by this milk protein.

NEW YORK CITY, N. Y. RECEIVED APRIL 24, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Abnormal Grignard Reactions. XIV.[1] Sterically Hindered Aliphatic Carbonyl Compounds. IV. Methyl Triethylcarbinyl Ketone and its Bromomagnesium Enolate

BY FRANK C. WHITMORE AND C. E. LEWIS[2]

An attempt to prepare 2-methyl-3,3-diethyl-2-pentanol by the reaction of methylmagnesium bromide with triethylacetyl chloride was unsuccessful. The action of the Grignard reagent with the acid chloride caused the evolution of one-half mole of methane for each mole of Grignard reagent used. The liquid products were methyl triethylcarbinyl ketone and bis-triethylacetyl-methane.

$$\underset{\text{I}}{Et_3CCOCl} + MeMgBr \longrightarrow \underset{\text{II}}{Et_3CCOCH_3} + MgBrCl \quad (1)$$

$$\underset{\text{II}}{} + MeMgBr \longrightarrow \underset{\text{III}}{Et_3CCOCH_2MgBr} + CH_4 \quad (2)$$

$$\underset{\text{III}}{} + \underset{\text{I}}{} \longrightarrow \underset{\text{IV}}{Et_3CCOCH_2COCEt_3} \quad (3)$$

Such a series of reactions is not new. Methyl-*t*-butylneopentylacetyl chloride[3] and dineopentylacetyl chloride[4] have both been found to give good yields of the corresponding methyl ketones with methylmagnesium bromide. These ketones give bromomagnesium enolates which react as true Grignard reagents.[3,4,5] Fuson and co-workers[6] had earlier shown that mesityl alkyl ketones give halomagnesium enolates which also react as true Grignard reagents.

Methyl triethylcarbinyl ketone gave 94% enolization and no addition when run in the Grignard machine[7] with methylmagnesium bromide. Thus, it is the lowest molecular weight ketone known which gives only enolization with the methyl Grignard reagent. The bromomagnesium enolate of methyl triethylcarbinyl ketone acts as a true Grignard reagent. Treatment of the enolate with carbon dioxide and formaldehyde gave the corresponding beta-keto acid and beta-ketol, respectively.

The few reactions studied indicate that the carbonyl of methyl triethylcarbinyl ketone is almost as sterically hindered as that of methyl methyl-*t*-butylneopentylcarbinyl ketone,[3] methyl dineopentylcarbinyl ketone[4] and acetomesitylene.[6] This is interesting when it is remembered that the reactions of pinacolone indicate only slight steric influence on the carbonyl. Thus, the remarkable difference in steric influence of the methyl and ethyl groups is clearly demonstrated.

We thank R. S. George of this Laboratory for his help on this paper.

Experimental

The Grignard reagents for this work were prepared in the usual manner. All fractionations were done with the usual type of column[8] having 12–18 theoretical plates. The triethylacetyl chloride was prepared by standard reactions as follows:

$$EtCO_2Pr \xrightarrow{EtMgBr} Et_3COH \xrightarrow{HCl} Et_3CCl \xrightarrow{Mg} Et_3CMgCl \xrightarrow{CO_2} Et_3CCO_2H \xrightarrow{SOCl_2} Et_3CCOCl$$

The chloride had b. p. 98° (65 mm.); $n^{20}D$ 1.4438.

(1) XIII, Whitmore and Lester, THIS JOURNAL, **64**, 1251 (1942).

(2) Present address: Calco Chem. Div., American Cyanamide Co., Bound Brook, New Jersey.

(3) Whitmore and Randall, THIS JOURNAL, **64**, 1242 (1942).

(4) Whitmore and Lester, *ibid.*, **64**, 1247 (1942).

(5) Whitmore and Lester, *ibid.*, **64**, 1251 (1942).

(6) Fuson and co-workers, *ibid.*, **52**, 5036 (1930); **61**, 2362 (1939); *J. Org. Chem.*, **4**, 111 (1939).

(7) Kohler, Stone and Fuson, THIS JOURNAL, **49**, 3181 (1927).

(8) Whitmore and Lux, *ibid.*, **54**, 3451 (1932).

Action of Methylmagnesium Bromide with Triethylacetyl Chloride (I).—To a solution of 157 g., 0.95 mole, of triethylacetyl chloride in ether was added 2 moles of 1.52 molar methylmagnesium bromide. About 0.5 mole of gas was evolved per mole of Grignard reagent added. The material was worked up as usual. Fractionation gave 45.6 g., 0.32 mole, or 34% of methyl triethylcarbinyl ketone (II), b. p. 90° (60 mm.), $n^{20}D$ 1.4318–9, and 39.9 g., 0.15 mole, or 32% of bis-triethylacetyl-methane (IV), b. p. 135–6° (8 mm.), $n^{20}D$ 1.4769–70. The *2,4-dinitrophenylhydrazone* and the *oxime* of the *monoketone*, both of which were prepared with difficulty, melted at 93–94.5° and 97–101°, respectively. The diketone gave a chelate copper derivative with ammoniacal cupric acetate. The derivative was a brilliant purple compound with m. p. 143–144°. The monoketone gave 94% enolization and no addition when run in the Grignard machine with methylmagnesium bromide.[7]

3-Keto-4,4-diethylhexan-1-ol.—To 16 g., 0.65 gram-atom, of magnesium in 200 cc. of dry ether was added 70 g., 0.65 mole, of ethyl bromide. When the reaction was completed 80 g., 0.56 mole, of methyl triethylcarbinyl ketone was added. The reaction mixture was stirred for twenty-four hours. Formaldehyde gas was then passed into the reaction flask until an excess had been added. The reaction mixture became viscous as the reaction proceeded, and heating was necessary to keep it fluid enough for adequate stirring. The material was worked up as usual. Fractionation gave 37.7 g., 0.22 mole, or 34% of 3-keto-4,4-diethylhexan-1-ol, b. p. 86° (2 mm.), $n^{20}D$ 1.4554–8; alpha-naphthylurethan, m. p. 120–122°. *Mol. wt.* Calcd. for $C_{10}H_{20}O_2$: mol. wt., 172. Found: mol. wt. (cryoscopic), 171.

3-Keto-4,4-diethylhexanoic Acid.—To 0.07 mole of ethylmagnesium bromide was added 10 g., 0.07 mole, of methyl triethylcarbinyl ketone. The reaction mixture was stirred three hours. Gas was evolved during the reaction. An excess of carbon dioxide gas was passed into the reaction mixture with continuous stirring. The material was worked up as usual. The oil layer was extracted with dilute sodium carbonate. The alkaline extract was acidified with sulfuric acid and the solid beta-keto acid was filtered off. The yield was 2.5 g., 0.014 mole, or 21%. The acid, m. p. 63–65°, decomposed on heating to give carbon dioxide and methyl triethylcarbinyl ketone.

Anal. Calcd. for $C_{10}H_{18}O_3$: neut. equiv., 186. Found: neut. equiv., 183, 185, 190.

Summary

1. The presence of three ethyl groups on the carbon adjacent to a carbonyl group has been found to have a pronounced influence on the reactions of the carbonyl.

2. The reaction of methyl triethylcarbinyl ketone with a Grignard reagent gives an enolate which reacts as a true Grignard reagent.

3. Methyl triethylcarbinyl ketone is the lowest molecular weight aliphatic ketone found to give only enolization with the methyl Grignard reagent.

STATE COLLEGE, PENNA. RECEIVED DECEMBER 18, 1941

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Grignard Reactions. XV.[1] Sterically Hindered Aliphatic Carbonyl Compounds. V. Enolization Studies. I

BY FRANK C. WHITMORE AND L. P. BLOCK[2]

Methylmagnesium halides have long been used as reagents for the determination of active hydrogen in organic compounds. Early work on such determinations has been reviewed by Courtot,[3] who pointed out that the method is applicable to the study of keto–enol tautomerism.

Kohler and co-workers[4] devised a new type of apparatus with which one can determine the amount of gas evolved with the methylmagnesium halide, and also measure the amount of reagent used in the reaction.

Enolization studies until recently have been confined almost entirely to ketones containing an aromatic group. The reason for this is probably because hindered ketones which would contain conjugated double bonds in the enol form almost invariably give enolization.[5] Thus acetomesitylene and related compounds[6] have been studied rather extensively.

A definite correlation between the branching in aliphatic ketones and the amount of enolization given with the methyl Grignard reagent is not yet entirely clear. The literature indicates that such ketones show little tendency to give enolization with simple Grignard reagents. However, several new aliphatic sterically hindered ketones[7] prepared in this Laboratory give as high as 100%

(1) Whitmore and Lewis, THIS JOURNAL, **64**, 1618 (1942).

(2) Present address: E. I. du Pont de Nemours and Co., Waynesboro, Va.

(3) Courtot, "Le Magnesium en Chemie Organique," 1926.

(4) Kohler, Stone and Fuson, THIS JOURNAL, **49**, 3181 (1927).

(5) (a) Fuson, Fisher and Fugate, *J. Org. Chem.*, **4**, 111 (1939); (b) Fuson, Fugate and Fisher, THIS JOURNAL, **61**, 2362 (1939).

(6) (a) Kohler and Baltzly, *ibid.*, **54**, 4015 (1932); (b) Smith and Guss, *ibid.*, **59**, 804 (1937).

(7) (a) Whitmore and Randall, *ibid.*, **64**, 1242 (1942); (b) Whitmore and Lester, *ibid.*, **64**, 1247 (1942); (c) Whitmore and Lewis, *ibid.*, **64**, 1618 (1942).

enolization and no addition with the methyl Grignard reagent.

The present work was undertaken to extend the studies on enolization of branched aliphatic ketones with the methyl Grignard reagent. The compounds studied are not sufficiently branched to prevent the addition reaction entirely. The results of the studies are given in Table I.

The Grignard machine used in this work is essentially the same as the one used by Kohler.[4] The amount of enolization was calculated from the amount of gas evolved by the action of methylmagnesium chloride with the carbonyl compound. The excess methylmagnesium chloride present was determined by observing the amount of gas evolved on the addition of water to the reaction flask. The amount of addition reaction was taken as the difference between the number of moles of methylmagnesium chloride added and the total moles of gas evolved by the enolization reaction and by the decomposition of the excess reagent. This is based on the assumption that the amount of condensation is negligible. The reaction flask was always heated to ensure optimum reaction conditions. The apparatus was enclosed in a case to protect it from changes in temperature caused by air currents. The usual corrections were made for the gas evolved due to the presence of moisture in the reaction flask.

TABLE I

Compound	Percentage Enolization	Addition
Methyl isopropyl ketone	0	100
Ethyl isopropyl ketone	0	100
Methyl *t*-butyl ketone	5	86
Ethyl *t*-butyl ketone	9	86
Pentamethylacetone	0	49
Methyl pinacolyl ketone	48	47
Ethyl pinacolyl ketone	62	33
Methyl *s*-butyl ketone	32	..
Propyl *s*-butyl ketone	53	40
2,2-Dimethyl-4-ethyl-3-hexanone	5	19
2,2,4,6,6-Pentamethyl-3,5-heptadione	27/2	129/2

From the above measurements it can be seen that the amount of enolization and addition is dependent upon the steric influence of the groups around the carbonyl. This was first pointed out by Conant and Blatt.[8] The carbonyls of methyl and ethyl isopropyl ketones are not sufficiently hindered to retard the normal addition reaction and allow time for the competing enolization reaction. It is interesting to note that although pentamethylacetone gave only 49% addition, no enolization took place. This recalls the failure of phenyl dineopentylcarbinyl ketone to give any enolate.[7b] All of the other ketones investigated gave both enolization and addition.

The steric influence of the ethyl group is shown to be much greater than that of the methyl group. The carbonyls of 2,2-dimethyl-4-ethyl-3-hexanone and 2,2,4,6,6-pentamethyl-3,5-heptadione are sterically hindered to such an extent that the sums of the enolization and addition reactions are 24% and 78%, respectively, of the calculated amount assuming complete reaction. It is thus apparent that steric hindrance in carbonyl compounds may retard, and in some cases prevent, either enolization or addition or both.

We thank R. S. George of this Laboratory for his help.

Experimental

The procedure used in making the enolization measurements has been described above. The compounds run in the Grignard machine were prepared by conventional procedures. The compounds, their physical properties and the method of preparation are given very briefly.

Methyl isopropyl ketone: dichromate oxidation of methylisopropylcarbinol; b. p. 92° (740 mm.) and $n^{20}D$ 1.3886.

Ethyl isopropyl ketone: dichromate oxidation of ethylisopropylcarbinol; b. p. 111–113° (740 mm.) and $n^{20}D$ 1.3975.

Methyl *t*-butyl ketone: reaction of acetyl chloride with *t*-butylmagnesium chloride; b. p. 103.5° (735 mm.) and $n^{20}D$ 1.3974.

Ethyl *t*-butyl ketone: oxidation of olefins; b. p. 124.5° (730 mm.) and $n^{20}D$ 1.4049.

Pentamethylacetone: diisopropyl ketone by reaction with sodamide and dimethyl sulfate; b. p. 135° (735 mm.) and $n^{20}D$ 1.4074.

Methyl pinacolyl ketone: ozonolysis of 3,4,5,5-tetramethyl-2-hexene; b. p. 144° (740 mm.).

Ethyl pinacolyl ketone: reaction of methyl-*t*-butylacetyl chloride with ethylmagnesium bromide; b. p. 87° (50 mm.) and $n^{20}D$ 1.4221.

Methyl *s*-butyl ketone: dichromate oxidation of methyl-*s*-butylcarbinol; b. p. 115.5° (733 mm.) and $n^{20}D$ 1.3988.

Propyl *s*-butyl ketone: dichromate oxidation of propyl-*s*-butylcarbinol; b. p. 154° (73 mm.) and $n^{20}D$ 1.4132.

2,2-Dimethyl-4-ethyl-3-hexanone: dichromate oxidation of 2,2-dimethyl-4-ethyl-3-hexanol; b. p. 120° (150 mm.) and $n^{20}D$ 1.4240.

2,2,4,6,6-Pentamethyl-3,5-heptadione: oxidation of triisobutylene; b. p. 91° (16 mm.) and $n^{20}D$ 1.4320.

Summary

1. Eleven aliphatic ketones have been analyzed in the Grignard machine with methylmagnesium chloride.

(8) Conant and Blatt, THIS JOURNAL, **51**, 1227 (1929).

2. Pentamethylacetone gave no enolization and 49% addition with the methyl Grignard reagent.

3. It has been confirmed that steric hindrance around the carbonyl retards both the enolization and addition reactions. Thus 2,2-dimethyl-4-ethyl-3-hexanone gave 5% enolization and 19% addition with the methyl Grignard reagent.

STATE COLLEGE, PENNSYLVANIA
RECEIVED DECEMBER 24, 1941

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

Carboxylation. III. The Peroxide-catalyzed Reaction of Oxalyl Chloride with the Side-chains of Aralkyl Hydrocarbons. A Preliminary Study of the Relative Reactivity of Free Radicals

BY M. S. KHARASCH, STEPHEN S. KANE[1] AND HERBERT C. BROWN

It has been suggested that the photochemical carboxylation[2] of the paraffin hydrocarbons with oxalyl chloride proceeds in the following manner.

Primary process

$$(A)\quad (COCl)_2 \xrightarrow{h\nu} 2\cdot COCl$$

and/or

$$(A')\quad (COCl)_2 \xrightarrow{h\nu} \cdot COCOCl + Cl\cdot$$

Secondary processes

$$(B)\quad \cdot COCl \longrightarrow CO + Cl\cdot$$

and/or

$$(B')\quad \cdot COCOCl \longrightarrow 2CO + Cl\cdot$$
$$(C)\quad RH + Cl\cdot \longrightarrow R\cdot + HCl$$
$$(D)\quad R\cdot + (COCl)_2 \longrightarrow RCOCl + \cdot COCl$$
$$(E)\quad \cdot COCl \longrightarrow CO + Cl\cdot$$

The experimental evidence upon which this mechanism is based has already been discussed.[3]

Study of the carboxylation of a number of representative hydrocarbons indicates that this reaction is general for the paraffins, the cycloparaffins and their halogen derivatives. However, attempts to extend this photochemical reaction to the carboxylation of the side chains of representative aralkyl hydrocarbons have thus far met with little success.

This observation can be interpreted in either of two ways: (1) the aromatic hydrocarbons containing side-chains are opaque to the radiation necessary for the chain-initiating step, which is the photolysis of the oxalyl chloride (A); or (2) the aralkyl free radicals which are formed (C) require a relatively high energy of activation to break the carbon-to-carbon bond in oxalyl chloride (D).

Considerable support for the belief that the first of these interpretations is of importance in the photochemical carboxylation reaction was furnished by a study of the carboxylation of cyclohexane in the presence of various diluents. Carbon tetrachloride, chloroform, and similar inert diluents exert but small effects upon the rate of carboxylation of cyclohexane. The slight decrease observed, approximately 20%, can easily be accounted for by decreased concentration of the reactants. On the other hand, the presence of comparable quantities of benzene in the reaction mixture causes a five-fold drop in the rate. It is evident, therefore, that in the *photochemical* carboxylation of the aralkyl hydrocarbons, the poor yields are largely due to the effect of the aromatic nucleus upon the radiation required to initiate the carboxylation reaction.

It is noteworthy, however, that this interpretation does not eliminate the second of the two possibilities mentioned above: namely, that the low degree of reactivity[4] of the aralkyl free radicals might also contribute to the sluggishness of the aralkyl hydrocarbons in the photochemical carboxylation reaction under discussion. The observation that the carboxylation reaction could be initiated thermally in the dark by the addition of several mole per cent. of an organic peroxide[3] offered a means of investigating this question.

Accordingly, a study of the peroxide-catalyzed carboxylation of a number of aralkyl hydrocarbons was undertaken. It is significant that low yields (about 5–10%) of the corresponding acid chlorides were obtained with such representative aralkyl hydrocarbons as toluene, *m*-xylene, and mesitylene. In these reactions, the inhibitory ef-

(1) This paper is part of a dissertation submitted by Stephen S. Kane to the Faculty of the Division of Physical Sciences of the University of Chicago in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) The authors have adopted the term carboxylation to describe the introduction of the chloroformyl (—COCl) group; see the first paper of this series (reference in footnote 3).

(3) Kharasch and Brown, THIS JOURNAL, **64**, 329 (1942).

(4) That is, low compared with the highly reactive normal alkyl free radicals.

fect exerted by the nucleus in the photochemical reaction is absent, since cyclohexane readily participates in the peroxide-catalyzed carboxylation reaction in the presence of as much as 50 mole per cent. of benzene. Therefore, the authors are led to the conclusion that the low reactivity of the aralkyl free radicals (resulting in comparatively short chain lengths) must be an important factor in the low conversions noted in the reaction of oxalyl chloride with aralkyl hydrocarbons. In other words, the reaction of the comparatively inactive aralkyl free radicals with oxalyl chloride (D) is so slow that the free radicals have greatly increased opportunity to disappear by participation in side reactions.[5]

An interesting question which is raised by these considerations is that of the relative reactivity of free radicals. If the organic free radicals differ markedly in chemical reactivity (as the results of the carboxylation studies indicate), it would be of considerable interest then to obtain information concerning their relative reactivity. This paper describes some preliminary experiments to establish a method for carrying out such studies.

There is at hand considerable experimental evidence to support the conclusion that the decomposition of the diacyl peroxides in solution proceeds through the formation of organic free radicals as intermediates.[6] The free radicals formed in this way may either react with the solvent or disappear by disproportionation, combination or other side reactions. The relative amount of any species of free radical which disappears by reaction with the solvent depends largely upon the nature of that solvent. Hence, by a judicious choice of solvent it should be possible to divide the free radicals into two groups which differ markedly in the extent of their attack upon the solvent in question. Obviously, these two groups could be further subdivided by the use of other solvents. In this way, a large number of organic free radicals might finally be arranged in the order of their relative activities.

As a preliminary study of the practicability of the method outlined, an investigation of the decomposition of several representative diacyl peroxides in carbon tetrachloride was undertaken.[7] Appreciable quantities of methyl, *n*-propyl and isopropyl chlorides were isolated from the reaction products of carbon tetrachloride, with diacetyl, di-*n*-butyryl and di-isobutyryl peroxides, respectively. On the other hand, no *t*-butyl or benzyl chloride could be found in the corresponding thermal decomposition products of di-trimethylacetyl or di-phenylacetyl peroxides in carbon tetrachloride. These results are interpreted, in accordance with the argument previously outlined, to mean that the methyl, *n*-propyl and isopropyl free radicals are of a higher order of reactivity than the benzyl or *t*-butyl free radicals. To the group of more active free radicals phenyl may be added, since dibenzoyl peroxide decomposes in carbon tetrachloride solution to form phenyl chloride and hexachloroethane[8]; triphenylmethyl, which crystallizes unchanged from carbon tetrachloride solution,[9] evidently belongs to the less reactive class.

These results are summarized in Table I.

TABLE I

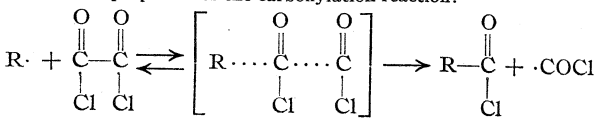
PRELIMINARY RESULTS ON A RELATIVE REACTIVITY SERIES OF ORGANIC FREE RADICALS

	Free radical	
Class I[a]		
More reactive free radicals	phenyl	$C_6H_5\cdot$
	methyl	$CH_3\cdot$
	n-propyl	$CH_3CH_2CH_2\cdot$
	isopropyl	$(CH_3)_2CH\cdot$
Class II[a]		
Less reactive free radicals	benzyl	$C_6H_5CH_2\cdot$
	t-butyl	$(CH_3)_3C\cdot$
	triphenylmethyl	$(C_6H_5)_3C\cdot$

[a] The arrangement of the free radicals within each of the two groups has not yet been verified experimentally.

It is perhaps too early to draw any theoretical

(5) This reactivity of the free radical must be intimately connected with the energy required for the formation of the activated complex, as indicated in the following equation, which is a more detailed representation of the processes involved in step D of the mechanism proposed for the carboxylation reaction:



That is, a free radical of "high" reactivity must require considerably less energy for the formation of the activated complex (shown in brackets above) than a free radical of "low" reactivity.

(6) Hey and Waters, *Chem. Rev.*, **21**, 169 (1937).

(7) Selection of carbon tetrachloride as the solvent in these preliminary experiments was dictated by a number of observations made at various times in this Laboratory that the decomposition of peroxides in this substance proceeds smoothly in accordance with the following equations:

$$(RCOO)_2 \longrightarrow 2R\cdot + 2CO_2$$
$$R\cdot + CCl_4 \longrightarrow RCl + Cl_3C\cdot$$
$$2Cl_3C\cdot \longrightarrow C_2Cl_6$$

The possibility of isolating and identifying both the organic chloride and the hexachloroethane offers a simple means of checking the results of any experiment. *Cf.* Böeseken and Gelissen, *Rec. trav. chim.*, **43**, 869 (1924); Kharasch, Kane and Brown, THIS JOURNAL, **63**, 526 (1941).

(8) Böeseken and Gelissen; unpublished work of Kharasch and Walling.

(9) Gomberg and Cone, *Ber.*, **37**, 2036 (1904).

conclusions from the chemical structures of the two groups of radicals. However, it is of considerable interest that this division of the free radicals closely follows the relative electronegativity series[10] of organic groups.[11] Thus the more reactive radicals are related to the more electronegative groups and the less reactive radicals to the less electronegative groups.

At first glance, it may appear somewhat surprising to find that the electronegativity series of organic groups, set up by a study of the hydrolytic splitting of unsymmetrical organomercurials, should correspond so closely to the arrangement of the free radicals according to their relative reactivities, as determined by the ease with which they react with carbon tetrachloride. Yet this correlation cannot be entirely fortuitous. The factors which tend to give an organic group such as phenyl or methyl a relatively high place in the electronegativity series, *i. e.*, which increase the tendency of the group to exist as a negative ion, probably also give the corresponding free radical a relatively high affinity for electrons.[12] Consequently, the free radical would fall into the more reactive class. By an obvious extension of the argument, the less electronegative groups may be identified with the less reactive free radicals. Whether other factors cause minor divergences between the two series remains to be settled by further experimentation. Until more definite information is available, however, the comprehensive classification of organic groups in the electronegativity series can probably be used as a rough indication of the relative reactivity of the organic free radicals. It is hoped to elaborate on these ideas in subsequent publications from this Laboratory.

Experimental Part

Attempt to Carboxylate the Aralkyl Hydrocarbons Photochemically.—A typical procedure utilizing toluene will be described. A mixture of 16.8 g. (0.2 mole) of toluene and 12.7 g. (0.1 mole) of oxalyl chloride was placed in an elongated flask and illuminated under the conditions previously described for the carboxylation of the paraffinic hydrocarbons.[13] After twenty hours, the reaction mixture was fractionated. Less than 0.4 g. of higher boiling material was isolated. With ammonia this material gave only a slight test for acid chloride groups. There was some indication of the presence of dibenzyl. Similar results were obtained with *m*-xylene, mesitylene, *p*-chlorotoluene, tetralin and β-methylnaphthalene. Under similar conditions, in a reaction mixture of cyclohexane and oxalyl chloride, approximately 50% of the oxalyl chloride is converted to the carboxylic acid derivative.

Photochemical Carboxylation of Cyclohexane in Presence of Diluents.—A number of reaction mixtures were made up using 0.1 mole of oxalyl chloride, 0.1 mole of cyclohexane and 0.1 mole of the diluent (benzene, carbon tetrachloride, chloroform, methylene chloride); these were illuminated for twenty hours by the standard procedure.[13] The yields of cyclohexane carboxylic acid chloride from those reaction mixtures containing the halogenated methanes as diluents were only slightly less (approximately 80%) than those obtained from reaction mixtures free from diluents. On the other hand, the yield of the acid chloride from the reaction mixture containing benzene as diluent was markedly lower—only 15% of the usual yield.

Peroxide-Catalyzed Carboxylation of the Aralkyl Hydrocarbons.—In the main, the experimental procedure was similar to that used for the peroxide-catalyzed carboxylation of the paraffin hydrocarbons.[14] A few modifications were, however, introduced. The hydrocarbon, oxalyl chloride, and dibenzoyl peroxide (3.0, 2.0, and 0.08 moles, respectively) were refluxed for twenty-four hours. The solution was then fractionated through a small column. The oxalyl chloride and most of the unreacted hydrocarbon was removed at ordinary pressure; the higher boiling material was fractionated under reduced pressure (approximately 20 mm.). Particular care was taken to separate benzoyl chloride (formed by the reaction of the peroxide on oxalyl chloride) from the acid chloride produced in the course of the reaction. The acid chloride thus obtained was identified by its boiling point, its neutral equivalent and the melting point of either the corresponding acid, or amide.

Under these experimental conditions, toluene produced an 8% yield of phenylacetyl chloride, *m*-xylene a 10% yield of 3-methylphenylacetyl chloride, mesitylene a 7% yield of 3,5-dimethylphenylacetyl chloride,[15] and *p*-chlorotoluene a 5% yield of 4-chlorophenylacetyl chloride.

No appreciable quantity of the carboxylic acid derivatives could be obtained from diphenylmethane, *p*-nitrotoluene and β-methylnaphthalene.[16]

Di-phenylacetyl Peroxide.—Phenylacetyl chloride, b. p. 99–103° (16 mm.), was prepared from phenylacetic acid and phosphorus pentachloride. The peroxide was made by slowly running 5 g. of the acid chloride into a vigor-

(10) Kharasch and Marker, THIS JOURNAL, **48**, 3131 (1926); Kharasch and Flenner, *ibid.*, **54**, 674 (1932). For leading references to the application of the electronegativity theory to the interpretation of organic reactions, see Kharasch, Reinmuth and Mayo, *J. Chem. Ed.*, **13**, 7 (1936).

(11) The term "groups" has been substituted for the original term "radicals." At the time the electronegativity series was set up, no particular significance had yet been attached to the term radical. At the present time, however, "radical" is used chiefly to refer to *neutral* organic aggregates and it seems advisable thus to restrict the use of this term.

(12) The correlation which exists between the electronegativity series and dipole moment data [Brown, THIS JOURNAL, **61**, 1483 (1939)] lends further support to the view that the position of an organic group in the electronegativity series is a measure of the affinity of the bonding carbon atom for electrons.

(13) Kharasch and Brown, *ibid.*, **64**, 331–332 (1942).

(14) Kharasch and Brown, *ibid.*, pp. 332–333.

(15) M. p. of the amide (not previously reported) is 154–154.5°. *Anal.* Calcd. for $C_{10}H_{13}ON$: N, 8.59. Found: N, 8.66.

(16) It may be recalled that these substances also failed to undergo the peroxide-catalyzed chlorination reaction with sulfuryl chloride [Kharasch and Brown, THIS JOURNAL, **61**, 2142 (1939)].

ously stirred solution of 4 g. of sodium peroxide in 100 cc. of water. The temperature was carefully maintained slightly below 5°. After thirty minutes, the granules formed were filtered off and immediately added to carefully purified carbon tetrachloride.[17] When the mixture was warmed, a vigorous reaction occurred which kept the carbon tetrachloride refluxing for several minutes. The carbon tetrachloride was then removed by distillation under ordinary pressure. The residue, 7 g., distilled from 115–200° (23 mm.). The combined distillate was washed with aqueous alkali and steam distilled. The solid obtained was identified as dibenzyl by its melting point of 52–53° (verified by the melting point of a mixture with an authentic sample). Acidification of the aqueous extract yielded a white crystalline precipitate, which, after recrystallization from water, was identified as phenylacetic acid from its m. p. of 75–76° and its neut. eq. of 140. Neither benzyl chloride nor hexachloroethane could be found in the reaction product.

Di-trimethylacetyl Peroxide.—Trimethylacetic acid was prepared by the Grignard reaction[18] and was transformed into its acid chloride by the use of benzoyl chloride.[19] The peroxide was prepared by the action of sodium peroxide on a solution of the acid chloride in ethyl ether.[20] This peroxide decomposed readily in warm carbon tetrachloride. Neither *t*-butyl chloride nor hexachloroethane could be identified in the reaction mixture.

From the less volatile constituents of the reaction product was obtained a liquid which distilled at 166–168°. It contained chlorine (28.54%) and appeared to be a C_8 derivative. Further identification was not attempted; the substance is probably formed by secondary reactions of the *t*-butyl free radicals.

Diacetyl, Di-*n*-butyryl, and Di-isobutyryl Peroxides.—These peroxides were prepared by methods similar to that described for di-trimethylacetyl peroxide. Their decomposition in hot excess carbon tetrachloride proceeded smoothly. From the reaction mixtures the corresponding alkyl chlorides[21] were isolated in yields of 10 to 20% and the presence of equivalent quantities of hexachloroethane was demonstrated.

(17) The carbon tetrachloride used in this work was washed with potassium permanganate solution, dried over Drierite, and distilled through an efficient column.

(18) "Organic Syntheses," Coll. Vol. I, p. 510.

(19) Brown, THIS JOURNAL, **60**, 1325 (1938).

(20) Procedure modified from that described by Gambayan, *Ber.*, **42**, 4008 (1909); see also Kharasch, Kane and Brown, THIS JOURNAL, **63**, 527 (1941).

(21) It is of considerable interest that *only* *n*-propyl chloride was obtained in the decomposition of *n*-butyryl peroxide and *only* isopropyl chloride was obtained from isobutyryl peroxide. This result suggests that the organic free radicals in solution do not isomerize to any appreciable extent. This point is of considerable importance for the further development of the chemistry of free radicals in liquid systems and has been discussed in detail in an earlier publication [Kharasch, Kane and Brown, *ibid.*, p. 526].

Summary

1. A number of aralkyl hydrocarbons (toluene, *m*-xylene, mesitylene, *p*-chlorotoluene) react with oxalyl chloride in the presence of dibenzoyl peroxide to form the corresponding acid chlorides. (The reaction is $RC_6H_4CH_3 + (COCl)_2 \rightarrow RC_6H_4CH_2COCl + CO + HCl$.) The conversions in the instances mentioned are low; they average 5–10% under conditions such that the carboxylation of representative paraffinic hydrocarbons is practically complete. Under the same conditions, some other aralkyl hydrocarbons (β-methylnaphthalene, diphenylmethane, *p*-nitrotoluene) are not appreciably carboxylated.

2. None of the aralkyl hydrocarbons were observed to undergo photochemical carboxylation with oxalyl chloride to any appreciable extent.

3. An important factor in the inhibition of the photochemical reaction of oxalyl chloride with the aralkyl hydrocarbons appears to be the effect of the aromatic nucleus on the radiation required for the photolysis of the oxalyl chloride, the chain-initiating step.

4. The low conversions in the peroxide-catalyzed reaction are ascribed to the comparatively low reactivity of the aralkyl free radicals, which results in a sluggish reaction of these intermediates with the oxalyl chloride.

5. Means of investigating the relative reactivity of aralkyl free radicals are discussed. Preliminary results indicate that the free radicals phenyl, methyl, *n*-propyl and isopropyl are more reactive than the benzyl, *t*-butyl and triphenylmethyl.

6. There is an interesting correspondence between the order of the free radicals when arranged according to their reactivities and the electronegativity series of organic groups. A plausible interpretation of this correspondence is advanced.

CHICAGO, ILL. RECEIVED MARCH 18, 1942

Some Mono- and Di-alkyl Ethers of Stilboestrol[1]

BY E. EMMET REID AND EDITH WILSON

For a study of the variation of the physical and pharmacological properties of the members of a series, the mono- and di-alkyl ethers of stilboestrol[2] (*trans*-4,4′-dihydroxy-α,β-diethylstilbene) seemed to be desirable. The parent compound has an intense physiological activity which can be determined readily and comparatively accurately. The dimethyl ether and several of the esters are known to have similar activity. The nonyl. The hexyl, octyl and decyl di-ethers have extremely low activity. The lower mono-ethers are 8 to 15 times as active as the corresponding di-alkylated compounds.[3] The figures given are the weights in gamma of the compounds which equal one rat unit as found by the Allan–Doisy method. The rat unit is the minimum amount of the estrogen required to produce cornification of the vaginal smear in 50% or more of a group of ten cas-

TABLE I

MELTING POINTS, ACTIVITIES AND ANALYSES OF THE MONO- AND DI-ALKYL ETHERS OF STILBOESTROL

The melting points were all taken on the same thermometer, calibrated for 3-inch immersion.

Alkyl	Melting points, °C. Mono-	Di-	Activity, γ Mono-	Di-	Analyses, mono- Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Analyses, di- Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Methyl	117[a]	124[b]	2.5[c]	20	...	...	...	...	...	...	...	...
Ethyl	99.5[d]	127.5[b]	5	50	81.08	80.62	8.11	8.10	81.48	81.10	8.64	8.82
Propyl	107	95.6[b]	17.5	250	81.29	80.97	8.39	8.27	81.81	81.66	9.09	9.44
Butyl	97.5	101.6	20	250	81.48	81.07	8.64	8.62	82.10	81.39	9.47	9.53
Amyl	82	64.6	48	600	81.65	81.69	8.87	8.81	82.35	82.17	9.81	9.91
Hexyl	72	74.6	45	30,000	81.81	81.05	9.09	9.04	82.56	82.38	10.09	10.13
Heptyl	87	50.4	45	750	81.96	81.84	9.29	9.38	82.75	82.58	10.34	10.37
Octyl	88.5	72.2	50	>50,000	82.10	81.80	9.47	9.75	82.92	82.97	10.56	10.54
Nonyl	76	57.4	50	5,000	82.23	81.88	9.64	9.63	83.07	83.05	10.76	11.01
Decyl	75	73.6	84	50,000	82.35	81.65	9.81	9.65	83.21	82.86	10.95	11.00
Undecyl	58.5	66.0	200	>40,000	82.46	81.68	9.95	9.89	83.33	82.71	11.11	11.01
Lauryl	83	80.0	100	.....	82.56	82.48	10.09	10.01	83.44	83.16	11.26	11.13
Tridecyl	67	73.2	...	.....	82.66	81.94	10.22	10.23	83.54	83.44	11.39	11.41
Myristyl	85	86.0	...	.....	82.75	82.81	10.34	10.68	83.63	83.67	11.51	11.94
Pentadecyl	73	77.0	...	.....	82.84	82.38	10.46	10.41	83.72	83.62	11.62	11.76
Cetyl	89	89.0	...	.....	82.92	81.93	10.56	10.27	83.80	83.64	11.73	12.06
Heptadecyl	78.5	82.0	...	.....	83.00	82.14	10.67	10.65	83.87	83.54	11.82	11.74
Octadecyl	94.3	94.0	...	.....	83.07	82.91	10.76	10.57	83.93	83.48	11.91	11.86

[a] The m. p. is 112–114° when it is recrystallized from aqueous alcohol and 116–117.5° from benzene–petroleum ether or from methylene chloride. *Anal.* Methoxyl calcd., 11.0; found, 10.9. [b] Sondern, Sealey and Kartsonis give 121–123°, 119–121° and 93–94° as the melting points of dimethyl, diethyl and dipropyl ethers, *Endocrinology*, **28**, 849 (1941). [c] Stilboestrol by same method 0.3 γ. [d] The mono-ethyl may have water of crystallization at times. One sample from aqueous alcohol, m. p. 105.5–107°, lost 6.0% on drying, calcd. for 1 water 5.7%, and then m. p. 99.5°.

mono-alkyl ethers appeared to be particularly interesting since, having one phenolic hydroxyl open, they might be expected to resemble the parent substance more closely than the dialkyl ethers.

We have prepared the mono- and di-ethers of stilboestrol using the normal alkyls from methyl to octadecyl. The melting points, activities and analyses are given in Table I and the melting points are plotted in Fig. 1.

In each series the estrogenic activity decreases as the alkyl increases in size, though in the mono-ethers there is not much change from amyl to

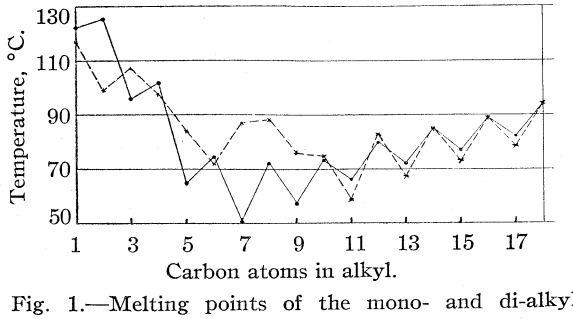


Fig. 1.—Melting points of the mono- and di-alkyl ethers of stilboestrol: —*——*—, mono-ethers; —●——●—, di-ethers.

(1) Read at the Atlantic City Meeting, September, 1941.

(2) E. C. Dodds, L. Goldberg, W. Lawson and R. Robinson, *Proc. Roy. Soc.* (London), **B127**, 152 (1939).

(3) Biological assays by C. F. Geschickter and Elizabeth W. Byrnes, published in part in *J. Clinical Endocrinology*, **2**, 19–25 (1942).

trated female rats. The melting points of the di-ethers show regular alternation; those of the mono- do so from the decyl up.

Experimental

These ethers were prepared in the conventional manner by heating stilboestrol in alcoholic solution with alkali and the required alkyl bromide (or iodide for the methyl). The preparation of the di-ethers presented no difficulty. These (particularly the high alkyl di-ethers) are much less soluble than the corresponding mono-ethers and can be purified by two or three recrystallizations from alcohol. To get rid of traces of mono-ether, alkali was usually added in the first recrystallization. The yields were high, usually above 90%. The mono-ethers proved to be difficult to prepare. The exclusive formation of a mono-ether could not be obtained by any attempted modification of the alkylation procedure. With less than one equivalent of alkyl halide and alkali the product always contained di-ether along with unreacted stilboestrol. Although stilboestrol is soluble in 0.1 *N* aqueous alkali and the mono-ethers only in alcoholic alkali, the separation, theoretically simple, is tedious in practice. Since the solubilities change greatly with the size of the alkyl, each mono-ether required special study. In some cases the separation was repeated as many as 10 times before a satisfactory product was obtained. For the monomethyl ether 0.4 *N* potassium hydroxide in 50% alcohol was used; the higher mono-ethers required stronger alcohol.

The monomethyl ether was recrystallized from 70% ethanol and then distilled *in vacuo*, b. p. 185–195° (0.3 mm.).

Summary

1. The normal mono- and di-alkyl ethers of stilboestrol from methyl to octadecyl have been prepared.

2. Their estrogenic activities have been determined.

BALTIMORE, MARYLAND RECEIVED APRIL 24, 1942

[CONTRIBUTION FROM THE WESTINGHOUSE RESEARCH LABORATORIES, EAST PITTSBURGH, PA.]

The Effect of Temperature on the Validity of Hudson's Rules of Isorotation

BY WALTER KAUZMANN*

Over thirty years ago, Hudson[1] proposed his "rules of isorotation" for use in calculating the optical rotatory powers of carbohydrate derivatives. Although these have since been of great use to the carbohydrate chemist in determining the structure of new derivatives, their reliability has been seriously reduced by the existence of a number of definite instances, notably but not solely in the mannose series, in which calculated rotations fail to agree at all satisfactorily with those observed. It has been felt that if the source of these discrepancies could be determined, the value of the rules as a tool in carbohydrate structure determination might be considerably enhanced. So far, the effects of different solvents and concentrations[2] and of wave length[3] on carbohydrate rotations have been studied, but the behavior of the anomalous cases with respect to these variables has not led to any clue as to the true nature of the difficulty. Previous theoretical considerations,[4] based upon the physical origin of optical rotation have led us to suspect that the real clue to the problem is to be found in temperature dependence of the rotation. In this paper we shall give the reasoning which leads to this conclusion and show by means of experimental data that there is indeed good reason to believe that this is actually the case.

In a previous paper[4] it was shown by relatively simple, essentially geometrical arguments that Hudson's rules may be expected to be valid if two conditions are fulfilled. (1) The vicinal actions between any two groups whose locations, conformations and relative orientations in a molecule are fixed must be unaffected by change in the spacial configurations of other groups in the molecule.[5] In order to state this more explicitly,

* Westinghouse Research Fellow. The experimental work in this paper was carried out at Frick Chemical Laboratory, Princeton University, Princeton, New Jersey.

(1) C. S. Hudson, THIS JOURNAL, **31**, 66 (1909).

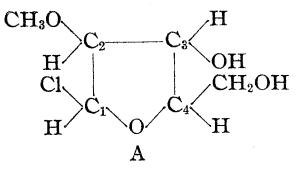
(2) P. Levene and I. Bencowitz, *J. Biol. Chem.*, **73**, 685 (1927).

(3) T. L. Harris, E. L. Hirst and C. E. Wood, *J. Chem. Soc.*, 2108 (1932).

(4) E. Gorin, W. Kauzmann and J. Walter, *J. Chem. Phys.*, **7**, 327 (1939).

(5) Vicinal actions are the optical interactions between groups in a molecule, the sum total of which results in the molecule's being able to rotate the plane of polarized light. For further details, see W. Kauzmann, J. Walter and H. Eyring, *Chem. Rev.*, **26**, 339 (1940).

consider the molecule shown as A. This condition then requires that the contribution to the optical rotation due to the interactions of, say, the methoxyl on C_2 and the chlorine on C_1 shall not be influenced by the configurations of the groups about C_3 and C_4, either directly, through the "higher order perturbations" considered in reference 5, or indirectly through, for instance, solvent and steric effects[6] on the methoxyl which might depend on the orientation of the groups about C_3. (2) The second condition which must be fulfilled in order that Hudson's rules may be valid is that the framework of the molecule have a plane of symmetry, such that when the configurations about any two asymmetric centers in the compound are simultaneously reversed, all of the contributions to the optical activity resulting from the interactions of the groups about the two centers with one another change their signs but not their absolute values. Referring again to compound A, this condition means that if we change the configurations about C_1 and C_2, the new *average* conformation which the molecule assumes must be merely the mirror image of the old one as far as C_1 and C_2 by themselves are concerned. In a plane, five-membered ring with tetrahedral carbon atoms this will be automatically true; in a puckered, six-membered ring this will only be true if the various possible "chair conformations" occur in equal amounts, and similarly if "bed conformations" are also present, so that the *average* conformation of the ring will be symmetrical.



A

As far as the vicinal actions themselves are concerned, condition (1) will very probably be well satisfied in the sugars. Evidence for this has been discussed elsewhere.[7] On the other hand, the effect of steric repulsions, solvent effects and other structural factors may not be such as to allow the molecule to conform with these requirements, and it is probably here that we should seek the reason for the observed discrepancies to the rules, as well as the failure of optical superposition rules more generally.

Now let us inquire what will be the effect of an increase in the temperature on these structural factors which tend to invalidate Hudson's rules. First of all, solvent effects are known to tend to decrease with increasing temperature, so that any trouble from this source must also decrease with increasing temperature. Secondly, increasing temperatures tend more or less to equalize the frequency of occurrence of all possible conformations of a molecule. This will tend to reduce the effects of "higher order steric interactions" which tend to invalidate the rules. It will also probably tend to equalize the amounts of the two possible chair forms of a six-membered ring, and it will tend to do the same for the bed forms. In short, except for the purely optical interactions (which would probably not lead to serious discrepancies anyway), an increase in the temperature should tend to bring about those conditions which result in Hudson's rules being valid.

Experimental.—The rotations of a number of sugar derivatives were measured at different temperatures and wave lengths. Since there was nothing particularly striking about the rotatory dispersion, however, these data will not be given here. The results at three temperatures for Na D light are given in Table I for various sugar derivatives. These derivatives were supplied by Dr. E. Pacsu, of Princeton University, or were prepared by standard procedures starting with materials furnished by him. The α-methyl mannofuranoside was supplied by Dr. A. Scattergood. The author wishes to express his gratitude for these materials.

The rotations recorded in Table I have been corrected for changes in the densities of the solutions on which the measurements were made. In all cases, rotations at room temperature were taken both before and after the readings at high temperatures in order to make sure that the observed changes with temperature were reversible. Practically all of the rotations changed very nearly linearly with the temperature in the range studied here.

Discussion.—It is obvious from the data of Table I that perhaps the conformations of, and certainly the solvent effects on, many of the sugars change with temperature sufficiently to cause, in some instances, very considerable changes in the optical rotation. Thus we see that there is no real justification for applying Hudson's rules indiscriminately to data obtained at room temperature, and serious errors might be expected from such a course.

(6) By the solvent effect here is meant the difference between the rotation in a given solvent and the rotation at the same temperature in the dilute vapor or (neglecting the internal field effect given by the factor $(n^2 + 2)/3$—see ref. 5) in an inert solvent.

(7) W. Kauzmann and H. Eyring, *J. Chem. Phys.*, **9**, 41 (1941).

TABLE I

VARIATION IN THE OPTICAL ROTATIONS OF CARBOHYDRATE DERIVATIVES WITH TEMPERATURE AND SOLVENT

Substance	Solvent	Concn., g./100 ml.	$[M]^{20}D$	$[M]^{70}D$	$[M]^{80}D$
α-Glucose pentaacetate	$C_2H_2Cl_4$	5.07	394.5	394.5	394.5
β-Glucose pentaacetate	$C_2H_2Cl_4$	4.98	16	25	26.5
α-Mannose pentaacetate	$C_2H_2Cl_4$	3.12	190.5	223	230.5
β-Mannose pentaacetate	$C_2H_2Cl_4$	5.04	−97.5	−90	−88.5
α-Methyl glucoside tetraacetate	$C_2H_2Cl_4$	4.80	439	461	465.5
α-Methyl glucoside tetraacetate	C_6H_6	5.30	623	583	(578)
β-Methyl glucoside tetraacetate	$C_2H_2Cl_4$	5.17	−80	−58.5	(−55)
β-Methyl glucoside tetraacetate	C_6H_6	4.85	−83.5	−73	(−70.5)
α-Methyl mannoside tetraacetate	C_6H_6	4.94	160.5	180	182.5
α-Methyl mannoside tetraacetate	$C_2H_2Cl_4$	5.06	221	218.5	(219)
α-Methyl glucopyranoside	H_2O	5.12	302	301.5	301
β-Methyl glucopyranoside	H_2O	5.00	−64.5	−61	−60.5
α-Methyl mannopyranoside	H_2O	4.93	150.5	152.5	153
α-Methyl mannofuranoside	H_2O	5.26	212	199	196.5

In order to see if our previous theoretical considerations are valid, values of $2A$ for the pentaacetates of glucose and mannose in acetylene tetrachloride were calculated at 20, 70 and 80°. The results are given in Table II. It is apparent that by increasing the temperature from 20 to 80° the agreement with Hudson's rules is improved by nearly 50%, and since at even the highest temperature the rotations were still rapidly changing with the temperature, it is easy to believe that at sufficiently high temperatures the agreement would be very nearly complete.

In Table III the values of $2A_{OMe}$ are given as determined from the methyl glucoside tetraacetates in benzene and acetylene tetrachloride as solvents. It is apparent that as the temperature is increased, the discrepancy due to the very large solvent effects here is considerably reduced. It is also apparent from Table I that when there are large differences in the rotation of one substance in different solvents, these differences tend to be reduced at higher temperatures, in accordance with a rule previously given.[7]

In the previous paper[4] it was recalled that there is a corollary to Hudson's rules[8] which predicts that, for instance, the difference in the rotations of α-methyl glucoside and α-glucose should be the same as that between α-methyl mannoside and α-mannose. It was shown that this corollary should and does tend to be very accurate when the partial rotations being compared (here A_{OH} and A_{OMe}) are due to optically similar groups, but that when optically dissimilar groups are compared (such as CH_3—O and CH_3—CO—O)[9] no good agreement should be expected, as is indeed found to be the case (Table VI, ref. 4). In Table IV this conclusion is tested further, and it is again seen that when dissimilar groups are involved, no general improvement in the discrepancy is found at higher temperatures. Even the apparent convergence for the glucose derivatives here is only temporary, since at the higher temperatures the rotations appeared to be still changing rapidly enough so that at about 100° their differences will probably become equal and then start to diverge.

The considerable temperature effects on the rotation of α-methyl mannofuranoside in water is of significance in connection with the poor agreement found for the mannofuranosides with respect to Hudson's rules.[10]

The temperature variation of the optical rotation offers a method for evaluating the F factors introduced by Pacsu[10,11] in order to improve the agreement with observed rotations of the rotations calculated using Hudson's rules: these factors at any given temperature should be given by the difference between the limiting rotation at high temperatures (insofar as the frequency of occurrence of all conformations is actually equalized at high temperatures) and the rotations at the given temperature. Pacsu[11] originally suggested that the factors arise from new types of isomerism, perhaps involving chair and bed forms of the sugar rings. More recently Scattergood and Pacsu[11] have suggested that they arise through "different

(8) C. S. Hudson, THIS JOURNAL, **47**, 271 (1925).

(9) By optically similar groups it is meant that the electronic transitions which play a predominant role in determining the contribution to the rotatory power by these groups acting as chromophores (see ref. 5, p. 351) are similar. Thus the first excited states in hydroxyl and methoxyl groups involve predominantly the same orbitals on the oxygen atom, so the groups are similar to one another in this sense, while the first excited state in the acetyl group involves the double bond of C=O, so this group is dissimilar to hydroxyl and methoxyl.

(10) A. Scattergood and E. Pacsu, THIS JOURNAL, **62**, 903 (1940).

(11) E. Pacsu, *ibid.*, **61**, 2669 (1939).

orientation [about the C—O bond] of the hydroxyl groups in the α- and β-isomers of certain sugars." In the light of the observed large solvent effects for some substances, it does not, however, seem profitable to ascribe all of these variations to any one such physical cause.

When the temperature dependence of the rotations of β-methyl mannoside tetraacetate in benzene and in acetylene tetrachloride and of β-methyl manno-pyranoside and -furanoside in water are known, it will be possible, with the data presented here, to find out if the values of $2A$ for these compounds, too, tend to agree any better at higher temperatures with the corresponding values of the glucose derivatives, just as we have shown is the case for the pentaacetates of the two sugars.

TABLE II

(FROM DATA ON THE PENTAACETATES)

t, °C.	$2A_{OAc}$(glucose)	$2A_{OAc}$(mannose)	Discrepancy
20	378.5	288	90.5
70	369.5	313	56.5
80	368	319	49

TABLE III

(FROM DATA ON THE METHYL GLUCOSIDE TETRAACETATES)

t, °C.	$2A_{OMe}$ (in acetylene tetrachloride)	$2A_{OMe}$ (in benzene)	Discrepancy
20	519	706.5	187.5
70	519.5	656	136.5
80	(520.5)	(648.5)	(128)

TABLE IV

(FROM DATA ON SOLUTIONS IN ACETYLENE TETRACHLORIDE)

t, °C.	α-Me gluc. tetraac.-α gluc. pentaac.	$-$(β-Me gluc. tetraac.-β gluc. pentaac.)	α-Me mann. tetraac.-α mann. pentaac.
20	44.5	96	−30
70	66.5	83.5	−43
80	71	82	(−48)

Conclusion.—From the evidence presented here it should be clear that for many of the derivatives of the carbohydrates there is a considerable dependence of the rotation on the temperature, so that structural influences on Hudson's rules must be important in affecting their validity, and it is not at all unlikely that these structural influences lie at the root of the major part of the observed discrepancies in those rules. It would be very desirable if, when a test is being made concerning the validity of Hudson's rules in a series of compounds, measurements of the effect of the temperature on the rotations as well as the rotations themselves were made. Then, if the rotations were found to be in disagreement with the rules, the influence of the temperature in making the rules better or worse could be ascertained, and we would gain considerably more insight into the origin of the discrepancy.

It would also be very interesting to have such temperature data for the menthyl amines investigated by Read,[12] since these should show superposition in the ordinary van't Hoff sense at higher temperatures. Similarly, the recent application of superposition rules to the γ-lactones by Hudson[13] should become more exact at higher temperatures, and no division of the γ-lactones into two classes should be necessary. By working at higher temperatures, superposition rules would undoubtedly be found to apply to many new types of compounds, possibly even to some open chain compounds.

Summary

It is shown from theoretical considerations that the clue to the discrepancies observed on the application of Hudson's rules of isorotation to the calculation of the optical rotations of carbohydrates is probably to be found in the temperature variation of the optical rotation for these compounds. Experimental measurements are made which support the prediction that as the temperature is increased, the rules should with certain restrictions tend to become more and more accurate.

EAST PITTSBURGH, PENNA. RECEIVED MARCH 20, 1942

(12) J. Read, *Trans. Faraday Soc.*, **26**, 441 (1930).

(13) C. S. Hudson, THIS JOURNAL, **61**, 1525 (1939).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Complex Ions. III. A Study of Some Complex Ions in Solution by Means of the Spectrophotometer[1]

BY ROBERT K. GOULD AND W. C. VOSBURGH

A modification of Job's method[2] of continuous variations for the identification of compounds formed in solution has been described by Vosburgh and Cooper.[3] The modification made it possible to apply the method to cases in which more than one compound is formed from the same components. It was thought desirable to test the method further on a wider variety of systems, and to investigate some more systems to determine how many different complex ions are formed from the same components.

The modified method consists of making a number of mixtures of equimolar solutions of the two reactants and measuring the optical densities of the mixtures at certain pre-selected wave lengths. From the density of each mixture is subtracted the density calculated by the law of mixtures assuming no reaction. The difference, Y, is a maximum or minimum for the mixture in which the two reactants have been brought together in the proportions in which they react.

When more than one compound is formed, particular wave lengths can be selected as the most favorable for obtaining evidence of the various compounds. Different wave lengths lead to different composition values for a maximum or minimum in Y when more than one compound is formed. If Y is a maximum or minimum at the same composition for all wave lengths, the probability is that only one compound is formed. The shapes of the curves obtained when the results are plotted help in deciding whether or not more than one compound is formed.

Theoretical

In the course of this work the question arose as to the effect of a second equilibrium in the system being investigated. For example, suppose that substance A in addition to reacting with B in accordance with the equation

$$A + nB \rightleftarrows AB_n \qquad (1)$$

reacts also with the substance D

$$A + rD \rightleftarrows AD_r \qquad (2)$$

Let us suppose that D is present in the equimolar solutions of A and B so that when these are mixed in varying proportions all mixtures contain the same concentration of D, and further that this concentration is large enough to remain practically constant in spite of Reaction 2. Then the concentration of AD_r is proportional to the concentration of A and can be set equal to Lc_1. The following equations can be set up, in which c_1, c_2 and c_3 are the concentrations of A, B and AB_n, respectively, and x is the volume of solution B added to the volume $1 - x$ of solution A to give unit volume of the mixture.

$$c_1 = M(1 - x) - c_3 - Lc_1$$
$$c_2 = Mx - nc_3$$
$$c_1c_2^n = Kc_3$$

On differentiation of each of these equations, setting dc_3/dx equal to zero, and solving the six equations simultaneously, the result is that when c_3 is a maximum, $n = x/(1 - x)$. This is the same as when there is no second equilibrium corresponding to Reaction 2.

If the compound AD_r is colored, but D is colorless, the difference Y between the actual optical density of the solution and the density calculated for no reaction is given by

$$Y = l(\epsilon_1 + \epsilon_4 L)\, c_1 + \epsilon_2 c_2 + \epsilon_3 c_3 - \epsilon_1 M(1 - x)/(1 + L) - \epsilon_2 Mx - \epsilon_4 LM(1 - x)/(1 + L)$$

in which ϵ_1, ϵ_2, ϵ_3 and ϵ_4 stand for the extinction coefficients of the substances A, B, AB_n, and AD_r, respectively, and l is the length of the path of light through the solution. Differentiating and equating dc_3/dx to zero shows that Y is either a maximum or minimum when c_3 is a maximum. Consequently, when a second substance is present that enters into reaction with Reactant A, the method of continuous variations may be used without the necessity of correcting for the second reaction. It should be noted that this is true only when the concentration of the second reactant is practically constant throughout the series of mixtures. Another restriction not mentioned is that the activity coefficients, if not cancelling from the equilibrium equations, must be held constant by constant ionic strength.

(1) Thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of Arts and Sciences of Duke University.

(2) Job, *Ann. chim.*, (10) **9**, 113 (1928).

(3) Vosburgh and Cooper, THIS JOURNAL, **63**, 437 (1941).

Ferric and Thiocyanate Ions.—Bent and French[4] and also Edmonds and Birnbaum[5] have shown that in dilute solutions the only compound formed from ferric and thiocyanate ions is the ion $FeCNS^{++}$. It was of interest to see whether or not the method of continuous variations would lead to the same conclusion.

Solutions containing iron(III) and thiocyanate ions, both at a concentration of 0.02 *M*, and other solutes as shown below, were prepared

Iron(III) ion solution, *M*	Thiocyanate solution, *M*
0.02 $Fe(NH_4)(SO_4)_2$	0.02 NH_4CNS
.06 H_2SO_4	.16 $(NH_4)_2SO_4$
.06 $(NH_4)_2SO_4$	

First, mixtures of the two solutions were made in the proportions of 1:1, 1:2 and 1:3 and their absorption spectra were measured by means of a Coleman Double Monochromator spectrophotometer. The slit width was 30 mμ, and by means of plungers in the sample tubes the length of the path of light through the solution was reduced to 2 mm. The spectra are shown in Fig. 1, in which the density values for the 1:1 mixture have been multiplied by 0.5 and those for the 1:2 mixture by 0.75. The curves are of the same shape and

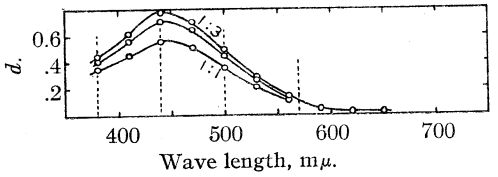


Fig. 1.—Absorption spectra of solutions containing iron(III) and thiocyanate ions in the ratios 1:1, 1:2 and 1:3. Dotted lines represent arbitrarily selected wave lengths.

are in agreement with the conclusion of Bent and French that only a single compound of low stability is formed. No particular wave lengths can be selected in accordance with the rules of Vosburgh and Cooper in this case, since the curves do not cross. A series of mixtures was therefore measured at four arbitrarily selected wave lengths. The values of *Y* as defined above were plotted against *x*, the volume of 0.02 *M* thiocyanate added to the volume $(1 - x)$ of 0.02 *M* iron(III) ion solution. The resulting curves are shown in Fig. 2. The curves all have a broad maximum in the vicinity of $x = 0.5$, indicating a compound $FeCNS^{++}$ which is considerably dissociated in solution, in agreement with Bent and French. There is no indication of the existence of any other compound under these conditions.

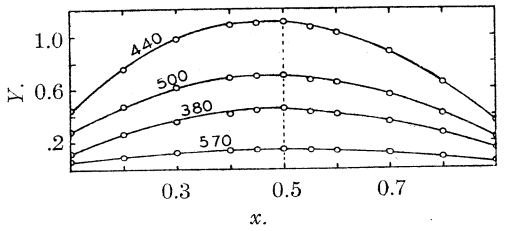


Fig. 2.—Iron(III) and thiocyanate ions; volume $(1 - x)$ of 0.02 *M* iron(III) ion solution plus *x* of 0.02 *M* thiocyanate ion solution.

It is shown in the theoretical part that the existence of a complex ion of iron and sulfate ions[6] would not affect this conclusion provided the sulfate ion concentration is held constant.

Iron(II) Ion and *o*-Phenanthroline.—Ferrari[7] has presented evidence that iron(II) ion forms only one complex ion with α,α′-dipyridyl in solution. Jaeger and van Dijk,[8] prepared solid complex sulfates with iron(II) ion and α,α′-dipyridyl in the proportions 1:1, 1:2 and 1:3. However, when it was attempted to convert these into chlorides by treatment with barium chloride, only the tridipyridyl iron(II) chloride was obtained. Vosburgh and Cooper[3] found evidence of three complex ions formed from nickel ion and *o*-phenanthroline in solution. Because of the similarity of α,α′-dipyridyl and *o*-phenanthroline, it was of interest to investigate compound formation between iron(II) ion and *o*-phenanthroline by the method of continuous variations.

A 0.004 *M* solution of ferrous ammonium sulfate was prepared by weighing the required amount of reagent grade material. A small amount of sodium bisulfite was included to prevent oxidation. A 0.004 *M* phenanthroline solution was prepared similarly from *o*-phenanthroline obtained from the G. Frederick Smith Chemical Co.

The two solutions were mixed in varying proportions, and the optical densities of the resulting solutions were measured at wave lengths 400, 500, 540 and 570 mμ with a length of path of 2 mm. The wave lengths were selected arbitrarily to cover the region of the spectrum absorbed by the iron $Fe(phen)_3^{++}$. The results are shown in Fig. 3, in which density is plotted against compo-

(4) Bent and French, THIS JOURNAL, **63**, 568 (1941).
(5) Edmonds and Birnbaum, *ibid.*, **63**, 1471 (1941).
(6) Kiss, Abraham and Hegedus, *Z. anorg. allgem. Chem.*, **244**, 98 (1940).
(7) Ferrari, *Gazz. chim. ital.*, **67**, 604 (1937).
(8) Jaeger and von Dijk, *Z. anorg. allgem. Chem.*, **227**, 273 (1936).

sition. Since the two original solutions were practically colorless, the density is equal to the difference Y. At all four wave lengths the maximum comes at composition 0.75, and each of the curves consists practically of two intersecting straight lines, indicating only one compound, $Fe(phen)_3^{+++}$, which is very stable.

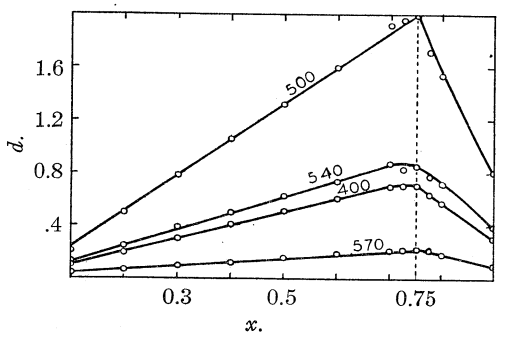


Fig. 3.—Iron(II) ion and *o*-phenanthroline; volume $(1 - x)$ of 0.004 M iron(II) sulfate solution plus x of 0.004 M *o*-phenanthroline solution.

The difference between the reaction of ferrous ion with phenanthroline and that of nickel ion is striking. There is another important difference between the ferrous phenanthroline and the three nickel phenanthroline ions: the ferrous phenanthroline ion is diamagnetic[9] while all three of the nickel phenanthroline ions are paramagnetic.[10]

The formation of a series of two or more complex ions from the same components is rather common. Bjerrum[11] has pointed out that this is to be expected theoretically, though the theory provides that in extreme cases a compound AB_n might be considerably more stable than the possible intermediate compounds. Bjerrum has investigated several series of ammines and ethylenediamine complex ions, finding in each case a series AB, AB_2, . . ., AB_n in which the stability decreases as n increases.

The ferrous phenanthroline complex ion seems to be exceptional in this respect, and the ion $Ni(CN)_4^=$ which is also diamagnetic seems to be another exception. Cambi, Cagnasso and Tremolada[12] have presented evidence from magnetic measurements that hydrated nickel cyanide, $Ni(CN)_2 \cdot nH_2O$ is in reality composed of the paramagnetic cation $Ni(H_2O)n^{++}$[7] and the diamagnetic anion $Ni(CN)_4^=$. Whether these two diamagnetic compounds are special cases or examples of a general rule can be determined by the examination of other ferrous and nickel complex ions.

Nickel and Dithio-oxalate Ions.—A highly colored complex salt formed from potassium dithio-oxalate and a nickel salt was shown by Jones and Tasker[13] to have the composition $K_2Ni(C_2O_2S_2)_2$. Cox, Wardlaw and Webster[14] showed that all atoms in the complex ion $Ni(C_2O_2S_2)_2^=$ are co-planar. According to Pauling, co-planar nickel compounds should be diamagnetic, and potassium nickel dithio-oxalate has been shown to conform.[15] Therefore, it was of interest to see if more than one complex ion formed from nickel and dithio-oxalate ions could be identified.

A 0.004 M solution of nickel sulfate was prepared by dilution of a stock solution made from reagent grade material and standardized gravimetrically. A 0.004 M solution of potassium dithio-oxalate was prepared by weight. The dithio-oxalate was obviously somewhat impure, and the concentration of the solution was somewhat lower than 0.004 M. However, it was felt that purification or standardization was unnecessary, since the main object was to see whether or not evidence could be found for more than one compound, and there was little doubt as to the formula of the known compound.

The two solutions were first mixed in the proportions of one part by volume of nickel sulfate solution to one, two, and three parts of dithio-oxalate solution. The optical densities were measured as described for the iron(III) and thiocyanate ions, and corrected to a nickel ion concentration of 0.001 M. The resulting absorption spectra are shown in Fig. 4. Since the curves do not cross in the visible region, wave lengths 440, 500 and 590 mμ were arbitrarily selected for the

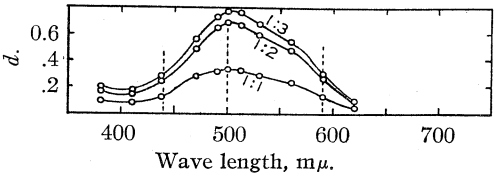


Fig. 4.—Absorption spectra of solutions containing nickel and dithio-oxalate ions in the ratios 1:1, 1:2 and 1:3. Dotted lines represent arbitrarily selected wave lengths.

(9) Cambi and Cagnasso, *Gazz. chim. ital.*, **63**, 767 (1933).
(10) Russell, Ph.D. Thesis, Duke University, 1941.
(11) Bjerrum, "Metal Ammine Formation in Aqueous Solution," P. Haase and Son, Copenhagen, Denmark, 1941, p. 130; *Chem. Abs.* **35**, 6527 (1941).
(12) Cambi, Cagnasso and Tremolada, *Gazz. chim. ital.*, **64**, 758 (1934).
(13) Jones and Tasker, *J. Chem. Soc.*, **95**, 1904 (1909).
(14) Cox, Wardlaw and Webster, *ibid.*, 1475 (1935).
(15) Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, p. 111.

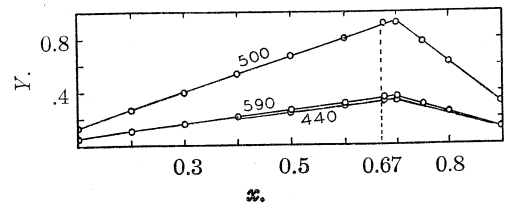


Fig. 5.—Nickel and dithio-oxalate ions; volume $(1 - x)$ of 0.004 M nickel sulfate solution plus x of 0.004 M potassium dithio-oxalate solution.

measurement of the usual series of mixtures. The results of these measurements are shown in Fig. 5. The straight lines, with the points of intersection all coming at about the same composition, indicate the formation of only one compound, which is quite stable. The difference between the 1:2 and 1:3 curves of Fig. 4 might appear to indicate some dissociation of the ion $Ni(C_2O_2S_2)_2^{=}$, but the error in concentration of the dithio-oxalate solution is responsible for at least part of the difference.

Copper and Aminoacetate Ions.—Copper aminoacetate, $Cu(OOCCH_2NH_2)_2$, was found by Ley[16] to be little dissociated in solution and was early recognized as a chelate compound.[17] Borsook and Thimann[18] found evidence for four different compounds of copper ion and aminoacetic acid or aminoacetate ion, two in the more acid solutions, one in neutral solution and a fourth in alkaline solutions. These were formed from either 1.5 or 2 moles of aminoacetic acid per gram atom of copper. Ley[19] has recognized the possibility of the stepwise dissociation of copper aminoacetate to give the ion $Cu(OOCCH_2NH_2)^+$. Application of the method of continuous variations to the study of compound formation from copper sulfate and sodium aminoacetate showed that two compounds were formed, with ratios of copper ion to aminoacetate ion of 1:1 and 1:2, respectively.

A 0.02 M copper sulfate solution was prepared from recrystallized material and standardized by iodometric determination of the copper. A 0.02 M sodium aminoacetate solution was prepared by weighing the twice recrystallized acid and adding the equivalent quantity of standard sodium hydroxide solution.

Absorption spectra were measured of a solution 0.01 M with respect to both copper sulfate and sodium aminoacetate, and of a solution 0.004 M with respect to copper sulfate and 0.08 M with respect to sodium aminoacetate. Circular sample tubes of 16 mm. diameter were used in the spectrophotometer. The optical densities of the second solution were corrected by multiplication by 2.5, and the data for the two solutions and for 0.01 M copper sulfate solution were plotted to give Fig. 6.

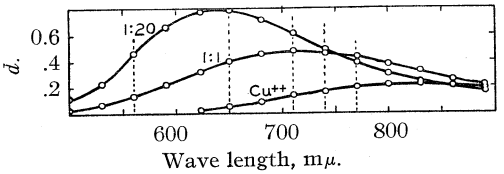


Fig. 6.—Absorption spectra of 0.01 M copper sulfate solution and solutions containing copper and aminoacetate ions in ratios of 1:1 and 1:20, with 0.01 M total copper.

The wave lengths indicated by the dotted lines in Fig. 6 were selected for use in the further investigation of the system. Measurement of a series of mixtures of the 0.02 M solutions described above at these wave lengths gave the data shown in Fig. 7. The Y-values for all of these curves were determined by the subtraction of the calculated densities for no reaction. This is wrong theoretically[3] for the curves with the maximum at $x = 0.67$. However, experience has shown that the position of the maximum is usually changed only a little when the correct subtraction is made instead of the one made in this case.

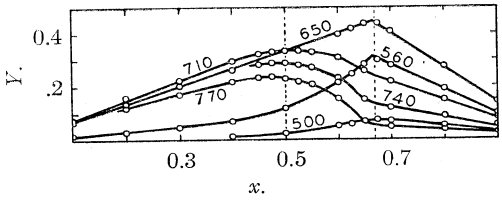


Fig. 7.—Copper and aminoacetate ions; volume $(1 - x)$ of 0.02 M copper sulfate solution plus x of 0.02 M sodium aminoacetate solution.

Figure 7 gives evidence of two compounds, the ion $Cu(OOCCH_2NH_2)^+$ postulated by Ley[19] and the neutral compound $Cu(OOCCH_2NH_2)_2$. It is interesting that the curve for wave length 650 mμ consists of two intersecting straight lines. Straight lines are generally found when only a single compound of high stability is formed. The straight line on the left for 650 mμ is the result of a coincidence, since it happens that at 650 mμ the molar extinction coefficient of the first compound is very nearly half that of the second.

(16) Ley, *Z. Elektrochem.*, **10**, 954 (1904).
(17) (a) Tschugaeff, *J. prakt. Chem.*, [2] **75**, 162 (1907); (b) Ley, *Ber.*, **42**, 354 (1909).
(18) Borsook and Thimann, *J. Biol. Chem.*, **98**, 671 (1932).
(19) Ley, *Z. anorg. allgem. Chem.*, **164**, 387 (1927).

At other wave lengths this is not true, and the curves for 500 and 560 mμ indicate the existence of a second compound, as do also the right-hand parts of the curves for 740 and 770 mμ. The wave length 740 mμ is the most favorable one for showing the existence of the first compound, and for this wave length the maximum in the *Y*-curve comes nearest to $x = 0.5$.

Nickel and Aminoacetate Ions.—Ley[19] has prepared a nickel aminoacetate and has found it to have the composition $Ni(OOCCH_2NH_2)_2 \cdot 2H_2O$. The method of continuous variations shows that in addition a compound is formed from three aminoacetate ions to one nickel ion. The new compound is presumably an anion in which the nickel has a coördination number of six.

A 0.2 *M* nickel sulfate solution was standardized gravimetrically. A 0.2 *M* sodium aminoacetate solution was prepared as described above in connection with the copper aminoacetate system. The two solutions were mixed in the ratios 1:1, 1:2 and 1:3, and the absorption spectra of the resulting mixtures measured in the circular sample tubes. The spectra corrected to a concentration of 0.1 *M* total nickel with the assumption of Beer's law are shown in Fig. 8. An outstanding feature

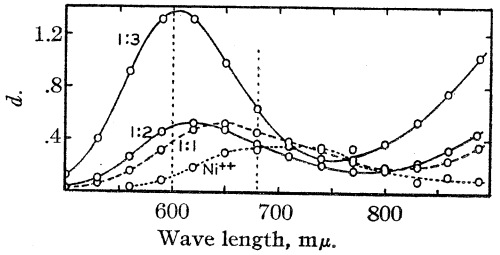


Fig. 8.—Absorption spectra of 0.1 *M* nickel sulfate solution and solutions containing nickel and aminoacetate ions in ratios of 1:1, 1:2 and 1:3, with 0.1 *M* total nickel.

of these curves is the large difference between the curve for the 1:3 ratio and the others. This curve lies above the others over so large a portion of the spectrum that it is difficult to select wave lengths that can be used to investigate the existence of other than the compound highest in aminoacetate content. In the region where the 1:1 curve is higher than the 1:3 curve, the curve for

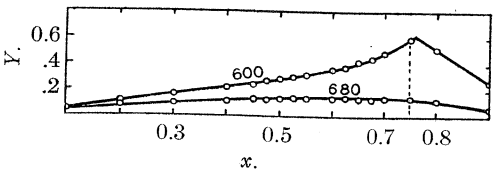


Fig. 9.—Nickel and aminoacetate ions; volume $(1 - x)$ of 0.2 *M* nickel sulfate solution plus x of 0.2 *M* sodium aminoacetate solution.

nickel ion almost coincides with the 1:1 curve, making this region useless. This system is one in which none but the compound highest in aminoacetate content can be determined with assurance. Wave length 600 mμ is favorable for showing the highest compound, and the only other that seemed worth while trying was 680 mμ. The usual series of mixtures was examined spectrophotometrically at these wave lengths and the results in Fig. 9 were obtained. At wave length 600 mμ the maximum comes slightly beyond the composition $x = 0.75$, indicating a compound of the composition $Ni(OOCCH_2NH_2)_3^-$. The curvature of the left-hand line suggests at least one other compound, and the *Y*-curve for 680 mμ has a maximum somewhere between $x = 0.5$ and $x = 0.75$, which also indicates another compound. These data give little indication of what the compound might be. Thus, it can be seen that the method of continuous variations does not always give full information about compound formation, and can be relied on for such only when conditions are favorable.

Summary

A number of systems have been examined by the method of continuous variations. In the three systems iron(III) and thiocyanate ions, iron(II) and *o*-phenanthroline, and nickel and dithio-oxalate ions, evidence was obtained for only one compound each, the compounds being already known. From copper and aminoacetate ions evidence of two compounds was obtained, with the components in ratios of 1:1 and 1:2, respectively. From nickel and aminoacetate ions evidence was obtained for a 1:3 compound and one other which could not be definitely identified.

DURHAM, N. C. RECEIVED MARCH 2, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE CATHOLIC UNIVERSITY]

Conductivity Studies. IV. The Limiting Ionic Mobilities of Several Univalent Ions at Temperatures between 15 and 45°

BY NORMAN C. C. LI AND WILHELM BRÜLL

Conductance data on aqueous solutions of potassium chloride at several temperatures are given in a paper preceding this one.[1] Allgood, LeRoy and Gordon[2] describe the accurate determination by moving boundary method of the transference numbers of aqueous solutions of potassium chloride at 15, 25, 35 and 45°. With these data on conductances and transference numbers at hand, we can calculate the equivalent conductances of ion constituents and the limiting ionic mobilities at different temperatures, with an accuracy of a part in several thousand.

Table I contains the assembled data on the equivalent conductances, Λ, of potassium chloride solutions and the corresponding transference numbers of the chloride ion, t_{Cl}, for 15, 25, 35 and 45°. The values of Λ are calculated from the equation

$$\Lambda = \Lambda_0' (1 - \alpha\sqrt{C}) - \beta\sqrt{C}$$

in which the theoretical coefficients α and β are calculated in the same way as described by Li and Fang[1] and Λ_0' is given by the equation

$$\Lambda_0' = \Lambda_0 + BC = \frac{\Lambda + \beta\sqrt{C}}{1 - \alpha\sqrt{C}}$$

The constants Λ_0 and B are either given in or interpolated from Table III of the preceding paper. The transference numbers as given by Allgood, LeRoy and Gordon are either the directly determined values or calculated by the equation

$$t_+^{\circ\prime} = t_+^\circ + AC = \frac{t_+\Lambda + {}^1/_2\beta\sqrt{C}}{\Lambda + \beta\sqrt{C}} \qquad (1)$$

where A is a disposable constant and β is the same theoretical coefficient as before, It is interesting to note that data on transference number and equivalent conductance can be treated in a similar way.

Column 4 of Table I gives the conductance of the chloride ion constituent $\lambda_{Cl} = \Lambda t_{Cl}$, and column 5 gives the values of λ_0' obtained by means of the equation

$$\lambda_0' = \lambda + {}^1/_2\beta\sqrt{C}/1 - \alpha\sqrt{C} = \lambda_0 + bC \qquad (2)$$

in which λ_0 is the limiting equivalent conductance of the ion species and b is an empirical constant.

(1) Li and Fang, THIS JOURNAL, **64**, 1544 (1942).

(2) Allgood, LeRoy and Gordon, *J. Chem. Phys.*, **8**, 421 (1940).

TABLE I

Λ_{Cl} FOR POTASSIUM CHLORIDE SOLUTIONS OF DIFFERENT CONCENTRATIONS

C	Λ_{KCl}	t_{Cl}	λ_{Cl}	λ_0'
		15°		
0.005	116.07	0.5074	58.89	61.50
.01	114.29	.5075	58.00	61.70
.02	111.97	.5076	56.84	62.09
.05	108.08	.5077	54.87	63.21
.10	104.73	.5079	53.19	65.12
		25°		
0.005	143.67	0.5097	73.23	76.58
.01	141.38	.5098	72.08	76.82
.02	138.41	.5099	70.62	77.33
.05	133.36	.5100	68.02	78.71
.10	128.98	.5100	65.78	81.06
		35°		
0.005	171.74	0.5113	87.81	91.96
.01	168.89	.5114	86.37	92.24
.02	165.17	.5115	84.48	92.80
.05	158.83	.5115	81.24	94.48
		45°		
0.005	199.72	0.5131	102.48	107.48
.01	196.26	.5132	100.72	107.81
.02	191.73	.5132	98.40	108.44
.05	183.96	.5131	94.37	110.33

This equation was first given by MacInnes, Shedlovsky and Longsworth.[3] Fig. 1 shows values of λ plotted against $\sqrt{C}$ and λ_0' against C. The

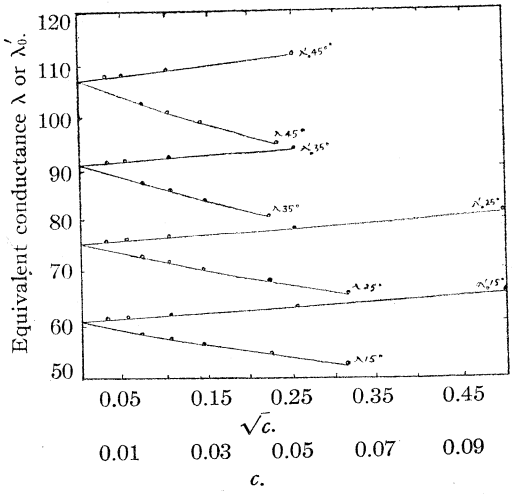


Fig. 1.—Variation of equivalent conductance with concentration.

(3) MacInnes, Shedlovsky and Longsworth, THIS JOURNAL, **54**, 2760 (1932).

values of λ_0 and b in Eq. 2 are obtained graphically and are listed in Table II.

TABLE II
LIMITING MOBILITIES OF THE CHLORIDE ION

t, °C.	b	λ_0 for Cl ion
15	40	61.30
25	48	76.34
35	56	91.68
45	64	107.16

The values of λ°_{Cl} can be calculated directly from the product of $\Lambda_{0\,KCl}$ and t°_{Cl}. Table III, columns 4 and 5 list the values of λ_0 for potassium and chloride ions, respectively, for 15, 25, 35 and 45°. The values of $\Lambda_{0\,KCl}$ are taken from Li and Fang[1] and t°_{+KCl} from Allgood, LeRoy and Gordon.[2]

TABLE III
LIMITING IONIC MOBILITIES

t, °C.	$\Lambda_{0\,KCl}$	$t^\circ_{+\,KCl}$	λ_K	λ°_{Cl}
15	120.88	0.4928	59.57	61.31
25	149.84	.4905	73.50	76.34
35	179.40	.4889	87.71	91.69
45	208.96	.4872	101.81	107.15

The values of λ°_{Cl} as seen agree very well with those listed in Table II and the very close agreements are somewhat surprising, since the transference numbers at very low concentrations are not known accurately. The relationship between λ° and temperature is linear so that the following equations can be applied

$$\lambda^\circ_{-1} = 38.50 + 1.519t$$
$$\lambda^\circ_K = 38.44 + 1.407t$$

The value of λ°_{Cl} at 25° agrees with that given by MacInnes, Shedlovsky and Longsworth.[3]

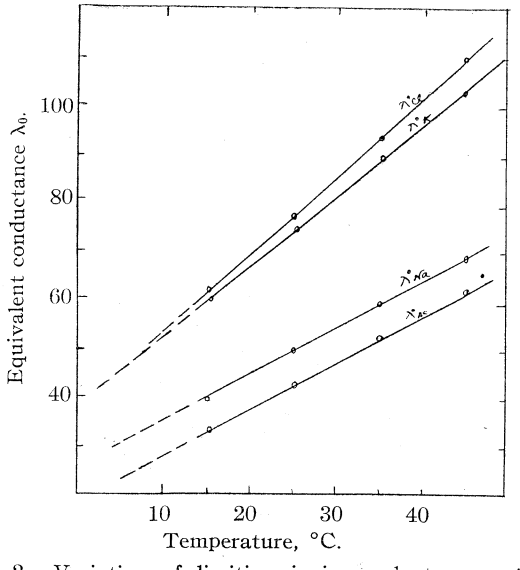


Fig. 2.—Variation of limiting ionic conductances with temperature.

From the values of λ°_K and λ°_{Cl} just given and the limiting conductances Λ_0 of sodium chloride and sodium acetate in water as given by Brescia, LaMer and Nachod,[4] the limiting ion conductances of sodium and acetate ions at different temperatures can be calculated from Kohlrausch's law of independent ion mobilities. The results obtained are shown in Table IV and in Fig. 2. The values for λ°_{Na} and λ°_{Ac} at 25° given by MacInnes, Shedlovsky and Longsworth[3] are 50.10 and 40.87, respectively, and differ considerably from the corresponding values given in Table IV, owing to the differences in the values of Λ°_{NaCl} and Λ°_{NaAc} used.

TABLE IV
LIMITING ION CONDUCTANCES AND LIMITING TRANSFERENCE NUMBERS

t, °C.	λ°_{Na}	λ°_{Ac}	t°_+ in NaCl	t°_+ in NaAc
15	39.70	32.80	0.3930	0.5476
25	49.29	42.07	.3923	.5395
35	58.57	51.65	.3898	.5314
45	67.72	61.36	.3872	.5256

The values of Λ°_{NaCl} and Λ°_{NaAc} given by Brescia, LaMer and Nachod,[5] however, are calculated from data in "International Critical Tables" and are not as accurate as the more recent values given by MacInnes, Shedlovsky and Longsworth. Using the equation

$$t^\circ_+ = \frac{\lambda^\circ_+}{\lambda^\circ_+ + \lambda^\circ_-} = \frac{\lambda^\circ_+}{\Lambda_0}$$

we have calculated the limiting transference numbers of aqueous solutions of sodium chloride and sodium acetate at the several temperatures and the results are shown in columns 3 and 4 of Table IV.

The cation transference numbers in aqueous solutions of sodium acetate are seen to decrease with rising temperature. This decrease is in accord with the well-known generalization that if the transference numbers are less than 0.5 they increase, and if greater than 0.5 they decrease with rise in temperature. The cation transference numbers in aqueous solutions of potassium and sodium chlorides, which are all less than 0.5, are seen to decrease with rising temperature and this is apparently contrary to the above generalization. Allgood, LeRoy and Gordon[2] have tentatively explained the anomaly of potassium chloride solutions as due to the hydration of the cation resulting in a different mechanism of transport for cation and anion. This difference may be-

(4) Brescia, LaMer and Nachod, THIS JOURNAL, **62**, 615 (1940).

come prominent because the anion and cation of potassium chloride have approximately the same mobility, but it is not sufficient to explain the case of sodium chloride, in which the mobilities of anion and cation are quite different. We believe that the apparent decrease in cation transference numbers in sodium chloride solutions with rise in temperature is due to the inaccurate conductivity data given in "International Critical Tables." Thus if we use the more recent value, $\Lambda_0 = 126.42$, for sodium chloride at 25°, the calculated value of t°_+ for aqueous solution of sodium chloride at 25° will be 0.3963 in agreement with the value found from direct transference data and in agreement with the above generalizations in that the limiting transference number at 25° is higher than at 15°. However, since the recent accurate conductivity data have been determined for 25° only, all the values given in Table IV for the four different temperatures are taken from the paper by Brescia, LaMer and Nachod which is based on the values given in "International Critical Tables." The older value for $\Lambda_{0\,NaCl}$ at 25° is 125.63, which is only 0.79 unit different from the new value. This illustrates the immense importance and need of obtaining accurate conductivity data at different temperatures, in order to obtain limiting ionic mobilities and limiting transference numbers with a high degree of accuracy.

Summary

Tables are given of the limiting mobilities of potassium and chloride ions at 15, 25, 35 and 45°, based on conductance data given by Li and Fang and transference data given by Allgood, LeRoy and Gordon. Approximate values for the limiting ionic mobilities of sodium and acetate as well as the limiting transference numbers in aqueous solutions of sodium chloride and sodium acetate for these temperatures are also given. The transference numbers calculated for sodium chloride solutions illustrate the necessity of obtaining accurate conductivity data not at one temperature, 25°, only, but at different temperatures.

PEIPING, CHINA RECEIVED APRIL 10, 1942

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

Studies of Lead Oxides.[1] VI. The Effect of Grinding on the X-Ray Diffraction Patterns of Mixtures Containing Lead Oxides

BY GEORGE L. CLARK AND STANLEY F. KERN

Of all the variables which are known to affect the nature of materials used in the lead storage battery, grinding, especially of mixtures, has been studied the least. Leblanc and Eberius[2] report, "A hard stroke with a spatula, leaving a brown-red trail in the yellow oxide, suffices for the conversion of Y-PbO (yellow, orthorhombic) into R-PbO (red, tetragonal), while the conversion of Pb_3O_4 (black) into Pb_3O_4 (red) proceeds only under the hardest grinding and crushing on the roughest surfaces." Clark and Rowan[3] have shown that the R-PbO obtained on grinding Y-PbO is different from the normal R-PbO in that it gives an X-ray diffraction pattern identical with a distorted R-PbO formed by the vacuum decomposition of lead carbonate, basic carbonate or white lead, or lead oxide hydrate, and in that it exhibits an abnormal chemical activity toward hydrogen peroxide and an increased heat of solution in perchloric acid over that of the normal R-PbO.

It has been observed previously in this Laboratory that intense grinding of normal R-PbO caused a slight broadening of some lines on the X-ray diffraction pattern. This non-uniform broadening is indicative of distortion.

Brown, Cook and Warner[4] have reported the effect of grinding upon the apparent density of Pb_3O_4 samples obtained by oxidation of three different lead oxides.

Procedure

Seven binary mixtures involving the lead oxides were investigated using six to eight different percentage compositions of each. These mixtures were ground with a rubbing or shearing action and in identical manner in an agate mortar and samples reserved after various times of

(1) For the fifth paper of this series, see Clark and Rowan, THIS JOURNAL, **63**, 1305 (1941).

(2) M. Leblanc and E. Eberius, *Z. physik. Chem.*, **A160**, 69 (1932); see also M. Petersen, THIS JOURNAL, **63**, 2617 (1941).

(3) Clark and Rowan, *ibid.*, **63**, 1302 (1941).

(4) O. W. Brown, S. V. Cook and J. C. Warner, *J. Phys. Chem.*, **26**, 477 (1922).

grinding for X-ray diffraction studies. In this manner, twenty to thirty patterns were obtained to describe each of the following mixtures

Y-PbO–PbO_2	$PbSO_4$–PbO_2
Y-PbO–SiO_2	R-PbO–PbI_2
R-PbO–PbO_2	Y-PbO–PbI_2
R-PbO–$PbSO_4$	

The grinding was carried out manually and in contact with the atmosphere in all cases except for a few samples of the PbO–PbO_2 system. Some of these were ground in an atmosphere of nitrogen and the rest in a vacuum. The same results could be obtained in times three times as long by grinding in the rod mill described by Clark and Rowan.[3]

Through holes bored in the sides of an air-tight box, rubber gloves were inserted and attached to the box in such a manner that these connections were also air tight. The gloves were used to operate the mortar and pestle inside the box. Nitrogen which previously had been passed through sulfuric acid and ascarite was passed through the box forming the nitrogen atmosphere used in these experiments.

For the vacuum grinding the mortar was placed in a glass jar having a flat brass cover. A rubber gasket was used between the brass cover and the glass jar to give a vacuum-tight contact. In the center of the cover was a hole fitted with a collar through which the pestle was operated. A length of rubber tubing fitting tightly around the collar and the pestle constituted the vacuum-tight connection at this point and allowed ample movement of the pestle to effect the grinding. Two smaller holes were on either side of the large central opening. One was connected to a Cenco-Hyvac pump and the other to a glass tube, one end of which was drawn into a capillary and sealed.

The sample of PbO was heated for several hours at 3 mm. pressure and 450° previous to grinding to ensure complete removal of any carbon dioxide present. A small amount of this PbO was mixed with an equal amount of PbO_2, the mixture placed in the mortar and the system evacuated within a minute after the PbO had been removed from the vacuum furnace. The sample was ground for twenty minutes and transferred to the capillary which was sealed off and used for X-ray diffraction studies.

All materials used were C. P. chemicals or made from C. P. reagents.

The X-ray diffraction patterns were registered in a cylindrical camera using a wedge-shaped sample holder for mounting the samples.[5] For the samples ground in vacuum the capillaries containing the sample were mounted directly. Radiation from a copper target X-ray tube was used throughout the investigation.

Results and Discussion

The description of some typical patterns will illustrate the phenomena observed when these mixtures were ground.

PbO–PbO_2 Mixtures.—For a mixture of 67% PbO_2 and 33% Y-PbO, after twenty minutes of grinding, the speckled lines of Y-PbO, easily observed for a mixture before grinding, are completely missing from the pattern, indicating that the Y-PbO has completely disappeared. Nor is there any evidence of R-PbO to which the yellow modification ordinarily is transformed on grinding. Other patterns were obtained from the following mixtures after they had been ground twenty minutes: 50% PbO_2–50% Y-PbO, 33% PbO_2–67% Y-PbO, 10% PbO_2–90% Y-PbO, 5% PbO_2–95% Y-PbO. *In each case both the Y-PbO and R-PbO patterns are completely missing.* On the other hand, corresponding mixtures ground with fine sand (SiO_2) as an abrasive invariably showed broad interferences of R-PbO.

The patterns of corresponding mixtures of PbO_2 and R-PbO up to a mixture of 10% PbO_2 and 90% R-PbO under the same conditions of grinding for twenty minutes disclosed only the pattern of PbO_2 with one extra line which could be attributed to $2PbCO_3 \cdot Pb(OH)_2$.

In attempting to determine what happened to the PbO on grinding, the following theories were proposed. First, the distorted (activated) PbO, formed on grinding, may have absorbed oxygen from the atmosphere and was oxidized to PbO_2. The high oxidation potential needed for such a reaction made this theory rather doubtful. Active oxygen analysis on the sample before and after grinding showed that there was no increase in active oxygen, as determined by the method of Diehl and Topf and recommended by Mrgudich and Clark.[6]

The second theory claimed that the PbO was incorporated into the PbO_2 lattice, giving either an interstitial solid solution of PbO in PbO_2 or a type of substitutional solid solution where the PbO_2 lattice remains but the ratio of oxygen to lead is less than two. The formation of an interstitial solid solution was immediately discounted as no parameter changes were observed on the PbO_2 pattern and because packing considerations would make this situation impossible.

The existence of an "oxygen-deficient" lattice of PbO_2 is well known. Clark and Rowan[1] have shown that sulfamic acid, although a very good solvent for PbO, is incapable of increasing the ratio of oxygen to lead in an oxygen-deficient lattice. However, after the ground mixture of PbO_2–PbO has been treated with sulfamic acid, an ac-

(5) G. L. Clark, "Applied X-Rays," 3rd ed., McGraw-Hill Book Co., 1940, p. 269.

(6) J. N. Mrgudich and G. L. Clark, *Ind. Eng. Chem., Anal. Ed.*, **9**, 256 (1937).

tive oxygen analysis on the residue showed that the residue was PbO_2 and therefore the PbO must have been removed. A precipitate of lead sulfate was obtained when sulfuric acid was added to the sulfamic acid extraction solution, thereby substantiating the conclusion that the divalent lead was removed from the ground mixture. In the light of these facts, there could be no appreciable incorporation of PbO into the PbO_2 lattice.

The final theory is a combination of two effects. It is known that grinding, in general, decreases the particle size of a crystalline material and in some cases introduces distortion. As mentioned previously, it has been observed in this Laboratory that R-PbO, as well as Y-PbO, when ground produces an X-ray diffraction pattern of distorted R-PbO. It is possible that grinding these mixtures decreases the particle size of the PbO and introduces such a large amount of distortion that Bragg scattering can no longer result. Thus, even a mixture of 90% PbO ground with 10% PbO_2 fails to produce the slightest diffraction evidence of PbO.

It has also been shown that this distorted PbO is highly active. In this highly distorted or activated state, some of the PbO could react rapidly with the carbon dioxide and water of the atmosphere to form a basic carbonate of lead. To substantiate this theory both R-PbO and Y-PbO were ground alone in air under the same conditions used for the mixtures, and the X-ray diffraction patterns obtained from the ground samples compared with the patterns of the basic carbonates. The patterns obtained from ground R-PbO, Y-PbO and the ground mixtures of PbO_2–PbO which contain a large percentage of R-PbO or Y-PbO always show one or more interferences characteristic of $2PbCO_3 \cdot Pb(OH)_2$ and thus indicate that this carbonate is being formed. Chemical analysis showed that the amount of carbon dioxide present in the ground samples was about 80% of that required for the complete conversion, of the PbO present, into $2PbCO_3 \cdot Pb(OH)_2$. These facts indicate that the effect of grinding on these mixtures is the activation of the PbO which then reacts with the carbon dioxide and water of the atmosphere to give $2PbCO_3 \cdot Pb(OH)_2$. However, the intensity of the diffraction interferences from this basic carbonate is far too small to account for 80% conversion of the PbO to the basic carbonate. Hence, we must conclude that either not all of the carbon dioxide in the mixture is in molecular union with the PbO or that the basic carbonate remains in a state of great dispersion and distortion. Since the diffraction interferences of the basic carbonate are very diffuse, it was more logical to accept the latter conclusion.

From these experiments, it was possible to conclude only that the absence of the PbO lines on patterns obtained from ground mixtures of PbO_2–PbO was accompanied by a large increase in carbon dioxide content of the sample. Whether the abnormal absorption or incorporation of the carbon dioxide into the mixture was a cause of the disappearance of the PbO pattern, or a result of the high activity introduced into the PbO on grinding, could not be ascertained from these experiments. To attempt to find facts favoring either explanation it was decided to grind the mixtures in an atmosphere as nearly free from carbon dioxide as possible.

The first attempt toward this goal was grinding in an atmosphere of nitrogen. The experimental procedure has been described above. X-Ray diffraction patterns taken of the samples after being ground in the nitrogen atmosphere were similar to those obtained from samples ground in air. Chemical analysis of these samples showed that they had absorbed some carbon dioxide, but to a far less degree than the samples ground in air. Although this experiment was unsuccessful in completely removing carbon dioxide from the atmosphere, it did indicate that the disappearance of the diffracting power of PbO was not primarily dependent on the amount of carbon dioxide absorbed.

Samples ground in vacuum gave X-ray patterns completely devoid of all PbO lines. Chemical analysis of the samples showed that there was less than 0.1% of carbon dioxide present in the ground sample. Hence, we are forced to conclude that the disappearance of the lines characteristic of PbO is not necessarily a function of the carbon dioxide absorbed.

Clark and Rowan[1] have shown that distorted PbO when annealed at a temperature above 300° was converted to the normal PbO. It was believed that if the PbO was present as a distinct phase annealing should restore it to the original form. A sample of PbO_2–PbO after being ground was annealed at 300° and an X-ray pattern taken of the product. The pattern showed the presence of a *large amount of the PbO* and a small amount of Pb_3O_4, as well as PbO_2, indicating that the PbO

was present in the ground sample in a form easily converted to the normal crystalline PbO.

These experiments prove that it is impracticable to place limits on the amount of PbO detectable in PbO_2 by the powder diffraction method, as too much depends upon the previous history of the sample.

R-PbO–$PbSO_4$ Mixtures.—Grinding experiments on these mixtures, followed by the X-ray method and chemical analysis, indicate that the PbO was converted into a poorly diffracting and, therefore, a highly distorted PbO.

In the unground mixture approximately 10% is the limit of detection of PbO in lead sulfate. This same limit can be said to hold for lead sulfate in PbO.

$PbSO_4$–PbO_2 Mixtures.—Grinding decreases the particle size of the lead sulfate but in no other way alters the pattern. The limit of detection of one component in the presence of the other is less than 5%.

PbO–PbI_2 Mixtures.—In direct opposition to the findings in the previous experiments it was found that grinding PbO in the presence of lead iodide does not destroy the PbO pattern. However, grinding does have an effect in that the pattern obtained from lead iodide tends to disappear. Chemical analysis of these samples before and after grinding shows no appreciable absorption of carbon dioxide on grinding.

In order to explain the apparent resistance of the PbO to reaction with carbon dioxide when ground with lead iodide, it is necessary to consider the differences between lead iodide and PbO_2. The PbO_2 lattice is made up of oxygen octahedra with a lead ion in the center of each octahedron. These octahedra are held together by shared corners and edges giving rise to strong bonding energies in each of the three directions. On the other hand, lead iodide exhibits a layer lattice composed of two layers of iodide ions to one layer of lead ions. The bonding force between the adjacent layers of iodine ions is weak and, as a result, the lead iodide crystal is easily sheared in this direction.

On grinding these mixtures, PbO_2–PbO and PbI_2–PbO, there is a tendency to set up a stress in the materials of the mixtures. In the PbO_2–PbO mixture there is a competition between the strong bonding forces between the octahedra in the PbO_2 lattice and the forces tending to keep the PbO lattice in the undistorted form as to which will yield to the applied stress. It is supposed that these forces for the latter are the weaker and, as a consequence, the PbO lattice is distorted by the stress of grinding. In the distorted form the PbO lattice is active and reacts with the carbon dioxide and moisture of the air and is partly converted into the basic carbonate. The PbO_2 seems to have more than a simple abrasive effect since silicon dioxide ground with PbO is not effective in destroying the PbO pattern or in producing a highly active oxide.

In the PbI_2–PbO mixtures the competition is between the forces of PbO and the relatively weak forces between the adjacent layers of iodide ions in the lead iodide lattice. In this case, we find that it is the bonds between these layers of iodine ions that yield to relieve the stresses introduced on grinding and thereby protect the PbO from distortion and the accompanying activation and reaction with carbon dioxide.

Summary

1. Grinding mixtures of PbO_2 with either R-PbO or Y-PbO results in the disappearance of the X-ray diffraction lines characteristic of PbO. This is not the case when PbO is ground with an abrasive like silicon dioxide. A. Active oxygen analysis on the samples before and after grinding showed that there was no increase in oxygen content in the mixture during grinding and, consequently, no oxidation of the PbO to PbO_2. B. The formation of a solid solution of PbO in PbO_2 or compound formation between them is improbable as the PbO is easily extracted from the ground mixture with sulfamic acid, no new lines indicative of compound formation are present on the pattern and, on annealing the ground sample, the PbO is restored to normal R-PbO. C. There is an abnormally high absorption of carbon dioxide by the PbO when ground with PbO_2. The absorption of carbon dioxide is not necessarily the cause of the disappearance of the PbO pattern as the PbO lines do not appear on patterns of samples ground in a vacuum and containing less than 0.1% carbon dioxide. D. The high absorption of carbon dioxide by the mixture when ground in air is further evidence of the increased activity of PbO when formed in the distorted form.

2. Lead oxide loses its diffracting power when ground with other compounds such as lead sulfate, although these are not so effective as PbO_2.

3. Grinding mixtures of lead iodide and PbO

results in the disappearance of the pattern of the lead iodide while the PbO pattern remains. The lead iodide acts as a lubricant and thereby protects the PbO from distortion. This lubricating action of the lead iodide arises from the weak forces existing between layers of iodide ions in the lead iodide crystals.

URBANA, ILLINOIS RECEIVED MARCH 26, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

Reproducible Contact Angles on Reproducible Metal Surfaces. III. Contact Angles of Saturated Aqueous Solutions of Different Organic Liquids on Silver and Gold

BY F. E. BARTELL AND PAUL H. CARDWELL

Recent communications from this Laboratory have presented the results obtained in studies of water–air contact angles on silver and gold,[1] and of organic liquid–water interfacial contact angles on these same solids.[2] For each of these systems explanations were suggested for the "hysteresis" of the contact angles. The system solid–saturated aqueous organic liquid solution–air reported upon in this paper is even more complex than the two types of systems previously discussed, and though angles can be reproduced readily by controlled procedures, the factors which may contribute to the "hysteresis" of these contact angles are more numerous and more complex than those encountered in the other systems.

The liquids used in this investigation were "conductivity" water, isoamyl alcohol, normal butyl acetate, benzene, α-bromonaphthalene and heptane. The organic liquids were of the same high degree of purity as those previously used. The procedure for the formation and measurement of contact angles and the method for preparing reproducible surfaces of silver and gold have been described in a previous paper.[1]

Three different groups of solution contact angles were measured. Angles formed by solution drops on initially fresh and clean surfaces of silver and gold comprised the first group, angles formed by solution drops on solids which had stood in air saturated with water and organic liquid vapors comprised the second, and angles formed by air bubbles on solids in saturated aqueous organic liquid solutions comprised the third group. The contact angles reported for both drop and bubble systems are the angles measured through the aqueous solution phase.

When a drop of saturated aqueous organic liquid solution was placed upon a fresh and clean solid surface, in a cell with air saturated with water vapor alone, the angle measured immediately after formation of the drop was not reproducible. Initial air adsorption upon the metal surface was so rapid that exact duplicates could not be obtained for these initial angles. When the solution drop was left stationary on the solid for a short period of time and was then caused to advance by adding solution to increase the volume of the drop, the value of the contact angle of the advanced drop was not the same as that of the original drop. This change in the contact angle appeared to be much greater than would have been caused by further adsorption of air by the solid during the short period of time that the solution drop was allowed to stand on the solid, since after the initial rapid air adsorption the rate of air adsorption appears to decrease.[1] It was concluded that organic liquid must have evaporated from the solution drop into the air of the closed cell and subsequently have been adsorbed by the solid and that this adsorbed organic liquid caused part of the change.

Reproducible contact angles of solution drops on silver and gold surfaces could be obtained when these metal surfaces were exposed for sufficient periods of time to air saturated with the vapors of the given aqueous organic liquid solution. Values obtained for angles measured in air saturated with the vapors of the given solutions are shown in Table I. The advancing angles of Table I are the angles measured immediately after the drops were formed upon the surfaces which had been allowed to stand in contact with the vapors. The receding angles were obtained by immediately withdrawing the solution-drop once it was formed. On solids exposed to the vapors for a few seconds only, the receding angles were smaller than the

(1) Bartell and Cardwell, THIS JOURNAL, **64**, 494 (1942).
(2) Bartell and Cardwell, *ibid.*, **64**, 1530 (1942).

TABLE I

CONTACT ANGLES

SOLID–SOLUTION DROP–AIR SATURATED WITH WATER VAPOR AND ORGANIC LIQUID VAPOR

Satd. aqueous soln. of org. liq.	Time metal surfaces were in contact with the vapors	Angle on silver Advancing	Angle on silver Receding	Angle on gold Advancing	Angle on gold Receding
Isoamyl alcohol	Few seconds	36	7	25	5
	12 hours	36.5	37	25	23
	18 hours			25	25
n-Butyl acetate	Few seconds	61	15.5	50	0
	12 hours	64.5	41	51	29
	18 hours			51	35.5
	6 days	64.5	64		
	7 days			51	51
Benzene	Few seconds	72	25	61.5	0
	12 hours	86	45	63	16.5
	18 hours			72.5	25
	6 days	90	90		
	7 days			83.5	83
α-Bromonaphthalene	Few seconds	71.5	14	61	0
	12 hours			80	7
	18 hours	95	69		
	6 days	96	90	94.5	76
	7 days				
Heptane	Few seconds	91	74	85.5	9
	12 hours	103.5	103		
	18 hours			101	71
	7 days			101	101

advancing angles. This was probably the result of a partial removal of an incomplete adsorbed film by the solution-drop. Solids on which there was maximum adsorption of the organic liquid vapors gave advancing and receding angles which were equal or nearly equal when the drop was receded immediately. Drops allowed to stand on the solids even for short periods of time before being receded gave receding angles somewhat smaller than those of Table I, while drops allowed to stand for long periods of time gave receding angles approaching zero, which indicates that the adsorbed films of the organic liquids on the solids were gradually being removed by the solution-drops. It is of interest to note that the values of the contact angles given by solution-drops on adsorbed organic liquid films increase progressively with the hydrophobic nature of the organic liquid.

Contact angles formed by air-bubbles on surfaces immersed in saturated aqueous organic liquid solutions are given in Table II. The solution receding contact angles reported in this table were those formed as soon as the air-bubbles were advanced. The magnitude of the angles formed when the air-bubbles were withdrawn, solution advancing, depended upon the length of time the air-bubbles were left on the metal surfaces. The longer the air-bubbles were allowed to stand on the solids before being withdrawn, the larger were the solution advancing angles. The solution advancing angles reported in Table II were obtained with air-bubbles which had stood on the metal surfaces for one minute before being withdrawn.

TABLE II

CONTACT ANGLES OF SOLID–SOLUTION–AIR BUBBLE

Satd. aqueous soln. of org. liq.	Angles on silver Advancing	Angles on silver Receding	Angles on gold Advancing	Angles on gold Receding
Isoamyl alcohol	47	22	43	21
n-Butyl acetate	58	36	48	33
Benzene	65	33	61	28
α-Bromonaphthalene	73	47.5	65	40
Heptane	74	37	66	34.5

Individual angle measurements for all angles reported showed a maximum variation of ± 1° and in many cases the variation was less than ± 0.5°.

Discussion of Results

In the water drop and air bubble systems previously studied,[1] drop and bubble measurements were identical, within the limits of experimental error, when corresponding states were reproduced. In the solid–liquid–liquid systems previously reported[2] corresponding water drop and organic

liquid drop measurements were also identical, within the limits of experimental error. The contact angle values obtained for solution drops and air bubbles in the present study were not identical.

In the solid–solution–air systems the air adsorption factor, operative also in solid–water–air systems, has an effect; and at the same time the organic liquid adsorption factor, operative also in solid–liquid–liquid systems, has *two* effects. Organic liquid appears to be adsorbed on the solid surface both from saturated air and from saturated solution. The solid appears to adsorb a more complete layer from saturated air than can exist in equilibrium under a saturated solution, however, and the solution accordingly tends to remove both adsorbed air and adsorbed organic liquid. Water adsorption appears to be a negligible factor in any of the three systems. With such varied processes of adsorption and such different rates of adsorption and desorption as the measurements indicate, exactly corresponding states for drop and bubble would be very difficult, if not impossible, to achieve. Corresponding states were not achieved in the present study and the measurements on drop and bubble were, therefore, not identical.

Factors capable of causing hysteresis of contact angles were numerous and were effective to different degrees for each change of system. It was possible to obtain advancing and receding angles of the same value, however, and the method of obtaining such angles was similar to that used with the two previously described less complex systems. On solids left for long periods of time in atmospheres saturated with organic liquid, solution drops gave advancing and receding angles of the same value when the solution was immediately receded after being advanced.

It has been realized from the beginning of work on contact angles in this Laboratory that the surface tension of identical solid surfaces does not always remain strictly constant when the solid is used in different systems. For some systems it probably is so nearly constant, or changes in the tension are so nearly identical, that combinations of equations effected by cancelling surface tension values of solid can give valuable information. The work reported in all three of the papers of this series re-emphasizes, however, that conclusions drawn from all such equations and from similar equations for solid–liquid–liquid systems must be subjected to careful analysis before their validity can be considered to be established.

Summary

Measurements have been made of the contact angles of drops of saturated aqueous organic liquid solutions on silver and gold in air and of air bubbles on silver and gold in saturated aqueous organic liquid solutions.

These measurements indicate that the metal surfaces adsorb air and adsorb also organic liquid both from air and from aqueous solution. A drop of solution caused to advance by stages over a fresh metal surface gives a different angle each time it is advanced because of evaporation of organic liquid into the air and subsequent adsorption of the vapor on the exposed metal.

Because of these complex adsorption conditions identical surface states for drop and bubble systems were not achieved, and, consequently, identical angles for the two systems were not obtained.

Identical advancing and receding angles were obtained for drops caused to recede immediately after they had been advanced on metal surfaces which had previously stood in the given aqueous solution vapors for sufficient time to attain adsorption equilibrium.

ANN ARBOR, MICH. RECEIVED APRIL 21, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

The Formal Oxidation–Reduction Potentials of Thallous–Thallic Salts in Aqueous Hydrochloric Acid Solutions. Formation of Chlorothallate Complex Ions[1]

BY RICHARD H. HUGHES AND CLIFFORD S. GARNER

The oxidation–reduction potentials of thallous–thallic salts have been investigated in aqueous solutions of hydrochloric,[2] sulfuric,[2,3,4] nitric[2,5] and perchloric[6] acids. These studies have shown that the formal potentials[7] differ in the presence of various anions, suggesting the formation of anion complexes with thallic ion.

In particular, the experiments of Spencer and Abegg[2] have indicated the probable formation of one or more chloride complexes of thallic ion. However, their data are not easily interpreted for several reasons: (1) because a 0.1 N calomel half-cell was used as a reference electrode, the results were complicated by the presence of relatively large liquid junction potentials which were not taken into account; (2) since the thallous–thallic solutions were always less than 0.2 f in hydrochloric acid, considerable hydrolysis of the thallic salts must have occurred in many of their solutions; and, (3) the chloride ion concentration was not varied independently of the hydrogen ion concentration and the ionic strength.

Since it seemed desirable to have more accurate values of the formal potentials in hydrochloric acid solutions and to study the formation of chloride complexes of thallic ion, the measurement of the electromotive forces of cells of the type

$$\mathrm{Pt,}\left\{\begin{array}{ll}\mathrm{TlCl} & (c_1 f)\\ \mathrm{TlCl_3} & (c_2 f)\\ \mathrm{HCl} & (c_3 f)\\ \mathrm{HClO_4} & (c_4 f)\end{array}\right\}\mathrm{,\ HCl}\ (c_3 + c_4 f),\ \mathrm{H_2}\ (p\ \mathrm{atm.}) + \mathrm{Pt}$$

has been undertaken. Conditions of concentration were chosen such that the difficulties referred to in the above paragraph were eliminated almost entirely.

For the above cell, the formal potential, $E^{0\prime\prime}$ (for the reaction $\mathrm{Tl^{I}} = \mathrm{Tl^{III}} + 2e^-$) has been derived by adding to the observed potential, $E_{\mathrm{obsd.}}$, the two following quantities

$$E_C = (RT/2F)\ln(c_2/c_1) \qquad (A)$$

to provide for equiformal concentrations of thallous and thallic salts, and

$$E_H = (RT/F)\ln\left(\sqrt{p}/\gamma(c_3 + c_4)\right) \qquad (B)$$

to refer the values to the molal hydrogen electrode, γ being the mean ionic activity coefficient of hydrogen ions in $c_3 + c_4 f$ hydrochloric acid, and p being the partial pressure of hydrogen in atmospheres. The liquid junction potential was made negligibly small by keeping the total salt concentration $(c_1 + c_2)$ less than 1% of the total acid concentration, which was the same in both half-cells.[8] This low salt concentration also made possible the maintenance of constant ionic strength in a given series of experiments. Hydrolysis of the thallic salts was reduced to a minimum by having the acid concentration 1 f or greater.

Since thallous ion appears to have no tendency to form chloride complexes,[9] the variation of the formal potential with changes in concentration of thallic ions or chloride ions may be interpreted in terms of the formation of chloride complexes of thallic ion.

Hence, two types of experiment were planned. In one (Series 1 and 2) the ratio of thallic to thallous salt concentration, c_2/c_1, was varied, and in the other (Series 3, 4 and 5) the ratio of hydrochloric to perchloric acid concentration, c_3/c_4, was altered, in both cases $c_3 + c_4$ and all other factors being held constant in a particular series.

Experimental

Preparation and Analysis of the Solutions.—"Chemically pure" thallous nitrate was recrystallized from water solution three times, dried in an oven at 120° and stored in

(1) Based on a thesis presented by R. H. Hughes to the Graduate Faculty of the University of Texas in partial fulfillment of the requirements for the degree of Master of Arts, June, 1942.

(2) Spencer and Abegg, *Z. anorg. Chem.*, **44**, 379 (1905).

(3) Grube and Hermann, *Z. Elektrochem.*, **26**, 291 (1920).

(4) Partington and Stonehill, *Trans. Faraday Soc.*, **31**, 1357 (1935).

(5) Noyes and Garner, THIS JOURNAL, **58**, 1268 (1936).

(6) Sherrill and Haas, *ibid.*, **58**, 952 (1936).

(7) The "formal potential" is the potential, referred to the standard molal hydrogen electrode, when the total concentrations of the reduced and oxidized substances (without reference to their possible incomplete ionization, hydrolysis, formation of complexes, etc.) are both 1.0 f.

(8) Although there is a liquid junction between hydrochloric and hydrochloric–perchloric acid solutions in some of the cells, the junction potential is negligible, for these two acids possess at 25° closely agreeing activity coefficients and almost identical equivalent conductances over the concentration range 1 to 4 f. See, for example, Latimer, "Oxidation Potentials," Prentice-Hall, Inc., New York, N. Y., 1938, p. 323, and "International Critical Tables," Vol. VI, McGraw-Hill Book Co., New York, N. Y., 1929, p. 241.

(9) Noyes, *Z. physik. Chem.*, **9**, 603 (1892), has shown that the solubility of thallous chloride in solutions of potassium chloride or hydrochloric acid at 25° decreases substantially in accordance with the solubility product principle, at least up to 0.8 f potassium chloride solution.

a desiccator. Analysis by the iodate method using the iodine monochloride end-point[10] showed the product to be 99.5% pure. It was used without further purification.

Thallous nitrate was dissolved in water, and a slight excess of hydrochloric acid was added. The precipitated thallous chloride was washed with water until the washings gave a negative test for nitrate ion with sulfuric acid and ferrous sulfate. A portion of this thallous chloride was dissolved in water. The resulting solution was standardized by the above iodate method, using a 0.01 *N* potassium iodate solution which had been prepared by weight and checked by titration against samples of Bureau of Standards arsenious oxide. The stock solution thus prepared was 0.004032 *f* in thallous chloride. All other thallous chloride solutions were made from it by weight dilution.

To prepare a stock thallic chloride solution a suspension of thallous chloride in hydrochloric acid was heated with an excess of C. P. potassium bromate. Thallic hydroxide was then precipitated by the addition of ammonium hydroxide, and was washed until the washings failed to give a positive test for bromide or chloride ion with nitric acid and silver nitrate. The moist thallic hydroxide was suspended in water and just enough hydrochloric acid added to dissolve it. Concordant analyses, made by methods described in an earlier paper,[5] showed the resulting stock solution to be 0.02508 *f* in thallic chloride and 0.0002403 *f* in thallous chloride (this small amount of thallous chloride was always taken into account in the preparation of the cell solutions). The amount of free hydrochloric acid was negligible. Other stock thallic chloride solutions were prepared in a similar way. Both the thallous and thallic stock solutions were checked at the end of this investigation and found to have undergone no appreciable change.

The hydrochloric and perchloric acid solutions were obtained by dilution of reagent grade concentrated acids, the impurities in which were stated to be negligible. These solutions were standardized by titrating portions of a sodium hydroxide solution which had been just standardized against Bureau of Standards potassium hydrophthalate.

Tank (electrolytic) hydrogen was purified by passing it successively through concentrated solutions of sulfuric acid, potassium hydroxide and sodium plumbite, then over electrically-heated platinized asbestos.

The Cell.—The assembled cell is shown in Fig. 1. A 180-ml. electrolytic beaker served as a container (A) for the thallous-thallic mixture, in which was immersed the hydrogen half-cell and two bright platinum wire electrodes (B). In some of the early experiments one of these electrodes was cathodically polarized and the other anodically polarized in 1 *f* hydrochloric acid; our experience, unlike that of Spencer and Abegg,[2] indicated that equilibrium was more quickly attained with non-polarized electrodes. The hydrogen half-cell vessel was made from a 25 × 200 mm. test-tube equipped with a standard taper ground-glass joint (C) which prevented appreciable liquid diffusion while allowing electrolytic contact. The liquid junction was made inside this joint by diffusion. Inside this vessel was the hydrochloric acid solution into which dipped two platinized platinum-foil electrodes (D) and the hydrogen entrance tube (E). Before entering the half-cell the hydrogen from the purification train passed through a long "bubbler" trap containing hydrochloric acid of the same concentration as that used in the half-cell. A small "bubbler" trap (F) was also provided at the hydrogen outlet.

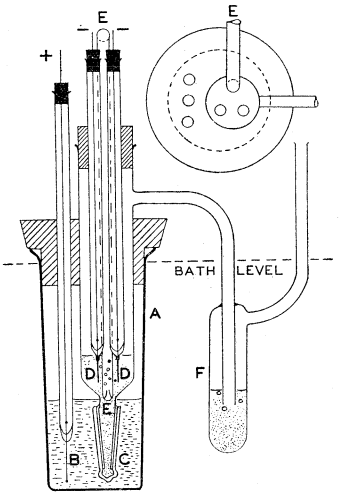


Fig. 1.—Cell for e. m. f. measurements.

All rubber stoppers and tubing were boiled in sodium hydroxide solution and rinsed well to remove sulfur.

The cell and "bubbler" traps were immersed in a kerosene-bath thermostated at the desired temperature to within ±0.05°.

Method of Potential Measurements.—A Leeds and Northrup Type K-1 potentiometer and Type R galvanometer were used for the e. m. f. measurements.[11] The Eppley standard cell used was checked several times during the investigation against a cell which had just been certified by the National Bureau of Standards.

Solutions of thallous chloride and of thallic chloride, both in 0.9952 *f* hydrochloric acid, were prepared by weight from the stock solutions, and mixed in varying proportions for the cells of Series 1 and 2. The cells of Series 3, 4 and 5 were prepared using a stock solution containing both thallous and thallic chlorides in water or in 4 or 2 *f* perchloric acid. To a given weight of one of these solutions was added a constant weight of water obtained by mixing in the desired proportion hydrochloric and perchloric acid solutions of the same concentration.

After the cells had attained thermal equilibrium (about half an hour was allowed), the potentials were measured at intervals over a period of two to fifty hours. In practically all cases equilibrium appeared to be reached within three hours, and thereafter readings were generally constant to 0.4 mv. or better. With rare exceptions, the readings taken with the duplicate electrodes in the same cell agreed to 0.1 mv. Occasionally some of the cells were agitated by hand, and this seldom produced an appreciable effect.

All volumetric apparatus, weights and thermometers employed in this research were calibrated, and all weighings were corrected to vacuum conditions. Distilled water was used in the preparation of all the solutions.

(10) Swift and Garner, THIS JOURNAL, **58**, 113 (1936).

(11) The authors wish to thank Professor W. A. Felsing for his kindness in making available to them this equipment.

TABLE I

ELECTROMOTIVE FORCES AT 25 AND 15° IN HYDROCHLORIC ACID SOLUTION

Series 1. 0.9952 f HCl (γ = 0.808) at 25°, μ = 1.00

TlCl, c_1	$TlCl_2$, c_2	$Tl^I + Tl^{III}$, $c_1 + c_2$	Tl^{III}/Tl^I, c_2/c_1	$E_{obsd.}$	E_C	E_H	$E^{0\prime\prime}$
0.0001814	0.00001886	0.0002001	0.1040	−0.7593 (1)	−0.0291	+0.0049	−0.7835
.0001016	.00009430	.0001959	0.9281	− .7862 (2)	− .0010	+ .0049	− .7823
.0001556	.0004715	.0006271	3.030	− .8019 (2)	+ .0142	+ .0051	− .7826
.0001097	.0009430	.001053	8.596	− .8148 (3)	+ .0276	+ .0049	− .7823
.00006390	.001415	.001479	22.14	− .8272 (4)	+ .0398	+ .0051	− .7823
.0001962	.004715	.004911	24.03	− .8289 (2)	+ .0408	+ .0050	− .7831
.0001452	.004715	.004861	32.32	− .8328 (1)	+ .0446	+ .0050	− .7832
.00001806	.001886	.001904	104.4	− .8468 (3)	+ .0597	+ .0049	− .7822
.00004515	.004715	.004760	104.4	− .8474 (1)	+ .0597	+ .0050	− .7827
.0001806	.01886	.01904	104.4	− .8489 (2)	+ .0597	+ .0049	− .7843
						Mean	− .7829

Series 2. 0.9952 f HCl (γ = 0.822) at 15°, μ = 1.00

0.0001814	0.00001886	0.0002001	0.1040	−0.7585 (1)	−0.0281	+0.0045	−0.7821
.0001016	.00009430	.0001959	.9281	− .7844 (2)	− .0010	+ .0045	− .7809
.00001806	.001886	.001904	104.4	− .8422 (1)	+ .0577	+ .0045	− .7800
.0001806	.01886	.01904	104.4	− .8456 (2)	+ .0577	+ .0045	− .7834
						Mean	− .7816

Results and Discussion

Potentials in Hydrochloric Acid Solution.—In Table I are presented the results of measurements made at 25 and 15° with cells in which perchloric acid was not present. The hydrochloric acid concentration was kept at 0.9952 f, corresponding to an ionic strength (μ) of 1.00. All concentrations have been expressed as weight formalities, f (formula weights per kilogram of water). Usually check cells were made up and measured. The values of $E_{obsd.}$ given in the table represent average values based on the number of cells indicated in the parentheses immediately following each value.[12] The values of $E^{0\prime\prime}$ were calculated as indicated earlier in this paper, the values of the activity coefficient of hydrochloric acid (given in parentheses following the concentration of the acid) being interpolated from the data of Harned and Ehlers,[13] and the partial pressure of hydrogen being computed from the corrected barometric pressure by subtraction of the vapor pressure of the acid solution at the given temperature[14] and addition of the hydrostatic head.

From the third, fourth and last columns of Table I it may be seen that the formal potential is not materially altered by changing the ratio c_2/c_1 or the formal concentration of the thallic salt one thousand-fold in the range indicated. One requirement of this constancy of $E^{0\prime\prime}$ is that there be only one thallium atom per thallic complex present in appreciable concentration.[15]

The cells of Series 1 and 2 give the average values of −0.7829 ± 0.0015 and −0.7816 ± 0.0015 volt for $E^{0\prime\prime}$ at 25 and 15°, respectively. From these values there are calculated for the cell reaction

$$Tl^+(0.9952\ f\ HCl) + 2H^+(a = 1m) = Tl^{III}\ (0.9552\ f\ HCl) + H_2(1\ atm.)$$

values of ΔF^0_{298} = 36.12 kcal., ΔH^0_{298} = 34.48 kcal., and ΔS^0_{298} = −0.0055 kcal./deg.[16]

Potentials in Mixtures of Hydrochloric and Perchloric Acid Solutions.—The measurements of Series 3, 4 and 5 were carried out with mixtures of hydrochloric and perchloric acid solutions so that the chloride ion concentration could be varied independently of hydrogen ion concentration and ionic strength. The results, together with the concentration conditions under which they were obtained, are given in Table II. Reference to columns one and six shows that the formal poten-

(12) The spread between extreme values was less than 0.5 mv. as a rule, but in a number of cases it was greater, becoming 3.7 mv. in the worst case.

(13) Harned and Ehlers, THIS JOURNAL, **55**, 2179 (1933).

(14) "International Critical Tables," Vol. III, McGraw-Hill Book Co., New York, N. Y., 1928, p. 301.

(15) If complexes of the type $Tl_xCl_y^{(y-3x)+}$ are important and stable in the solutions studied, then

$$E^{0\prime\prime} = (RT/2F)(1 - 1/x) \ln c_2 + \text{constant}$$

where x is the average number of thallium atoms per complex. For example, if x were 2, the thousand-fold variation in c_2 would have produced a change of 44 mv. in $E^{0\prime\prime}$ at 25°.

(16) From the relatively large variation in the values of $E^{0\prime\prime}$ at 15° it would appear that the entropy change is unreliable. However, by taking the temperature coefficients of the six cells involved and averaging them the value −0.00012 volt per degree was obtained, the mean deviation from the mean being 0.00002 volt per degree.

TABLE II

ELECTROMOTIVE FORCES AT 25° IN MIXTURES OF HYDROCHLORIC AND PERCHLORIC ACID SOLUTIONS

HCl, c_3	$\log_{10} c_3$	$E_{obsd.}$	E_C	E_H	$E^{0\prime\prime}$	$E^{0\prime\prime\prime}$
Series 3. Total acid concentration, 4.007 f (γ = 1.762), μ = 4.01 ($c_1 = 2.070 \times 10^{-4} f$, $c_2 = 4.520 \times 10^{-4} f$, c_2/c_1 = 2.184)						
1.003	+0.0013	−0.7260 (2)	+0.0100	−0.0506	−0.7666	−0.7667
0.8020	− .0958	− .7357 (2)	+ .0100	− .0506	− .7763	− .7664
.6017	− .2206	− .7472 (1)	+ .0100	− .0508	− .7880	− .7652
.4013	− .3965	− .7682 (2)	+ .0100	− .0509	− .8091	− .7681
.2010	− .6968	− .8008 (4)	+ .0100	− .0507	− .8415	− .7694
						Mean − .7672
Series 4. Total acid concentration, 2.000 f (γ = 1.010), μ = 2.00 ($c_1 = 2.070 \times 10^{-4} f$, $c_2 = 4.520 \times 10^{-4} f$, c_2/c_1 = 2.184)						
1.001	+0.0004	−0.7691 (2)	+0.0100	−0.0188	−0.7779	−0.7779
0.8006	− .0966	− .7785 (2)	+ .0100	− .0188	− .7873	− .7773
.6006	− .2214	− .7912 (2)	+ .0100	− .0189	− .8001	− .7772
.5006	− .3005	− .7991 (1)	+ .0100	− .0188	− .8079	− .7768
.4006	− .3973	− .8091 (2)	+ .0100	− .0189	− .8180	− .7769
.2006	− .6977	− .8413 (2)	+ .0100	− .0189	− .8502	− .7780
						Mean − .7774
Series 5. Total acid concentration, 0.9952 f (γ = 0.808), μ = 1.00 ($c_1 = 2.099 \times 10^{-4} f$, $c_2 = 1.866 \times 10^{-4} f$, c_2/c_1 = 0.8890)						
0.9952	−0.0021	−0.7871 (1)	−0.0015	+0.0050	−0.7836	−0.7834
.7464	− .1270	− .7991 (2)	− .0015	+ .0051	− .7955	− .7824
.4976	− .3031	− .8204 (2)	− .0015	+ .0050	− .8169	− .7855
.3483	− .4581	− .8348 (1)	− .0015	+ .0050	− .8313	− .7839
.2488	− .6042	− .8465 (2)	− .0015	+ .0049	− .8431	− .7806
.1742	− .7590	− .8644 (1)	− .0015	+ .0051	− .8608	− .7822
.0995	−1.002	− .8938 (1)	− .0015	+ .0049	− .8904	− .7867
						Mean − .7835

tial, $E^{0\prime\prime}$, is a function of chloride ion or perchlorate ion concentration. Since the work of Sherrill and Haas[6] has indicated that perchlorate ions have little or no tendency to form complexes with thallic ion over the range 0.5 to 1.2 f perchloric acid, this variation in $E^{0\prime\prime}$ may be interpreted in terms of the formation of complexes involving chloride and thallic ions.

Conceivably, a solution of thallic chloride in hydrochloric acid may contain complexes such as $TlCl^{++}$, $TlCl_2^{+}$, $TlCl_3$, $TlCl_4^{-}$, . . ., $TlCl_i^{(i-3)-}$, having equilibrium dissociation constants K_1, K_2, K_3, . . ., K_i, respectively. Assuming that the relatively high acid concentrations employed in these studies prevent the formation of hydrolytic complexes such as $TlOH^{++}$ and $Tl(OH)_2^{+}$, and that the concentration of free (hydrated) Tl^{+++} is very small compared to that of the complexes,[17] then

$$c_2 = (TlCl^{++}) + (TlCl_2^{+}) + \ldots + (TlCl_i^{(i-3)-}) \quad (1)$$

In terms of the dissociation constants, (1) becomes

$$c_2 = (Tl^{+++}) \sum_{i=1}^{n} (Cl^-)^i/K_i \quad (2)$$

Now, the formal potential is related to the molal thallous–thallic potential, E^0, by the equation

$$E^{0\prime\prime} = E^0 - (RT/2F) \ln (\gamma_{Tl^{+++}}/\gamma_{Tl^{+}}) + (RT/2F) \ln c_2/(Tl^{+++}) \quad (3)$$

Substitution of (2) into (3) and the collection of all terms which are constant under the conditions of Series 3, 4 or 5, leads to the following relation for the variation of $E^{0\prime\prime}$ with chloride ion concentration:

$$E^{0\prime\prime} = (RT/2F) \ln \sum_{i=1}^{n} (Cl^-)^i/K_i + \text{constant} \quad (4)$$

Within the accuracy of the results described in this paper, the sum term may be replaced by the term $(Cl^-)^y/K_y$, where y is a weighted average of the number of chlorine atoms per complex.[18] Equa-

(17) The latter assumption seems justified in view of the fact that the formal potentials in hydrochloric acid solutions are about 0.5 volt more positive than the corresponding potentials in perchloric acid solution.

(18) The condition for the replacement is that

$$(Cl^-)^y = \frac{a(Cl^-) + b(Cl^-)^2 + \ldots + n(Cl^-)^n}{ab.....n}$$

where the coefficients are products of suitable dissociation constants. Consequently, the value of y is a function of chloride ion concentration as well as of the exponents, but for our experiments the change in y for a ten-fold change in (Cl^-) is less than 10%. This change in slope cannot be detected in our graphs, and for all practical purposes y is a constant.

tion (4) then becomes

$$E^{0\prime\prime} = y(RT/2F)\ln(Cl^-) + \text{constant} \qquad (5)$$

Accordingly, a straight line should be obtained if $E^{0\prime\prime}$ is plotted against log c_3, the slope being 2.303 $(RT/2F)y$.

In order to investigate this power dependence of $E^{0\prime\prime}$ upon the chloride ion concentration, plots were made of the data from Series 3, 4 and 5, and these are given in Fig. 2. Within the experimental error the points fall on straight lines the slopes of which are almost identical. The average number of chlorine atoms per thallic complex was thus found to be 3.5 ± 0.2, indicating that chlorothallate anions exist in appreciable concentrations under the given conditions. Definite conclusions regarding the formulas of such complex ions cannot be deduced from these data, however.[19]

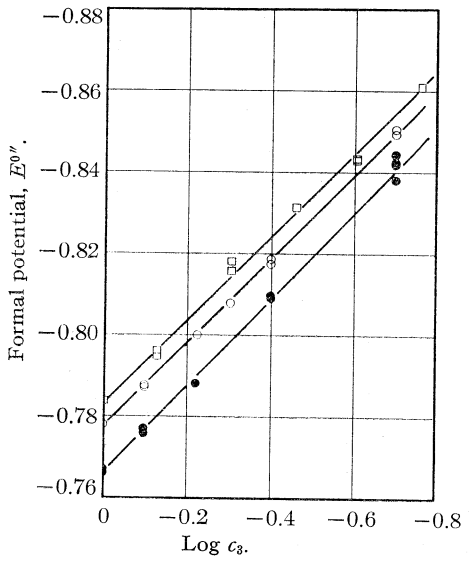


Fig. 2.—Power dependence of formal potential upon the chloride ion concentration: ●, μ = 4.01; ○, μ = 2.00; □, μ = 1.00.

In the last column of Table II are given values of $E^{0\prime\prime\prime}$, the formal potential for the reaction

$$Tl^+ + 3.5Cl^- = TlCl_{3.5}^{0.5-} + 2e^-$$

Using the average of the values at each ionic strength, the following relation has been derived for the temperature of 25°

$$E^{0\prime\prime\prime} = -0.7880 + 0.00508\,\mu \qquad (6)$$

Equation (6) reproduces within 1 mv. the values of $E^{0\prime\prime\prime}$ over the range μ = 1 to μ = 4.

Equation (6) may be combined with the standard free-energy of ionization of solid thallous chloride[20] to give for the reaction

$$TlCl(s) + 2.5Cl^- = TlCl_{3.5}^{0.5-} + 2e^-$$

the formal potential, $E^{0\prime\prime\prime\prime}$, at 25°

$$E^{0\prime\prime\prime\prime} = -0.8902 + 0.00508\,\mu \qquad (7)$$

This value should replace that estimated by Latimer.[21]

Summary

1. The formal oxidation–reduction potential, $E^{0\prime\prime}$, of thallous–thallic salts in 0.9952 f hydrochloric acid has been determined at 25 and 15°. $E^{0\prime\prime} = -0.7829 \pm 0.0015$ volt for the reaction $Tl^I = Tl^{III} + 2e^-$ at 25° in the above acid solution and for a thousand-fold variation of thallic salt concentration. The thermodynamic constants for the reaction Tl^+ (0.9952 f HCl) + $2H^+$ (a = 1m) = Tl^{III} (0.9952 f HCl) + H_2 (1 atm.) were found to be: $\Delta F^0_{298} = 36.12$ kcal., $\Delta H^0_{298} = 34.48$ kcal., and $\Delta S^0_{298} = -0.0055$ kcal./deg.

2. Measurements have been made of the potentials in mixtures of hydrochloric and perchloric acid solutions of constant total acid concentration and constant ionic strength. The results were interpreted in terms of the formation of chlorothallate anions of the type $TlCl_4^-$ and $TlCl_6^{---}$. Most of the thallic ions are bound in the form of such complexes, there being one thallium atom and, on the average, 3.5 chlorine atoms per complex in the range of hydrochloric acid concentration from 0.1 to 1 f.

3. For the half-cell reaction $Tl^+ + 3.5Cl^- = TlCl_{3.5}^{0.5-} + 2e^-$, the formal potential at 25° was found to be given by the relation $E^{0\prime\prime\prime} = -0.7880 + 0.00508\,\mu$, over the range of ionic strength from μ = 1 to μ = 4. The corresponding formal potential, $E^{0\prime\prime\prime\prime}$, for the reaction TlCl(s) + $2.5Cl^- = TlCl_{3.5}^{0.5-} + 2e^-$ is $E^{0\prime\prime\prime\prime} = -0.8902 + 0.00508\,\mu$.

AUSTIN, TEXAS RECEIVED APRIL 21, 1942

(19) It has been reported that a solid with the composition $TlCl_3 \cdot 3TlCl$ may be prepared from thallous and thallic chlorides (see, for example, Spencer and Abegg, *loc. cit.*). If this solid is a compound it may be thallous hexachlorothallate, in which event $TlCl_6^{---}$ ions presumably could exist in solution as well as in the crystal lattice. Covalent complexes of this type could probably be formed by use of the 6s and 6p orbitals ($TlCl_4^-$, sp^3) or with the 6s, 6p and two 6d orbitals ($TlCl_6^{---}$, sp^3d^2); these two complexes would then resemble $SnCl_4$ and $SnCl_6^{--}$, since it is likely that the latter make use of the corresponding 5s, 5p and 5d orbitals in bond formation. There would probably be an appreciable amount of ionic character to such bonds.

(20) TlCl(s) = Tl^+(aq.) + Cl^-(aq.); $\Delta F^0_{298} = 5.086$ kcal. Latimer, "Oxidation Potentials," Prentice-Hall, Inc., New York, N. Y., 1928, p. 152.

(21) Latimer, *ibid.*, p. 154.

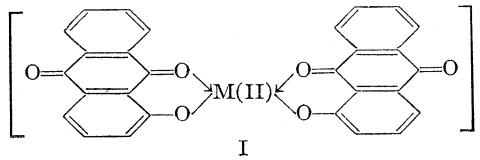
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WASHINGTON]

Preparation and Properties of Some Peri-Hydroxyquinone Inner Complexes[1]

BY BRADFORD P. GEYER[2] WITH GEORGE MCP. SMITH

Little work has been done on the preparation and characterization of simple inner complexes of compounds containing the C,C,C–O,OH chelating group.[3] Such inner complexes are of interest because of their structural relationship to the color lakes derived from alizarin and related substances. Because of the remarkable difference in color of these inner complexes compared to the color of the quinone and the metal ion involved, the preparation of several inner complexes of some peri-hydroxyquinones was undertaken with a view to determining, by absorption spectra, the relationship between color and structure.

1. 1-Hydroxyanthraquinone Inner Complexes.—Only three inner complexes of 1-hydroxyanthraquinone (9,10-anthracenedion-1-ol) have been described. Machemer[4] has prepared the cobalt(II) and copper(II) complexes of this quinone. Pfeiffer and co-workers[5] have made the dipyridinonickel(II) compound. We have prepared the four-coördinate cobalt(II), copper(II), magnesium, manganese(II), nickel(II), diaquonickel(II), and uranyl inner complexes of 1-hydroxyanthraquinone, with the general structure I.



I

Starting Material.—1-Hydroxyanthraquinone was prepared by a method similar to that of Roemer.[6] To 10 g. of 1-aminoanthraquinone in 500 ml. of glacial acetic acid, a cold solution of 3.5 g. of sodium nitrite in 25 ml. of 36 *N* sulfuric acid was added gradually. After forty-two hours the solution was concentrated, a large volume of cold water added, and the solid filtered off after nine hours. By treating the crude acetoxy compound with 100 ml. of 3 *N* sodium hydroxide under reflux for three hours and then acidifying with 6 *N* hydrochloric acid, 1-hydroxyanthraquinone was obtained. Sublimation of the product yielded 4.6 g. (46%) of pure yellow-orange hydroxyquinone; m. p. 193–194°. A sample of the crude 1-acetoxyanthraquinone, recrystallized from chloroform, formed pale-yellow crystals; m. p. 175–176°.

Inner Complexes: 9,10-Anthracenedion-1-olato-cobalt (II).—A cold, filtered solution of 0.25 g. of $Co(OAc)_2 \cdot 4H_2O$ in 50 ml. of methanol was added to a hot, filtered solution of 0.45 g. of 1-hydroxyanthraquinone in 200 ml. of methanol. The dark red mixture was heated under reflux for one-half hour, the solid filtered off when cool, washed with hot methanol, and dried at 100° to a brown powder.

9,10-Anthracenedion-1-olato-copper(II).—A cold solution of 0.40 g. of $Cu(OAc)_2 \cdot H_2O$ in 100 ml. of water was added to 400 ml. of a warm 95% ethanol solution of 0.90 g. of 1-hydroxyanthraquinone The solid was filtered off after twelve hours, washed with ethanol and water, and dried at 105°. It was purified by extraction with 95% ethanol for seven hours, followed by extraction with water, and dried at 105° to a bright brownish-red powder.

9,10-Anthracenedion-1-olato-magnesium.—To a warm solution of 0.90 g. of 1-hydroxyanthraquinone in 400 ml. of ethanol was added 100 ml. of a cold, water solution of 0.43 g. of $Mg(OAc)_2 \cdot 4H_2O$. Six *N* ammonium hydroxide was added dropwise until a definite precipitate persisted. After standing overnight, the excess 1-hydroxyanthraquinone was removed by decanting the reheated solution from the solid. This solid was washed with hot ethanol, followed by hot water, dried at 100°, and extracted with 95% ethanol. This inner complex is a deep red powder.

9,10-Anthracenedion-1-olato-manganese(II).—A cold solution of 0.98 g. of $Mn(OAc)_2 \cdot 4H_2O$ in 50 ml. of methanol was mixed with a warm solution of 0.90 g. of 1-hydroxyanthraquinone in 300 ml. of ethanol. The solution was concentrated under reduced pressure. After cooling, the solid formed was collected by filtration, washed with cold water and ethanol, and dried at 105°. To remove excess quinone, the solid was heated for one hour under vacuum in a drying pistol at 205°. The compound was obtained as a dark olive-brown powder.

9,10-Anthracenedion-1-olato-nickel(II).—The four-coordinate nickel complex was prepared exactly as was the cobalt compound, using identical quantities. The unsolvated complex is an orange-brown powder.

Diaquo-9,10-anthracenedion-1-olato-nickel(II).—The six-coördinate diaquo nickel complex was prepared by the method used for the copper(II) complex, using 0.50 g. of $Ni(OAc)_2 \cdot 4H_2O$, the other quantities being the same; red-violet powder.

9,10-Anthracenedion-1-olato-uranyl.—One hundred ml. of a warm methanol solution of 1.70 g. of $UO_2(OAc)_2 \cdot 2H_2O$ was added slowly to 300 ml. of a warm methanol solution of 0.90 g. of 1-hydroxyanthraquinone. After several days, the crystals were removed, washed with cold methanol, and dried at 105°. The complex was heated in the drying pistol at 204° for one hour; purple-brown crystals.

These compounds are stable at high temperatures, highly colored, insoluble in water, and in the common organic solvents at room temperature. Strong acids de-

(1) This paper represents an abstract of a portion of a thesis presented by Bradford P. Geyer to the University of Washington in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Present address: Shell Development Company, Emeryville, Calif.

(3) Haendler and Geyer, THIS JOURNAL, **60**, 2813 (1938).

(4) Machemer, *J. prakt. Chem.*, **127**, 109 (1930).

(5) Pfeiffer, Breith, Lübbe and Tsumaki, *Ann.*, **503**, 84 (1933).

(6) Roemer, *Ber.*, **15**, 1793 (1882).

TABLE I

ANALYTICAL AND SPECTRAL DATA FOR THE INNER COMPLEXES

Inner complex	Formula	Percentage of Metal Calcd.	Found	Yield, %	Maximum mμ	ε
9,10-Anthracenedione-1-olato-Co(II)	$C_{28}H_{14}O_6Co$	11.7	11.5	86	410, 480	6080, 3190
9,10-Anthracenedione-1-olato-Cu(II)	$C_{28}H_{14}O_6Cu$	12.5	12.3	91	400, 500	4830, 940
9,10-Anthracenedione-1-olato-Mg	$C_{28}H_{14}O_6Mg$	5.2	5.0	57	400, 500	3160, 1440
9,10-Anthracenedione-1-olato-Mn(II)	$C_{28}H_{14}O_6Mn$	11.0	10.9	14		
9,10-Anthracenedione-1-olato-UO_2	$C_{28}H_{14}O_6UO_2$	33.2	33.8	80	410, 510	13900, 2020
9,10-Anthracenedione-1-olato-Ni(II)	$C_{28}H_{14}O_6Ni$	11.6	11.7	51	400, 500	8100, 6990
Diaquo-9,10-anthracenedione-1-olato-Ni(II)	$C_{28}H_{14}O_6Ni\cdot 2H_2O$[a]	10.8	10.9	86		
2-Acetoxy-9,10-anthracenedione-1-olato-Cu(II)	$C_{32}H_{18}O_{10}Cu$	10.2	9.7	89	400, 530	2380, 2810
3-Nito-9,10-anthracenedion-2(1)-ol-1(2)-olato-Cu(II)	$C_{28}H_{12}O_{12}N_2Cu$	10.1	10.8	57	500	3720

[a] H_2O calcd.: 1:2. Found: 1:2.1; 1:1.9.

compose the complex with liberation of the quinone. The analytical data for the complexes are in Table I.

2. 1-Acetylalizarin Inner Complexes.—It has been reported[7] that alizarin, 1,2-dihydroxyanthraquinone, upon direct interaction with metal acetates, forms normal salts. Acetylation of the more active 2-hydroxy group should permit chelation through the other, or 1-hydroxy, group. As was expected, 2-acetylalizarin (2-acetoxy-9,10-anthracenedion-1-ol) did form an inner complex with copper(II) ion. The complex was similar in color and behavior to the corresponding complex of 1-hydroxyanthraquinone.

Starting Material.—2-Acetylalizarin was prepared according to Perkin[8]; m. p. 197–198°.

Inner Complex: 2-Acetoxy-9,10-anthracenedion-1-olato-copper(II).—A warm solution of 0.20 g. of $Cu(OAc)_2\cdot H_2O$ in 30 ml. of absolute alcohol was added dropwise to a warm solution of 0.56 g. of 2-acetylalizarin in 20 ml. of nitrobenzene, with stirring. After five hours, the solid was filtered off, washed with hot ethanol, then with ether, and dried. The dry powder was heated for six hours in the drying pistol at 210°, followed by extraction with chlorobenzene and reheating at 210°; red-brown powder.

3. 3-Nitroalizarin Inner Complexes.—The hydrogen bonding of peri-hydroxyquinones[9] and of *o*-nitrophenols would suggest the possibility of inner complex formation through either of the two chelating groups in 3-nitroalizarin (3-nitro-9,10-anthracenedion-1,2-diol). This proved to be the case, for a copper(II) compound, which exhibited typical inner complex behavior, was prepared from the nitro compound.

Starting Material.—Crude 3-nitroalizarin was recrystallized from glacial acetic acid; m. p. 244–245°, with decomposition.

Inner Complex: 3-Nitro-9,10-anthracenedion-2(1)-ol-1(2)-olato-copper(II).—A cold solution of 0.20 g. of $Cu(OAc)_2\cdot H_2O$ in 100 ml. of absolute alcohol was added slowly to a suspension of 0.57 g. of 3-nitroalizarin in 100 ml. of cold, absolute alcohol contained in a 3-neck flask fitted with mercury-seal stirrer, condenser with anhydrone-filled drying tube, and dropping funnel. The mixture was stirred and heated under reflux for seven hours, and while still hot was filtered. The solid was washed with cold ether, air-dried, and then heated for ninety minutes in the drying pistol at 255° to give purplish-brown microcrystals.

Absorption Spectra

The absorption of these inner complexes was measured in the visual range following the same procedure as in our earlier publication.[10] In the case of the inner complexes of 1-hydroxy-anthraquinone, absorption occurs over one narrow band in the violet and another narrow, but less intense, band in the blue-green. As in the phthiocol series of inner complexes previously described[10] the intensity of absorption is dependent upon the metal present. The absorption curves for the four-coördinate 1-hydroxyanthraquinone complexes are all similar in shape. Table I shows the wave lengths at which maximum absorption occurs and the corresponding molecular extinction coefficients.

From 370–410 mμ, the absorption of the cobalt(II), copper(II), magnesium, and nickel(II) inner complexes show the same relationships observed among the corresponding phthiocol complexes. From 470–580 mμ the absorption characteristics of the cobalt(II), copper(II), and nickel(II) complexes are again similar to the phthiocol compounds. The color of the inner complexes is caused more by the formation of the chelate ring than by the presence of a particular metal. This latter fact has been observed in all of the studies on the absorption spectra of *o*-quinone monoxime, *o*-hydroxyazo dye, and *o*-hydroxyquinone inner complexes prepared in this Laboratory.[10,11]

The absorption spectra curves for 2-acetylalizarin and 3-nitroalizarin, with those for their

(7) Crossley, THIS JOURNAL, **41**, 2081 (1919).
(8) Perkin, *J. Chem. Soc.*, **75**, 447 (1899).
(9) Hilbert, Wulf, Hendricks and Liddel, THIS JOURNAL, **58**, 548 (1936).
(10) Geyer with Smith, *ibid.*, **63**, 3071 (1941).
(11) Haendler with Smith, *ibid.*, **62**, 1669 (1940).

copper(II) complexes, are similar in gross detail to the corresponding hydroxyanthraquinone curves.

Experimental

The experimental procedure for absorption spectra measurements[12] was the same as that described in our earlier publication.[10] The concentrations of the *n*-butanol solutions ranged from 0.00003 to 0.0002 *M*. Values of the extinction coefficients were calculated by Beer's law.

Catalytic Behavior of the Inner Complex[10]

It was found that certain of the inner complexes prepared could catalyze the chemiluminescent oxidation of luminol (3-amino-phthalhydrazide) by hydrogen peroxide. The cobalt(II) and copper(II) complexes of 1-hydroxyanthraquinone and the copper(II) complexes of 2-acetylalizarin and 3-nitroalizarin all exhibit decreasing degrees of catalytic activity, in that order. The free quinones are inactive.

The 1-hydroxyanthraquinone-cobalt(II) complex produces a bluish violet-white luminescence, lasting over three hours, but not as intense as the light produced with the cobalt(II) complex of phthiocol. The copper(II) complex produces a blue-white light of three-hour duration, but of lower intensity than either the 1-hydroxyanthraquinone cobalt(II) complex or the phthiocol copper(II) complex. Solubility and stability of the complex appear to be the governing factors in the catalysis of chemiluminescent oxidation.

(12) With H. M. Haendler.

Summary

1. The preparation and properties of the cobalt(II), copper(II), magnesium, manganese(II), nickel(II), diaquonickel(II), and uranyl inner complexes of 1-hydroxyanthraquinone, as well as the copper(II) inner complexes of 2-acetylalizarin and 3-nitroalizarin have been described.

2. The absorption spectra of these inner complexes in *n*-butanol solution have been determined in the visual region.

3. The color of the complex is due to the chelation of the quinone with the metal.

4. The cobalt(II) and copper(II) inner complexes of 1-hydroxyanthraquinone and the copper(II) inner complexes of 2-acetylalizarin and 3-nitroalizarin catalyze the chemiluminescent oxidation of luminol by hydrogen peroxide.

SEATTLE, WASHINGTON RECEIVED NOVEMBER 24, 1941

[CONTRIBUTION FROM THE IOWA AGRICULTURAL EXPERIMENT STATION]

The Molecular Weights of the Schardinger Alpha and Beta Dextrins[1]

BY DEXTER FRENCH AND R. E. RUNDLE

The work of Freudenberg[2] and others[3] indicates that the Schardinger dextrins are composed solely of glucose residues bonded by α-1,4-glucosidic linkages as in starch. Though these dextrins are of much lower molecular weight than starch, they are completely non-reducing. The only structure which appears to be consistent with these chemical properties is a cyclic structure.[4]

Several molecular species with the chemical properties given above are known to occur in the dextrin mixture obtained by the *B. macerans* enzymolysis of starch. The main components of the mixture have been separated and characterized by Freudenberg and Jacobi.[5] The molecular weights which these authors suggest for these species were determined by cryoscopic methods, but since these dextrins are of comparatively high molecular weight and are very difficult to free from low molecular weight impurities (solvent of crystallization and inorganic ash), the cryoscopic molecular weights can be expected to be but rough approximations.

A method better adapted to the determination of the molecular weights of high molecular weight crystalline compounds is X-ray diffraction combined with crystal density measurement. In this method low molecular weight impurities are of minor importance, and their contribution to the crystal density can be determined and corrected for with satisfactory accuracy.

By this method we have found Schardinger's

(1) Journal Paper No. J-979 of the Iowa Agricultural Experiment Station, Ames, Iowa. Project No. 639. Supported in part by a grant from the Corn Industries Research Foundation.

(2) K. Freudenberg, G. Blomquist, L. Ewald and K. Soff, *Ber.*, **69**, 1258 (1936).

(3) J. C. Irvine, H. Pringsheim and J. MacDonald, *J. Chem. Soc.*, **125**, 942 (1924).

(4) K. Freudenberg, *Ann. Rev. Biochem.*, **8**, 81 (1939).

(5) K. Freudenberg and R. Jacobi, *Ann.*, **518**, 102 (1935).

α-dextrin to contain six glucose residues per molecule and the β-dextrin to contain seven glucose residues per molecule, whereas Freudenberg and Jacobi[5] report five and six, respectively.[6] That the cryoscopic values are too low is not unexpected.

Naming of the Compounds.—The chemical properties of the α- and β-dextrins together with the molecular weights reported here leave no doubt as to the gross structure of these compounds. Their present names have no structural significance, nor have the names been standardized in usage.[7] The term amylose has been generally applied to those compounds possessing the α-1,4-glucosidic linkage of starch. The prefix *cyclo* adequately describes the distinguishing structural characteristics of this class of compounds, and the usual Greek terms can be used to identify the members of the class through the number of glucose residues in the ring. We therefore propose that Schardinger's α-dextrin be named cyclohexaamylose, and the β-dextrin be named cycloheptaamylose.

Experimental

Preparation of the Cycloamyloses.—The cycloamyloses were prepared by enzymolysis of potato starch as described by Schoch,[8] and were separated and purified by the method of Freudenberg and Jacobi.[5] The authors are indebted to Drs. T. J. Schoch and R. W. Kerr of Corn Products Refining Company for part of the material used in this investigation. Crystals of cyclohexaamylose were prepared by adding 95% ethanol to a hot, 30% aqueous solution of the cyclohexaamylose until the concentration of alcohol reached 60–80%. On cooling, crystals deposited in large, glass-clear, orthorhombic prisms. For anhydrous cyclohexaamylose $[\alpha]_D$ is 151.4 ± 0.5°. Crystals of cycloheptaamylose were prepared by evaporation of a saturated, aqueous solution at room temperature. For anhydrous cycloheptaamylose $[\alpha]_D$ is 161.9 ± 0.5°. The identity of these compounds with the α- and β-dextrins was confirmed by the formation of characteristic iodine addition products: blue-black hexagonal prisms and greenish needles from the cyclohexaamylose, and red-brown prisms from the cycloheptaamylose.

X-Ray Diffraction Patterns.—Twenty degree oscillation patterns were taken about all three axes of both crystals reported here. They were obtained using Ni filtered Cu Kα radiation and a cylindrical camera of 5-cm. radius. Reciprocal lattice goniometer patterns[9] were also made with Cu Kα radiation and a sample to film distance of $2\sqrt{3}$ cm., with the axis of rotation inclined 60° to the X-ray beam.

Cyclohexaamylose.—The density, measured by flotation in a mixture of chloroform and toluene, was 1.436 ± 0.004. The amount of volatile matter (water and/or alcohol of crystallization) amounted to 12.2 ± 0.1% of the weight of the crystals, and an ash determination showed the presence of 1.63 ± 0.02% inorganic impurity. The average value for the carbohydrate density is then 1.237 ± 0.005.

The primitive translations of the lattice, as obtained by layer line separations on oscillation patterns, are a_0 = 15.49 Å.; b_0 = 24.06 Å.; c_0 = 13.93 Å. The volume of the orthorhombic unit is 5195 cu. Å. Since the molecular weight of a glucose residue is 162.1, the number of glucose residues per unit cell is

$$\frac{5195 \times 1.237 \times 6.06 \times 10^{-1}}{162.1} = 24.02 \cong 24$$

The crystal has orthorhombic symmetry as shown by oscillation and goniometer diffraction patterns. Since the molecules are optically active only those space groups isomorphous with the point group V-222 are allowed. Many reflections from all types of planes eliminate all space groups based on any but the primitive orthorhombic lattice. The possible space groups are then V^1-$P222$, V^2-$P222_1$, V^3-$P2_12_12$, and V^4-$P2_12_12_1$. Examination of the ($h00$), ($0k0$), and ($00l$) reflections on intense oscillation and goniometer patterns reveals that all odd orders of these reflections are missing. It was possible to observe 16 orders of ($h00$), 26 orders of ($0k0$), and 14 orders of ($00l$), so that the space group is doubtless V^4-$P2_12_12_1$. This space group requires a multiple of four molecules per unit cell regardless of molecular symmetry. The number of glucose residues per molecule is then 6, 3, or 2. The latter two possibilities may be excluded on the basis of the chemical behavior of this compound and the fact that a ring of three or two glucose residues is sterically impossible. Moreover, it is quite unusual for a unit cell to contain a number of molecules greater than that required by the crystal symmetry.[10]

Cycloheptaamylose.—Crystals were obtained having a density of 1.444 ± 0.004 and a water content of 14.18 ± 0.02%. The carbohydrate density is therefore 1.240 ± 0.004. The crystals exhibit monoclinic symmetry as shown by oscillation and reciprocal lattice patterns. The unit translations determined by layer line separations are a_0 = 15.27 Å.; b_0 = 10.24 Å.; c_0 = 20.93 Å. The monoclinic angle β = 68.0° ($\sin\beta$ = 0.9272) was determined by direct measurement on reciprocal lattice patterns and confirmed by Laue patterns. The volume of the unit cell is

(6) O. Kratky and B. Schneidmesser [*Ber.*, **71**, 1413 (1938)], claim to have found five glucose residues per molecule of the alpha-dextrin, but their work contains a discrepancy. The possible space groups which they find for their crystal are V^3 – $P2_12_12$ and V^4 – $P2_12_12_1$. V^4 requires four asymmetric molecules per cell, and V^3 requires four asymmetric molecules or two molecules possessing a two-fold axis. They find for their unit cell two molecules of five glucose residues each, molecules which cannot possess the required symmetry.

(7) Schardinger called these compounds "crystallized amylose" and "crystallized amylopectin" [*Zentr. Bakt. Parasitenk. II*, **22**, 98 (1908)]. Pringsheim used the name "polyamylose," and referred to the individual compounds as α-tetraamylose, β-hexaamylose, etc. [*Ber.*, **47**, 2565 (1914)]. Freudenberg and Jacobi (ref. 5) refer to these compounds as α-dextrin, β-dextrin, etc., and later as pentaosan, hexaosan, etc. [K. Freudenberg and H. Boppel, *Ber.*, **73**, 609 (1940)].

(8) T. J. Schoch, Report to the Corn Industries Research Foundation (1940). This method is an adaptation of the method of E. B. Tilden and C. S. Hudson, THIS JOURNAL, **61**, 2900 (1939).

(9) The instrument used was the Clark–Gross modification of the reciprocal lattice X-ray goniometer described by W. F. deJong and J. Bouman, *Z. Krist.*, **98**, 456 (1938); **99**, 326 (1938).

(10) A. E. H. Tutton, "Crystalline Form and Chemical Constitution," The Macmillan Co., London, 1926, p. 31.

3032 cu. Å. The number of glucose residues per unit cell is then

$$\frac{3032 \times 1.240 \times 6.06 \times 10^{-1}}{162.1} = 14.05 \cong 14$$

The monoclinic space groups allowed for an optically active molecule are C_2^1-$P2$, C_2^2-$P2_1$, and C_2^3-$C2$. Many reflections of the form (hkl) with $(h + k)$ odd are present so that C_2^3-$C2$ is eliminated. Intense reciprocal lattice goniometer patterns were made rotating the crystal about the zone [100]. All reflections of the form $(0kl)$ were observed to $(\sin\theta)/\lambda = 0.56$, except the odd orders of $(0k0)$, through (090), which were absent. The space group can then be taken as C_2^2-$P2_1$. This space group requires an even number of molecules per unit cell so we must have two molecules of seven glucose residues each.

Summary

1. The molecular weights of the Schardinger α- and β-dextrins have been accurately determined by X-ray diffraction and crystal density measurements.

2. The α-dextrin contains six glucose residues per molecule and has been renamed cyclohexaamylose; the β-dextrin contains seven glucose residues and has been renamed cycloheptaamylose.

AMES, IOWA RECEIVED FEBRUARY 17, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. CXLVII. Sapogenins. LXI. The Bio-reduction of Steroids

BY RUSSELL E. MARKER, R. B. WAGNER AND PAUL R. ULSHAFER

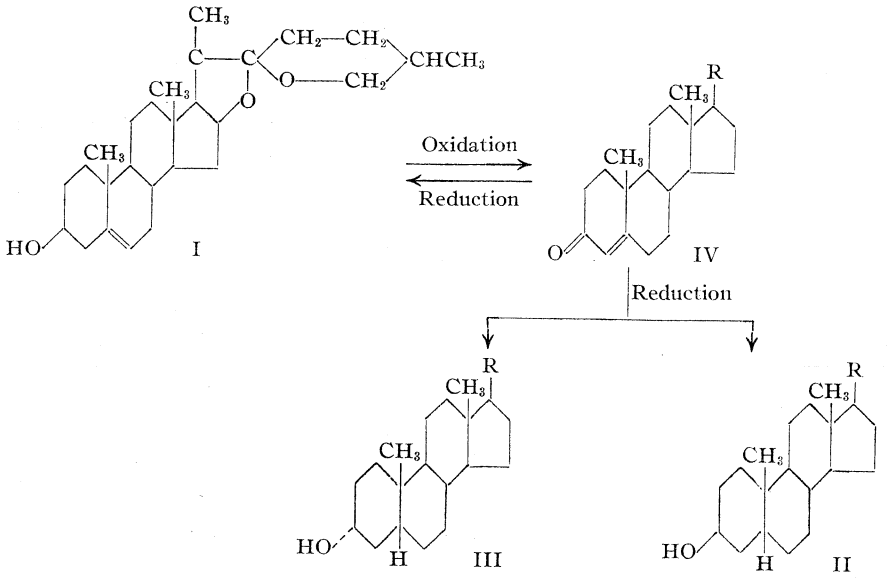
It has been postulated that Δ^5-3-hydroxysteroids arise as reduction products of Δ^4-3-ketosteroids under biological conditions.[1] Using Δ^4-dehydrotigogenone as a model substance for the bio-reduction process, we[3] have recently shown that this when administered to a dog on a biscuit diet gave diosgenin (I), smilagenin (iso-sarsasapogenin) (II) and *epi*-smilagenin (*epi*-iso-sarsasapogenin) (III). These results not only support our hypothesis, but also support the conception that cholestenone is an intermediate in the formation of coprosterol in the organism[1,5] since the products, (I), (II) and (III) correspond in nuclear structure to cholesterol, coprosterol and *epi*-coprosterol. The sapogenin derivatives having the characteristic side-chain act as effective indicators and are not subject to the suggestions of Fieser and Wolfe.[2]

We have now extended this work along the line of that of Rosenheim and Webster[4] who showed that β-sitosterol administered together with brain-powder to rats was converted into an isomeride of sitostanol which they named *copro*-sitostanol. The latter agrees in composition and properties with 24-ethylcoprostanol-3(β). Since a coprostane derivative has not been obtained directly from a Δ^5-3-hydroxysteroid by chemical action Rosenheim and Webster's experiment indicates a Δ^4-3-ketosteroid as a very probable intermediate for the formation of the *copro*-sitostanol.

Accordingly, diosgenin (I) was administered to a dog fed on a meat diet containing small portions of pig brain. The non-saponifiable fraction of the feces gave smilagenin (II) and *epi*-smilagenin (III) products which correspond to coprosterol and its epimer. This and the previous conversion support the hypothesis of Schoenheimer[5] that there is a reversible biological reaction of the type cholestenone $\rightleftarrows$ cholesterol. Δ^4-Dehydrotigogenone (IV) may be reduced by one enzyme system to smilagenin (II) and *epi*-smilagenin (III) or by another enzyme system converted to diosgenin (I). The present work indicates the reversible reaction involving the following oxidation–reduction mechanism; diosgenin (I) $\underset{[R]}{\overset{[O]}{\rightleftarrows}}$ Δ^4-dehydrotigogenone (IV) $\xrightarrow{[R]}$ smilagenin (II) and *epi*-smilagenin (III). These reactions are summarized in the accompanying chart.

Another observation in the present work is that the bio-reduction of keto-sapogenins gives hydroxy compounds of both alpha and beta configuration. This is contrary to the earlier statements[1] that reduction *in vivo* of 3-ketosteroids appears to give only alpha compounds. Tigogenone and sarsasapogenone having the cholestane and the coprostane configuration, respectively, were administered to a dog fed on a meat diet. In the case of the tigogenone the feces contained both

(1) Marker, THIS JOURNAL, **60**, 1725 (1938).
(2) Fieser and Wolfe, *ibid.*, **63**, 1485 (1941).
(3) Marker, Wittbecker, Wagner and Turner, *ibid.*, **64**, 818 (1942).
(4) Rosenheim and Webster, *J. Soc. Chem. Ind.*, **XL**, 486 (1941)
(5) Schoenheimer, Rittenberg and Graff, *J. Biol. Chem.*, **111**, 185 (1935).



tigogenin and *epi*-tigogenin. Similarly, the sarsasapogenone gave both sarsasapogenin and its epimer.

We thank Parke, Davis and Company for their assistance.

Experimental Part

The Biological Conversions of Diosgenin.—A 10-kg. dog was fed daily a mixture of 150 g. of meat, 50 g. of pig-brain and 3 g. of diosgenin for three consecutive days. After these feedings the dog was maintained for three additional days on a meat diet. Its feces were collected during the entire period and immediately ground up in acetone. The residue was further extracted with ether. The solvent was removed and the residue hydrolyzed with alcoholic potassium hydroxide. The product was extracted with ether and the ethereal solution washed with water. The solvent was removed and the residue was refluxed with 30 cc. of acetic anhydride for thirty minutes. After cooling the crystalline product was filtered and washed with cold ether; m. p. and mixed m. p. with an authentic sample of diosgenin acetate, 197–200°; yield 5.2 g.

The filtrate was vacuum distilled and the residue was refluxed for thirty minutes with alcoholic potassium hydroxide. Water was added and the product extracted with ether. The solvent was removed and the residue was heated on a steam-bath for two hours with 50 cc. of pyridine and 10 g. of succinic anhydride. After cooling, ether was added and the pyridine was removed by washing the ethereal solution with dilute hydrochloric acid. The ether layer was then washed well with potassium carbonate solution. The aqueous layer was acidified and extracted with ether. The solvent was removed and the residue was refluxed with alcoholic potassium hydroxide for thirty minutes. Water was added and the product was extracted with ether. The solvent was removed and the residue was dissolved in a small amount of 95% alcohol. To this was added a solution of 15 g. of digitonin in 700 cc. of 95% ethanol. After standing for two hours in the ice-box the digitonide was filtered and washed well with alcohol. The filtrate was concentrated to about 50 cc., ether was added and the excess digitonin filtered off. The filtrate was washed well with water, the solvent was removed and the residue was crystallized from methanol, m. p. and mixed m. p. with an authentic sample of *epi*-smilagenin 217–220°; yield 0.2 g. of good material.

When refluxed with acetic anhydride it gave an acetate which was crystallized from methanol and from acetone; m. p. and mixed m. p. with an authentic sample of *epi*-smilagenin acetate, 158–160°.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.9; H, 10.1. Found: C, 76.0; H, 10.2.

The digitonide was decomposed with pyridine and the product thus obtained was converted to the acetate and crystallized from ether to give an additional crop of diosgenin acetate. The filtrate from this was fractionally crystallized from methanol and from acetone to give a product; m. p. and mixed m. p. with an authentic sample of smilagenin acetate, 127–130°; yield 0.1 g. of good material.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.9; H, 10.1. Found: C, 75.8; H, 10.0.

Sarsasapogenone.—The dog was fed meat containing 7 g. of sarsasapogenone divided into three daily feedings. Its feces were collected for six consecutive days and immediately ground up with acetone. After a thorough extraction with acetone the feces were extracted with ether. The combined extracts were evaporated and the residue was hydrolyzed with alcoholic potassium hydroxide for thirty minutes. Water was added and the product was extracted well with ether. The solvent was removed and the residue was heated on a steam-bath for two hours with 25 cc. of pyridine and 10 g. of succinic anhydride. Ether was added and the pyridine was removed by washing the ethereal solution with dilute hydrochloric acid. The succinates were removed by shaking with potassium carbonate solution. The aqueous layer was acidified, extracted with ether and the solvent removed. The residue was hydrolyzed by refluxing with alcoholic potassium hydroxide. The neutral fraction was extracted with ether and the solvent was removed; yield 2.7 g.

The residue was dissolved in alcohol and 10 g. of digitonin in 500 cc. of ethanol was added. After standing at room temperature for several hours the digitonide was filtered, washed with alcohol and dried. It was then decomposed by warming on a steam-bath for one hour with pyridine. Ether was added and the digitonin was filtered. The filtrate was washed well with water and dilute hydrochloric acid. The solvent was evaporated and the residue was crystallized from ethanol and from methanol; m. p. and mixed m. p. with an authentic sample of sarsasapogenin, 199–200°.

When refluxed with acetic anhydride it gave sarsasapogenin acetate; m. p. and mixed m. p. 126–128°.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.9; H, 10.1. Found: C, 75.8; H, 10.2.

The filtrate from the digitonide was evaporated to about 50 cc. Ether was added and the digitonin was filtered off. The filtrate was washed well with water and the solvent removed. The residue was crystallized from methanol; m. p. and mixed m. p. with *epi*-sarsasapogenin, 205–209°. When refluxed with acetic anhydride it gave a product which was crystallized from methanol; m. p. and mixed m. p. with *epi*-sarsasapogenin acetate, 190–195°.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.9; H, 10.1. Found: C, 76.0; H, 10.3.

Tigogenone.—The dog was fed a meat diet containing 7 g. of tigogenone. The feces were extracted and worked up as described above. The digitonin precipitable fraction gave a product which was crystallized from methanol; m. p. and mixed m. p. with tigogenin, 200–202°. This gave tigogenin acetate; m. p. and mixed m. p. with tigogenin acetate, 197–199°.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.9; H, 10.1. Found: C, 76.2; H, 10.3.

The fraction not precipitated by digitonin was crystallized from acetone; m. p. and mixed m. p. with an authentic sample of *epi*-tigogenin, 242–244°. This product gave *epi*-tigogenin acetate; m. p. and mixed m. p., 199–201°.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.9; H, 10.1. Found: C, 75.7; H, 10.1.

Summary

1. Diosgenin has been biologically converted to smilagenin and *epi*-smilagenin.

2. Similarly tigogenone and sarsasapogenone have been converted to the carbinols of both the alpha and beta configurations.

3. The significance of these facts has been discussed.

STATE COLLEGE, PENNA. RECEIVED MARCH 5, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. CXLVIII. Sapogenins. LXII. The Structure of the Side Chain in the Dihydro-pseudosapogenins[1]

BY RUSSELL E. MARKER, D. L. TURNER AND PAUL R. ULSHAFER

When dihydro-pseudosarsasapogenin (I) was oxidized with chromic anhydride at 15–18°, two products were obtained,[2] a C-27 keto acid (II) and 16-pregnenedione-3,20 (V). The latter arises from an acid oxidation intermediate which is hydrolyzed on extraction from ethereal solution with alkali.[3] In the same manner the oxidation of dihydropseudotigogenin gives an isomeric C-27 keto acid (VIII) together with 16-*allo*-pregnenedione-3,20 (VII).

On oxidation with chromic acid the two keto-acids, like the corresponding dihydropseudosapogenins, are converted to 16-pregnenedione-3,20 (V) and 16-*allo*-pregnenedione-3,30 (VII), respectively. This suggested that the formation of the keto acids involves only the oxidation of the two hydroxyl groups at C-3 and C-27. The presence of a single carbonyl group in each acid was indicated by the analyses of the oximes and semicarbazones.[4]

Clemmensen reduction of the acid (VIII) from dihydro-pseudotigogenin removed only one oxygen to give the 3-desoxy acid (IX). Catalytic reduction of both keto acids in neutral solution gave the corresponding 3-hydroxy acids (IV), (VI), (X). In the case of the acid from dihydro-pseudosarsasapogenin, a mixture of the epimeric carbinols resulted, the 3(α)-carbinol being present in greater quantity. The acid of the *allo* series gave the 3(β) carbinol. Bouveault reduction of the methyl ester of the acid (II) from dihydro-pseudosarsasapogenin gave *epi*-dihydro-pseudosarsasapogenin (III), identified as its *bis-p*-nitrobenzoate.[5]

These results establish definitely that the two keto acids are mono-ketones. The reactions can best be represented as in the accompanying chart.

The various reactions of the pseudosapogenins which have been reported[2,3,6,7] from this Laboratory are all consistent with the dihydrofuran formulation of the side-chain in these substances (XI).

(1) Original manuscript received June 25, 1941.

(2) Marker and Rohrmann, THIS JOURNAL, **62**, 521 (1940).

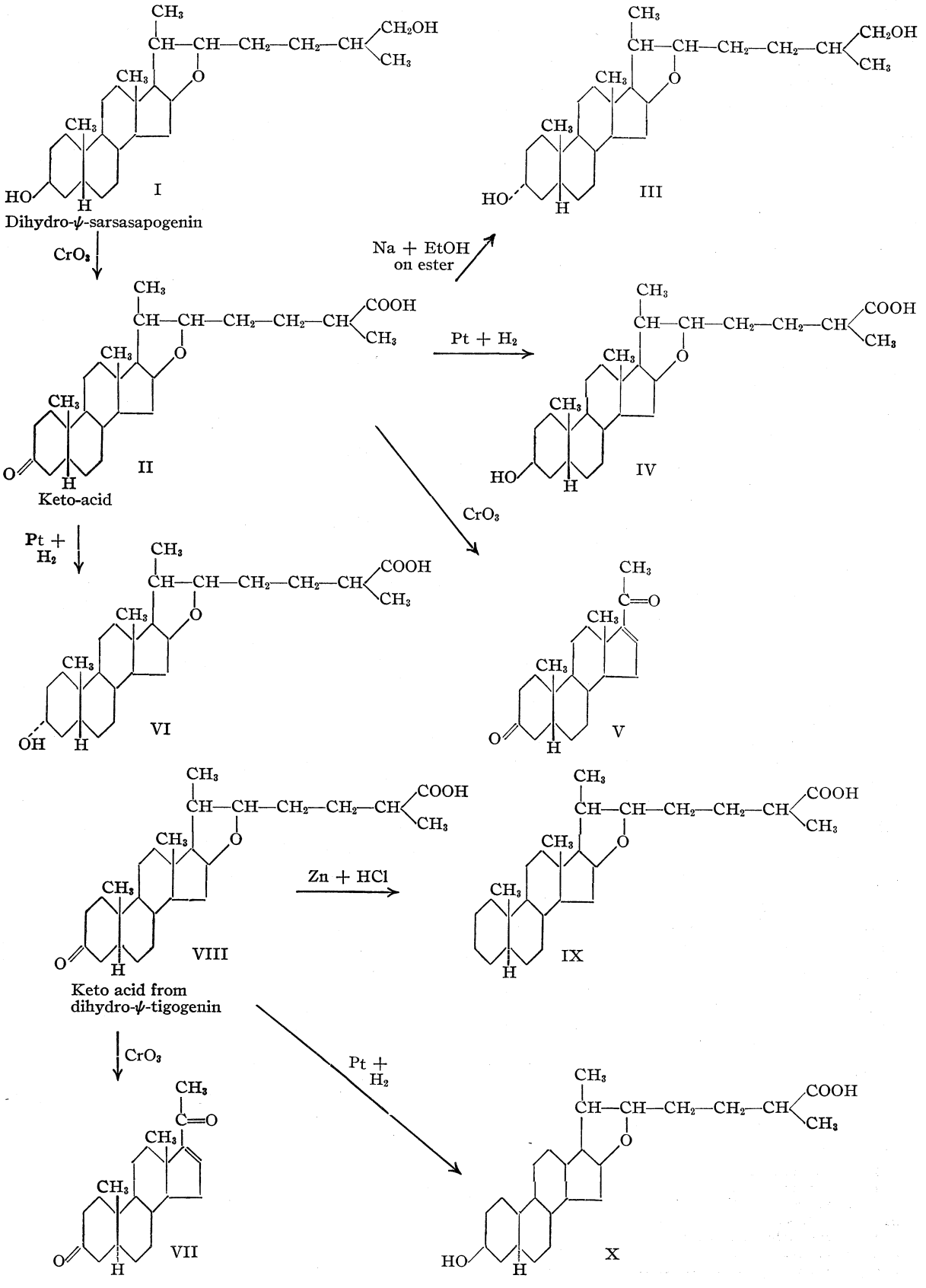
(3) (a) Marker, *et al.*, *ibid.*, **63**, 774 (1941); (b) Marker *et al.*, *ibid.*, **63**, 779 (1941).

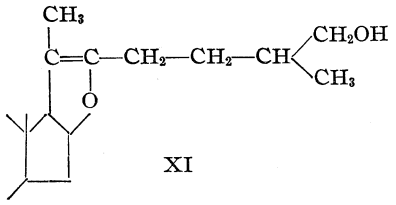
(4) We are unable to duplicate the preparation of the *bis*-semicarbazone previously reported.[2] The analytical data as previously given for the acid and ester are correct for the mono-keto compound.

(5) Marker, Rohrmann and Jones, THIS JOURNAL, **62**, 648 (1940).

(6) Marker and Rohrmann, *ibid.*, **62**, 896 (1940).

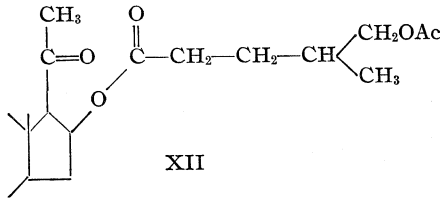
(7) Marker, Jones and Kreuger, *ibid.*, **62**, 2532 (1940).


I
Dihydro-ψ-sarsasapogenin
CrO3
Na + EtOH
on ester
III
II
Keto-acid
Pt + H2
IV
CrO3
Pt +
H2
VI
V
VIII
Keto acid from
dihydro-ψ-tigogenin
Zn + HCl
IX
CrO3
Pt +
H2
VII
X



XI

The structure of the side-chain in the oxidation products has been established as (XII).[2,3] Con-



XII

sequently the oxide bridge must be assumed to be present in dihydro-pseudosapogenins as well as in the pseudosapogenins. That the third oxygen atom is of oxide function is also indicated by the formation of diacetates from the dihydro-pseudosapogenins and by the properties of the C_{27} keto acids described in the present paper. This leads to a structure for the side-chain of dihydro-pseudosapogenins (I) which is identical with one previously assigned to the dihydrosapogenins.[8,9] The dihydrosapogenins can be oxidized to monoketo acids, anhydrotetrahydro-sarsasapogenoic acid[9] and anhydrotetrahydrotigogenoic acid,[10,11] which were assigned constitutions identical with these of the acids described in the present paper. Oxidation of the diacetates of the dihydrosapogenins at higher temperatures gave the same products which were obtained from the sapogenins: the C_{22} lactone, the sapogenoic acid, the 16-keto acid, etc.,[9,10] in extreme contrast to the behavior of the dihydro-pseudosapogenins on oxidation. This may be due to a difference of configuration at C-20 and C-22. Sterols differing only stereochemically are known to give different products of oxidation in other cases.[12]

We thank Parke, Davis and Company for their assistance.

Experimental Part

Oxidation of Dihydropseudotigogenin.—To a solution of 8 g. of dihydropseudotigogenin in 400 cc. of acetic acid at 15° was added a solution of 6.4 g. of chromic anhydride in 50 cc. of 60% acetic acid. The temperature was maintained at 10–15° for thirty minutes. The product was poured into water and then extracted with ether. The ethereal solution was washed free of acetic acid with water. The acid was then removed with 10% sodium hydroxide solution. The alkaline layer was allowed to stand for thirty minutes and then reëxtracted with ether. The C_{27} keto acid separated in the alkaline layer as an insoluble sodium salt. This was filtered and decomposed with dilute hydrochloric acid. It was taken up in ether and crystallized after evaporation to a small volume; yield about 0.8 g. It was recrystallized from ethyl acetate, m. p. 207–209°.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.3; H, 9.6. Found: C, 75.2; H, 9.7.

The neutral fraction from the above oxidation gave material which was crystallized from acetone, m. p. 211–213°. When mixed with 16-*allo*-pregnene-3,20-dione (m. p. 210–212°) there was no depression in melting point.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 80.1; H, 9.7.

Semicarbazone of the Above *allo*-Keto-acid (VIII).—This was prepared in the usual manner by boiling for two hours in aqueous ethanol with semicarbazide hydrochloride and potassium acetate; recrystallized from ethanol, m. p. 210–213° dec.

Anal. Calcd. for $C_{28}H_{45}O_4N_3$ (mono-semicarbazone): C, 68.9; H, 9.3. Calcd. for $C_{29}H_{46}O_4N_6$ (bis-semicarbazone): C, 64.2; H, 8.5. Found: C, 68.9; H, 9.2.

Oxime of *allo*-Keto-acid (VIII).—This was prepared by a method similar to that used for the semicarbazone and recrystallized from methanol as colorless needles which decomposed at 232–234°.

Anal. Calcd. for $C_{27}H_{43}O_4N$: C, 72.8; H, 9.7. Found: C, 72.8; H, 9.7.

Methyl Ester of *allo*-Keto-acid (VIII).—This was prepared in ether with diazomethane and recrystallized from methanol, m. p. 138°.

Anal. Calcd. for $C_{28}H_{44}O_4$: C, 75.6; H, 10.0. Found: C, 75.3; H, 9.8.

Oxidation of *allo*-Keto-acid (VIII).—To a solution of 1.4 g. of the above keto-acid in 115 cc. of acetic acid was added a solution of 1.4 g. of chromic anhydride in 28 cc. of 80 per cent acetic acid at 28°. The mixture was allowed to stand for seventy-five minutes at 28–30°. It was poured into water and extracted with ether. The ethereal solution was washed to remove acetic acid. The acid fraction was extracted with 20% potassium hydroxide solution; it was allowed to stand for one hour and then re-extracted with ether. The united ether extracts gave crystalline material on evaporation. This was recrystallized from acetone, m. p. 212–213°. When mixed with 16-*allo*-pregnene-3,20-dione, there was no depression in melting point.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 80.0; H, 9.5.

Oxidation of Dihydropseudosarsasapogenin (I).—This followed the procedure given for the oxidation of dihydropseudotigogenin except that the sodium salt was not sepa-

(8) Marker and Rohrmann, THIS JOURNAL, **61**, 846 (1939).
(9) Marker and Rohrmann, *ibid.*, **61**, 2072 (1939).
(10) Marker, Turner and Ulshafer, *ibid.*, **63**, 763 (1941).
(11) Anhydrotetrahydro-tigogenoic acid was incorrectly designated "tetrahydroanhydro-tigogenoic acid" in the theoretical section of the paper of ref. 10.
(12) *Cf.* Marker *et al.*, *ibid.*, **61**, 3317 (1939).

rated by filtration. The acid product was crystallized from acetone, m. p. 233–236°. When mixed with the acid previously prepared[2] there was no depression in melting point.

To a solution of 300 mg. of the acid in 70 cc. of ethanol was added a solution of 1.0 g. of semicarbazide hydrochloride in 5 cc. of water and a solution of 1.0 g. of potassium acetate in 5 cc. of water. This was refluxed for two hours. The mixture was poured into water, the product was filtered and washed with water and ether. It was recrystallized from ethanol and decomposed at 236°.

Anal. Calcd. for $C_{28}H_{45}O_4N_3$: C, 68.9; H, 9.3. Found: C, 68.7; H, 9.3.

The **oxime** was prepared similarly. It was recrystallized from methanol and melted at 232–234°.

Anal. Calcd. for $C_{27}H_{43}O_4N$: C, 72.8; H, 9.7. Found: C, 72.4; H, 9.6.

Methyl Ester of the Above Keto-acid (II).—This was prepared with diazomethane in ether and was recrystallized from pentane as prismatic needles, m. p. 116.5°. Upon standing for two years the ester previously described had changed in melting point from 85–87° to 112°, apparently changing crystalline form. This gave no depression with the above sample.

Anal. Calcd. for $C_{28}H_{44}O_4$: C, 75.6; H, 10.0. Found: C, 75.6; H, 10.0.

Semicarbazone of the Methyl Ester of the Above Keto Acid (II).—This was prepared in the usual manner and recrystallized from methanol. It decomposed at 225°.

Anal. Calcd. for $C_{29}H_{47}O_4N_3$: C, 69.4; H, 9.4. Found: C, 69.3; H, 9.4.

Bouveault Reduction of the Methyl Ester of (II).—Sodium (2.5 g.) was added to a solution of 2.0 g. of methyl ester in 20 cc. of absolute ethanol (dried over magnesium methylate). The mixture was boiled for one hour, then an additional 25 cc. of absolute ethanol and 2 g. of sodium was added. After boiling for two additional hours the mixture was poured into water and extracted with ether. The ethereal solution was washed with water and evaporated. The residue was a mixture difficult to separate. It was dissolved in dry pyridine and treated with an excess of *p*-nitrobenzoyl chloride. The *p*-nitrobenzoate was isolated in the usual manner and crystallized from acetone, m. p. 206–208°. Mixed with the bis-*p*-nitrobenzoate of epidihydropseudosarsasapogenin, m. p. 208–9°, the m. p. was 206–208°, yield 0.5 g.

Anal. Calcd. for $C_{41}H_{54}O_9N_2$: C, 68.5; H, 7.6. Found: C, 68.7; H, 7.4.

Clemmensen Reduction of the Keto-acid (II) from Dihydropseudosarsasapogenin.—To a refluxing solution of 1 g. of the keto acid in 250 cc. of ethanol containing 40 g. of amalgamated zinc (20-mesh) was added 70 cc. of concentrated hydrochloric acid during a period of three hours. The mixture was refluxed for an additional hour, poured into water and extracted with ether. The residue remaining after evaporation was crystallized from methanol, m. p. 81.5–82.5.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.8; H, 10.6. Found: C, 78.1; H, 10.7.

Catalytic Reduction of the Keto-acid (II) from Dihydropseudosarsasapogenin.—A mixture of 1.0 g. of acid and 0.5 g. of platinum oxide catalyst in 200 cc. of absolute ethanol was shaken with hydrogen at 3 atm. for two hours. The catalyst was removed and 200 cc. of ethanol was added together with a hot solution of 8.0 g. of digitonin in 500 cc. of 85% ethanol. The digitonide which separated was decomposed with pyridine in the usual manner. The 3(β)-hydroxy acid was crystallized from acetone, m. p. 189–190°.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.9; H, 10.25. Found: C, 74.6; H, 10.3.

The fraction which did not precipitate with digitonin was crystallized from ether, m. p. 181–183°. This is the 3(α)-hydroxy acid.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.9; H, 10.25. Found: C, 74.6; H, 10.3.

The **acetate** was prepared by treatment with acetic anhydride in pyridine in the usual manner. It was crystallized from methanol, m. p. 197–199°.

Anal. Calcd. for $C_{29}H_{46}O_5$: C, 73.4; H, 9.8. Found: C, 73.5; H, 9.6.

Catalytic Reduction of the Keto-acid (VIII) from Dihydropseudotigogenin.—The keto acid was reduced by the procedure given for the reduction of the acid from dihydropseudosarsasapogenin except that the digitonin separation was unnecessary. The product was crystallized from methanol, m. p. 240–241°.

It was quite insoluble in acetone, ethyl acetate and chloroform.

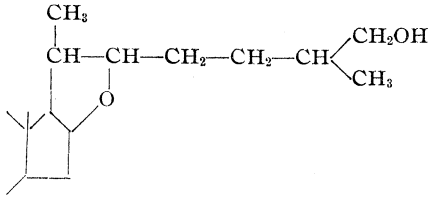
Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.9; H, 10.25. Found: C, 75.1; H, 10.3.

The **acetate** was prepared by refluxing with acetic anhydride. It was recrystallized from ethyl acetate, m. p. 179–181°.

Anal. Calcd. for $C_{29}H_{46}O_5$: C, 73.4; H, 9.8. Found: C, 73.7; H, 9.7.

Summary

Evidence has been presented indicating that the side chain in the dihydropseudosapogenins has the structure



STATE COLLEGE, PENNA. RECEIVED APRIL 22, 1942

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY OF THE NATIONAL RESEARCH COUNCIL]

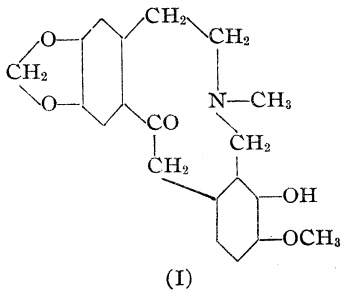
The Alkaloids of Papaveraceous Plants. XXXIV. *Hunnemannia fumariaefolia Sweet* and the Constitution of a New Alkaloid, Hunnemanine

BY RICHARD H. F. MANSKE, LÉO MARION AND ARCHIE E. LEDINGHAM

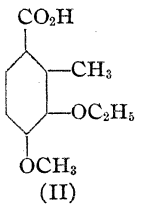
Hunnemannia is a mono-typic genus being represented only by *H. fumariaefolia Sweet*, the so-called tulip poppy. It is native to Mexico and has been successfully introduced into more temperate regions as an ornamental.

There seems to be no record of this plant having been chemically examined. Such an examination seemed to the authors particularly interesting on account of the lone position which the plant occupies in the *Papaveraceae* family.

Four alkaloids have been isolated, two of which, namely protopine and allo-cryptopine, are well-known constituents of many plants of the same family. The remaining two alkaloids appear to be new. One of these, *alkaloid F58*, is non-phenolic and is best represented by $C_{22}H_{21}O_5N$ containing two methoxyl groups. The amount available was too small for further immediate investigation. The second of the new alkaloids (F59) is now termed *hunnemanine* and its constitution has been determined. It is empirically represented by $C_{20}H_{21}O_5N$. It is a mono-hydric phenol, one methoxyl group is present, and on methylation with diazomethane it yields allo-cryptopine ($C_{21}H_{23}O_5N$). This simple observation establishes that hunnemanine is one of the two possible O-desmethyl-allo-cryptopines. That the free hydroxyl is in the sterically hindered 9-position in analogy with many other phenolic alkaloids was highly probable. On this assumption formula (I) has been adopted as a basis for degradative and subsequent synthetic experiments. The degradation of alkaloids of this nuclear type as represented by cryptopine is readily carried out by the procedure first detailed by Perkin,[1] but the yield of the final products is not always good. The O-ethyl ether of hunnemanine on subjection to the necessary series of reactions yielded two fragments. Since the isolation of one of these, 4,5-methylenedioxy-2-β-dimethylaminoethylbenzaldehyde, could give us no new information, it was not exhaustively purified. The second fragment was isolated in a pure condition and shown by a synthesis to be 2-methyl-3-ethoxy-4-methoxybenzoic acid (11), thus proving formula (I) for hunnemanine. It is pertinent to point out that this alkaloid is the first known example of a phenolic base of the protopine type. The synthesis of the above acid was effected by a very simple route but not until a variety of previous attempts had failed. Oxidation of the mono-basic acid to the known 3-ethoxy-4-methoxyphthalic acid was not practical on account of the small amount available.



(I)



(II)

The successful synthesis of the above acid was readily achieved by oxidizing the corresponding aldehyde. The synthesis of the aldehyde from 2-ethoxy-3-methoxytoluene proceeded smoothly and with good yield by Gattermann's method. It is worthy of note that in this synthesis the sole product was the desired one since the acid obtained from the crude aldehyde was pure even without recrystallization. It is to be observed in this connection that the nitration of 2,3-dimethoxybenzaldehyde gives the 6-nitro-derivative[2] almost exclusively, whereas the nitration of 2-ethoxy-3-methoxybenzaldehyde yields for the most part the 5-nitro-compound.[3] It is, of course, obvious that the synthetic and degradative acids cannot be identical unless the assigned formula is the correct one. The 2-ethoxy-3-methoxytoluene was prepared by the Clemmensen reduction of the corresponding aldehyde which was obtained by ethylating 2-hydroxy-3-methoxybenzaldehyde.

For the last the authors are greatly indebted to the Monsanto Chemical Co., St. Louis, Missouri, who generously donated a liberal amount of it.

Experimental

Isolation of the Alkaloids.—The plant material for this investigation was grown in part in a local garden. The

(1) Perkin, *J. Chem. Soc.*, **109**, 815 (1916).

(2) Perkin and Robinson, *ibid.*, **105**, 2389 (1914).

(3) Davies and Rubenstein, *ibid.*, **123**, 2839 (1923).

greater portion, however, was kindly supplied by Bodger Seeds, Limited, El Monte, California, and special thanks are due to Miss Elizabeth M. Bodger of this firm who personally supervised the collecting and drying of the material. There was available a total of 12 kg. which included the roots. Nearly all of the material was collected during the early flowering stages of the plant. In the course of the chemical examination of the plant it was observed that there were present practically no alkaloids whose hydrochlorides were extractable from aqueous solution by means of chloroform. The procedure devised by one of us[4] yielded only two fractions, namely, -BS, non-phenolic bases (protopine, allo-cryptopine, and alkaloid F58) and BSE + EES, phenolic bases (hunnemanine).

Protopine and Allo-cryptopine.—The dried base, representing fraction BS, was boiled with methanol and the protopine which then crystallized was filtered off. After recrystallizing it from chloroform–methanol the protopine was obtained in brilliant colorless crystals melting at 209–210°[5] either alone or in admixture with an authentic specimen. Including a small amount obtained from the mother liquor the total yield of protopine was 0.14%.

The methanolic filtrate from the protopine was filtered with the aid of charcoal and evaporated somewhat. The crystals which then separated consisted primarily of allo-cryptopine with some protopine. The mixture was dissolved in dilute hydrochloric acid and the sparingly soluble protopine hydrochloride which then separated was filtered off. The filtrate was basified and the separated base recrystallized from chloroform–methanol. It then melted at 160° either alone or in admixture with an authentic specimen of allo-cryptopine. The yield was 0.03%.

Alkaloid F58.—The final mother liquor from which no more protopine or allo-cryptopine could be crystallized was acidified with hydrochloric acid, boiled to expel the solvents, filtered, basified with ammonia, and the liberated base extracted with ether. The washed extract was evaporated to dryness and the resin treated with an excess of oxalic acid in methanol. The sparingly soluble oxalate which then separated in orange colored plates was converted to free base by shaking with ammonia in the presence of ether. The washed ether solution left a colorless resinous base which crystallized in contact with methanol. The washed base (alkaloid F58) was recrystallized from chloroform–methanol and then consisted of aggregates of colorless fine prisms melting at 174°. It dissolved in sulfuric acid to yield an orange colored solution which changed to a dirty pink color only on heating to a high temperature. Found: C, 69.48, 69.27; H, 5.35, 5.23; N, 3.50, 3.77; OCH_3, 18.39, 18.37. Calcd. for $C_{22}H_{21}O_5N$: C, 69.65; H, 5.54; N, 3.69; OCH_3, 16.36.

Hunnemanine.—The phenolic base (BSE) precipitated by means of carbon dioxide from its solution in an excess of aqueous sodium hydroxide was dried and boiled with methanol. The cooled mixture was filtered and the crystalline solid recrystallized first from chloroform–methanol and then from a large volume of boiling methanol. Hunnemanine was thus obtained in large colorless rectangular prisms which melted at 209°. A trace of the alkaloid dissolved in sulfuric acid yielded an intensely lilac colored solution which on gentle heating changed to an olive color. Found: C, 67.95, 67.63; H, 5.93, 5.76; N, 3.51, 3.91; OCH_3, 9.19, 9.27. Calcd. for $C_{20}H_{21}O_5N$: C, 67.60; H, 5.92; N, 3.94; OCH_3, 8.73. The total yield of hunnemanine was 0.18%.

A small portion of the base was methylated by treating its suspension in methanol with an ethereal solution of diazomethane. The alkaloid dissolved as the brisk evolution of nitrogen proceeded. The non-phenolic product isolated in the usual way was recrystallized from hot methanol and then melted sharply at 160°. In admixture with allo-cryptopine it melted at the same temperature. Calcd. for $C_{21}H_{23}O_5N$: OCH_3, 16.62. Found: OCH_3, 17.46, 17.53.

Hunnemanine-O-ethyl Ether.—The ethylation of hunnemanine suspended in absolute ethanol was carried out with an ethereal solution of diazo-ethane. The yield was not quite quantitative but no difficulty was experienced in obtaining the non-phenolic base in a pure condition. When recrystallized from hot methanol it was obtained in colorless stout prisms which melted sharply at 168°. From 5 g. of the phenolic base there was obtained 4.3 g. of the ethyl ether. Calcd. for $C_{22}H_{25}O_5N$; $OCH_3 + OC_2H_5$ as OCH_3, 16.19. Found: OCH_3, 16.72, 16.82.

Hunnemanine-O-ethyl Ether Methosulfate.—Hunnemanine-O-ethyl ether was added to freshly distilled methyl sulfate and the mixture kept on the steam-bath for thirty minutes. The mixture was then cautiously heated over a small flame until the few remaining crystals had dissolved. The resulting thick, dark sirup was dissolved in a little boiling ethyl acetate, from which solution the methosulfate crystallized in colorless needles melting at 196°.

Tetrahydromethylhunnemanine-O-ethyl Ether.—The methosulfate dissolved in 5% sulfuric acid was reduced with sodium amalgam according to the procedure of Perkin.[1] The product consisted of a thick, light-brown, oily base.

Anhydrotetrahydromethylhunnemanine-O-ethyl Ether.—The oily tetrahydromethylhunnemanine-O-ethyl ether was refluxed for thirty minutes with acetyl chloride. After removal of the excess acetyl chloride, the oily residue was dissolved in hot water, the solution filtered, basified with strong sodium hydroxide and the precipitated base extracted with ether. The ether extract was washed with water and dried over anhydrous potassium carbonate. The oily residue from this solution did not crystallize and failed to yield a crystalline picrolonate.

Oxidation of Anhydrotetrahydromethylhunnemanine-O-ethyl Ether.—Anhydrotetrahydromethylhunnemanine-O-ethyl ether (1.29 g.) was dissolved in purified acetone (100 cc.) and the stirred and cooled (3°) solution treated with finely ground potassium permanganate (1.3 g.) added in small portions. When the oxidation had been completed, the mixture was filtered and the solid washed with acetone. The combined filtrate and washings were distilled under diminished pressure and the viscous residue dissolved in ether. The filtered ether solution was extracted repeatedly with small quantities of dilute acid (1 vol. hydrochloric acid: 3 vol. water), washed with water and extracted with two portions of dilute sodium hydroxide. The combined sodium hydroxide solutions were acidified with hydrochloric acid and the precipitated acid collected in ether.

(4) Manske, *Can. J. Research*, **8**, 210 (1933).

(5) All melting points are corrected.

The ether solution was washed with water, dried over sodium chloride and distilled. The crystalline residue after repeated recrystallization from ether–hexane was finally obtained as short white needles melting at 175°. Calcd. for $C_{11}H_{14}O_4$: C, 62.86; H, 6.67. Found: C, 62.88; H, 6.88. A further quantity of the same acid was obtained by digesting with hot water the manganese dioxide sludge which had been filtered out. The aqueous solution was evaporated down to a volume of *ca.* 25 cc. and acidified with hydrochloric acid. The chalky precipitate was filtered, dissolved in 5% sodium bicarbonate, the solution filtered and again acidified with hydrochloric acid. The precipitate was dissolved in dilute ammonia and boiled thirty minutes with a little barium chloride. The insoluble barium salt which precipitated was filtered out and the filtrate acidified and extracted with ether. The ether solution, after washing and drying, yielded an acid melting at 168° which after several recrystallizations from ether–hexane melted at 175° and was identical with that obtained as above. A mixture of this acid with a synthetic specimen of 2-methyl-3-ethoxy-4-methoxy-benzoic acid melted at 176–177°.

2-Ethoxy-3-methoxy-toluene.—A mixture of 2-ethoxy-3-methoxybenzaldehyde (50 g.), amalgamated zinc (100 g.), toluene (100 cc.) and hydrochloric acid (275 cc.) was boiled under reflux for twenty-four hours. The separated toluene solution was washed with successive portions of aqueous sodium bisulfite, the solvent distilled off, and the residue fractionated *in vacuo*. The portion boiling at 72–74° (4 mm.) weighed 20 g. and consisted substantially of 2-ethoxy-3-methoxytoluene. Calcd. for $C_{10}H_{14}O_3$: C, 72.29; H, 8.43. Found: C, 71.56; H, 8.82.

2-Methyl-3-ethoxy-4-methoxybenzaldehyde.—Aluminum chloride (25 g.) was added to a cooled solution of 2-ethoxy-3-methoxytoluene (17 g.) in dry benzene (50 cc.). To the stirred and cooled mixture was then added anhydrous hydrogen cyanide (17 g.), and a stream of dry hydrogen chloride passed in to saturation. The temperature was then raised to 40° and maintained there for two hours. After remaining at room temperature overnight, the mixture was decomposed with ice, and the aldehyde distilled in a current of steam. It was extracted from the distillate and fractionated *in vacuo*. As thus obtained 2-methyl-3-ethoxy-4-methoxybenzaldehyde was a colorless oil boiling at 121–123° (3 mm.). On cooling it formed a mass of colorless needles which when pressed out on filter paper melted at 24°. The yield was 14 g. Calcd. for $C_{11}H_{14}O_3$: C, 68.04; H, 7.21. Found: C, 68.35; H, 7.65.

The *oxime* was prepared in aqueous methanol and recrystallized from ether–hexane. It consisted of colorless pearly plates melting at 88°. Calcd. for $C_{11}H_{15}O_3N$: C, 63.15; H, 7.18; N, 6.70. Found: C, 63.36; H, 7.05; N, 7.09.

2-Methyl-3-ethoxy-4-methoxybenzoic Acid.—A suspension of the aldehyde in warm water was vigorously stirred and treated with a saturated solution of potassium permanganate until the color was permanent for five minutes. The solution was then boiled, filtered, decolorized with a little sulfur dioxide, and while still warm acidified with hydrochloric acid. The filtered, washed, and dried acid melted at 176°. It was recrystallized from hot acetone, in which it is only moderately soluble. The large brilliant highly refracting plates thus obtained melted sharply at 177°. The yield was virtually quantitative. Calcd. for $C_{11}H_{14}O_4$: C, 62.86; H, 6.67. Found: C, 63.02; H, 6.83.

Summary

Hunnemannia fumariaefolia Sweet has yielded four alkaloids, two of which, protopine and allocryptopine, are well known. A third, *alkaloid F58*, represented as $C_{22}H_{21}O_5N$, was obtained in only minute amounts. The main alkaloid now termed hunnemanine, $C_{20}H_{21}O_5N$, is phenolic, contains one methoxyl group, and on methylation yielded allo-cryptopine. O-Ethylation gave a non-phenolic base which on appropriate degradation yielded 2-methyl-3-ethoxy-4-methoxybenzoic acid, identical with a specimen synthesized for purposes of comparison. Hunnemanine is therefore 9-desmethyl-allo-cryptopine. It is the first alkaloid of the protopine type known to contain a free hydroxyl group.

OTTAWA, CANADA RECEIVED MARCH 30, 1942

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, UNIVERSITY OF MISSOURI]

Orientation Effects in the Alkylation of *m*-Xylene by Various Procedures and Reagents

BY DOROTHY NIGHTINGALE, H. D. RADFORD AND O. G. SHANHOLTZER

Investigations of the alkylation of substituted aromatic hydrocarbons by an alcohol and 70–85% sulfuric acid[1,2] have led to the belief, but apparently without definite proof in some cases, that the normal orientation effects of alkyl groups are always exerted when this procedure is used. Thus, *i*-propylbenzene has been reported to yield 1,2,4-tri*iso*propylbenzene, and the dialkylbenzenes obtained from benzene or toluene have been reported to be the *o*- and *p*-isomers. In their investigation of the action of aluminum chloride on the 1,3-dimethyl-4-butylbenzenes, Nightingale and Smith[3] assumed that the products obtained from *m*-xylene and *t*-butyl alcohol by the sulfuric acid procedure had the 1,3,4 orientation, although it was observed that the trinitro derivatives of the 1,3-dimethyl-4-*t*-butyl- and -5-*t*-butylbenzene melted at 112 and 113°, respectively, and gave only small depressions in melting points when mixed.

During further work with these compounds, the similarity in melting points and the small depressions in the mixed melting points of other derivatives of the two hydrocarbons led to the conviction either that the 1,3,4-hydrocarbon did not have this orientation, but was mainly the 1,3,5-isomer, or that a rearrangement of the 1,3,4- to the 1,3,5-isomer occurred during the preparation of the derivatives. In order to decide between these alternatives we have reinvestigated the nature of the products obtained when *m*-xylene is alkylated by *t*-butyl alcohol and 85% sulfuric acid, and it has been found that the previous work[3] was in error in that the trialkylbenzene from this reaction is a mixture consisting of approximately two parts of 1,3-dimethyl-5-*t*-butylbenzene and one part of the 1,3,4-isomer.

The study has been extended to include the trialkylbenzenes formed from *m*-xylene by alkylation with other butyl compounds in the presence of boron trifluoride or ferric chloride as catalysts. The results showed that the abnormally oriented trialkylbenzene (1,3,5) was obtained not only from 75 and 85% sulfuric acid, but with boron trifluoride and with ferric chloride, when *t*-butyl compounds were used. The abnormally oriented product with boron fluoride was unexpected, for 1,2,4-tri*iso*propylbenzene is reported from benzene, *i*-propyl alcohol and this catalyst.[4] The normally oriented trialkylbenzene (1,3,4) was obtained from *m*-xylene, *s*-butyl alcohol and either 85% sulfuric acid or boron trifluoride as the catalyst.

The structures of the hydrocarbons were established by oxidation rather than by conversion to the trinitro derivatives in order to avoid any chance that a rearrangement might occur during the preparation of the derivatives. The oxidation product of 1,3-dimethyl-5-*t*-butylbenzene (Friedel–Crafts) proved to be 5-*t*-butyl-isophthalic acid, m. p. 343°, rather than trimesic acid, and the trialkylbenzene from *m*-xylene, *t*-butyl alcohol and 85% sulfuric acid yielded a mixture of 4-*t*-butyl-isophthalic acid and 5-*t*-butyl isophthalic acid. The 4-*t*-butylisophthalic acid is soluble in the aqueous pyridine solution in which the oxidation was carried out, whereas the 5-isomer is only slightly soluble, and this fact made it possible to separate the mixture of acids.

To establish the identity of the 5-*t*-butylisophthalic acid, the compound was synthesized by the method of Doebner[5] from pyruvic acid, trimethylacetaldehyde and barium hydroxide. The acid so obtained melted at 343° and did not depress the melting point of the acid formed by oxidation.

The 1,3-dimethyl-4-*t*-butylbenzene was synthesized by coupling the Grignard reagent from 1,3-dimethyl-4-iodobenzene with *t*-butyl chloride.[6] Oxidation of this hydrocarbon with potassium permanganate in aqueous pyridine yielded 4-*t*-butyl-isophthalic acid.

The stability of the tertiary radical toward potassium permanganate is surprising. In one experiment, more than enough permanganate was used to oxidize the *t*-butyl group and the two methyl groups of the 1,3,5-hydrocarbon and the mixture was refluxed gently. The product was

(1) Meyer and Bernhauer, *Monatsh.*, **53**, 721 (1929).
(2) Kirrmann and Graves, *Bull. soc. chim.*, (5) **1**, 1494 (1934).
(3) Nightingale and Smith, THIS JOURNAL, **61**, 101 (1939).
(4) McKenna and Sowa, *ibid.*, **59**, 470 (1937).
(5) Doebner, *Ber.*, **24**, 1748 (1891).
(6) Smith and Perry, THIS JOURNAL, **61**, 1411 (1939).

nearly pure 5-*t*-butylisophthalic acid in almost quantitative yield. Oxidation of *p*-*t*-butyltoluene with excess permanganate likewise yielded only *p*-*t*-butylbenzoic acid.

These results do not invalidate the work of Nightingale and Smith,[3] for both 1,3-dimethyl-4-*t*-butyl- and 4-*s*-butylbenzene synthesized through the Grignard route are converted to the 5-*t*-butyl isomer by the action of aluminum chloride.

The abnormal orientation of these trialkylbenzenes made it desirable to verify the structure of the trialkylbenzene from *m*-xylene, *s*-butyl alcohol and 85% sulfuric acid or boron trifluoride. The 1,3-dimethyl-4-*s*-butylbenzene was synthesized through 2,4-dimethylacetophenone and ethylmagnesium bromide. The carbinol was dehydrated to the olefin, which was reduced with hydrogen and Raney nickel under pressure. The trialkylbenzenes were identical. This hydrocarbon could be oxidized to 4-*s*-butylisophthalic acid, but the 5-*s*-butyl isomer yielded trimesic acid.

It may or may not be significant that three of the condensing agents which lead to abnormally oriented trialkylbenzenes, sulfuric acid, aluminum chloride and ferric chloride, can also cleave a *t*-butyl group from the benzene ring.[7]

Results from the alkylation of *m*-xylene with *t*-amyl alcohol and either 85% sulfuric acid or boron trifluoride are not so clean-cut. Analyses and neutral equivalents of the acids obtained by oxidation of the trialkylbenzene fraction correspond to a *t*-amylisophthalic acid, as do their methyl esters. The fact that these compounds melt higher than 5-*t*-amylisophthalic acid and its methyl ester is difficult to explain. Mixtures of the acids with 5-*t*-amylisophthalic acid melt between the two, as do mixtures of the methyl esters. The reaction products from *t*-amyl alcohol are undoubtedly more complicated mixtures than in the case of the butyl compounds. By analogy with the reaction products from *t*-butyl alcohol the trialkylbenzenes should have the 1,3,5 orientation. *t*-Amylbenzene was unaffected by potassium permanganate in aqueous pyridine solution.

Oxidation of 1,3-dimethyl-5-*t*-amylbenzene (Friedel–Crafts) yielded 5-*t*-amylisophthalic acid, identical with 5-*t*-amylisophthalic acid synthesized by Doebner's method. Unfortunately the Grignard reagent from 1,3-dimethyl-4-iodobenzene would not couple with *t*-amyl chloride and a Fittig synthesis was likewise unsuccessful, so 4-*t*-amylisophthalic acid could not be made to complete the series.

In an effort to find solid derivatives of these alkylbenzenes which would avoid the use of nitric or sulfuric acid, the hydrocarbons were chloromethylated. The substituted benzyl chlorides were converted to the corresponding acetamides by heating with acetamide, and to the benzyl alcohols.

The reactions were useful only with 1,3-dimethyl-5-*t*-butylbenzene. The 2,4-dimethyl-6-*t* butylbenzylacetamide separated readily as a solid, and 2,4-dimethyl-6-*t*-butylbenzyl alcohol is a solid. The other amides were viscous and would not crystallize readily. The other benzyl alcohols were liquids. Careful oxidation of 2,4-dimethyl-6-*t*-butylbenzyl alcohol to the corresponding known monocarboxylic acid[8] served to establish the location of the —CH_2Cl group as between the methyl and *t*-butyl radicals rather than between the two methyl groups.

Experimental[9]

Most of the trialkylbenzenes were prepared by procedures previously described.[3] The preparation of 1,3-dimethyl-4-*s*-butylbenzene has been improved by increasing the amount of *s*-butyl alcohol to 100 cc., and reducing the reaction time to seven hours. The hydrocarbons were vacuum distilled through columns packed with single turn glass helices.

The diacetamino derivative of 1,3-dimethyl-4-*t*-butylbenzene, not previously described, melts at 331°.

Anal. Calcd. for $C_{16}H_{24}O_2N_2$: N, 10.14. Found: N, 10.00.

Preparation of 1,3-Dimethyl-5-*t*-butylbenzene. (a) **With Ferric Chloride as Catalyst.**—*m*-Xylene (144 g.) and anhydrous ferric chloride (12.2 g.) were placed in a 3-necked flask cooled with an ice–salt mixture and fitted with a sealed stirrer and dropping funnel. *t*-Butyl chloride (25 g.) was added at such a rate that the temperature of the reaction mixture did not rise above −4.5°. Stirring was continued an additional four hours. The reaction mixture was decomposed as for a Friedel–Crafts reaction; yield, 29.6 g.; b. p. 88° (14 mm.).

(b) **With Boron Fluoride as Catalyst.**—*m*-Xylene (106 g.) was alkylated with *t*-butyl alcohol (74 g.) and boron fluoride (41 g.) by the method of McKenna and Sowa[4] using a 3-necked conical flask. The boron fluoride was admitted into the reaction mixture during six hours. The flask was cooled with water at the beginning of the reaction. The hydrocarbon layer was separated, washed and dried; yield, 27.5 g.; b. p. 78–79° (8 mm.).

(c) **With 75% Sulfuric Acid as Catalyst.**—The experimental conditions were those of Meyer and Bernhauer.[1]

(7) Ipatieff and Corson, THIS JOURNAL, **59**, 1417 (1937).

(8) Bauer, *Ber.*, **33**, 2562 (1900).

(9) Semimicro analyses by D. R. Smith and E. Milberger.

The *m*-xylene (184 g.) and *t*-butyl alcohol (123 g.) were placed in a 3-necked flask in a water-bath at 65–70°. A solution of concentrated sulfuric acid (1060 cc.) and water (540 cc.) was added during an hour while the reaction mixture was stirred mechanically. The hydrocarbon layer was washed, dried and distilled. The following fractions were obtained at 13 mm. after removal of *m*-xylene: (I) 24 g. up to 85°; (II) 3 g. 85–89°; (III) 8.2 g. 89–92°; (IV) 5 g. 92–97°. Fraction (III) is the trialkylbenzene.

Oxidation of 1,3-Dimethyl-5-*t*-butylbenzene.—The hydrocarbon (5 g.) from *t*-butyl chloride and aluminum chloride was dissolved in pyridine (40 cc.) and water (20 cc.) in a 3-necked flask. Finely powdered potassium permanganate (21.5 g.) was added in small portions during two hours with the temperature maintained around 80°. The mixture was heated until the purple color disappeared. The mixture was stirred mechanically during the entire period.

The manganese dioxide was separated by filtration and the filtrate acidified strongly with hydrochloric acid. The 5-*t*-butylisophthalic acid precipitated. A small amount of acid was extracted from the manganese dioxide. The combined acids (6.5 g.) were recrystallized from glacial acetic acid; m. p. 343°. Since the acid begins to sublime below the melting point, the sample was packed into the tube and the tube sealed.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.84; H, 6.30; neut. eq., 111. Found: C, 64.73; H, 6.49; neut. eq., 110.

The methyl ester was prepared with diazomethane, m. p. 97°.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.20; H, 7.20. Found: C, 67.08; H, 7.29.

Only 5-*t*-butylisophthalic acid was obtained by the oxidation of the hydrocarbons from the three alkylations described above.

Oxidation of 1,3-Dimethyl-4-*t*-butylbenzene.—A 7-g. sample of the hydrocarbon (Grignard synthesis[6]) was oxidized in aqueous pyridine solution. After separation of the manganese dioxide, most of the pyridine was distilled from the solution before acidifying; yield, 5 g.; m. p. 230°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.84; H, 6.30; neut. eq., 111. Found: C, 64.77; H, 6.39; neut. eq., 112.5.

Oxidation of the Trialkylbenzene from *m*-Xylene, *t*-Butyl Alcohol and 85% Sulfuric Acid.—The hydrocarbon (10.8 g.) was oxidized with excess permanganate. The 5-*t*-butylisophthalic acid (9.7 g.) separated when the solution was acidified after removal of the manganese dioxide. The filtrate was made basic and most of the pyridine distilled off. The solution in the distilling flask was again acidified and the 4-*t*-butylisophthalic acid (5.2 g.) separated. The purified acids melted at 343° and 230°, respectively, and did not depress the melting points of authentic samples.

Synthesis of 5-*t*-Butylisophthalic Acid.—Trimethylacetaldehyde[10] (23.7 g.), pyruvic acid (50 g.), barium hydroxide (120 g.) and 1000 cc. of water were refluxed gently for one hundred hours.[5] To free the crude 5-*t*-butylisophthalic acid from oxalic acid, the solid was suspended in a little water and potassium permanganate solution added in the cold until the purple color persisted. Hydrochloric acid was added and the manganese dioxide removed with sulfur dioxide; yield, 4.1 g.; m. p. 343°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.86; H, 6.30; neut. eq., 111. Found: C, 64.63; H, 6.54; neut. eq., 112.5.

Preparation of 1,3-Dimethyl-4-*s*-butylbenzene. (a) **Through the Grignard Reaction.**—A solution of 2,4-dimethylacetophenone (155 g.) in ether was added to the Grignard reagent from 86 g. of ethyl bromide. The complex was decomposed in the usual manner.

The crude carbinol was added to 250 g. of acetic anhydride containing ten drops of concentrated sulfuric acid. The anhydride was distilled off at a somewhat reduced pressure and the residue fractionated. The olefin distilled at 102° (1 mm.). To purify the olefin, it was heated with sodium, vacuum distilled, and again vacuum distilled from Raney nickel.

The olefin (45 g.) was reduced in methyl alcohol solution with Raney nickel at 80–90° (2000 lb.). After removal of the solvent and catalyst, the hydrocarbon was heated with sodium and fractionated; yield, 38 g.; b. p. 82° (1 mm.).

The diacetamino derivative of this hydrocarbon melted at 270° and did not depress the melting point of diacetamino-1,3-dimethyl-4-*s*-butylbenzene prepared by the sulfuric acid procedure.

(b) **With Boron Fluoride as the Catalyst.**—*m*-Xylene (106 g.) was alkylated with *s*-butyl alcohol and boron fluoride (49 g.); yield, 30 g.; b. p. 91–93° (13 mm.).

The diacetamino derivative of this hydrocarbon melted at 270° and did not depress the melting point of the derivative of the hydrocarbon from the Grignard reaction. Careful oxidation of 1,3-dimethyl-4-*s*-butylbenzene (10 g.) at 70° yielded 2 g. of 4-*s*-butylisophthalic acid; m. p. 188°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.86; H, 6.30; neut. eq., 111. Found: C, 64.81; H, 6.30; neut. eq., 111.7.

Synthesis of 5-*t*-Amylisophthalic Acid.—The 2,2-dimethylbutyraldehyde was prepared by adding the Grignard reagent from 425 cc. of *t*-amyl chloride to 460 cc. of methyl formate.[10] The reaction temperature was maintained at −50° to −55°; yield, 53.7 g. (26%).

A mixture of pyruvic acid (45 g.), 2,2-dimethylbutyraldehyde (24.5 g.), barium hydroxide (106 g.) and 900 cc. of water was refluxed for one hundred hours. The acid was purified as described above; yield, 7.5 g.; m. p. 307°.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.10; H, 6.78; neut. eq., 118. Found: C, 66.19; H, 6.67; neut. eq., 115.

The methyl ester melted at 81°.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.18; H, 7.20. Found: C, 68.34; H, 7.51.

Oxidation of 4 g. of 1,3-dimethyl-5-*t*-amylbenzene (Friedel–Crafts) yielded 5-*t*-amylisophthalic acid; m. p. 307°; yield, 5 g.

The methyl ester melted at 78°.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.10; H, 6.78; neut. eq., 118. Found: C, 66.10; H, 7.11; neut. eq., 123.

Alkylation of *m*-Xylene with *t*-Amyl Alcohol. (a) With Boron Fluoride as Catalyst.—*m*-Xylene (200 cc.) was alkylated with *t*-amyl alcohol (200 cc.) and 30–50 g. of boron fluoride as described above. The reaction mixture was stirred for four hours. The following fractions were obtained at 16 mm. after removal of *m*-xylene: (I) 4.5

(10) Campbell, THIS JOURNAL, **59**, 1980 (1937).

TABLE I

CHLOROMETHYL DERIVATIVES AND BENZYL ALCOHOLS

Alkylbenzene, 1,3-dimethyl-	Chloromethyl derivative[a] B. p. °C.	Mm.	C, %	H, %	Benzyl alcohol[b] B. p. °C.	Mm.	C, %	H, %
5-*s*-Butyl	115	1	74.25	9.36	158–162	14	81.20	10.15
5-*t*-Butyl	111–116	6	74.14	9.59	m. p. 99		81.18	10.12
4-*n*-Butyl	103–108	1	74.66	9.40	135–140		81.13	10.10
4-*s*-Butyl	100–106	4	74.25	9.32	145–150	10	81.16	10.40

[a] Calcd. for $C_{13}H_{19}Cl$: C, 74.28; H, 9.04. [b] Calcd. for $C_{13}H_{20}O$: C, 81.25; H, 10.41.

g. 91–94°; (II) 15 g. 94–96°; (III) 15 g. 96–104°; (IV) 29 g. 100–135°; residue 15 g.

Oxidation of 4 g. of the trialkylbenzene (II) yielded 6 g. of a dicarboxylic acid, m. p. 330°, corresponding to a *t*-amylisophthalic acid.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.10; H, 6.78; neut. eq., 118. Found: C, 65.85; H, 6.99; neut. eq., 113.

(b) **With 85% Sulfuric Acid as Catalyst.**—This alkylation was carried out as previously described.[11] The dibenzamino derivative of the trialkylbenzene from this reaction melted at 305°. A mixture of this derivative and the dibenzamino derivative (m. p. 303°) of 1,3-dimethyl-5-*t*-amylbenzene (Friedel–Crafts) melted at 298°.

Oxidation of this hydrocarbon yielded an acid melting at 320–325°, which, mixed with the acid (m. p. 330°) from the trialkylbenzene prepared with boron fluoride, melted at 319°. The neutral equivalent was 116.

The method of oxidation of alkylbenzenes such as durene containing only methyl radicals or methyl radicals and *t*-alkyl radicals with potassium permanganate in aqueous pyridine solution has been generally successful with other compounds such as 4-methyl-2′-methoxydiphenyl ether. Yields are much higher than in aqueous solution. Bumping is avoided, for it is not necessary to boil the mixture and in some cases the temperature must be kept at 80° or lower. *t*-Butylbenzene and *t*-amylbenzene were unaffected even after long heating with excess permanganate. The ethylbenzenes gave indefinite oxidation products.

Chloromethyl Compounds and Derivatives.—The hydrocarbons were chloromethylated by the method of v. Braun and Nelles.[12] Boiling points and analytical data are summarized in Table I. Derivatives were prepared from 2,4-dimethyl-6-*t*-butylbenzyl chloride as follows:

The acetate was prepared by refluxing 4.2 g. of the chloride, 2.5 cc. of acetic anhydride, 7.5 cc. of acetic acid and 2.5 g. of potassium acetate. The mixture was poured onto ice, washed, and dried over sodium sulfate. The ether was distilled leaving the crude ester.

The crude ester (2.5 g.) was refluxed three hours with potassium hydroxide (6.6 g.) in alcohol (25 cc.) and water (35 cc.). The oily top layer solidified on cooling. The carbinol was separated by filtration and recrystallized from 28–30° petroleum ether; yield, 2.25 g.; m. p. 99°.

(11) Nightingale and Shanholtzer, *J. Org. Chem.*, **6**, 6 (1942).
(12) v. Braun and Nelles, *Ber.*, **67**, 1094 (1934).

The carbinol was oxidized to the corresponding monocarboxylic acid with potassium permanganate at 0 to 20°. The 2,4-dimethyl-6-*t*-butylbenzoic acid melted at 168°, the recorded value.[8]

2,4-Dimethyl-6-*t*-butylbenzylacetamide was prepared by heating a mixture of the chloride (2.1 g.) and acetamide (1.2 g.) in an oil-bath at 210° for thirty-five minutes. The solid was boiled with water to remove acetamide and recrystallized from a mixture of chloroform and petroleum ether; yield, 2.2 g.; m. p. 197°.

Anal. Calcd. for $C_{15}H_{23}NO$: N, 6.00. Found: N, 6.25.

Nitrations.—All efforts in this Laboratory to prepare the trinitro derivatives, by the use of the nitrating mixture previously described,[3] have been fruitless. A nitrating mixture in the ratio of 15 g. of nitric acid sp. gr. 1.5 and 30 g. of 15% fuming sulfuric acid has been satisfactory, although this mixture is not as smooth a nitrating agent as the mixture originally used. We can give no explanation for this difference.

Summary

Abnormally oriented trialkylbenzenes (1,3,5 rather than 1,3,4) are formed when *m*-xylene is alkylated with *t*-butyl alcohol in the presence of 75–85% sulfuric acid or boron trifluoride, and with *t*-butyl chloride and anhydrous ferric chloride as the catalyst.

The normally oriented trialkylbenzene (1,3,4) is formed when *m*-xylene is alkylated with *s*-butyl alcohol and either 85% sulfuric acid or boron trifluoride.

Abnormally oriented trialkylbenzenes are formed from *m*-xylene and *t*-amyl alcohol and *t*-amyl chloride under the same conditions as for the *t*-butyl compounds.

The 1,3-dimethyl-4-*t*-butyl, 5-*t*-butyl and 5-*t*-amylbenzenes can be oxidized in aqueous pyridine solution to the corresponding *t*-butyl and *t*-amyl isophthalic acids.

COLUMBIA, MO. RECEIVED FEBRUARY 10, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

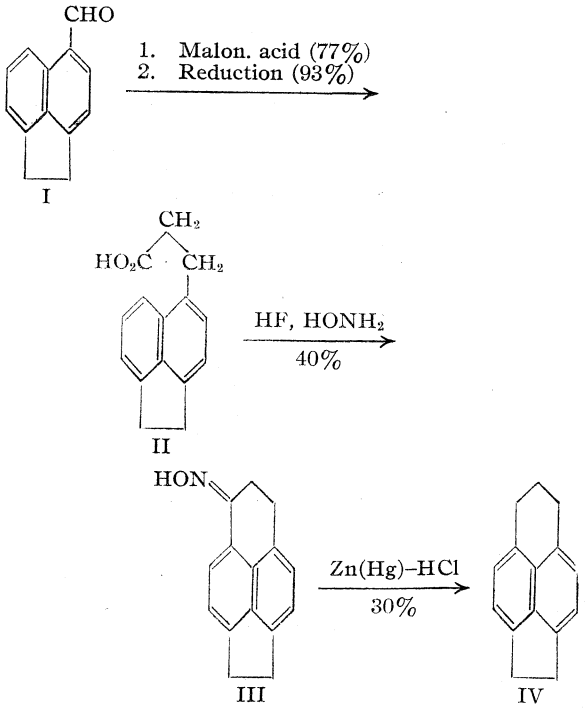
The N-Methylformanilide Synthesis of Aldehydes

BY LOUIS F. FIESER AND J. ELMORE JONES

Vilsmeier and Haack[1] discovered that secondary and tertiary aromatic amines can be converted into aldehydo derivatives by the action of N-methylformanilide and phosphorus oxychloride, a reaction reminiscent of the Bischler–Napieralski synthesis of isoquinolines. In a series of patents, Kalischer, Scheyer and Keller[2] reported that the reaction is applicable to certain phenol ethers and aromatic hydrocarbons, and these claims were verified by Wood and Bost[3] to the extent of noting that β-naphthol ethyl ether and anthracene can be formylated by the method described, and detailed procedures for conducting these reactions have subsequently been published.[4]

Following the observations of Vollmann, *et al.*,[5] that pyrene-3-aldehyde can be obtained in excellent yield by the methylformanilide method, the reaction was applied in this Laboratory to a few carcinogenic and related hydrocarbons. With the use of *o*-dichlorobenzene as the solvent,[5] 3,4-benzpyrene was found to react[6] with the same degree of readiness as pyrene[5] and anthracene[4,7] and to afford the 5-aldehyde in 90% yield; 1,2-benzanthracene was converted into the 10-derivative somewhat less smoothly[7] (64%), and 1,2,5,6-dibenzanthracene failed to react.[7] In exploring other cases, we have found the reaction to be less generally applicable to aromatic hydrocarbons than claimed in the patents.[2] No trace of aldehyde could be obtained from hydrindene, α-methylnaphthalene, phenanthrene, or chrysene in condensations conducted at temperatures from 20 to 150°, and the solid hydrocarbons were recovered in good yield. 9-Methylanthracene reacted satisfactorily without added solvent, since it melts at the reaction temperature, and gave the 10-aldehyde. Acenaphthene and perinaphthane possess adequate nuclear reactivity but are highly sensitive to the action of phosphorus oxychloride and yielded only tars when condensed at 95 and 25°, respectively.

In the condensation with acenaphthene a satisfactory conversion was accomplished by controlling the temperature to 25° and allowing a reaction period of six days. The product was purified effectively if slowly by steam distillation and obtained in 85% yield. It melted at 105–107° and was identified as 3-acenaphthaldehyde (I) by oxidation to the corresponding acid.[8] Hinkel, Ayling and Beynon[9] obtained a lower melting product (87°) by the Gattermann synthesis, but the constants for the oxime and semicarbazone are comparable. 3-Acenaphthaldehyde was converted to the corresponding alcohol by hydrogenation in the presence of Adams catalyst and ferrous chloride, and it yielded 3-methylacenaphthene when heated in an autoclave with hydrazine hydrate at 200°, according to Vollmann, *et al.*[5] The aldehyde was also utilized for the synthesis of the tetracyclic hydrocarbon IV.



Condensation with malonic acid and reduction

(1) Vilsmeier and Haack, *Ber.*, **60**, 119 (1927).

(2) Kalischer, Scheyer and Keller (I. G. Farbenind. A.-G.), German Patents 514,415 (1930) and 519,444 (1931); French Patent 648,069 (1928); U. S. Patent 1,807,693 (1931) [*Chem. Zentr.*, **100**, I, 2528 (1929); **102**, II, 3394 (1931)].

(3) Wood and Bost, THIS JOURNAL, **59**, 1721 (1937).

(4) Wood and Bost (2-ethoxy-1-naphthaldehyde), Fieser, Hartwell and J. E. Jones (9-anthraldehyde), "Organic Syntheses," **20**, 11 (1940).

(5) Vollmann, Becker, Corell and Streeck, *Ann.*, **531**, 1 (1937).

(6) Fieser and Hershberg, THIS JOURNAL, **60**, 2542 (1938).

(7) Fieser and Hartwell, *ibid.*, **60**, 2555 (1938).

(8) Fieser and Hershberg, *ibid.*, **62**, 49 (1940).

(9) Hinkel, Ayling and Beynon, *J. Chem. Soc.*, 339 (1936).

either catalytically or with sodium amalgam afforded the propionic acid II, and cyclization with hydrogen fluoride gave a tarry product from which the ketone was best isolated in the form of the oxime (III). Under the conditions of the Clemmensen reaction the oxime suffered hydrolysis and the ketone was reduced. The point of ring closure was established by oxidation of the ketone to the known naphthalene-1,4,5,8-tetracarboxylic acid. The hydrocarbon obtained as the end-product of the synthesis (m. p. 121.4–122°) can thus be assigned the structure of 3,4-aceperinaphthane (IV).

3-Methylacenaphthene and 3-methylpyrene were found to react smoothly with N-methylformanilide, but no satisfactory methods were found for separating the resulting mixtures of isomers.

Experimental Part[10]

9-Methyl-10-anthraldehyde.—A mixture of 9-methylanthracene[7] (m. p. 77.9–78.4°), 2.7 g. of N-methylformanilide,[11] and 2.7 g. of phosphorus oxychloride was heated with stirring on the steam-bath under protection from moisture for forty-five minutes, during which time the hydrocarbon dissolved. The cooled mixture was treated with 5.6 g. of crystalline sodium acetate in 50 cc. of water and stirred for a few minutes to decompose the excess oxychloride and any intermediate complex. The collected solid product on crystallization from acetic acid gave 1.84 g. (84%) of orange needles; m. p. 170–171.4°. After three recrystallizations from benzene–ligroin the substance melted at 171.9–172.6°.

Anal. Calcd. for $C_{16}H_{12}O$: C, 87.25; H, 5.49. Found: C, 87.34; H, 5.61.

Oxidation of the aldehyde with chromic oxide in acetic acid gave anthraquinone (mixed m. p.) in 86% yield.

The **oxime** was obtained from the aldehyde with aqueous hydroxylamine hydrochloride and alkali, with enough ethanol to effect solution; after heating at the boiling point for ten minutes, the oxime separated in deep yellow plates; m. p. 210°, dec.; (94% yield).

Anal. Calcd. for $C_{16}H_{13}ON$: C, 81.68; H, 5.57. Found: C, 81.52; H, 5.60.

The **hydrazone** was prepared by adding 0.5 g. of hydrazine hydrate to a solution of 0.5 g. of the aldehyde in 70 cc. of hot alcohol, boiling the solution for ten minutes, and adding water to saturation; on cooling 0.37 g. (69%) of orange needles separated; m. p. 175.1–175.8°. A mixture with the aldehyde showed a 10°-depression. The hydrazone is stable in the solid state but decomposes on attempted crystallization.

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02. Found: C, 82.26; H, 6.29.

A mixture of 0.25 g. of the hydrazone with a solution of 0.05 g. of sodium in 16 cc. of absolute ethanol was shaken in a sealed tube until uniform and heated at 200–210° for twenty-four hours. The product was collected after dilution with water and neutralization with acetic acid and crystallized from ethanol, giving 0.17 g. (74%) of light yellow plates, m. p. 183–183.7°; the picrate formed dark red needles, m. p. 175.6–176.3°. The constants agree with those reported for **9,10-dimethylanthracene** (m. p. 180–181°)[12] and its picrate (m. p. 175–176°).[13]

3-Acenaphthaldehyde (I).—A mixture of 43 g. of acenaphthene, 90 cc. of N-methylformanilide, 60 cc. of phosphorus oxychloride, and 50 cc. of *o*-dichlorobenzene was shaken thoroughly to effect solution and allowed to stand at room temperature for six days, during which time the solution turned deep red and hydrogen chloride was evolved slowly. For hydrolysis, 150 g. of crystalline sodium acetate in 150 cc. of water was added slowly to prevent violent reaction, and the mixture was subjected to efficient steam distillation. The solvent was removed in about one-half hour, and the product then distilled very slowly. Filtration of the large volume of cooled distillate afforded 40.2 g. (85%) of the aldehyde; m. p. 105–107°. The best sample, purified by repeated crystallization from dilute acetic acid and sublimation at 110° (2 mm.), formed pale greenish needles; m. p. 107.4–108°.

Anal. Calcd. for $C_{13}H_{10}O$: C, 85.69; H, 5.53. Found: C, 85.95; H, 5.50.

A sample of the oxime melted at 126.8–127.9°, and the semicarbazone melted at 247.8–248.8°; Hinkel, *et al.*,[9] recorded the constants 126.5° and 234°. For oxidation, 0.3 g. of the aldehyde in 5 cc. of dioxane was treated slowly with 8 cc. of 30% hydrogen peroxide, followed by 10% sodium hydroxide. The mixture was heated on the steam-bath for ten minutes, filtered from a trace of unreacted aldehyde (0.04 g.), and acidified. Crystallization of the voluminous precipitate from acetic acid yielded 0.22 g. (78%) of **acenaphthene-3-carboxylic acid;** m. p. 219–221° (no depression with an authentic sample).[8]

3-Hydroxymethylacenaphthene.—Hydrogenation of 1.16 g. of 3-acenaphthaldehyde in 100 cc. of absolute ethanol in the presence of 25 mg. of Adams catalyst and 10 mg. of ferrous chloride proceeded to completion in one hour, and in this time a quantity of the alcohol had crystallized in colorless needles. This was dissolved by warming, and the solution was filtered and evaporated and the product crystallized from benzene, yielding 0.86 g. (73%) of needles; m. p. 153.4–154.2°. The best sample melted at 153.8–154.8°.

Anal. Calcd. for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.52; H, 6.66.

3-Methylacenaphthene.—A mixture of 18 g. of the aldehyde and 55 g. of hydrazine hydrate was heated in an autoclave under a nitrogen pressure of 2250 lb. at 200–210° for eight hours. The well washed reaction product on sublimation at atmospheric pressure at 100° yielded 10.4 g. (63%) of colorless blades; m. p. 95.6–95.9°. The hydrocarbon crystallized from ethanol in long, colorless needles of the same melting point (20°-depression with acenaphthene). Considerable azine was formed in the reaction and was left as a residue in the sublimation.

(10) All melting points are corrected.

(11) Fieser and Jones, "Org. Synth.," **20**, 66 (1940).

(12) Gibson and Johnson, *J. Chem. Soc.*, 753 (1931); Bachmann and Chemerda, *J. Org. Chem.*, **4**, 583 (1939).

(13) Barnett and Matthews, *Ber.*, **59**, 1437 (1926).

Anal. Calcd. for $C_{13}H_{12}$: C, 92.82; H, 7.18. Found: C, 92.57; H, 7.38.

The **picrate** crystallized from alcohol in bright red needles; m. p. 163°, dec.

Anal. Calcd. for $C_{19}H_{15}O_7N_3$: C, 57.42; H, 3.81. Found: C, 57.59; H, 3.82.

3-Acenaphthalacetic Acid.—A mixture of 40.2 g. of the aldehyde, 42 g. of malonic acid, and 30 cc. of pyridine was heated on the steam-bath for eight hours and the solid product which separated was collected after cooling and dissolved in 200 cc. of 10% sodium carbonate solution by heating. The filtered solution was acidified and the pale yellow precipitate was washed thoroughly and dried for six hours at 50° (20 mm.). This material had no distinct melting point and appeared to be the **dihydrate;** yield 47.8 g. (83%).

Anal. Calcd. for $C_{15}H_{12}O_2 \cdot 2H_2O$: neut. equiv., 260. Found: 256.

Crystallization from ethanol (Norit) yielded 38.4 g. (77%) of pale yellow needles of the anhydrous acid; m. p. 250°, dec. On further purification the substance melted at 251.3–251.8° with gas evolution.

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.33; H; 5.39; neut. equiv., 224. Found: C, 80.43; H, 5.51; neut. equiv., 219.

The acid seemed to undergo some decarboxylation on melting, but attempts to isolate a pure reaction product after vacuum distillation or treatment with copper bronze were unsuccessful.

The **methyl ester,** prepared with diazomethane, distilled at 204° at 6 mm. and crystallized from ligroin in large yellow cubes; m. p. 104.4–105.4°. A second modification was obtained by rapid cooling of the melted ester; this melted at 73–74°, solidified and remelted at the higher temperature.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.34; H, 5.99.

β-3-Acenaphthylpropionic Acid (II).—A solution of 22.4 g. of the unsaturated acid in 200 cc. of 0.5 *N* sodium hydroxide was shaken with 450 g. of 2% sodium amalgam for three hours and the filtered solution was acidified. Crystallization of the precipitated material from benzene gave 21.0 g. (93%) of colorless needles, m. p. 188–190°, and repeated recrystallization raised the melting point to 191.7–192°.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.44; H, 6.46.

The **methyl ester,** prepared by hydrogenation of the unsaturated ester in ethanol (Adams catalyst) formed colorless needles from methanol; m. p. 50.7–51.7°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.92; H, 6.94.

3,4-Aceperinaphthanone-7.—A solution of 5 g. of the saturated acid in 50 g. of liquid hydrogen fluoride was poured onto ice after twenty minutes. The tarry, yellow-green product which separated solidified after about three hours and was washed thoroughly and dried at 50° (20 mm.) for three hours. Extraction with ligroin from a residual green tar and clarification with Norit gave 2.5 g. (54%) of clusters of yellow plates; m. p. 92–97°. Further purification was best accomplished through the oxime (III), which was prepared by treating a solution of the crude ketone in ethanol with the filtrate from a mixture of 13 g. of hydroxylamine hydrochloride and 14 g. of sodium carbonate which had been ground with 50 cc. of ethanol. After standing for several hours the mixture was heated to boiling, the separated solid was brought into solution with more solvent, and the solution was clarified with Norit and allowed to cool. Repeated crystallizations of the material which separated afforded 1.9 g. (40%) of colorless needles, m. p. 245–246°, dec., with darkening at 225° (even in an evacuated capillary).

Anal. Calcd. for $C_{15}H_{13}ON$: C, 80.69; H, 5.87. Found: C, 80.93; H, 5.98.

Steam distillation of a mixture of the oxime and dilute sulfuric acid yielded in the distillate 1.36 g. of the ketone (77% from the oxime, 31% from the acid). The substance crystallized from ligroin in clusters of yellow plates; m. p. 102.6–103.4°. The ketone darkened on exposure to sunlight.

Anal. Calcd. for $C_{15}H_{12}O$: C, 86.51; H, 5.80. Found: C, 86.59; H, 5.79.

The **semicarbazone** separated from a boiling solution of the components in ethanol in the form of microcrystals which turned green when introduced into a bath at 260° and melted at 268° (evacuated capillary). The substance was very sparingly soluble in the usual solvents.

Anal. Calcd. for $C_{16}H_{15}ON_3$: C, 72.43; H, 5.70. Found: C, 72.54; H, 5.86.

Oxidation of the ketone was accomplished by gradually adding 10 g. of chromic oxide in 20 cc. of 50% acetic acid to 1.5 g. of the ketone in 10 cc. of acetic acid. After the initial reaction had subsided the solution was refluxed for one hour and poured into water. The mixture was boiled to coagulate the dark brown solid, and this crude product was then dissolved in 20 cc. of 10% sodium hydroxide and refluxed with 3 g. of potassium permanganate for three hours. The mixture was poured into 100 cc. of water containing 20 cc. of concentrated sulfuric acid, sodium bisulfite was added until the manganese dioxide was dissolved, and the solution was evaporated to a volume of 75 cc. The gray product which separated was sublimed at 320° (3 mm.) and yielded 0.15 g. (7.7%) of **naphthalene-1,4,5,8-tetracarboxylic dianhydride.**[14] This was identified by the formation of the diimide and its sodium salt, by the characteristic solubility in sulfuric acid and precipitation with water, and by the analysis.

Anal. Calcd. for $C_{14}H_4O_6$: C, 62.70; H, 1.50. Found: C, 62.94; H, 1.72.

3,4-Aceperinaphthane (IV).—A mixture of 0.75 g. of the oxime, 12 cc. of 6 *N* hydrochloric acid, 6 cc. of acetic acid, 12 cc. of toluene, and 4 g. of amalgamated zinc was refluxed vigorously for six hours, after which another charge of zinc and acid was added and refluxing continued for thirty-six hours longer. The aqueous layer was extracted with ether, combined with the toluene layer, and evaporated to dryness. The residue was a greenish tar from which the hydrocarbon was obtained by sublimation at 135° (8 mm.) in the form of colorless needles. Two crystallizations from

(14) Bamberger and Philip, *Ann.*, **240**, 147 (1887); Freund and Fleischer, *ibid.*, **399**, 182 (1913).

ligroin afforded 0.2 g. (30%) of material melting at 121.4–122°.

Anal. Calcd. for $C_{15}H_{14}$: C, 92.75; H, 7.26. Found: C, 92.72; H, 7.24.

Attempts to prepare a pure picrate were unsuccessful, the best sample sintering at 121° and melting over the range 127–130°. The **trinitrobenzene derivative** crystallized from ethanol in orange needles; m. p. 147–148°.

Anal. Calcd. for $C_{21}H_{17}O_6N_3$: C, 61.91; H, 4.21. Found: C, 61.98; H, 4.50.

Other Trials.—3-Methylacenaphthene (10 g.) was condensed with N-methylformanilide under the conditions used in the reaction with acenaphthene. Steam distillation gave 8.0 g. (68%) of a mixture of aldehydes, m. p. 67–100°, but no satisfactory method of separation was found. 3-Methylpyrene[5] (9 g.) was submitted to the reaction in *o*-dichlorobenzene solution at the steam-bath temperature, and the reaction mixture when processed through the bisulfite addition product yielded 7.5 g. (73%) of a mixture of aldehydes, m. p. 98–108°, but this again proved intractable. The semicarbazone mixture did not seem favorable for fractionation and the regeneration proceeded poorly. Extensive fractionation of the aldehyde mixture from alcohol and from benzene-ligroin afforded only a small amount of possibly homogeneous orange needles; m. p. 138–140°.

Anal. Calcd. for $C_{17}H_{10}O$: C, 88.50; H, 4.99. Found: C, 88.60; H, 4.95.

Summary

The reaction of aromatic hydrocarbons with N-methylformanilide to give aldehydes is limited to substances having a particularly reactive nuclear position and not too sensitive to be destroyed by the condensing agent (phosphorus oxychloride). Acenaphthene has been formylated by this method and the product utilized for the synthesis of 3,4-aceperinaphthane.

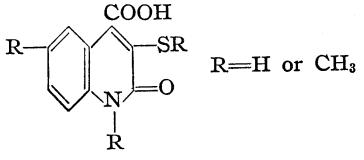
CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 1, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

The Synthesis from Rhodanine-oxindoles of Keto and Mercapto Derivatives of Cinchoninic Acid[1]

BY RUFUS VERNON JONES[2] AND HENRY R. HENZE

Although the preparation of derivatives of ketocinchoninic acids has been studied to a considerable extent, little attention has been directed to the synthesis of mercapto derivatives of the type



In fact, only two examples of this type have been reported, namely, the unsubstituted keto-mercapto acid and its 1-methyl derivative, prepared, respectively, by the alkaline hydrolysis of the appropriate rhodanine-($\Delta^{5,3'}$)-oxindole.[3]

We have resynthesized these two rhodanine-oxindoles and, in addition, have prepared the 5-methyl and the 1,5-dimethyloxindole analogs, by condensation of rhodanic acid and appropriate derivatives of isatin, in order to study their conversion into keto and mercapto derivatives of cinchoninic acid. A comparison of behavior upon hydrolysis of rhodanine-($\Delta^{5,3'}$)-oxindole and its 5-methyl homolog was of special interest since it had been shown[4] that the closely related hydantoin-(5,3')-oxindole and its 5'-methyl homolog had formed markedly different products on alkaline hydrolysis, in that the former yielded 1,2-dihydro-2-ketocinchoninic acid and the latter 5-methyloxindole.

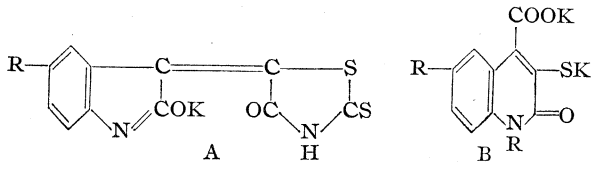
In the present investigation, rhodanine-($\Delta^{5,3'}$)-oxindole and three methyl derivatives were hydrolyzed by alkali to form derivatives of 1,2-dihydro-2-keto-3-mercaptocinchoninic acid. The behavior of these compounds toward further hydrolysis, methylation and reduction was studied. It was found that rhodanine-($\Delta^{5,3'}$)-oxindole and its 5'-methyl homolog by treatment with one molecular proportion of potassium hydroxide are converted into mono-potassium salts of the type (A) which can be hydrolyzed to regenerate the oxindoles but cannot be methylated. With an excess of alkali, rhodanine-($\Delta^{5,3'}$)-oxindole was converted into the dipotassium salt of 1,2-dihydro-2-keto-3-mercaptocinchoninic acid, and the three methyl derivatives formed analogous dipo-

(1) Presented before the Division of Organic Chemistry at the 99th meeting of the American Chemical Society at Cincinnati, Ohio, April 9–11, 1940.

(2) From the Ph.D. dissertation of R. V. Jones, June, 1937. Present address of R. V. J., East Texas State Teachers College, Commerce, Texas.

(3) (a) Gränacher and Mahal, *Helv. Chim. Acta*, **6**, 467 (1923); (b) Gränacher and Kouniniotis, *ibid.*, **11**, 1241 (1928).

(4) Henze and Blair, THIS JOURNAL, **55**, 4624 (1933).



tassium salts of type (B). The latter upon acidification form the corresponding 1,2-dihydro-2-keto-3-mercaptocinchoninic acid derivatives. These, in turn, when treated with dimethyl sulfate were converted into 1,2-dihydro-2-keto-3-methylmercaptocinchoninic acid analogs.

Experimental

Rhodanine-($\Delta^{5,3'}$)-1'-methyloxindole (II).—This compound was synthesized in a manner similar to rhodanine-($\Delta^{5,3'}$)-oxindole (I),[5] by heating for five hours at 140° a solution of 30 g. (0.185 mole) of 1-methylisatin,[6] 24.6 g. (0.185 mole) of rhodanine, 30 g. (0.36 mole) of fused sodium acetate, 400 cc. of glacial acetic acid and 4 cc. of acetic anhydride. Upon cooling, dark red crystalline plates separated which, after drying, weighed 51 g. (99% yield). This compound is virtually insoluble in the common organic solvents and does not melt or decompose at 300°. It yields a positive test with Feigl's reagent, (=C=C(SH)⇌=CH—C(=S)),[7] and dissolved in alkaline solution but is not reprecipitated unchanged upon acidification.

Anal. Calcd. for $C_{12}H_8N_2O_2S_2$: N, 10.14; S, 23.20. Found: N, 9.76; S, 23.31.

Rhodanine-($\Delta^{5,3'}$)-5'-methyloxindole (III).—Prepared in the same manner as the above but from 5-methylisatin, this compound possesses a copper-brown color with a metallic luster and is very sparingly soluble in ordinary organic solvents. Its physical and chemical behavior is similar to that of the 1'-isomer.

Anal. Calcd. for $C_{12}H_8N_2O_2S_2$: S, 23.20. Found: S, 22.82.

Rhodanine-($\Delta^{5,3'}$)-1',5'-dimethyloxindole (IV).—Prepared as above from 1,5-dimethylisatin[8] in 76% yield, the compound is a satin-black colored, fluffy solid with physical and chemical properties like those of the monomethyl analogs.

Anal. Calcd. for $C_{13}H_{10}NO_2S_2$: N, 9.65. Found: N, 9.83.

The same compound was obtained in 69% yield by condensing 1,5-dimethylisatin and rhodanine in ethyl alcohol solution using diethylamine as the catalyst.

Methylation of Rhodanine-($\Delta^{5,3'}$)-oxindoles.—In an attempt to convert (I) into (II), the former (0.05 mole) was mixed with dimethyl sulfate (0.05 mole) in alcoholic solution made basic with potassium hydroxide, and then was heated with an equal quantity of dimethyl sulfate for one hour. The solution was acidified and the solid which separated was purified and then melted at 216–217° with decomposition. Analysis proved the material to be **1,2-dihydro-2-keto-3-methylmercaptocinchoninic acid** (XIII), indicating that mere methylation had not occurred.

Anal. Calcd. for $C_{11}H_9NO_3S$: N, 5.95. Found: N, 5.94.

When compound I was treated with two equivalents of dimethyl sulfate in a 5% alcoholic solution, addition of 25% potassium hydroxide solution produced a red precipitate. The latter was filtered, dissolved in excess of the same alkaline solution and, upon acidification with hydrochloric acid, hydrogen sulfide was evolved. From the solution was obtained light yellow crystals melting at 345° (cor.); mixed with an authentic sample of **1,2-dihydro-2-ketocinchoninic acid** (XVII), the mixture melted unchanged.

Attempted methylation of I, suspended in methanol, by means of dimethyl sulfate and alcoholic potash for two hours at 100° was unsuccessful and I was recovered unchanged. The monopotassium salt of I was refluxed for fifteen hours with methyl iodide, but without reaction.

Likewise, no apparent change occurred when the monopotassium salt of III was suspended in dry ether and heated for several hours with dimethyl sulfate in an attempt to form IV. Even when this salt was heated for eighty hours at 100° with dimethyl sulfate, instead of methylation, hydrolysis and desulfurization produced **1,2-dihydro-2-keto-6-methylcinchoninic acid** (XVIII); m. p. 235–236° (cor.).

Anal. Calcd. for $C_{11}H_9NO_3$: N, 6.90. Found: N, 6.96.

Potassium Hydroxide on Rhodanine-($\Delta^{5,3'}$)-oxindoles.—To a well-stirred alcoholic suspension of I was added one equivalent of potassium hydroxide and the mixture was heated for one hour. The suspended, dark colored material became red and then was but slightly soluble in alcohol, ether or water. Suspended in water the salt rapidly hydrolyzed (accelerated by acid) to regenerate I. The red solid does not melt or decompose at 300°, is a monopotassium salt, and gives a positive test with the Feigl reagent.[7]

Anal. Calcd. for $C_{11}H_5KN_2O_2S_2$: N, 9.26. Found: N, 8.94.

Addition of three equivalents of potassium hydroxide to an alcoholic suspension of I caused a change of color, first to a deep red, and after a while to yellow. The mixture was boiled for one hour, cooled and filtered, yielding a canary yellow, crystalline solid. The latter is extremely soluble in water but is only slightly so in absolute alcohol or ether. The salt gave a positive Feigl test.[7] A 3% solution yields precipitates of characteristic color with many cations; these cannot be distinguished from those produced by the dipotassium salt of **1,2-dihydro-2-keto-3-mercaptocinchoninic acid (V).**

Anal. Calcd. for $C_{10}H_5K_2NO_3S$: S, 10.78. Found: S, 10.43.

A solution of this dipotassium salt in water at 0° was acidified yielding an orange colored amorphous precipitate. After drying, the product (81% yield) was recrystallized from toluene as feathery, orange crystals melting at 165–

(5) Andreasch, *Monatsh.*, **38**, 138 (1917).

(6) Heller, *Ber.*, **40**, 1300 (1907); an easier method of preparing N-methylisatin involves conversion of N-methylaniline into methylisonitrosoacetanilide and warming the latter with concentrated sulfuric acid at 40–50°.

(7) Feigl, *Mikrochemie*, **XV**, (N. F. IX), 1 (1934).

(8) Hegel [*Ann.*, **232**, 217 (1885)] reported m. p. 148°; we found m. p. 150–152° (cor.).

166° (cor.). These data are in exact agreement with that reported for **1,2-dihydro-2-keto-3-mercaptocinchoninic acid**[9] (VI).

Anal. Calcd. for $C_{10}H_7NO_3S$: neut. equiv., 110.6; N, 6.33. Found: neut. equiv., 109.5; N, 6.36.

Unsuccessful attempts were made to synthesize VI from isatin (a) with thioglycolic acid in alcohol refluxed with diethylamine and (b) with thioglycolic acid heated in glacial acetic acid containing acetic anhydride and fused sodium acetate.

Boiling the dipotassium salt (V) with glacial acetic acid caused the separation of elementary sulfur and from the solution was obtained a curdy, light yellow mass. After solution in alkali, acidification yielded material (62%) melting at 345° (cor.). This material was mixed with an authentic sample of **1,2-dihydro-2-ketocinchoninic acid**[10] (XVII) and the melting point remained unchanged.

The 1-methyl, 5-methyl and 1,5-dimethyl derivatives of rhodanine-($\Delta^{5,3'}$)-oxindole appear to be more readily hydrolyzed by action of potassium hydroxide solution and are converted into the dipotassium salts of the corresponding methylated 1,2-dihydro-2-keto-3-mercaptocinchoninic acids (VII), (IX) and (XI). These salts do not appear to decompose at 300°.

Anal. Dipotassium salt from rhodanine-($\Delta^{5,3'}$)-1'-methyloxindole (VII). Calcd. for $C_{11}H_7K_2NO_3S$: N, 4.50; S, 10.29. Found: N, 4.64; S, 9.85.

This salt was converted in 79% yield by acidification into **1,2-dihydro-2-keto-3-mercapto-1-methylcinchoninic acid** (VIII), m. p. 145° (cor.) (dec.).[11]

Anal. Calcd. for $C_{11}H_9NO_3S$: N, 5.96. Found: N, 5.73.

A monopotassium salt was obtained by interaction of rhodanine-($\Delta^{5,3'}$)-5'-methyloxindole (III) and one equivalent of potassium hydroxide in alcohol. The red salt is hydrolyzed readily by hot water, regenerating the original oxindole derivative.

Anal. Calcd. for $C_{12}H_7KN_2O_2S_2$: N, 8.92; S, 20.40. Found: N, 8.87; S, 20.10.

When the oxindole derivative III is allowed to stand in the cold with alcoholic potassium hydroxide solution, or more rapidly by warming, canary yellow needle-like crystals of a dipotassium salt (IX) are obtained in 90% yield. The compound is very soluble in water, yielding a solution neutral to phenolphthalein, but is rather sparingly soluble in 95% alcohol.

Anal. Calcd. for $C_{11}H_7K_2NO_3S$: C, 42.42; H, 2.27; N, 4.50; S, 10.29. Found: C, 42.04; H, 3.01; N, 4.47; S, 10.40.

From a chilled, aqueous solution of this salt (IX), acidification caused separation (93% yield) of an orange colored solid, so finely divided as to be filtered with extreme difficulty. It is quite soluble in alcohol, acetone and ethyl acetate, but is best recrystallized from glacial acetic acid as a bright red product; m. p. 193–196° (cor.) (dec.). **1,2-Dihydro-2-keto-3-mercapto-6-methylcinchoninic acid** (X) is rather insoluble in cold water but is decomposed by continued contact with boiling water.

Anal. Calcd. for $C_{11}H_9NO_3S$: neut. equiv., 117.6; N, 5.96; S, 13.63. Found: neut. equiv. (phenolphthalein), 117.6; N, 6.01; S, 13.75.

Compound IV was heated with slightly more than two equivalents of potassium hydroxide in water (20% solution); the black compound became red in color and dissolved. Upon dilution of the solution with ethyl alcohol a yellow, crystalline dipotassium salt (XI) separated and was filtered and dried (90% yield). This salt is extremely soluble in water and is quite hygroscopic.

Anal. Calcd. for $C_{12}H_9K_2NO_3S$: N, 4.30; S, 9.85. Found: N, 4.32; S, 10.03.

This salt (XI) upon acidification formed the corresponding **1,2-dihydro-2-keto-3-mercapto-1,6-dimethylcinchoninic acid** (XII) in 87% yield. Out of toluene, the orange-brown feathery crystals melt with decomposition at 157–159° (cor.).

Anal. Calcd. for $C_{12}H_{11}NO_3S$: neut. equiv., 124.6; N, 5.62; S, 12.86. Found: neut. equiv., 125.1 (phenolphthalein); N, 5.79; S, 12.66.

In order to further characterize X, 2 g. of the latter was heated with 1.2 g. of benzyl chloride, 5 g. of sodium hydroxide and 50 cc. of alcohol until solution was complete. On cooling, sodium chloride separated and was removed by filtration. The filtrate was diluted with a large volume of water, boiled to remove much of the alcohol, again cooled, extracted with ether, and upon acidification there was precipitated **1,2-dihydro-2-keto-3-benzylmercapto-6-methylcinchoninic acid;** purified by crystallization from diluted alcohol it melts with decomposition above 200°.

Anal. Calcd. for $C_{18}H_{15}NO_3S$: N, 4.31. Found: N, 4.29.

Following the method of Johnson, Pfau and Hodge,[12] 11 g. of chloroacetic acid was dissolved in 20 cc. of water, 5 g. of X was added and the mixture was boiled for one hour. The black, suspended material was removed and dissolved in alcohol with separation of elementary sulfur. Dilution of the filtrate caused precipitation of **1,2-dihydro-2-keto-6-methylcinchoninic acid** (XVIII). The latter was recrystallized from 80% alcohol and melted with decomposition at 235–236°. The acid is insoluble in water, but is fairly soluble in alcohol, ether and glacial acetic acid.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.47; N, 6.90. Found: C, 65.21; H, 4.61; N, 6.88.

Formation of 1,2-Dihydro-2-keto-3-methylmercaptocinchoninic Acids.—A solution of 60 g. (0.22 mole) of the yellow dipotassium salt V in 200 cc. of water was cooled to 0° and treated with 60 g. (0.475 mole) of dimethyl sulfate with subsequent addition of 20% potassium hydroxide solution as needed to maintain the mixture alkaline to litmus. A yellow precipitate was filtered and recrystallized from boiling water. The solid did not melt at 300° and yielded a negative test with the Feigl reagent.[7]

Anal. Calcd. for $C_{11}H_8KNO_3S$: S, 11.73. Found: S, 11.57.

Upon acidifying the filtrate from this potassium salt, or a cold aqueous solution of the salt, bright yellow leaflets

(9) Gränacher and Kouniniotis, ref. 3b.

(10) Borsche and Jacobs, *Ber.*, **47**, 362 (1914).

(11) Gränacher and Kouniniotis, ref. 3b, report m. p. 146–150° (dec.). The temperature of decomposition of this acid is greatly influenced by the rate of heating during the m. p. determination.

(12) Johnson, Pfau and Hodge, THIS JOURNAL, **34**, 1041 (1912).

were obtained which could be recrystallized from dilute alcohol. Thus purified, **1,2-dihydro-2-keto-3-methylmercaptocinchoninic acid** (XIII) melts with decomposition at 219–220° (cor.).

Anal. Calcd. for $C_{11}H_9NO_3S$: neut. equiv., 235.3; N, 5.95; S, 13.63. Found: neut. equiv. (phenolphthalein), 238.9; N, 5.98; S, 13.84.

In the same manner, (VII) was converted into **1,2-dihydro-2-keto-3-methylmercapto-1-methylcinchoninic acid** (XIV), melting with decomposition at 229–230° (cor.).

Anal. Calcd. for $C_{12}H_{11}NO_3S$: neut. equiv., 249.3; N, 5.62. Found: neut. equiv. (phenolphthalein), 245.4; N, 5.87.

From the dipotassium salt (IX) there was prepared a monopotassium salt which was recrystallized from 80% alcohol.

Anal. Calcd. for $C_{12}H_{10}KNO_3S$: N, 4.88; S, 11.16. Found: N, 5.00; S, 11.16.

A sample of this monopotassium salt was dissolved in water and treated with cold, dilute hydrochloric acid causing separation of a glistening yellow solid. After recrystallization from dilute alcohol, **1,2-dihydro-2-keto-3-methylmercapto-6-methylcinchoninic acid** (XV) was obtained as an orange crystalline material melting with decomposition at 221–222° (cor.).

Anal. Calcd. for $C_{12}H_{11}NO_3S$: neut. equiv., 249.3; N, 5.62. Found: neut. equiv. (phenolphthalein), 246.2; N, 5.57.

Dimethyl sulfate converted the dipotassium salt XI into a monopotassium salt which did not melt at 300° and which did not give a positive test with Feigl reagent.[7]

Anal. Calcd. for $C_{13}H_{12}KNO_3S$: N, 4.65. Found: N, 4.35.

This salt upon acidification yielded yellow, crystalline material. Recrystallized from dilute alcohol, **1,2-dihydro-2-keto-3-methylmercapto-1,6-dimethylcinchoninic acid** (XVI) melts with decomposition at 224–225° (cor.).

Anal. Calcd. for $C_{13}H_{13}NO_3S$: neut. equiv., 263.3; N, 5.32. Found: neut. equiv. (phenolphthalein), 258.0; N, 5.61.

Reduction of 1,2-Dihydro-2-keto-3-methylmercaptocinchoninic Acids.—Six grams of XIII, 5 g. of red phosphorus and 50 cc. of hydriodic acid (sp. gr. 1.7) were refluxed for seven hours at 150°. After removal of the phosphorus by filtration and most of the acid by steam distillation, the solution was made alkaline with potassium hydroxide and then faintly acidic with hydrochloric acid; upon cooling, light yellow crystals (2 g. or 41% yield) were obtained. A mixture of this material with an authentic sample of **1,2,3,4-tetrahydro-2-ketocinchoninic acid** (XIX)[13] melted at 215–216° (cor.).

Anal. Calcd. for $C_{10}H_9NO_3$: N, 7.33. Found: N, 7.16.

Three grams of XIV was heated with 25 cc. of hydriodic acid and 2 g. of red phosphorus for eight hours at 150°, a gas with mercaptan-like odor being evolved. The gum which formed could not be caused to crystallize, but did not contain sulfur.

From heating a sample of XV with concentrated hydriodic acid for ten hours at 150° there was obtained white needles of **1,2,3,4-tetrahydro-2-keto-6-methylcinchoninic acid** (XX) melting at 219–220° (cor.). This melting point was not altered by mixture with an authentic sample.[14]

Anal. Calcd. for $C_{11}H_{11}NO_3$: N, 6.86. Found: N, 6.74.

Two attempts were made to reduce 1,2-dihydro-2-keto-3-methylmercapto-1,6-dimethylcinchoninic acid (XVI) with hydriodic acid alone or with red phosphorus; in neither case was it possible to secure a crystalline product.

Summary

The preparation of ketomercaptocinchoninic acids from rhodanine-($\Delta^{5,3'}$)-oxindoles has been studied. As a result it has been possible to synthesize examples of 1,2-dihydro-2-keto-3-methylmercaptocinchoninic acids, a type not previously reported in the chemical literature.

(13) Hill, Schultz and Lindwall [THIS JOURNAL, **52**, 773 (1930)] reported m. p. 217–218°.

(14) Henze and Blair, ref. 4.

AUSTIN, TEXAS RECEIVED DECEMBER 8, 1941

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Hydantoins Containing a Tetrahydropyranyl Substituent[1]

BY HENRY R. HENZE AND ROBERT L. MCKEE

Until quite recently, the clinical utilization of hydantoin derivatives had been limited wholly to the use of ethylphenylhydantoin (Nirvanol)[2] in the treatment of convulsions of the type of St. Vitus dance. However, the sodium salt of diphenylhydantoin (Dilantin)[3] has come now to be considered as virtually a specific for control of epileptic seizures. Treatment with this substituted hydantoin does not effect a cure of epilepsy, hence the necessity for further research seeking additional anticonvulsants.

A few hydantoin derivatives containing an alkoxy substituent[4] have been prepared in this Laboratory and shown elsewhere to possess vary-

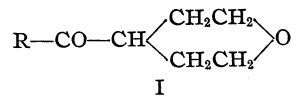
(1) Presented before the Medicinal Division of the American Chemical Society at Memphis, April, 1942.

(2) Swiss Patent 72,561 (Sept. 16, 1916).

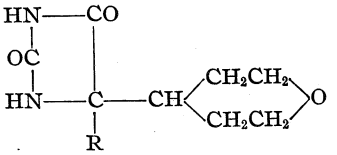
(3) (a) Putnam and Merritt, *Science*, **85**, 526 (1937); (b) Merritt and Putnam, *J. Am. Med. Assoc.*, **111**, 1068 (1938); (c) Putnam, *ibid.*, **112**, 2190 (1939).

(4) (a) Rigler with Henze, THIS JOURNAL, **58**, 474 (1936); (b) Speer with Henze, *ibid.*, **61**, 3376 (1939); (c) Rogers and Henze, *ibid.*, **62**, 1758 (1940).

ing degrees of activity as anticonvulsants. A careful survey of the chemical literature fails to disclose evidence of the synthesis of any hydantoin possessing a cyclic ether grouping as a substituent. With these facts in mind, this research was begun with the intention to synthesize a series of cyclic keto ethers of the type (I) in which the —R grouping should be alkyl or phenyl, and, further, from these ketones to prepare a similar series of 5,5-disubstituted hydantoins of the type (II) in which the —R groupings should correspond to those of the parent ketones.



I



II

Only two examples of cyclic keto ethers (I) were known, namely, the methyl and ethyl tetrahydropyranyl ketones,[5] which were reported to be formed by action of the appropriate zinc alkyls upon the acid chloride of tetrahydropyran-4-carboxylic acid. In the present investigation, reaction of 4-cyanotetrahydropyran with appropriate Grignard reagents has been utilized in the resynthesis of these methyl and ethyl ketones, and in the initial preparation of six homologs and of the cyclohexyl and phenyl analogs. No appreciable quantity of ketone could be obtained from 4-cyanotetrahydropyran and either isopropylmagnesium bromide or *s*-butylmagnesium bromide.

Each of these ten acyl derivatives of tetrahydropyran has been converted into the corresponding hydantoin by interaction with potassium cyanide and ammonium carbonate in diluted alcohol solution. Through the courtesy of Parke, Davis and Company two of these new compounds, in the form of their sodium salts, have received preliminary pharmacological testing; 5-isoamyl-5-tetrahydropyranylhydantoin and its 5-phenyl analog were found to exhibit mild anticonvulsant activity and to be devoid of any hypnotic action.

Experimental

Ethyl 4-Cyanotetrahydropyran-4-carboxylate.—To a suspension of sodium ethylate, prepared from 31.5 g. of sodium and 450 cc. of absolute ethanol, was added 155 g. of ethyl cyanoacetate[6] followed by 97 g. of 2,2′-dichloroethyl ether. This mixture was heated under a reflux condenser for three hours and later allowed to stand for an additional twelve hours. After filtration from sodium chloride, the solution was fractionated and the material boiling 105–140° (16 mm.) was collected. Upon redistillation there was obtained 37 g. (31% yield) of ethyl 4-cyanotetrahydropyran-4-carboxylate boiling at 135° (16 mm.)[7]; $n^{20}D$ 1.4539; d^{20}_4 1.1109; y^{20} 37.4; *MR* calcd. 44.68; *MR* found 44.66; *P* calcd. 413.9; *P* found 407.9.

Anal. Calcd. for $C_9H_{13}NO_3$: C, 58.95; H, 7.15; N, 7.65. Found: C, 58.77; H, 7.29; N, 7.71.

This ester was subsequently hydrolyzed by allowing a mixture of 32 g. of ester, 10.8 g. of potassium hydroxide, 9 cc. of water and 192 cc. of methanol to stand at room temperature for fifteen hours. Carbon dioxide was passed through the solution while the latter was concentrated on a water-bath. When solid matter began to separate it was redissolved and acidified with hydrochloric acid, causing separation of the organic acid. After recrystallization from the least amount of water, **4-cyanotetrahydropyran-4-carboxylic acid** (yield quantitative) melted at 163–164° (cor.).[8]

Anal. Calcd. for $C_7H_9NO_3$: neut. equiv., 155.1; N, 9.03. Found: neut. equiv. (phenolphthalein), 156.5; N, 9.12.

Tetrahydropyran-4-nitrile.—The carboxylic acid (28.5 g.) was heated under a reflux condenser in an oil-bath at 180–200° until evolution of carbon dioxide ceased. On fractionation of the residue, the nitrile distilled at 82–83° (10 mm.)[9] and left a small amount of solid product, which on further heating at 210–220° gave an additional amount of the nitrile. The total yield was 18.4 g. or 90%; $n^{20}D$ 1.4521; d^{20}_4 1.0343; y^{20} 40.7; *MR* calcd. 29.11; *MR* found 28.99; *P* calcd. 267.9; *P* found 272.0.

Preparation of Acyl 4-Tetrahydropyrans.—The ketones were prepared by addition of a molar proportion of tetrahydropyran-4-nitrile in absolute ether to 1.2–2.0 molar proportions of an appropriate Grignard reagent; the hydrolysis could be effected equally well with cold solutions of either ammonium chloride or hydrochloric acid. The ether extracts, after drying, were fractionated through an eight-inch (21 cm.) column containing a nichrome wire spiral. The purified ketones were water-white liquids having a sweet odor, and were miscible with ethanol or ethyl ether but immiscible with water. The compounds appear to be stable on standing and readily formed semicarbazones and 2,4-dinitrophenylhydrazones.

Preparation of 5-(4-Tetrahydropyranyl)-5-substituted Hydantoins.—A given ketone, together with 1.8 molar equivalents of potassium cyanide and 3.6 molar equivalents of ammonium carbonate (U. S. P. cubes), was dissolved in about 150 cc. of 50% ethyl alcohol and heated under a reflux condenser at 58–60° for twelve hours. The solution was evaporated to about one-half its original

(5) Prelog, Cerkovnikov and Heimbach, *Collection Czech. Commun.*, **10**, 399 (1938).

(6) "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. I, 1932, p. 249.

(7) Gibson and Johnson [*J. Chem. Soc.*, 2528 (1930)] report b. p. 125° (16 mm.), but no other data.

(8) *Ibid.*, p. 2529, reported m. p. 160–162°.

(9) *Ibid.*, reported b. p. 82–83° (10 mm.).

TABLE I

4-ACYLTETRAHYDROPYRANS, R—CO—CH(CH$_2$CH$_2$)$_2$O

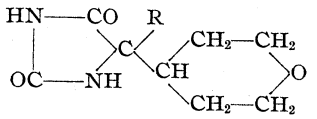
—R	Yield, %	B. p. °C. (cor.)	Mm.	$n^{20}D$	d^{20}_4	γ^{20}	Mol. refract. Calcd.	Found
Methyl[a]	53	205–207	144	1.4530	1.0243	35.8	33.98	33.84
Ethyl[b]	72	101	20	1.4541	1.0016	37.2	38.60	38.40
n-Propyl	57	85–88	5	1.4545	0.9828		43.22	43.08
n-Butyl	67	100	5	1.4551	.9700		47.83	47.61
Isobutyl	69	90–92	6	1.4545	.9648	33.2	47.83	47.83
n-Amyl	64	106–107	5	1.4573	.9589	33.3	52.45	52.39
Isoamyl	65	116–117	7	1.4567	.9562	32.9	52.45	52.46
n-Hexyl	61	134–135	6	1.4569	.9446		57.07	57.12
Cyclohexyl	46	142	5	1.4839	1.0262		54.87	54.72
Phenyl	67	57–58[c]						

—R	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Semicarbazone M. p., °C. (cor.)	2,4-Dinitrophenylhydrazone M. p., °C. (cor.)
Methyl	65.57	65.21	9.43	9.58	178	160–161[d]
Ethyl	67.55	67.28	9.92	10.08	151	146–147[e]
n-Propyl	69.18	68.87	10.32	10.54	145–146	
n-Butyl	70.54	70.21	10.66	10.68	180	99
Isobutyl	70.54	70.40	10.66	10.78	187–188	122
n-Amyl	71.69	71.39	10.94	10.95	117	89–90
Isoamyl	71.69	71.60	10.94	10.93	158–159	134–135
n-Hexyl	72.68	72.67	11.18	11.19	161	
Cyclohexyl	73.42	73.43	10.27	10.19	213–214	
Phenyl	75.76	75.62	7.42	7.65		(*f*)

[a] Prelog, Cerkovnikov and Heimbach, ref. 5, reported b. p. 90–94° (15 mm.); we found b. p. 91–92° (15 mm.). [b] *Ibid.*, reported b. p. 103° (15 mm.). [c] M. p. of the solid ketone. [d] Prelog, Cerkovnikov and Heimbach, ref. 5, reported m. p. 160.0–160.5°. [e] *Ibid.*, reported m. p. 146.0–146.5°. [f] Did not form; the ketone was recovered unchanged.

TABLE II

HYDANTOINS CONTAINING A TETRAHYDROPYRANYL SUBSTITUENT



—R	M. p., °C. (cor.)	Yield, %	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
Methyl	250	51	54.53	54.79	7.12	7.30	14.13	14.14
Ethyl	246	70	56.59	56.25	7.60	7.69	13.20	13.34
n-Propyl	223	66	58.39	58.41	8.02	8.18	12.38	12.19
n-Butyl	195	49	59.98	59.74	8.39	8.48	11.66	11.60
Isobutyl	222	53	59.98	59.76	8.39	8.50	11.66	11.55
n-Amyl	171–172	79	61.39	61.30	8.72	8.74	11.02	11.15
Isoamyl	195–196	68	61.39	61.22	8.72	8.77	11.02	10.97
n-Hexyl	169	48	62.66	62.58	9.01	9.04	10.48	10.61
Cyclohexyl	304–306	65	63.12	63.01	8.33	8.40	10.52	10.63
Phenyl	253	72	64.57	64.23	6.20	6.39	10.77	10.88

volume and then was acidified with hydrochloric acid causing separation of the hydantoin. In general, two recrystallizations from 20% alcohol produced crystalline white material, seemingly quite insoluble in water, but readily soluble in alkaline solution. Sodium salts of the hydantoins could be prepared readily by addition of the calculated amount of sodium ethylate to an alcoholic solution of the hydantoin and evaporation to dryness.

Summary

1. Eight new cyclic ether ketones, containing the tetrahydropyran nucleus, have been prepared.

2. The initial synthesis is reported of ten examples of a novel type of hydantoin containing a cyclic ether (tetrahydropyranyl) grouping.

AUSTIN, TEXAS RECEIVED MAY 4, 1942

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

Copolymerization of Alkyl Acrylates and Alkyl Maleates. Some Kinetic Studies on Copolymerization[1]

BY C. S. MARVEL AND ROBERT L. FRANK[2]

In order to learn more about copolymerization an attempt has been made to extend the method of kinetic study of the polymerization of optically active monomers[3] to mixtures of monomers. The work reported in this communication deals with copolymers of acrylates and maleates. These were selected for study because of ready availability and because it was thought that when these two monomer units entered a growing chain, they would do so in a 1:1 ratio as this seemed to be the tendency for such heteropolymers as styrene–maleic anhydride, stilbene–maleic anhydride[4] and the less closely related olefin–sulfur dioxide[5] copolymers. It was to be expected that excess acrylate units might appear in the polymer but the maleate being unable to polymerize alone should never exceed the 1:1 ratio.

The polymerization of various mixtures of *l*-monomenthyl maleate and ethyl acrylate was carried out in water-jacketed polarimeter tubes at 55° and the change in rotation was followed to determine the rate of each reaction. The change in concentration of the maleate could then be calculated by means of the equation

$$C_T = \frac{C_0(\gamma_T - \gamma_p)}{\gamma_m - \gamma_p}$$

in which C_T is the concentration of the maleate at time T (in grams per 100 cc.), C_0 is the initial concentration, and γ_m, γ_p, and γ_T are the specific rotations of the monomer, the polymer, and the solution at time T, respectively. It should be noted that what is being measured here is not necessarily the rate of polymer formation, but the rate of entrance of the maleate units into the chain.

Benzoyl peroxide was used to catalyze the polymerizations, and rather large amounts (up to 5% of the solutions) were employed in order to eliminate as much as possible the induction period and to speed up the polymerizations. Anhydrous dioxane was the solvent and the solutions contained from 6 to 16% of the combined monomers.

The entrance of maleate units into the polymer chains appears to be a zero order reaction and gives a straight line when the change in concentration ($C_0 - C_T$) is plotted against time (Fig. 1, Curve 1). This indicates that the rate should be independent of the concentration of the maleate, and this was found to be the case. When the concentration of the maleate was varied, the slope of the straight line did not change (Figs. 1 (Curve 2) and 2).

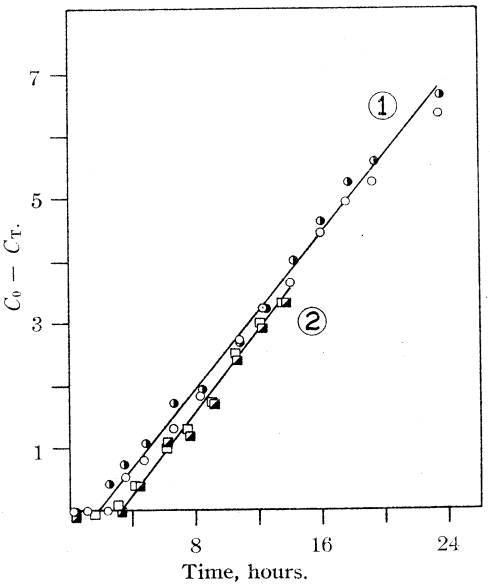


Fig. 1.—Curve 1: 0.26 molar ethyl acrylate, 0.26 molar *l*-monomenthyl maleate, 5% benzoyl peroxide; Curve 2: 0.26 molar ethyl acrylate, 0.13 molar *l*-monomenthyl maleate, 5% benzoyl peroxide.

When two equivalents of *l*-monomenthyl maleate to one of ethyl acrylate were used, it was expected that the rotation would change until half the maleate had copolymerized with the acrylate, to give a 1:1 polymer, and that the rotation would then show no further change, as indicated by the dotted line in Fig. 2. As shown by the curve obtained in Fig. 2, this was not the case. The rotation changed according to zero order kinetics until one equivalent of maleate had been used up, and then continued to decrease slowly.

(1) This is the thirteenth communication on vinyl polymers. For the twelfth see THIS JOURNAL, **64**, 92 (1942).

(2) du Pont Post-Doctorate Research Assistant, University of Illinois, 1940–1941.

(3) (a) Marvel, Dec and Cooke, THIS JOURNAL, **62**, 3499 (1940); (b) Price and Kell, *ibid.*, **63**, 2798 (1941).

(4) Wagner-Jauregg, *Ber.*, **63**, 3213 (1930).

(5) Frederick, Cogan and Marvel, THIS JOURNAL, **56**, 1815 (1934).

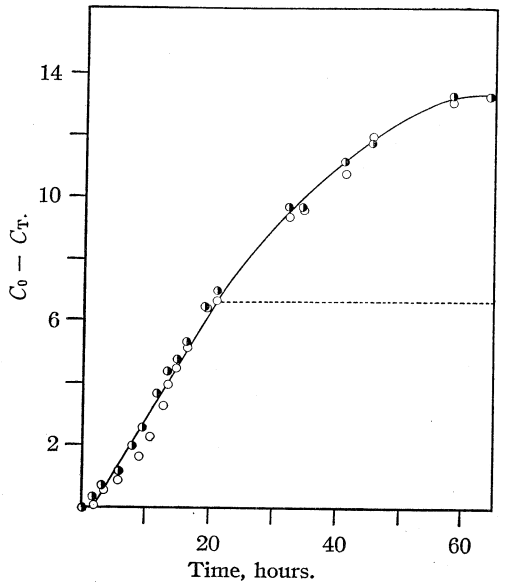


Fig. 2.—0.26 molar ethyl acrylate, 0.52 molar *l*-monomenthyl maleate, 5% benzoyl peroxide.

In order to investigate this behavior, *l*-monomenthyl maleate was heated in dioxane alone for a week to determine whether or not an ester interchange might be taking place. The rotation was unchanged at the end of this time.

The maleate was then treated with benzoyl peroxide without having any acrylate present. The rotation changed and, when the data were plotted, a first-order curve was obtained (Fig. 3). This result indicated that the maleate was polymerizing itself or that perhaps the monomer was reacting in some way with the benzoyl peroxide. In experiments using a limited amount of peroxide it was found that the latter alternative was the correct one. When less than one mole of peroxide was used for two of maleate, the rotation changed only in proportion to the amount of peroxide which would combine in this ratio. When the acrylate is present, this first order reaction is apparently superseded by the zero-order copolymerization, but takes place when the acrylate is absent. This reaction is being investigated further.

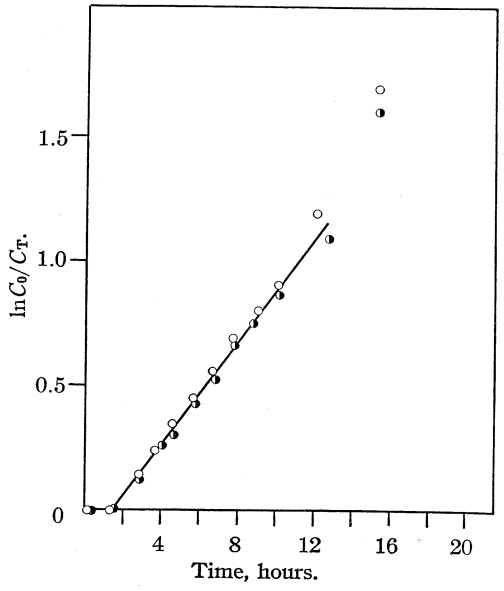


Fig. 3.—0.26 molar *l*-monomenthyl maleate, 0.21 (5%) molar benzoyl peroxide.

By doubling the concentration of acrylate and keeping the peroxide and maleate concentrations the same as in the experiments plotted in Fig. 1, it was found that the rate of reaction is independent of the acrylate concentration (Fig. 4, Curve 1).

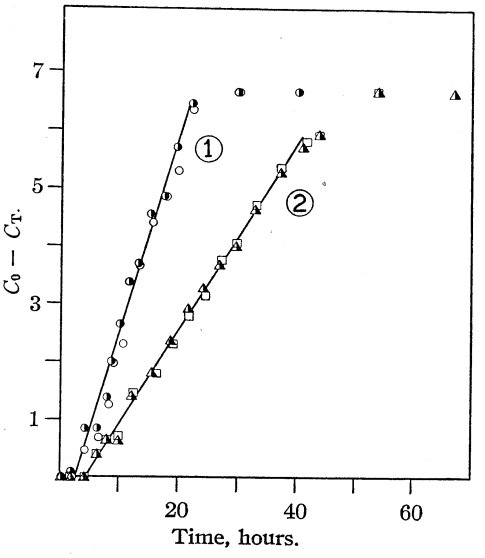


Fig. 4.—Curve 1: 0.52 molar ethyl acrylate, 0.26 molar *l*-monomenthyl maleate, 5% benzoyl peroxide; Curve 2: 0.26 molar ethyl acrylate, 0.26 molar *l*-monomenthyl maleate, 2.5% benzoyl peroxide.

When mole per mole of acrylate and maleate were used at the same concentration as in Fig. 1, and the peroxide concentration was halved, the rate of reaction was also cut in half, as illustrated in Fig. 4, Curve 2. Thus the rate of this polymerization appears to be directly proportional to peroxide concentration and not to the square root of the peroxide concentration as found by Price and Kell for *d*-*s*-butyl α-chloroacrylate.[3b]

It is possible to explain these kinetics, zero order with respect to maleate, if one makes the assumption that the reaction of *l*-monomenthyl maleate with the growing polymer chains occasionally forms a non-polymerizing product.

Polymers were isolated from the reaction mixtures containing equimolar amounts of acrylate and maleate and also from the mixtures containing two moles of maleate for one of acrylate. These polymers were found to have specific rotations of $-29.2°$ and $-39.2°$, respectively. By calculating the specific rotation of a 1:1 copolymer from the actual rotation of the reaction mixtures at the end of the reaction, a figure of $-43.2°$ is obtained, which is higher than the values found. This would indicate that the polymer chains contain less than one maleate unit for each acrylate unit, even when the maleate monomer is used in excess. This conclusion is in agreement with the analytical data obtained for the copolymers.

A second series of experiments was carried out with *l*-menthyl acrylate and ethyl maleate, in order to study the kinetics of the entrance of acrylate units into the polymer chain. These reactions, however, did not give clean-cut curves and it was impossible to ascertain whether the reactions were zero order or first order. *l*-Menthyl acrylate alone was found to polymerize according to first-order kinetics, as shown in Fig. 5. This is the expected result and similar to the polymerization of *s*-butyl α-chloroacrylate and vinyl β-phenylbutyrate.[3a]

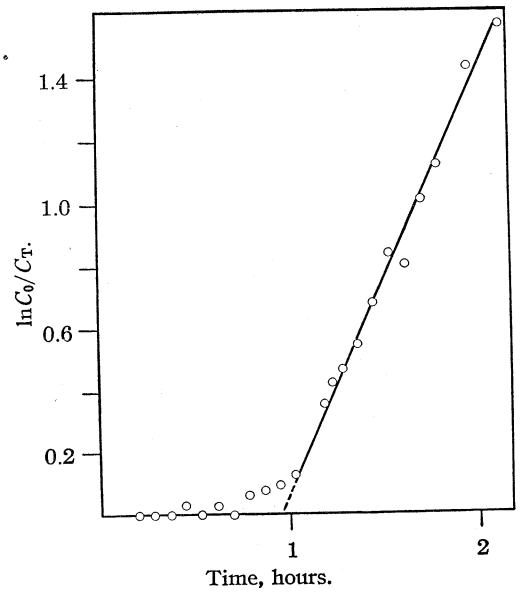


Fig. 5.—0.26 molar *l*-menthyl acrylate, 5% benzoyl peroxide.

Experimental

Kinetic Studies on Polymerization of Optically Active Esters.—Special water-jacketed 1-dm. polarimeter tubes of Pyrex glass were used for the rotation studies. These were made by the Macalaster Bicknell Company of Cambridge, Massachusetts. Between polarimeter readings these tubes were kept in a constant temperature bath at 55°. When a reading was to be taken, a tube was removed from the bath and connected by means of rubber tubing to a small centrifugal pump. Water from the bath was then circulated through the jacket.

Some difficulty was experienced in the readings at 55° because of convection currents, but by averaging a number of readings it was possible to obtain reproducible results. All the experiments were carried out in duplicate except the polymerization of *l*-menthyl acrylate.

The first experiment was made with 0.750 g. of benzoyl peroxide, 0.999 g. of *l*-monomenthyl maleate, and 0.403 g. of ethyl acrylate in 15 ml. of dry dioxane solution. The data are plotted in Fig. 1, Curve 1.

The second experiment was carried out with 0.750 g. of benzoyl peroxide, 0.499 g. of *l*-monomenthyl maleate, and 0.399 g. of ethyl acrylate in 15 ml. of dry dioxane solution. These results are plotted in Fig. 1, Curve 2.

In the third kinetic study 0.750 g. of benzoyl peroxide, 2.000 g. of *l*-monomenthyl maleate, and 0.402 g. of ethyl acrylate in 15 ml. of dry dioxane were used. These data are plotted in Fig. 2.

The reaction between peroxide and maleate alone was carried out using 0.500 g. of benzoyl peroxide and 0.667 g. of *l*-monomenthyl maleate in 10 ml. of dry dioxane solution. The results are plotted in Fig. 3.

The data represented in Curve 1 of Fig. 4 were obtained with a 15-ml. solution of dry dioxane containing 0.750 g. of benzoyl peroxide, 1.000 g. of *l*-monomenthyl maleate, and 0.787 g. of ethyl acrylate. These are represented in Fig. 4, Curve 1.

In the experiment represented by Curve 2 of Fig. 4, the reaction was carried out with a 15-ml. dry dioxane solution containing 0.375 g. of benzoyl peroxide, 1.000 g. of *l*-monomenthyl maleate, and 0.394 g. of ethyl acrylate. The results are shown in Fig. 4, Curve 2.

The final experiment, the polymerization of *l*-menthyl acrylate, was made using a 5-ml. dry dioxane solution of 0.250 g. of benzoyl peroxide and 0.277 g. of *l*-menthyl acrylate. These data are represented in Fig. 5.

The final reading in each experiment was taken after the cell had been heated overnight in order to determine the rotation of the polymer itself.

***l*-Monomenthyl Maleate.**—This was prepared by the method of Wassermann[6] and on recrystallization from petroleum ether melted at 86–87° ($[\alpha]^{28}D$ $-74.3°$, 0.1053 g. in 5 cc. of ethanol solution). The yield was 38.6%.

Ethyl Acrylate.—Röhm and Haas ethyl acrylate was distilled once through a modified Widmer column at atmospheric pressure; b. p. 98–99°.

***l*-Menthyl β-Chloropropionate.**—To 125 g. of *l*-menthol dissolved in 200 cc. of dry benzene was added 98.2 g. of β-chloropropionyl chloride. The reaction mixture became warm and hydrogen chloride was evolved. The reaction flask, fitted with a calcium chloride tube, was allowed to stand for forty-eight hours.

The reaction mixture was fractionally distilled under reduced pressure through a modified Widmer column. The main fraction distilled at 105–107° (4 mm.) and weighed

(6) Wassermann, *Ann.*, **488**, 211 (1931).

146.4 g. (77%); $n^{20}D$ 1.4642; d^{25}_4 1.011; $[\alpha]^{26}D$ +25.8° (no solvent).

Anal. Calcd. for $C_{13}H_{23}ClO_2$: C, 63.30; H, 9.39. Found: C, 63.55; H, 9.60.

l-Menthyl Acrylate.—A mixture of 30 g. of *l*-menthyl β-chloropropionate and 66 g. of quinoline was heated for three hours at a bath temperature of 170–180°. Crystalline quinoline hydrochloride separated from the reaction mixture on cooling. One hundred cubic centimeters of benzene was added and the solution was extracted with three 100-cc. portions of water and five 60-cc. portions of 50% sulfuric acid. It was then washed with ten 50-cc. portions of water, in order to remove the last traces of quinoline salts.

The dark oily solution was fractionally distilled through a modified Widmer column and 10.2 g. (39.5%) of product boiling at 64–67° (3 mm.) was obtained. This was redistilled at 78–80° (5 mm.); $n^{20}D$ 1.4628; d^{20}_4 0.927; $[\alpha]^{28}D$ −80.2° (1.002 g. in 10 cc. of dioxane solution).

Anal. Calcd. for $C_{13}H_{22}O_2$: C, 74.29; H, 10.55. Found: C, 74.53; H, 10.57.

Isolation of Polymers.—The collected washings from all the polarimeter tubes containing 1:1 ethyl acrylate and *l*-monomenthyl maleate were evaporated nearly to dryness and the viscous mixture was dissolved in 50 cc. of methanol. This was poured into 100 cc. of water and the mixture became milky. Polymer droplets adhered to the sides of the beaker and the milky supernatant liquid was poured off. This procedure was repeated and the polymer was then dried overnight at 70°. The result was a clear, light yellow, tacky plastic mass, $[\alpha]^{55}D$ −29.2° (0.0992 g. in 5 cc. of dioxane solution).

Anal. Found: C, 63.15; H, 8.39.

The contents of the two polarimeter tubes used in the experiments described in Fig. 2 (two parts maleate and one part acrylate) were washed into a beaker with dioxane. Water was added and the polymer separated as an oil which stuck to the bottom and sides of the beaker. The milky supernatant liquid was poured off. This procedure was repeated once with dioxane and once with acetone, in which the polymer was soluble. The polymer was then dried overnight at 70°, yielding a clear, amber, brittle resin (0.4 g.); $[\alpha]^{55}D$ −39.5° (0.1030 g. in 5 cc. of dioxane solution).

Anal. Found: C, 64.42, 64.48; H, 8.55, 8.57.

Summary

Some preliminary kinetic studies on mixtures of ethyl acrylate and *l*-monomenthyl maleate and of ethyl maleate and *l*-menthyl acrylate have been recorded. Evidence that *l*-monomenthyl maleate reacts with benzoyl peroxide to give a non-polymeric product has been reported.

URBANA, ILLINOIS RECEIVED MARCH 11, 1942

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 882]

The Synthesis of the Three Isomeric *dl*-β-Pyridylalanines

BY CARL NIEMANN, RICHARD N. LEWIS AND JOHN T. HAYS

The knowledge that the known α-amino acids containing heterocyclic ring systems are intimately associated with a number of important biological processes[1] has led us to consider the chemical and physiological properties of α-amino acids containing the pyridine nucleus, a heterocyclic ring system which, to date, has not been found in any naturally occurring α-amino acid,[2] but which is present in other compounds isolated from natural sources.[1,4] In this communication we wish to describe the synthesis of *dl*-β-(2-pyridyl)-alanine, *dl*-β-(3-pyridyl)-alanine, and *dl*-β-(4-pyridyl)-alanine, and to record some of the properties of these amino acids.

Overhoff, Boeke and Gorter,[5] starting with (2-pyridyl)-methyl chloride, prepared *dl*-β-(2-pyridyl)-alanine *via* the phthalimidomalonic ester synthesis of Sörensen.[6] The authors also reported that all attempts to prepare the amino acid from β-(2-pyridyl)-α-chloropropionic acid or from picolinaldehyde were unsuccessful. Our experiences have been similar to those described above, but we have found that *dl*-β-(2-pyridyl)-alanine can be prepared in considerably better yield than that reported by Overhoff, Boeke and Gorter[5] by substituting the benzamidomalonic ester synthesis of Redemann and Dunn[7] for the procedure of Sörensen.[6] The failure of picolinaldehyde to condense with hippuric acid[5] or with diketopiperazine in the desired fashion is not due to a lack of reac-

(1) M. Guggenheim, "Die biogenen Amine," S. Karger, Basel, 1940.

(2) It has been suggested[3] that the compound mimosine, obtained from the leaves of *Mimosa pudica*, is a dihydroxypyridylalanine, but this characterization has not been confirmed.

(3) (a) H. Nienburg and K. Tauböck, *Z. physiol. Chem.*, **250**, 80 (1937); (b) J. Renz, *ibid.*, **244**, 153 (1936).

(4) T. A. Henry, "The Plant Alkaloids," 3rd edition, Blakiston's Sons, Philadelphia, Pa., 1939.

(5) J. Overhoff, J. Boeke and A. Gorter, *Rec. trav. chim.*, **55**, 293 (1936).

(6) S. P. L. Sörensen, *Z. physiol. Chem.*, **44**, 448 (1905).

(7) C. E. Redemann and M. S. Dunn, *J. Biol. Chem.*, **130**, 341 (1939).

tivity, but rather to side reactions which lead to loss of aldehyde through tar formation. It appears that those aldehydes which undergo condensation with derivatives of glycine, to form azlactones or analogous compounds, in satisfactory yields are aldehydes in which additional stabilization is brought about by the possibility of resonance among excited structures.[8]

A comparison of the various structures that can be written for nicotinaldehyde and for picolinaldehyde[8,9] leads one to the conclusion that nicotinaldehyde has the greater resonance energy and consequently more closely resembles the aromatic aldehydes than does picolinaldehyde. One would therefore expect that nicotinaldehyde could be converted into *dl*-β-(3-pyridyl)-alanine by the Erlenmeyer procedure,[10] or modifications thereof.[11] This expectation was realized when it was found that nicotinaldehyde readily condenses with hippuric acid, diketopiperazine, hydantoin, thiohydantoin, and acetylthiohydantoin. Since the azlactone is not readily purified and the hydantoins are not readily hydrolyzed, the amino acid was prepared from the diketopiperazine-nicotinaldehyde condensation product by the method of Sasaki.[12]

The condensation of (4-pyridyl)-methyl bromide hydrobromide with benzamidomalonic ester[7] was not very satisfactory but hydrolysis of the small amount of condensation product that was obtained gave *dl*-β-(4-pyridyl)-alanine.

During this investigation we attempted to prepare the three isomeric pyridylaldehydes from the corresponding pyridine monocarboxylic acids by the method of McFadyen and Stevens.[13] In the case of nicotinic acid and picolinic acid the method proved to be satisfactory but when applied to isonicotinic acid only traces of isonicotinaldehyde were obtained. McFadyen and Stevens[13] found that *p*-nitrobenzoic acid could not be converted into *p*-nitrobenzaldehyde by their procedure although *m*-nitrobenzaldehyde was readily obtained from *m*-nitrobenzoic acid. Our observation of the difference in the behavior of nicotinic acid and isonicotinic acid in the McFadyen–Stevens reaction provides still another example of the parallel behavior of derivatives of pyridine and nitrobenzene.[9,14] The conversion of picolinic acid to picolinaldehyde by the McFadyen–Stevens reaction cannot be taken as an exception to the above generalization because with picolinic benzenesulfonhydrazide there is an excellent possibility that an intramolecular hydrogen bond is formed between the pyridine nitrogen atom and one of the nitrogen atoms present in the side chain thereby causing a decided structural modification which would preclude any direct comparison of the behavior of the alpha and gamma compounds.

A preliminary determination of the apparent dissociation constants[11] of the three isomeric *dl*-β-pyridylalanines[15] led to results which may be interpreted as follows. Considering first the zwitterionic structures, one would expect that in all of the amino acids the positively charged ammonium nitrogen atom would try to get as close as is structurally possible to the negatively charged pyridine nitrogen atom. In the case of *dl*-β-(2-pyridyl)-alanine this tendency would lead to the formation of a strong intramolecular hydrogen bond between the ammonium nitrogen atom and the pyridine nitrogen atom. It is obvious that this situation makes it difficult to add a proton to the pyridine nitrogen atom or to remove one from the ammonium nitrogen atom. Therefore one would predict that the pyridine nucleus, in all three *dl*-β-pyridylalanines, would be less basic than pyridine, and that the basicity of the pyridine nucleus would increase as the amino acid side chain is shifted progressively from the 2 to the 4 position with the greatest increment accompanying the shift from the 2 to the 3 position. The observed apparent basic dissociation constants ascribable to the pyridine nucleus are generally in accord with these predictions. Similarly the observed apparent acid dissociation constants are compatible with the idea that it is more difficult to remove a proton from the ammonium nitrogen atom in *dl*-β-(2-pyridyl)-alanine than in *dl*-β-(3-pyridyl)-alanine. However, they also show that the amino group is less basic in these amino acids than in the simple monoamino-monocarboxylic acids. The observed values for the second apparent basic dissociation constants

(8) L. Pauling, "The Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, N. Y., 1940.

(9) V. Schomaker and L. Pauling, THIS JOURNAL, **61**, 1769 (1939).

(10) (a) E. Erlenmeyer, Jr., *Ann.*, **271**, 137 (1892); (b) *ibid.*, **275**, 1 (1893).

(11) C. L. A. Schmidt, "The Chemistry of the Amino Acids and Proteins," C. C. Thomas, Springfield, Ill., 1938.

(12) T. Sasaki, *Ber.*, **54**, 163 (1921).

(13) J. S. McFadyen and T. S. Stevens, *J. Chem. Soc.*, 584 (1936).

(14) (a) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," Oxford University Press, New York, 1937, pp. 522–523; (b) C. Naegeli, W. Kündig and H. Brandenburger, *Helv. Chim. Acta*, **22**, 912 (1939).

(15) In the case of *dl*-β-(4-pyridyl)-alanine a complete titration curve was not determined because of the small amount of amino acid available.

of *dl*-β-(2-pyridyl)-alanine and *dl*-β-(3-pyridyl)-alanine make it clear that the carboxyl group is more acidic in the case of the *dl*-β-pyridylalanines than in the case of the simple monoamino-monocarboxylic acids. This increase in acid strength as well as the decrease in basic strength of the amino group can be explained in terms of the inductive effect of the pyridine nucleus. Summing all of the above effects one finds that the values for the isoelectric points of these amino acids (pI = 6.6–6.8) are more acid than one would expect upon casual examination.

Experimental[16]

***dl*-β-(2-Pyridyl)-alanine.**[5]—Sodium nitrite, 4 g., in 6 ml. of water, was added dropwise, with stirring, to a well-cooled solution of 5.4 g. of (2-pyridyl)-methylamine,[17] b. p. 87–89° (2.2 mm.), in 25 ml. of concentrated hydrochloric acid. Forty grams of powdered potassium hydroxide was then added to the cold reaction mixture, the solution quickly filtered, and the filtrate extracted with ether. The ethereal solution was dried, filtered, the solvent removed by evaporation *in vacuo*, and the residue dissolved in 50 ml. of absolute ethanol. This solution was added to a warm solution of 12.1 g. of benzamidomalonic ester[7] and 1.56 g. of sodium in 76 ml. of absolute ethanol and the mixture refluxed for four hours. The ethanol was removed by evaporation *in vacuo*, the residue taken up in dilute aqueous hydrochloric acid, and the excess benzamidomalonic ester removed by extraction with ether. The aqueous phase was made alkaline, extracted with ether, the ethereal phase dried, filtered, and the solvent removed to give 5.6 g. (30%) of oily (2-pyridyl)-methylbenzamidomalonic ester. This condensation product was refluxed for eight hours with 25 ml. of 49% hydrobromic acid. The hydrolysate was diluted with 150 ml. of water, the solution cooled to 25°, and the liberated benzoic acid removed by extraction with ether. The aqueous phase was evaporated to dryness, the residue taken up in water, the solution freed of inorganic ions with the aid of silver carbonate and hydrogen sulfide, and evaporated to dryness. The residue was collected, washed with a mixture of absolute ethanol and isopropyl ether and then recrystallized from a mixture of isopropyl ether and 80% aqueous ethanol to give 1.38 g. (17%) of *dl*-β-(2-pyridyl)-alanine; m. p. 205.5–206°. Overhoff, Boeke and Gorter[5] give 216° as the melting point.

Anal. Calcd. for $C_8H_{10}O_2N_2$ (166.2): C, 57.8; H, 6.1; N, 16.9. Found: C, 58.0; H, 6.2; N, 16.8.

The addition of ninhydrin to an aqueous solution of *dl*-β-(2-pyridyl)-alanine resulted in the formation of a violet color.

Picolinic Benzenesulfonhydrazide.—Benzenesulfonyl chloride (5 ml.) was added, with stirring, to a chilled solution of 4.62 g. of picolinic hydrazide[18] in 35 ml. of pyridine.[13] The clear red solution was allowed to stand for four hours before the pyridine was removed by evaporation *in vacuo*. When the sirupy residue was stirred with a large volume of cold water a solid separated. This was washed with water, a small amount of cold ethanol, and finally with ether to give picolinic benzenesulfonhydrazide, m. p. 202–203.5°, after recrystallization from ethanol. The yield of crude product was practically quantitative.

Anal. Calcd. for $C_{12}H_{11}O_3N_3S$ (277.3): C, 52.0; H, 4.0; N, 15.2. Found: C, 52.4; H, 4.1; N, 15.1.

Picolinaldehyde.[19]—The procedure of McFadyen and Stevens[13] was modified as follows: 25 g. of picolinic benzenesulfonhydrazide, 24 g. of anhydrous sodium carbonate and 100 ml. of C. P. glycerol were heated to 160° and maintained at that temperature for two minutes. One hundred ml. of water was added to the reaction mixture, the solution saturated with sodium nitrate, filtered, and the filtrate extracted with ether in a continuous extractor for ten hours. The ethereal phase was dried, filtered, and the solvent evaporated to give 1.99 g. (20%) of picolinaldehyde. The liquid aldehyde was converted into the phenylhydrazone hydrochloride; m. p. 194.5–197°. Lénárt[19] gives a melting point of 196° for this compound. All attempts to condense the above picolinaldehyde with diketopiperazine were unsuccessful.

Nicotinic Benzenesulfonhydrazide.—The addition of 230 g. of benzenesulfonyl chloride to a suspension of 169 g. of nicotinic hydrazide[20] in 1.2 liters of technical pyridine gave 328 g. (96%) of nicotinic benzenesulfonhydrazide, m. p. 186–186.5° after recrystallization from 95% ethanol.

Anal. Calcd. for $C_{12}H_{11}O_3N_3S$ (277.3): C, 52.0; H, 4.0; N, 15.2. Found: C, 51.7; H, 4.2; N, 15.2.

Nicotinaldehyde.[21]—Nicotinic benzenesulfonhydrazide (177 g.) was decomposed, in 25-g. portions, to give 14.3 g. (22.5%) of nicotinaldehyde; b. p. 97–99° (26 mm.). The liquid aldehyde was converted into the phenylhydrazone; m. p. 157.5–158°. Harries and Lénárt[21] give a melting point of 158° for this compound.

5-(3-Pyridylmethyl)-thiohydantoin.—One gram of acetylthiohydantoin,[22] 0.53 g. of dry sodium acetate, both finely powdered, 0.67 g. of nicotinaldehyde, and 5 ml. of acetic anhydride were heated in an oil-bath at 110–115° for thirty minutes. The solid reaction product was extracted with hot water leaving 1.2 g. of a light yellow solid as a residue. This product was refluxed for six hours with 6 ml. of acetic anhydride, 6 ml. of hydriodic acid (d. 1.7) and 1.3 g. of red phosphorus. The hydrolyzate was filtered, the acetic anhydride and hydriodic acid removed by repeated evaporation, following the addition of water, and the residue dissolved in 20 ml. of ethanol. The addition of 6 *N* aqueous ammonium hydroxide to the filtered alcoholic solution precipitated an oil which solidified in contact with methanol. This product was recrystallized from aqueous ethanol to give 0.8 g. (60%) of 5-(3-pyridylmethyl)-thiohydantoin; m. p. 249–252°.

Anal. Calcd. for $C_9H_9ON_3S$ (207.2): C, 52.2; H, 4.4; N, 20.3. Found: C, 52.3; H, 4.7; N, 20.3.

(16) Microanalyses by Dr. G. Oppenheimer and G. A. Swinehart.

(17) H. G. Kolloff and J. H. Hunter, THIS JOURNAL, **63**, 492 (1941).

(18) H. Meyer and J. Mally, *Monatsh.*, **33**, 393 (1912).

(19) G. Lénárt, *Ber.*, **47**, 808 (1914).

(20) T. Curtius and E. Mohr, *ibid.*, **31**, 2493 (1898).

(21) C. Harries and G. H. Lénárt, *Ann.*, **410**, 115 (1915).

(22) T. B. Johnson and B. H. Nicolet, THIS JOURNAL, **33**, 1973 (1911).

Dinicotinaldiketopiperazine.—Nine grams of diketopiperazine, 27 g. of fused sodium acetate, 14.3 g. of nicotinaldehyde, and 25 ml. of acetic anhydride were heated in an oil-bath at 120–125° for five hours.[12] The solid reaction product was digested with hot water, the digest cooled, filtered, and the residue digested with hot ethanol to give 9.7 g. (50%) of crude dinicotinaldiketopiperazine. After two recrystallizations from pyridine the condensation product was obtained in the form of fine yellow needles; m. p. >300°.

Anal. Calcd. for $C_{16}H_{12}O_2N_4$ (292.3): C, 65.8; H, 4.1; N, 19.2. Found: C, 66.0; H, 4.3; N, 19.3.

***dl*-β-(3-Pyridyl)-alanine.**—A mixture of 9.7 g. of dinicotinaldiketopiperazine, 6.7 g. of red phosphorus, 67 ml. of hydriodic acid (d. 1.7), and 67 ml. of acetic anhydride was refluxed for six hours. The reaction product was filtered and the volatile acids removed by repeated evaporation, following the addition of water. The residue remaining after the final evaporation was dissolved in water and the solution freed of inorganic ions with the aid of silver carbonate and hydrogen sulfide. The solution was then evaporated to dryness and the solid residue collected with the aid of ethanol to give 7.6 g. (69%) of crude *dl*-β-(3-pyridyl)-alanine; m. p. 258–260°. The crude amino acid was recrystallized from 80% aqueous ethanol to give *dl*-β-(3-pyridyl)-alanine; pearly flakes; m. p. 262–263°.

Anal. Calcd. for $C_8H_{10}O_2N_2$ (166.2): C, 57.8; H, 6.1; N, 16.9. Found: C, 57.6; H, 6.2; N, 16.9.

dl-β-(3-Pyridyl)-alanine has a very sweet taste, gives a violet color when treated with ninhydrin, and forms a dipicrate, needles, m. p. 187–189°, after recrystallization from a dilute aqueous solution of picric acid.

Anal. Calcd. for $C_{20}H_{16}O_{16}N_8$ (624.4): C, 38.5; H, 2.6; N, 18.0. Found: C, 38.5; H, 2.7; N, 18.1.

Isonicotinic Benzenesulfonhydrazide.—A suspension of 13 g. of isonicotinic hydrazide,[22] m. p. 170.5–171.5°,[23] in 90 ml. of pyridine was treated with 18 g. of benzenesulfonyl chloride and the reaction mixture worked up as previously described to give 24.5 g. (93%) of isonicotinic benzenesulfonhydrazide; m. p. 193–194° after recrystallization from water.

Anal. Calcd. for $C_{12}H_{11}O_3N_3S$ (277.3): C, 52.0; H, 4.0; N, 15.2. Found: C, 52.2; H, 4.2; N, 15.3.

All attempts to prepare isonicotinaldehyde by decomposing the above sulfonhydrazide in the presence of glycerol and sodium carbonate, as described previously, failed in that only traces of the aldehyde were formed.

(4-Pyridyl)-carbinol Hydrochloride.[24]—A solution of 3.8 g. of (4-pyridyl)-methylamine,[17] b. p. 99–101° (24 mm.), was treated with silver nitrite according to the directions of Graf.[24] The crude carbinol hydrochloride was recrystallized from absolute ethanol to give 2.5 g. of (4-pyridyl)-carbinol hydrochloride; m. p. 167–172°.

Anal. Calcd. for C_6H_8ONCl (145.6): N, 9.6. Found: N, 9.5.

(4-Pyridyl)-methyl Bromide Hydrobromide.[25]—(4-Pyridyl)-carbinol hydrochloride (1.8 g.) was refluxed with 15 ml. of 49% hydrobromic acid, the solution evaporated to dryness, and the residue washed with absolute ethanol to give 2.8 g. of crude (4-pyridyl)-methyl bromide hydrobromide; m. p. 145–150°. The compound had a very irritating action on the skin.

Anal. Calcd. for $C_6H_7NBr_2$ (253.0): N, 5.5. Found: N, 5.8.

***dl*-β-(4-Pyridyl)-alanine.**—(4-Pyridyl)-methyl bromide hydrobromide (2.8 g.) was refluxed with a solution of sodiobenzamidomalonic ester[7] prepared by adding 0.54 g. of sodium to 5 g. of benzamidomalonic ester dissolved in 50 ml. of toluene. The reaction mixture was filtered, the filtrate extracted with 4 *N* hydrochloric acid, a slight excess of aqueous potassium hydroxide added to the aqueous phase, and the latter extracted with ether. The ethereal solution was dried, filtered, the solvent removed from the filtrate, and the residue recrystallized from aqueous ethanol to give 0.24 g. of condensation product; m. p. 106–107°.[26] The condensation product (0.24 g.) was hydrolyzed as previously described to give 0.11 g. of *dl*-β-(4-pyridyl)-alanine, m. p. 235–236°, after recrystallization from a mixture of isopropyl ether and 80% aqueous ethanol.

Anal. Calcd. for $C_8H_{10}O_2N_2$ (166.2): C, 57.8; H, 6.1; N, 16.9. Found: C, 56.9; H, 6.2; N, 17.0.

The addition of ninhydrin to an aqueous solution of *dl*-β-(4-pyridyl)-alanine resulted in the formation of a red color.

Preliminary Titration Data.—Samples of the amino acids dissolved in 10 ml. of water were titrated at 23° with 0.1 *N* hydrochloric acid and sodium hydroxide. The *p*H measurements were made with a Beckman Laboratory Model *p*H Meter equipped with external shielded electrodes. In the titration of *dl*-β-(2-pyridyl)-alanine and *dl*-β-(3-pyridyl)-alanine the mean volumetric error was less than 0.1% but in the titration of *dl*-β-(4-pyridyl)-

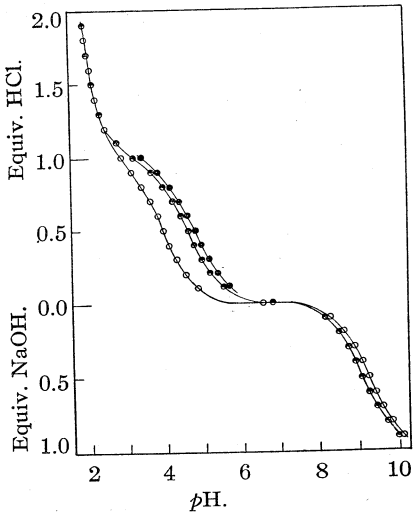


Fig. 1.—O, *dl*-β-(2-Pyridyl)-alanine, volume of solution containing 63.2 mg. of the amino acid after 1.5 equiv. of acid had been added = 17.0 ml.; ◐, *dl*-β-(3-pyridyl)-alanine, volume of solution containing 165.5 mg. of the amino acid after 1.5 equiv. of acid had been added = 27.0 ml.; ●, *dl*-β-(4-pyridyl)-alanine.

(23) Meyer and Mally[18] give a m. p. of 163°.

(24) R. Graf, *J. prakt. Chem.*, **146**, 88 (1936).

(25) All attempts to obtain (4-pyridyl)-methyl chloride directly from (4-pyridyl)-methylamine by treating the latter compound with nitrous acid in the presence of hydrochloric acid were unsuccessful.

(26) A similar yield and a comparable product was obtained when the condensation was carried out in absolute ethanol.

alanine, this error was of the order of 1%. The *p*H measurements were reproducible to within 0.02 of a *p*H unit and in the case of the base titration correction was made for the presence of sodium ion. The titration curves are given in Fig. 1 and the apparent dissociation constants, K_A, K_{B_1}, and K_{B_2}, in Table I.

TABLE I

APPARENT DISSOCIATION CONSTANTS

Amino acid	$K_{B_1} \times 10^{-10}$	$K_{B_2} \times 10^{-13}$	$K_A \times 10^{-10}$
dl-β-(2-Pyridyl)-alanine	0.89 ± 0.05	2 ± 1	6 ± 1
dl-β-(3-Pyridyl)-alanine	3.7 ± .5	5 ± 1	8 ± 1
dl-β-(4-Pyridyl)-alanine	6 ± 1		

Summary

1. The three isomeric *dl*-β-pyridylalanines have been synthesized and their apparent acid and basic dissociation constants determined. The effect of structure on acid and base strength is discussed.

2. Picolinaldehyde and nicotinaldehyde have been synthesized by the McFadyen–Stevens reaction and the applicability of this reaction to the pyridine series is discussed.

PASADENA, CALIFORNIA RECEIVED APRIL 21, 1942

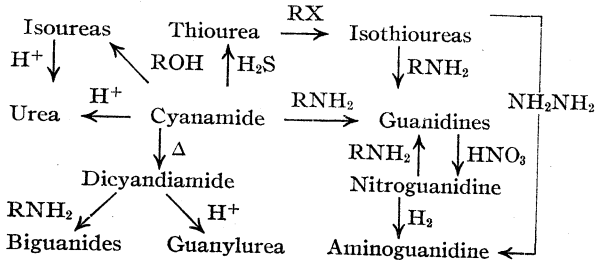
[CONTRIBUTION FROM THE STAMFORD RESEARCH LABORATORIES OF THE AMERICAN CYANAMID COMPANY]

Studies in Chemotherapy. V. Sulfanilylcyanamide and Related Compounds[1]

BY PHILIP S. WINNEK, GEORGE W. ANDERSON, HARRY W. MARSON, H. ELDRIDGE FAITH AND RICHARD O. ROBLIN, JR.

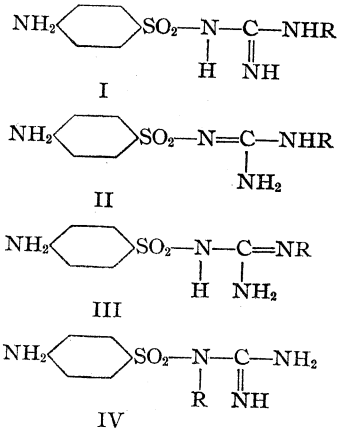
Shortly after sulfanilylguanidine was described in a preceding paper of this series,[2] Marshall and co-workers[3] reported the compound independently. On the basis of a comprehensive bacteriological and pharmacological study, they suggested its use for the treatment of intestinal infections.

Guanidine is one of a large group of compounds which may be prepared from cyanamide. Because of the somewhat unusual characteristics of sulfaguanidine, it appeared to be of interest to investigate the sulfanilyl derivatives of cyanamide and a number of related compounds including a series of substituted guanidines. The following diagram illustrates some of the inter-relationships among this group of substances



Many of the same relationships have been found to exist among the sulfanilyl derivatives of these compounds (Table I). Thus, in addition to the more obvious method, sulfanilylguanidines were prepared from the sulfanilyl derivatives of cyanamide, nitroguanidine and isothioureas. Similarly, sulfanilylcyanamide was converted to the urea or isourea compounds. *p*-Nitrobenzenesulfonyl chloride and isoureas also led to the formation of sulfanilylisoureas, which in turn could be hydrolyzed to the urea derivative.[4] Other similar reactions such as the conversion of sulfanilyldicyandiamide to guanylurea and biguanide derivatives were also investigated.

Because of the alkali insolubility of many of the substituted sulfanilylguanidines (Table I), it was not possible to establish their structure directly when they were prepared through acetylsulfanilyl chloride and the substituted guanidines. For example, the sulfanilylalkylguanidines might have any of the following structures



(1) Presented in part before the Division of Medicinal Chemistry, Memphis meeting of the American Chemical Society, April 22, 1942.

(2) Roblin, Williams, Winnek and English, THIS JOURNAL, **62**, 2002 (1940).

(3) Marshall, Bratton, White and Litchfield, *Bull. Johns Hopkins Hosp.*, **67**, 163 (1940).

(4) *Cf.* Cox and Raymond, THIS JOURNAL, **63**, 300 (1941).

TABLE I

PROPERTIES OF SULFANILYL COMPOUNDS

Compound, sulfanilyl-	M. p.,[a] °C. (cor.)	Water[b] soly. 37°	Alk.[c] soly.	Max. blood[b] level[d]	*In vitro* activity[e]	Method of prepn.	Ref. to interm.	Formula	Analyses,[f] % Calcd. C	H	N	Found C	H	N
Cyanamide	292–5	384	sol.	3.7	Less	A	*i*	$C_7H_7O_2N_3S$	42.6	3.6	21.3	42.5	3.7	21.2
Urea	140–4	811	sol.	7.4	Equal	B, C	*j*	$C_7H_9O_3N_3S$	39.1	4.2	19.5	39.1	4.1	19.2
Methylisourea	172–3	157	sol.	22.6	Equal	D, E	*j*	$C_8H_{11}O_3N_3S$	41.9	4.8	18.3	42.1	4.8	18.3
Ethylisourea	126–7	199	sol.	16.0	Equal	D	*j*	$C_9H_{13}O_3N_3S$	44.4	5.4	17.3	44.7	5.4	17.2
Methylisothiourea	184–5	33	sol.	8.6	Equal	F	*k*	$C_8H_{11}O_2N_3S_2$	39.2	4.5	17.1	39.2	4.5	17.2
Ethylisothiourea	154–5	30	sol.	6.4	Equal	F	*l*	$C_9H_{13}O_2N_3S_2$	41.7	5.0	16.2	41.8	5.1	16.2
Guanidine[g]	189–90	190	in.	2.6[h]	Standard									
Nitroguanidine	194–5	44	sol.	2.8	Less	G	*i*	$C_7H_9O_4N_5S$	32.4	3.5	27.0	32.5	3.6	27.0
Aminoguanidine	209–10	188	in.	2.8	Greater	H, m	*j*	$C_7H_{11}O_2N_5S$	36.7	4.8	30.6	36.7	4.7	30.8
Ethylguanidine	160–1	226	in.	4.2	Equal	G	*n*	$C_9H_{14}O_2N_4S$	44.6	5.8	23.1	44.4	5.7	23.5
Propylguanidine	147–8	429	in.	12.0	Sl. less	G	*o*	$C_{10}H_{16}O_2N_4S$	46.9	6.2	21.9	46.8	6.0	21.6
Butylguanidine	184–6	28	in.	6.9	Less	G, H	*p*	$C_{11}H_{18}O_2N_4S$	48.9	6.7	20.7	49.1	6.7	20.7
Phenylguanidine	231–3	24	in.	1.6	Equal	I, J	*j*	$C_{13}H_{14}O_2N_4S$	53.8	4.8	19.3	53.8	4.7	19.6
p-Aminophenylguanidine	200–1	205	in.	2.4	Equal	J	*j*	$C_{13}H_{15}O_2N_5S$	51.1	4.9	22.9	51.1	4.6	22.6
p-Carboxyphenylguanidine	234–5	19	sol.	0.8	Less	J	*j*	$C_{14}H_{14}O_4N_4S$	50.3	4.2	16.8	50.2	4.1	16.6
2-Pyridylguanidine	239–41	2.6	in.	3.4	Sl. less	J	*j*	$C_{12}H_{13}O_2N_5S$	49.5	4.5	24.0	49.5	4.3	23.6
Dicyandiamide	236–7	255	sol.	1.2	Less	G	*i*	$C_8H_9O_2N_5S$	40.2	3.8	29.3	40.3	3.8	29.2
Guanylurea	225–6	20	sol.	1.3	Sl. less	B, G	*q*	$C_8H_{11}O_3N_5S$	37.3	4.3	27.2	37.2	4.4	27.4
Biguanide	244–5	134	in.	1.3	Less	G	*r*	$C_8H_{12}O_2N_6S$	37.4	4.7	32.8	37.6	4.9	33.1
Butylbiguanide	214–5	5.4	in.	2.8	Less	G	*r*	$C_{12}H_{20}O_2N_6S$	46.1	6.4	26.9	46.4	6.4	26.6
Dimethylbiguanide	191–2	28	in.	3.0	Equal	G	*s*	$C_{10}H_{16}O_2N_6S$	42.2	5.6	29.6	42.2	5.7	29.5
o-Tolylbiguanide	214–6	8.0	in.	1.5	Less	G, I	*t*	$C_{16}H_{18}O_2N_6S$	52.0	5.2	24.3	52.5	5.1	24.6

[a] With decomposition. [b] Mg./100 cc. [c] Sol. indicates greater solubility in alkali than in water; in., no greater than in water. [d] White mice; dosage 0.5 g./kg. body weight. [e] Relative bacteriostatic activity compared with sulfaguanidine against *B. coli* in a synthetic medium. [f] Microanalyses were carried out in these Laboratories by Mrs. Thelma Kirk and the Misses Helen Chubb, Margaret Oliver, Rebecca Teston and Lucy Vandervort. [g] Refs. 2 and 3. [h] Average of large number of determinations. [i] American Cyanamid Co., New York, N. Y. [j] This paper. [k] Arndt, *Ber.*, **54B,** 2236 (1921). [l] Taylor, *J. Chem. Soc.*, **111,** 656 (1917). [m] Also prepared by iron reduction of sulfanilylnitroguanidine; m. p. N^4-acetylsulfanilylaminoguanidine 256–7°. [n] Schenck and Kirchhof, *Z. physiol. Chem.*, **154,** 292 (1926). [o] Piovano, *Gazz. chim. ital.*, **58,** 245 (1928). [p] Davis and Elderfield, THIS JOURNAL, **54,** 1499 (1932). [q] Söll and Stutzer, *Ber.*, **42,** 4534 (1909). [r] Rackmann, *Ann.*, **376,** 169 (1910). [s] Slotta and Tscheschi, *Ber.*, **62,** 1400 (1929). [t] U. S. Patent 2,195,073.

However, the synthesis of a sample of sulfanilylbutylguanidine from N^4-acetylsulfanilylmethylisothiourea and butylamine[5] identical with the product obtained from acetyl sulfanilyl chloride and butylguanidine served to eliminate formula IV as a possibility. We have not attempted to differentiate conclusively among formulas I, II and III, because they are potentially tautomeric isomers. With the possible exception of sulfanilyl-*p*-carboxyphenylguanidine, alkali solubility would seem to favor I, since there appears to be a general tendency against the formation of III.[6]

The use of sulfaguanidine for intestinal infections is based on the fact that, while it has a reasonable degree of water solubility and therapeutic activity, it is poorly absorbed. These properties result in a high concentration in the intestinal tract without a correspondingly high level in the blood and tissues. The most important properties for compounds of this type then appear to be activity against the coliform group of organisms, degree of absorption and solubility. Given these data for a new substance, it should be possible to determine whether or not it merits further investigation. These properties for the compounds reported in this paper are recorded in Table I.[7]

It is interesting that in general the presence of a guanidyl radical resulted in low absorption. An exception to this were the alkyl guanidines, which were more completely absorbed. Other closely related compounds which lacked the guanidyl group were also absorbed.

Sulfanilylaminoguanidine was the only substance in this group which was more active *in vitro* against *B. coli* than sulfaguanidine. From the standpoint of absorption in mice and water solubility there appears to be little to choose between these two compounds. Since the preliminary results indicate that the amino derivative is bacteriostatic at higher dilutions than sulfaguanidine, it is possible that a further study of sulfanilylaminoguanidine may demonstrate it to be useful in the treatment of intestinal infections.

(5) *Cf.* Phillips and Clarke, THIS JOURNAL, **45,** 1755 (1923).

(6) Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 2nd ed., 1940, p. 213.

(7) The bacteriological and pharmacological studies were carried out in this Laboratory under the direction of Dr. W. H. Feinstone.

Experimental

A number of different procedures have been used in preparing the sulfanilyl derivatives reported in this paper. In most cases only one example of each method is described in detail. Other derivatives prepared by the same general procedure are designated in Table I. Whenever the same compound was prepared by more than one method, the identity of the different samples was established by mixed melting points as well as separate analyses.

(Method A) Sulfanilylcyanamide.—Commercial calcium cyanamide (220 g. of minimum hydrated) was stirred in 1300 cc. of water for three hours at 25–30°. To the filtrate from this mixture (about a 10% solution of $Ca(HNCN)_2$) was added with stirring, over a period of forty-five minutes, 200 g. (0.855 mole) of acetylsulfanilyl chloride at a temperature of 25–30°. The reaction mixture was kept alkaline by adding 40% sodium hydroxide solution as required. Stirring was continued for two hours, during which time a precipitate separated. After filtering the cooled mixture, the precipitate was washed with cold water and then with acetone. A yield of 162 g. (73%) of calcium acetylsulfanilyl cyanamide was obtained. Without further purification the product analyzed as follows: Ca (calcd.) 7.75%; Ca (found) 7.73%.

Thirteen grams (0.025 mole) of the acetyl derivative was refluxed with 60 cc. of 10% sodium hydroxide solution for thirty-five minutes and filtered while hot. The cooled filtrate was then made strongly acid with concentrated hydrochloric acid to separate the sulfanilyl cyanamide. It was purified by dissolving in alkali, treating with activated charcoal, filtering and precipitating with hydrochloric acid. The yield amounted to 9.8 g. (95%).

Sulfanilylcyanamide was also prepared by treating *p*-nitrobenzenesulfonyl chloride with free cyanamide in an aqueous medium in the presence of an excess of sodium hydroxide. The resulting sodium *p*-nitrobenzenesulfonylcyanamide was reduced to sulfanilylcyanamide with iron powder and 5% acetic acid.

(Method B) Sulfanilylurea.—Three grams (0.0058 mole) of calcium acetylsulfanilylcyanamide and 20 cc. of 4 *N* hydrochloric acid were warmed together on a steam-bath until solution was complete (fifteen to twenty minutes). When the solution was cooled a gummy solid separated. It was filtered off and dried. A yield of 2 g. (82%) of crude sulfanilylurea was obtained. The product was purified by repeated crystallization from water.

(Method C) Sulfanilylurea was also prepared from sulfanilylmethylisourea (see Methods D and E) by hydrolysis with concentrated hydrochloric acid on a steam-bath.[4]

(Method D) Sulfanilylmethylisourea.—14.9 g. (0.06 mole) of sodium *p*-nitrobenzenesulfonylcyanamide was added to 100 cc. of absolute methanol; most of the salt dissolved. Eight grams (0.22 mole) of hydrochloric acid gas was bubbled in from a cylinder in fifteen to twenty minutes with ice cooling. A white precipitate formed immediately. After one and one-half hours of standing in a stoppered flask at room temperature, the solid was filtered off and washed with methanol. It was then slurried with 25 cc. of water, made alkaline with ammonium hydroxide, filtered off and washed with 25 cc. of water, then with methanol. A yield of 14.4 g. (93%) of crude *p*-nitrobenzenesulfonylmethylisourea was obtained. It was purified by recrystallizing twice from methanol. Sulfanilylmethylisourea was produced in 81% yield by reduction of the purified nitro compound with iron powder in 5% acetic acid.

Sulfanilylmethylisourea was made more simply by the reaction of calcium acetylsulfanilylcyanamide with methanol and dry hydrochloric acid. Hydrolysis of the acetyl group apparently took place during the reaction, since the final compound was isolated directly from the reaction mixture.

(Method E) Sulfanilylmethylisourea was obtained also from *p*-nitrobenzenesulfonyl chloride and methylisourea hydrochloride following the general method of Cox and Raymond.[4] The nitro group was reduced as described under Method D.

(Method F) Sulfanilylmethylisothiourea was prepared from acetylsulfanilyl chloride and methylisothiourea sulfate by the general procedure described in a previous paper.[8] A mixture of 10 g. (0.035 mole) of acetylsulfanilylmethylisothiourea obtained by this procedure, 20 cc. of concentrated hydrochloric acid and 100 cc. of 95% ethanol was heated to boiling and the boiling continued for two minutes after all solid material had dissolved. The reaction mixture was then neutralized with 20% sodium hydroxide and cooled. The resulting precipitate of sulfanilylmethylisothiourea was purified by crystallization from water; yield 3.6 g. (42%).

(Method G) Sulfanilylpropylguanidine.—Fifteen grams (0.1 equiv.) of propylguanidine sulfate was suspended in 120 cc. of acetone and 10 g. (0.25 mole) of sodium hydroxide dissolved in 20 cc. of water was added. The mixture was cooled to 20°, and 25 g. (0.107 mole) of acetylsulfanilyl chloride was added gradually with stirring, while the temperature was maintained at 18–22°. After the reaction mixture had been stirred for four hours at room temperature, it was allowed to stand overnight. It was then diluted with 200 cc. of water and neutralized with acetic acid. Acetylsulfanilylpropylguanidine separated as a white solid, which was filtered off, washed with water and dried. The yield was 23 g. (78%) of crude product.

Nine grams (0.03 mole) of the crude acetyl compound was suspended in 21 cc. of 4 *N* hydrochloric acid and the mixture heated to boiling. All solid material was dissolved after five minutes and boiling was continued for three minutes. At this point a precipitate started to form. The mixture was at once diluted with two volumes of ice and the cold solution stirred for one hour with activated charcoal. The filtrate from this mixture was neutralized in the cold with 20% sodium hydroxide solution. Crude sulfanilylpropylguanidine separated as a gum which on stirring in the cold turned to a white solid. It was purified by crystallizing twice from hot water. A yield of 3 g. (40%) was obtained.

(Method H) Sulfanilylbutylguanidine.—4.1 g. (0.014 mole) of *p*-acetylsulfanilylmethylisothiourea was suspended in 20 cc. of 50% ethanol in a 3-necked flask fitted with a mercury-sealed stirrer and a reflux condenser leading through wash-bottles containing dilute hydrochloric

(8) Roblin and Winnek, THIS JOURNAL, **62**, 1999 (1940).

acid and sodium hydroxide solution; 0.86 g. (0.012 mole) of butylamine was added and the mixture warmed slowly with stirring on a steam-bath. There was a slow evolution of gas and after two hours the solid had dissolved. Heating was continued for one hour and the reaction mixture was then diluted with water and the acetylsulfanilylbutylguanidine separated as a solid; yield 3.5 g. (94%). Hydrolysis to sulfanilylbutylguanidine was accomplished by the method described under Method G except that 50% ethanol was employed as the medium.

(Method I) Sulfanilylphenylguanidine.—21.1 grams (0.07 mole) of acetylsulfanilylnitroguanidine, 13 g. (0.14 mole) of aniline, and 60 cc. of dioxane were refluxed for seven hours. All the solids had dissolved after the first half hour and the dark solution was allowed to stand overnight. Dilution with 200 cc. of water gave a sticky precipitate. The mixture was made slightly alkaline with ammonium hydroxide to dissolve any unreacted acetylsulfanilylnitroguanidine. After standing in the refrigerator for several hours, the oily material completely solidified. This was filtered off, washed with very dilute ammonia, and dried. The yield was 12.6 g. (54%). It was purified by crystallization from dilute alcohol. Deacetylation was carried out as described under Method G.

(Method J) Sulfanilyl-*p*-aminophenylguanidine.—7.5 grams (0.05 mole) of *p*-aminoacetanilide (Eastman Kodak Co., Rochester, N. Y.) was suspended in 50 cc. of water and 4 cc. of concentrated hydrochloric acid and 13 g. (0.025 mole) of calcium acetylsulfanilylcyanamide was added. A thick slurry resulted, which on heating to boiling dissolved. The mixture was refluxed for one-half hour and during the last fifteen minutes a light yellow precipitate separated. After cooling the product was filtered off, washed with water and dried. The crude acetylsulfanilyl-*p*-acetylaminophenylguanidine obtained in this manner amounted to 13 g. (67%). It was hydrolyzed as described under Method G in 54% yield.

Sulfanilyl-2-pyridylguanidine was obtained by a modification of the above method. Equivalent quantities of 2-aminopyridine hydrochloride and calcium acetylsulfanilylcyanamide were heated together at 200° for fifteen minutes. The resulting acetylsulfanilyl-2-pyridylguanidine was deacetylated by refluxing with 4 *N* hydrochloric acid. The yield of purified product was about 10%.

Sulfanilyldicyandiamide.—The acetyl derivative of this compound was obtained through the courtesy of Dr. D. W. Kaiser of this Laboratory. It was prepared by him using Method G. Sulfanilyldicyandiamide resulted from the alkaline hydrolysis of the intermediate acetyl derivative by the procedure described under Method A.

Sulfanilylguanylurea was prepared both by Method G and from the acid hydrolysis of acetylsulfanilyldicyandiamide employing the procedure described in Method B for the conversion of the cyanamide to the urea derivative. The product obtained by the latter method was somewhat difficult to purify. Only after fractional precipitation from alkaline solution was the melting point as high as that of the product obtained by Method G. Since only one product can be obtained from the dicyandiamide derivative, this method of synthesis in conjunction with the alkali solubility served to indicate the structure of sulfanilylguanylurea.

Sulfanilylbiguanides were produced by the same process that was employed for a number of the guanidines (Method G). In addition, sulfanilyl-*o*-tolylbiguanide was obtained by the reaction of acetylsulfanilyldicyandiamide and *o*-toluidine followed by hydrolysis. The conditions were the same as those described under Method I. This method helped to establish the structure of the *o*-tolyl derivative and by analogy the structure of the other sulfanilylbiguanides.

Summary

A group of sulfanilyl derivatives of cyanamide and related compounds has been prepared. The interrelationships among this group of compounds have made it possible to obtain many of them by more than one method. On the basis of this and other evidence the structure of the sulfanilyl derivatives is discussed.

The absorption, water solubility and bacteriostatic activity of these substances compared with sulfaguanidine are reported. These preliminary data suggest that sulfanilylaminoguanidine may be worth further investigation.

STAMFORD, CONNECTICUT RECEIVED APRIL 9, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF MOUNT HOLYOKE COLLEGE]

A Further Study of the Cyclization of Ureido Derivatives of Unsymmetrical Iminodibasic Acids Together with the Synthesis of Certain Hydantoins and Other Related Compounds[1]

BY DORIS R. SEEGER AND ANNE MACMILLAN

Observations have been reported separately to the effect that neither the acyclic ureidic derivative of phenylalanine-N-acetic acid,[2] $NH_2CON(CH_2COOH)CH(CH_2C_6H_5)COOH$, nor the corresponding phenylureide of tyrosine-N-acetic acid,[3] $C_6H_5NHCON(CH_2COOH)CH(CH_2C_6H_4OH)COOH$, has ever been obtained in pure condition. Indeed both appear to be so unstable that when formed by the hydrolysis of their esters or salts, they suffer ring closure almost instantly with the elimination of water and the formation of the corresponding hydantoin derivatives. Attention has not yet been called, however, to the fact that the dimethyl esters of such compounds also show a tendency to cyclization, in this case with the elimination of one molecule of alcohol and the formation of an acetic ester derivative of the corresponding hydantoin.[4] Even more significant is the observation that under all conditions and in the case of all of these diesters and acids only one of the two carboxyl groups enters into a reaction with the ureidic hydrogen atom, although theoretically unsymmetrical dibasic acids of this kind might be expected to form a mixture of two isomeric hydantoins, *i. e.*

(1*a*) $HOOCCH_2\overline{NCONHCOCHCH_2C_6H_5}$ and

(2*a*) $HOOC(CH_2C_6H_5)CH\overline{NCONHCOCH_2}$, or

(1*b*) $HOOCCH_2\overline{NCON(OC_6H_5)COCHCH_2C_6H_4OH}$ and

(2*b*) $HOOC(CH_2C_6H_4OH)CH\overline{NCON(C_6H_5)COCH_2}$

Actually hydantoins of the second type have never been isolated except under conditions which precluded the participation of the substituted acetic acid group in the condensation.[5]

The present investigation was undertaken in order to determine whether a phenylureide of phenylalanine-N-acetic acid, $C_6H_5NHCON(CH_2COOH)CH(CH_2C_6H_5)COOH$, would behave in the same way as the corresponding derivative of tyrosine-N-acetic acid and thus furnish additional evidence in support of the assumption that, in general, substituted acetic acid residues tend to dissociate their hydroxyl groups much more readily than unsubstituted residues. Accordingly a dimethyl ester of the above ureide was prepared by treating the free dimethyl ester of phenylalanine-N-acetic acid, dissolved in absolute ether, with phenyl isocyanate

$$\begin{matrix} & CH_2COOCH_3 \\ NH & \\ & CH(CH_2C_6H_5)COOCH_3 \end{matrix} + C_6H_5NCO \longrightarrow C_6H_5NHCON\begin{matrix} CH_2COOCH_3 \\ CH(CH_2C_6H_5)COOCH_3 \end{matrix}$$

Under these conditions the product separated almost instantly in exceptionally pure condition and in quantitative amounts. Its conversion into methyl N-3-phenyl-C-5-benzylhydantoin-N-1-acetate was effected with equal ease since solution in absolute methyl alcohol containing one equivalent of sodium methoxide[6] was followed within five minutes by precipitation of the calculated quantity of the pure ester. On the other hand, the corresponding hydantoin acid

(1*c*) $HOOCCH_2\overline{NCON(C_6H_5)COCHCH_2C_6H_5}$,

was obtained by the action of aqueous hydrochloric acid upon the acyclic ester. In both cases the condensations were exactly analogous to those previously reported.

The configuration of the hydantoin (1*c*) was subsequently established by means of a separate synthesis which involved the following series of transformations

(1) $NH_2CH_2COOH + C_6H_5NCS \longrightarrow \overline{NHCSN(C_6H_5)COCH_2}$ [7]

(2) $\overline{NHCSN(C_6H_5)COCH_2} + C_6H_5CHO \longrightarrow \overline{NHCSN(C_6H_5)COC{=}CHC_6H_5}$ [8]

(3) The product, N-3-phenyl-2-thio-5-benzalhy-

(1) Grateful acknowledgment is due Dr. Dorothy A. Hahn for suggesting and coöperating in this research.

(2) Hahn and Endicott, THIS JOURNAL, **60**, 1040 (1938).

(3) Ware, *ibid.*, **60**, 2653 (1938).

(4) Hahn, McLean and Endicott, *ibid.*, **62**, 1087 (1940); *cf.* Ware, ref. 3, p. 2655.

(5) Hahn, McLean and Endicott, ref. 4, pp. 1087, 1090, 1091.

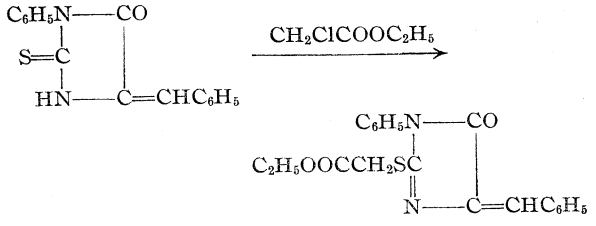
(6) Compare Hahn, McLean and Endicott, ref. 4, p. 1088, footnote 8.

(7) Brautlecht, *J. Biol. Chem.*, **10**, 142 (1911); cf. Aschan, *Ber.*, **16**, 1544 (1883) and **17**, 424 (1884); also Marckwald, Neumark and Stelzner, *ibid.*, **24**, 3276 (1891).

(8) Wheeler and Brautlecht, *Am. Chem. J.*, **45**, 448 (1911).

dantoin, which will be referred to again in another connection, was then converted into the corresponding oxy-compound, $\overline{NHCON(C_6H_5)COC}=CHC_6H_5$,[9] by first preparing the ethyl mercapto derivative and then hydrolyzing this in the presence of hydrochloric acid. (4) and (5) The preparation of ethyl N-3-phenylbenzalhydantoin-N-1-acetate[10] was carried out in the usual way[11] and the product then reduced and hydrolyzed simultaneously under the action of hydrogen iodide and red phosphorus.[12] The product finally obtained as a result of the above series of transformations was N-3-phenyl-5-benzylhydantoin-N-1-acetic acid. That it was identical with the compound (1*c*) previously obtained from the corresponding acyclic ureide, was established by a mixed melting point as well as by a detailed comparison of the properties of the two substances.

Supplementary work undertaken during the course of this investigation will now be outlined briefly since, although minor in character, it adds a few facts to what has been previously reported regarding the behavior of three of the substances which have been mentioned. Of these, N-3-phenyl-2-thiobenzalhydantoin[8] and ethyl N-3-phenylbenzalhydantoin-N-1-acetate[10] will be considered first.[13] The thiohydantoin has been observed, for example, to condense readily not only with ethyl chloride to form a mercapto derivative in the manner described by Wheeler and Brautlecht, but also to react almost instantly with α-halogen derivatives of esters of the fatty acids. In the case of ethyl chloroacetate, the reaction takes place as follows



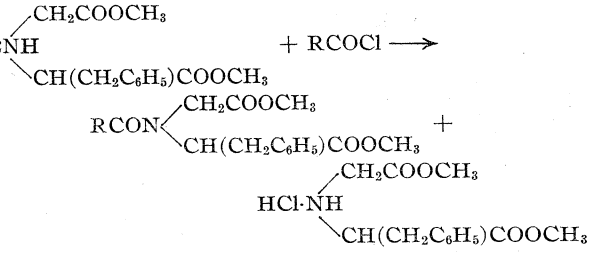
and in the presence of ethyl phenylbromoacetate or ethyl bromopropionate analogous compounds may be obtained. That all of these compounds are true mercapto derivatives was demonstrated by the fact that each, like 2-ethylmercapto-3-phenyl-5-benzalhydantoin, was converted into N-3-phenyl-2-oxybenzalhydantoin when hydrolyzed in the presence of hydrochloric acid.

A study of ethyl N-3-phenylbenzalhydantoin-N-1-acetate revealed that it reacted in a manner closely analogous to ethyl N-3-methylbenzalhydantoin-N-1-acetate when treated with bromine under certain specific conditions,[14] and that two isomeric unsaturated monobromo derivatives were formed. These appear to represent geometric modifications of a compound possessing the following structure

$$C_2H_5OOCCH_2\overline{NCON(C_6H_5)COC}=CBrC_6H_5$$

and may, therefore, be assumed to have resulted from the elimination of hydrogen bromide from a primary dibromo addition product.[15]

A third and somewhat more extended investigation was concerned with an effort to prepare N-acyl derivatives of phenylalanine-N-acetic acid, but in this case only a few positive results were obtained. The free dimethyl ester was first used as a starting point and the experiments carried out by applying Fischer's method of procedure[16]



Since the reaction takes place in an absolute ether solution, its progress can be followed by the separation of the insoluble hydrochloride. However, from among a number of different reagents employed in these experiments positive reactions were observed only in the case of three, namely, acetyl chloride, benzoyl chloride and 3,5-dinitrobenzoyl chloride. Even then only one primary product, *i. e.*

$$3,5\text{-}(NO_2)_2C_6H_3CON(CH_2COOCH_3)CH(CH_2C_6H_5)COOCH_3$$

could be obtained in pure crystalline condition

(9) Wheeler and Brautlecht, ref. 8, p. 451. The product, N-3-phenylbenzalhydantoin, was also prepared by condensing N-3-phenylhydantoin with benzaldehyde according to the method of Wheeler and Hoffman [*Am. Chem. J.*, **45**, 368 (1911)], a reaction which though mentioned as practical by Johnson and Brautlecht [THIS JOURNAL, **33**, 1531 (1911)], was never described in detail. The compound prepared in this way was found to be identical with that prepared by the method of Wheeler and Brautlecht.

(10) Halogen derivatives of this compound will be considered later.

(11) and (12) Compare Litzinger, THIS JOURNAL, **56**, 673, 675 (1934).

(13) Investigations concerning derivatives of these two substances were carried out, respectively, by Shirley M. Vincent and Marian L. Blanchard in connection with work that led to the B.A. degree with Honors in June, 1941.

(14) McLean and Seeger, THIS JOURNAL, **62**, 1416 (1940).

(15) Hahn, McLean and Murphy, *ibid.*, **60**, 1927 (1938); also *cf.* Litzinger, refs. 11, 12, p. 677.

(16) Fischer and Otto, *Ber.*, **36**, 2112 (1903); *cf.* Kossel, *ibid.*, **24**, 4153 (1891).

and in quantitative yields, all other products separating from their ether solution in the form of oils. Of these the acetyl derivative dissociated readily into its components since when its ether solution was treated with dry hydrogen chloride, the hydrochloride of the imino ester was precipitated quantitatively. The benzoyl derivative, on the other hand, was sufficiently stable to admit of transformation into the corresponding disodium salt. The latter formed a well defined crystalline compound which was subsequently identified by comparison with a product resulting from the application of the Schotten–Baumann reaction to phenylalanine-N-acetic acid itself. It may be added that although the latter method of acylation was applied in the case of other reagents, the only compound which was obtained in a condition sufficiently pure for analysis was *m*-nitrobenzoylphenylalanine-N-acetic acid, *m*-$NO_2C_6H_4$-$CON(CH_2COOH)CH(CH_2C_6H_5)COOH \cdot 2H_2O$.

Experimental

The phenylalanine-N-acetic acid[17] and the hydrochloride of the corresponding dimethyl ester[18] were prepared by methods previously reported. However, the yields of the latter were increased from 70% to nearly 100% by surrounding the reaction flask with an ice-bath during saturation with dry hydrogen chloride and then allowing the closed flask to remain for four days at room temperature. The product, when recrystallized from boiling acetone, melted at 144–144.5° with an evolution of gas.

Dimethyl phenylalanine-N-acetate, $NH(CH_2COOCH_3)$-$CH(CH_2C_6H_5)COOCH_3$, was prepared by treatment of the corresponding hydrochloride with an exact equivalent of aqueous sodium carbonate and extraction with ether. It boiled sharply at 182° (10 mm.).

Anal. Calcd. for $C_{13}H_{17}O_4N$: C, 62.13; H, 6.82; N, 5.58. Found: C, 62.11; H, 6.78; N, 5.73.

Dimethyl Ureidophenylalanine-N-acetate, NH_2CON-$(CH_2COOCH_3)CH(CH_2C_6H_5)COOCH_3$, was prepared by adding 0.88 g. of powdered potassium cyanate to a solution of 2 g. of the above ester hydrochloride in 5 cc. of water. The product, an oil which crystallized on stirring, consisted of a mixture of the ureide and methyl 5-benzylhydantoin-N-1-acetate,[19] the latter having formed by ring closure. Although it was impossible to effect complete separation of these two substances, a crystalline compound (m. p. 125–126°) was obtained from absolute methyl alcohol.[20]

Anal. Calcd. for $C_{14}H_{18}O_5N_2$: C, 57.12; H, 6.16; N, 9.52. Found: C, 58.80; H, 5.77; N, 9.52.

Dimethyl Phenylureidophenylalanine-N-acetate, $C_6H_5NHCON(CH_2COOCH_3)CH(CH_2C_6H_5)COOCH_3$, was obtained by adding 1.3 cc. of phenyl isocyanate, dropwise under cooling and stirring, to a solution of 2 g. of dimethyl phenylalanine-N-acetate in 200 cc. of absolute ether. The heavy white crystalline precipitate which began to form almost immediately and was complete at the end of two hours, weighed 1.7 g. and melted to a clear liquid at 124.5–125°. Additional amounts recovered from the filtrate made the yield quantitative.

Anal. Calcd. for $C_{20}H_{22}O_5N_2$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.42; H, 5.78; N, 7.83.

The ureidic ester is very soluble in methyl alcohol, acetone and chloroform; moderately soluble in ether, carbon tetrachloride and boiling water and almost insoluble in cold water. The corresponding acyclic dibasic acid was never obtained since hydrolysis of the ester in the presence of aqueous hydrochloric acid is accompanied simultaneously by ring closure.

$CH_3OOCCH_2\overline{NCON(C_6H_5)COCHCH_2C_6H_5}$, **Methyl N-3-phenyl-5-benzylhydantoin-N-1-acetate,** m. p. 97–97.5°, was obtained by dissolving 3 g. of dimethyl phenylureidophenylalanine-N-acetate in absolute alcohol which contained one equivalent of sodium methoxide (0.19 g. of sodium in 12 cc.).[21] The product precipitated immediately as fine white needles (2.21 g.) and was recrystallized from 50% methyl alcohol (1 g. in 4.4 cc. boiling). Since additional quantities could not be separated from the filtrate, the latter was evaporated to dryness and the residue dissolved in aqueous hydrochloric acid, when 0.45 g. of the corresponding hydantoin acid, m. p. 159–160°, separated, thus bringing the total yield to 98% of the theoretical.

Anal. Calcd. for $C_{19}H_{18}O_4N_2$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.50; H, 5.22; N, 8.55.

This ester is very soluble in methyl alcohol (1 g. in 0.3 cc. boiling and in 1.2 cc. at 20°) and in acetone (1 g. in 0.5 cc. boiling and in 3.5 cc. at 20°). It is extremely stable in the presence of 10% hydrochloric acid (less than 40% being hydrolyzed as a result of heating an aqueous alcohol solution for eight hours) while in the presence of alkali its hydrolysis was accompanied by the formation of decomposition products.[22]

$HOOCCH_2\overline{NCON(C_6H_5)COCHCH_2C_6H_5} \cdot 2H_2O$, **N-3-Phenyl-5-benzylhydantoin-N-1-acetic acid** (1*c*), was obtained in a number of different ways. As previously stated, it resulted from the hydrolysis of dimethyl phenylureidophenylalanine-N-acetate, since the corresponding acyclic acid, $C_6H_5NHCON(CH_2COOH)CH(CH_2C_6H_5)$-$COOH$, is unstable and suffers ring closure the moment it is liberated. The same hydantoin acid was also synthesized from phenylalanine-N-acetic acid by dissolving the latter (5 g.) in aqueous sodium bicarbonate and treating the ice-cold solution with phenyl isocyanate (4 g.) added over a period of four hours under constant stirring, after which the mixture was allowed to stand overnight at room temperature. Following the removal of a small amount of *sym*-diphenyl urea, the clear liquid was diluted to a volume of 500 cc. and treated with 20 cc. of concentrated hydrochloric acid when a heavy oil separated. The latter was transformed into fine white crystals (6.75 g.) by heating

(17) Hahn and Endicott, ref. 2, p. 1042.

(18) Hahn, McLean and Endicott, ref. 4, p. 1089.

(19) Hahn and Endicott, ref. 2, p. 1044.

(20) This compound on hydrolysis suffered ring closure and passed quantitatively into 5-benzylhydantoin-N-1-acetic acid. *Cf.* Hahn and Endicott, ref. 2, p. 1043.

(21) *Cf.* Bailey and Snyder, THIS JOURNAL, **37**, 391 (1915).

(22) That hydrolysis was extensive is shown by the fact that a sodium salt of phenylalanine-N-acetic acid was isolated.

the reaction mixture, and additional quantities obtained from the filtrate made the yield quantitative. The acid, crystallized from boiling water, separated in large transparent prisms which decrepitate at 95° with an evolution of a gas and on exposure to the air, slowly decompose and become opaque. Heated at 110° they lost two molecules of water rapidly, passing into the anhydrous form which melts sharply at 159.5–160°.

Anal. Calcd. for $C_{18}H_{16}O_4N_2 \cdot 2H_2O$: C, 59.99; H, 5.59; N, 7.78; H_2O, 9.91. Found: C, 59.86; H, 5.69; N, 8.20; H_2O, 9.96. Calcd. for $C_{18}H_{16}O_4N_2$: C, 66.68; H, 4.97; N, 8.64. Found: C, 66.87; H, 4.99; N, 8.80.

Since the acid is only slightly soluble in water (1 g. in 400 cc. of boiling and in 2500 cc. at 20°) while very soluble in alcohol (1 g. in 0.4 cc. of boiling and in 2 cc. at 20°), it was conveniently recrystallized from 50% alcohol. It is also very soluble in boiling methyl alcohol (1 g. in 1.8 cc.) and in cold acetone (1 g. in 1.5 cc.), glacial acetic acid and chloroform. It is readily transformed into the corresponding methyl ester when dissolved in methyl alcohol and treated with dry hydrogen chloride.

The configuration of both N-3-phenyl-5-benzylhydantoin-N-1-acetic acid and its methyl ester was finally established by means of a separate synthesis as follows.

$NHCON(C_6H_5)COC{=}CHC_6H_5$, **N-3-Phenyl-5-benzalhydantoin,** m. p. 252–252.5°, was prepared by condensing N-3-phenylhydantoin[23] with benzaldehyde according to the method of Wheeler and Hoffman[24] which consisted in refluxing a mixture of 75 g. of phenylhydantoin, 52 g. of freshly distilled benzaldehyde, 78 g. of fused sodium acetate and 350 cc. of glacial acetic acid for eleven hours. The reaction mixture was then diluted with an equal volume of water, and the product, N-3-phenyl-5-benzalhydantoin[25] (91.78 g.), was freed from traces of the reactants by washing first with boiling water and then with cold alcohol.

The compound is almost insoluble in boiling water; slightly soluble in boiling alcohol (1 g. in 400 cc.) and very soluble in glacial acetic acid (1 g. in 33 cc. boiling and in 224 cc. at 20°) from which it was recrystallized.

Anal. Calcd. for $C_{16}H_{12}O_2N_2$: C, 72.71; H, 4.57; N, 10.60. Found: C, 72.85; H, 4.40; N, 10.78.

$C_2H_5OOCCH_2NCON(C_6H_5)COC{=}CHC_6H_5$, **Ethyl N-3-phenyl-5-benzalhydantoin-N-1-acetate,** m. p. 88.5–89°, was obtained by treating a solution of N-3-phenyl-5-benzalhydantoin (30 g.) in 225 cc. of absolute alcohol containing 3.3 g. of sodium, with freshly distilled ethyl chloroacetate (19.5 g.) and refluxing for eighteen hours after which the precipitate (largely sodium chloride) was filtered and washed with boiling alcohol in which the ester is very soluble. Dry hydrogen chloride gas was then passed into the alkaline solution in order to precipitate phenylbenzalhydantoin (in all 6.5 g. was recovered) from any N-1 sodium salt that remained in solution. The hot filtrate from this second precipitate (volume 850 cc.) when concentrated deposited the product in theoretical amounts, calculated on the phenylbenzalhydantoin that had reacted. The ester crystallized from alcohol as white transparent plates.

Anal. Calcd. for $C_{20}H_{18}O_4N_2$: C, 68.56; H, 5.17; N, 8.00. Found: C, 68.69; H, 5.06; N, 8.22.

The product is readily soluble in alcohol (1 g. in 3 cc. boiling and in 100 cc. at 20°), cold acetone, ether and chloroform. All attempts to prepare a geometric isomer of this ester were fruitless although two modifications are theoretically possible and have been isolated in other cases.[26]

The transformation of this unsaturated ester into the corresponding saturated acid, which served to establish the configuration of the latter, was accomplished in the following way. The ester (20 g.), mixed with hydrogen iodide (54 cc., sp. g. 1.7) and red phosphorus (3.5 g.), was heated over a metal bath kept at a temperature of 140–145° until no further distillate was given off after which the excess hydrogen iodide was removed under reduced pressure. The residue was then extracted with boiling water and finally the product was extracted from the red phosphorus with boiling alcohol. The filtrate was concentrated to 100 cc. and treated with an equal volume of boiling water. On cooling it deposited 16.8 g. of the crystalline hydrate additional quantities of which were recovered from the filtrate, indicating a quantitative reaction. This acid was not only identical in all respects with that obtained from the interaction of phenylalanine-N-acetic acid and phenyl isocyanate, but it formed a methyl ester which was the same as that obtained from dimethyl phenylureidophenylalanine-N-acetate as a result of ring closure.

As stated in the introduction, two of the unsaturated hydantoins which were prepared during the course of the above investigation were made the subjects of special study. Of these the first, N-3-phenyl-2-thiobenzalhydantoin,[8] was transformed into three new mercapto derivatives and the second, ethyl N-3-phenyl-5-benzalhydantoin-N-1-acetate,[10] into two isomeric monobromo substitution products. A description of the experimental work follows.

N-3-Phenyl-2-thio-5-benzalhydantoin, prepared according to the method of Wheeler and Brautlecht,[8] was first transformed into the corresponding 2-ethylmercapto derivative[27] as a check on subsequent experiments. It was then treated with ethyl chloroacetate, ethyl phenylbromoacetate and ethyl α-bromopropionate, respectively, under exactly analogous conditions, *i. e.*, 10 g. of the hydantoin, dissolved in 75 cc. of absolute alcohol containing 1.1 equivalents of sodium, reacting with a slight excess of the reagent. In each case the transformation was either instantaneous or complete after the mixture had been heated for thirty minutes, and on cooling the product separated in almost pure condition in the form of pale yellow needles or plates. Yields varied from 86 to 96% of the theoretical value depending somewhat upon the solubility of the compound, which was recrystallized from alcohol. The melting points, solubilities in alcohol and analyses of the individual products are listed below.

(23) Prepared according to the method developed by Paal, *Ber.*, **27**, 975 (1894), and Mouneyrat, *ibid.*, **33**, 2393 (1900).

(24) Wheeler and Hoffman, *Am. Chem. J.*, **45**, 368 (1911). This reaction was mentioned as practical by Johnson and Brautlecht (ref. 9) but never described in detail.

(25) This compound, when prepared from N-3-phenyl-2-thio-5-benzalhydantoin, was reported by Wheeler and Brautlecht (ref. 8, p. 451) to melt between 242° and 243°. This melting point can be raised ten degrees by repeated recrystallizations.

(26) Compare Litzinger, ref. 11, p. 673; Hahn and Gilman, THIS JOURNAL, **47**, 2953–61 (1925).

(27) Wheeler and Brautlecht, ref. 8, p. 450.

$\overline{N{=}CS(CH_2COOC_2H_5)N(C_6H_5)COC}{=}CHC_6H_5$, **Ethyl N-3-phenyl-5-benzalhydantoin-2-mercaptoacetate,** m. p. 142–144°; 1 g. in 21 cc. boiling and in 325 cc. at 20°.

Anal. Calcd. for $C_{20}H_{18}O_3N_2S$: C, 66.55; H, 4.95; N, 7.65; S, 8.75. Found: C, 66.51; H, 5.31; N, 7.72; S, 8.68.

$\overline{N{=}CS[CH(C_6H_5)COOC_2H_5]N(C_6H_5)COC}{=}CHC_6H_5$, **Ethyl N-3-phenyl-5-benzalhydantoin-2-mercaptophenylacetate,** m. p. 156–156.5°; 1 g. in 40 cc. boiling and in 400 cc. at 20°.

Anal. Calcd. for $C_{26}H_{22}O_3N_2S$: C, 70.57; H, 5.01; N, 6.33; S, 7.25. Found: C, 70.14; H, 5.06; N, 6.55; S, 7.24.

$\overline{N{=}CS[CH(CH_3)COOC_2H_5]N(C_6H_5)COC}{=}CHC_6H_5$, **Ethyl N-3-phenyl-5-benzalhydantoin-2-mercaptopropionate,** m. p. 111–112°; 1 g. in 7 cc. of boiling and in 150 cc. at 20°.

Anal. Calcd. for $C_{21}H_{20}O_3N_2S$: C, 66.30; H, 5.30; N, 7.36; S, 8.43. Found: C, 65.76; H, 5.07; N, 7.41; S, 8.08.

All three compounds when dissolved in alcohol and boiled for fifteen minutes with concentrated hydrochloric acid passed quantitatively into N-3-phenyl-5-benzalhydantoin,[9] their behavior being analogous to that of 2-ethylmercapto-N-3-phenyl-5-benzalhydantoin.

$C_2H_5OOCCH_2\overline{NCON(C_6H_5)COC}{=}CBrC_6H_5$, **Ethyl N-3-phenyl-5-α-bromobenzalhydantoin-N-1-acetate,** exists in two isomeric modifications: *a*, m. p. 124–125°, and *b*, m. p. 98–100°, which were formed simultaneously when ethyl N-3-phenyl-5-benzalhydantoin-N-1-acetate,[10] dissolved in glacial acetic acid, was treated with a molecular equivalent of bromine.[28] During the process of eliminating hydrogen bromide from the reaction mixture the acetic acid was gradually displaced by carbon tetrachloride. On evaporation of the solvent, the product separated as a heavy oil which was partially resolved into its components by fractional crystallization from 60% alcohol, the ester *a* being relatively less soluble than *b*. Purification was complicated by the fact that both compounds are extremely soluble in all solvents and tend to form oily mixtures. Moreover, the substance[10] from which they were obtained is almost equally soluble.

Anal. Calcd. for $C_{20}H_{17}N_2O_4Br$: C, 55.44; H, 3.99; N, 6.53; Br, 18.61. Found: *a*, m. p. 124–125°, C, 56.30; H, 3.60; N, 6.84; Br, 18.42. Found: *b*, m. p. 98–100°, C, 55.98; H, 3.92; N, 6.98; Br, 18.89.

As stated in the introduction, dimethyl phenylalanine-N-acetate was treated successively with a number of different acyl chlorides. The procedure, which was the same in all cases, consisted in treating a solution of 2 g. of the free ester in 200 cc. of ether with one-half of a molecular equivalent of the acid chloride. In cases where a reaction took place, separation of the hydrochloride of the ester began immediately and was complete at the end of two hours; in cases where no precipitate had formed at the end of five hours, the original ester was recovered in quantitative amounts in the form of its hydrochloride by passing dry hydrogen chloride into the solution.

(28) *Cf.* McLean and Seeger, ref. 14, p. 1418.

$(NO_2)_2C_6H_3CON(CH_2COOCH_3)CH(CH_2C_6H_5)COOCH_3$, **Dimethyl 3,5-dinitrobenzoylphenylalanine-N-acetate,** m. p. 102–103°, formed in quantitative yield and crystallized from absolute alcohol in fine white needles growing in clusters.

Anal. Calcd. for $C_{20}H_{19}O_9N_3$: C, 53.91; H, 4.30; N, 9.43. Found: C, 53.57; H, 4.21; N, 9.71.

Attempts to transform this product into either the corresponding acid or salt were unsuccessful.

Dimethyl benzoylphenylalanine-N-acetate, $C_6H_5CON(CH_2COOCH_3)CH(CH_2C_6H_5)COOCH_3$, was obtained in the form of a heavy oil which refused to crystallize. That the product consisted exclusively of an ester of the benzoyl derivative was shown by the fact that an ether solution of the oil gave no precipitate when treated with dry hydrogen chloride. Moreover, when warmed with two equivalents of sodium hydroxide dissolved in aqueous alcohol, the ester passed quantitatively into the corresponding disodium salt. The latter, recrystallized from aqueous alcohol, melted at 288–289° (dec.) and was identified by means of the following synthesis.

Disodium benzoylphenylalanine-N-acetate, $C_6H_5CON(CH_2COONa)CH(CH_2C_6H_5)COONa\cdot 2H_2O$, m. p. 288–289° (dec.), was prepared by treating a solution of 5 g. of phenylalanine-N-acetic acid and two equivalents (3.8 g.) of sodium bicarbonate in 45 cc. of water with three equivalents of benzoyl chloride and six equivalents of sodium bicarbonate, the reagents being added alternately over a period of twelve hours. Concentrated hydrochloric acid was then added in excess, the precipitated gum taken up in ether and the solution extracted with the same solvent. In this way the benzoic acid and the benzoyl derivative of phenylalanine-N-acetic acid were separated from any imino dibasic acid which had failed to react (1.06 g.),[29] the latter remaining in solution as the hydrochloride. The combined ether extractions were then extracted with 10% sodium hydroxide, and the salt solution was concentrated to 10 cc. and treated with an equal volume of boiling absolute alcohol. Upon standing overnight 2.19 g. of thin, white, glistening plates separated and when absolute alcohol was added to successively concentrated filtrates, additional quantities (3.5 g.) of the same substance were obtained.[30] The salt was purified by treating its cold aqueous solution (1 g. in 2 cc.) with an equal volume of absolute alcohol.

Anal. Calcd. for $C_{18}H_{15}O_5NNa_2\cdot 2H_2O$: C, 53.09; H, 4.70; N, 3.44; Na, 11.29. Found: C, 53.01; H, 4.45; N, 3.64; Na, 11.06.

During the process of recrystallization an isomeric salt *b*, which melted sharply at 272–273° (dec.), was isolated. The latter, which appeared to be much more soluble in 50% alcohol than the compound, m. p. 288–289°, also separated as white, glistening plates. The configuration of these salts is uncertain. It may be noted also that neither on heating at 110° loses its water of crystallization, although the presence of two molecules is indicated from the results of analysis.

(29) This was identified following the hydrolysis of the hydrochloride; *cf.* Hahn and Endicott, ref. 2, p. 1041, footnote 4.

(30) In all, the yield corresponded to 86% of the theoretical as calculated upon the number of grams of imino acid which had reacted.

Anal. b. Calcd. for $C_{18}H_{15}O_5NNa_2 \cdot 2H_2O$: C, 53.09; H, 4.70; Na, 11.29. Found: C, 53.09; H, 4.41; Na, 11.26.

***m*-Nitrobenzoylphenylalanine-N-acetic acid,** $NO_2C_6H_4CON(CH_2COOH)CH(CH_2C_6H_5)COOH \cdot 2H_2O$, was obtained in two different crystalline modifications, one of which (*a*) melts at 90–92° and decomposes with the evolution of a gas at 105°, while the other (*b*) remains unchanged until 105° when it decrepitates with the evolution of a gas, melting at 130–131° (dec.). Both substances were formed under the conditions described above except that potassium hydroxide was used in place of the sodium bicarbonate and it was found expedient to spread the addition of the *m*-nitrobenzoyl chloride and alkali over a period of thirty-six hours. Moreover, following the addition of hydrochloric acid, a gum was precipitated which crystallized on treatment with ether, yielding 3.81 g. of the product *a* in the form of thin creamy-white, glistening plates. Additional quantities obtained from the filtrate brought the percentage yield to approximately 65% of the theoretical value. The product was recrystallized from water (1 g. soluble in 50 cc. boiling and in 100 cc. at 20°).

The product *b*, isolated in small quantities during the process of recrystallizing *a*, has the same crystalline form but is more soluble in water.

Anal. Calcd. for $C_{18}H_{16}O_7N_2 \cdot 2H_2O$: C, 52.91; H, 4.94; N, 6.88. Found: *a*, C, 52.71; H, 4.79; N, 7.19. Found: *b*, C, 52.20; H, 5.02; N, 7.25.

Summary

Both dimethyl phenylureidophenylalanine-N-acetate and the corresponding acyclic dibasic acid undergo condensation, with the elimination of one molecule of methyl alcohol and one molecule of water, respectively, to form in each case only one of the two isomeric cyclic compounds which might be expected on the basis of purely theoretical considerations. These results agree with previous observations in showing that a marked difference exists between the reactivities of the two acid complexes present in certain unsymmetrical iminodibasic acids. Moreover, the configuration of the product, which has been definitely established in each case, indicates that in all instances so far reported ring closure always takes place in the same general sense.

New derivatives of N-3-phenyl-2-thiobenzalhydantoin and of ethyl N-3-phenylbenzalhydantoin-N-1-acetate are described, together with others obtained by the action of certain acyl chlorides upon phenylalanine-N-acetic acid and its dimethyl ester.

SOUTH HADLEY, MASS. RECEIVED APRIL 7, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF RICHMOND]

Local Anesthetics. I. β-Monoalkylaminoethyl Esters of Alkoxybenzoic Acids[1]

BY J. STANTON PIERCE, J. M. SALSBURY AND J. M. FREDERICKSEN

The majority of the synthetic local anesthetics are alkamine esters of the type $XC_6H_4COO(CH_2)_yNR_2$ in which X usually is the primary amino group, *y* is 2 or 3, and R is an alkyl group. Goldberg and Whitmore[2] have demonstrated that the tertiary amino group, above, can be replaced advantageously by a secondary amino group. Other investigators[3] have shown that in the above type formula, X can be an alkoxy group. This investigation takes up the preparation of alkamine esters of the type $ROC_6H_4COOCH_2CH_2NHR'$.

Most of the alkoxybenzoic acids reported in this work have been made by previous investigators.[4] For this investigation the alkoxybenzoic acids not obtainable from Eastman Kodak Co. were made from the methyl or ethyl ester of the phenolic acid, according to the method of Cohen and Dudley,[4a] by the alkylation of the ester with alkyl bromide and hydrolysis of the ester.

The alkoxybenzoyl chlorides were prepared from the alkoxybenzoic acids and phosphorus pentachloride in all but one case, that of *p*-allyloxybenzoic acid, when phosphorus trichloride was used.

Most of the β-monoalkylaminoethanols were prepared by the reaction of an alkyl halide with a large excess of ethanolamine, without a solvent. Goldberg[5] recommends the use of approximately equimolar quantities of alkyl bromide and ethanolamine, in alcohol solution. This procedure was not found to be satisfactory for the formation of β-mono-*n*-butylaminoethanol, β-mono-*n*-propylaminoethanol, β-monoallylaminoethanol, and β-

(1) Acknowledgment is made to Dr. E. Emmet Reid, Research Adviser to the Chemistry Department of the University of Richmond, for his advice during the course of this work.

(2) Goldberg and Whitmore, THIS JOURNAL, **59**, 2280 (1937).

(3) Wildman and Thorp, U. S. Patent 1,193,650 (1916); C. Rohmann and Scheurle, *Arch. Pharm.*, **274**, 110–126 (1936).

(4) (a) J. B. Cohen and H. W. Dudley, *J. Chem. Soc.*, 1732–1751 (1910); (b) A. E. Bradfield and B. Jones, *ibid.*, 2660–2661 (1929); (c) B. Jones, *ibid.*, 1874 (1935); (d) Bennett and Jones, *ibid.*, 420 (1939); (e) Lauer, Sanders, Leekley and Ungnade, THIS JOURNAL, **61**, 3050 (1939).

(5) S. D. Goldberg, U. S. Patent 2,139,818 (1938).

mono-isopropylaminoethanol. β-Mono-isopropylaminoethanol and β-mono-*n*-dodecylaminoethanol were produced in poor yields when no solvent was used, but with dioxane as solvent (and with *n*-dodecyl iodide instead of bromide[6]), fair results were obtained. Allyl bromide reacted so vigorously with ethanolamine that it formed mainly diallylaminoethanol. Ethyl bromide gave a poor yield of β-monoethylaminoethanol when it reacted with ethanolamine. Therefore, β-monoallylaminoethanol and β-monoethylaminoethanol were prepared by the reaction of β-chloroethyl chlorocarbonate with the appropriate amine, followed by hydrolysis of the carbamate with alcoholic potash.[7]

The alkoxybenzoyl chlorides were condensed with hydrochlorides of β-monoalkylaminoethanols to form hydrochlorides of β-monoalkylaminoethyl alkoxybenzoates.

Pharmacological tests on these compounds are being made by Dr. H. B. Haag and Mr. I. L. Silverstein of the Medical College of Virginia. The results will be reported elsewhere.

Experimental

Alkoxybenzoic Acids.—In a typical experiment, 11.5 g. of sodium was dissolved in 175 ml. of absolute ethyl alcohol. To this alcoholate was added 0.5 mole of methyl- or ethylhydroxybenzoate and then 0.5 mole of alkyl bromide. The mixture was refluxed eight to twelve hours, cooled, and filtered from inorganic salts. About half of the alcohol was vacuum evaporated and the precipitated inorganic salt was filtered off. A solution of 1 g. of sodium hydroxide in 10 ml. of alcohol was added and the mixture was treated with 150 ml. of ether and 50 ml. of water. The ether layer and a second ether extract were combined. The ether was distilled off and the residue was vacuum distilled. The ether ester thus obtained was saponified by refluxing from 1.5 to 8 hours with aqueous sodium hydroxide or alcoholic potash. The alkaline solution was poured into from two to four volumes of water and the unchanged ester was extracted with ether. The *o*-alkoxybenzoic acids and the *m*-*n*-butoxybenzoic acid were isolated by acidification of the aqueous layer, ether extraction, and vacuum distillation. *m*-Ethoxybenzoic acid, *m*-*n*-amyloxybenzoic acid, and the *p*-alkoxybenzoic acids were isolated by acidification of the aqueous layer and filtration. The solid alkoxybenzoic acids were purified by recrystallization from ethyl alcohol and water.

Alkoxybenzoyl Chlorides.—In most cases, the alkoxybenzoyl chlorides were made by treating the corresponding alkoxybenzoic acid with 1.05 equivalents of phosphorus pentachloride and heating for one hour on a boiling water-bath. The phosphorus oxychloride formed was distilled off and the alkoxybenzoyl chloride was vacuum distilled. The alkoxybenzoyl chlorides which were decomposed by the above method were obtained in satisfactory yields by the following modification. A vacuum was applied as soon as the phosphorus pentachloride was added. When the initial vigorous reaction subsided, the phosphorus oxychloride was vacuum distilled from the reaction mixture and the alkoxybenzoyl chloride was vacuum distilled.

Phosphorus pentachloride decomposed *p*-allyloxybenzoic acid, so this compound was treated with 0.67 mole of phosphorus trichloride and was heated for two hours on a water-bath. The reaction mixture was extracted with anhydrous ether and the ether layer was filtered. The ether was removed by distillation and the *p*-allyloxybenzoyl chloride was vacuum distilled.

β-Monoalkylaminoethanols.—A typical experiment is given to illustrate the method used to form the β-monoalkylaminoethanols.

β-Mono-*n*-butylaminoethanol[8] was prepared by adding slowly 1 mole (137 g. of 93%) butyl bromide, over a period of about four hours, to 160 g. (2.54 moles) of vigorously stirred ethanolamine, in a water-bath at 50–60°. A solution of 112 g. (2 moles) of potassium hydroxide in 100 ml. of water was added and the mixture was stirred with a mechanical stirrer from five to fifteen minutes. The precipitated inorganic salt was filtered off with suction. If the filtrate did not separate into two layers, a hot concentrated solution of potassium carbonate was added until two layers were formed. The upper layer was treated in a continuous extractor with petroleum ether (preferably 65–110°) for from eight to sixteen hours. The petroleum ether was distilled off and the residue fractionated.

β-Mono-*n*-propylaminoethanol and β-mono-isobutylaminoethanol were prepared similarly. In the case of β-mono-*n*-heptylaminoethanol, it was found necessary to use several moles of ethanolamine to avoid dialkylation. β-Mono-*n*-dodecylaminoethanol was formed by heating *n*-dodecyl iodide with an excess of ethanolamine in dioxane solution for sixty hours at 102° or for sixteen hours at 140° in a sealed tube. Also, dioxane was used as solvent for the reaction of isopropyl bromide and ethanolamine. β-Mono-*n*-amylaminoethanol and the higher homologs were separated readily from excess aminoethanol by ether extraction.

The β-monoalkylaminoethanols were analyzed by titration with standard hydrochloric acid with methyl red as indicator.

Hydrochlorides of β-Monoalkylaminoethyl Alkoxybenzoates.—For the preparation of β-monoalkylaminoethyl alkoxybenzoates, an excess of hydrochloric acid was added to the amino alcohol and the solution was evaporated to dryness in a vacuum. An equimolar quantity of the alkoxybenzoyl chloride was added and the mixture was heated on a water-bath for about one hour under reduced pressure. The hydrochloride of the β-monoalkylaminoethyl alkoxybenzoate was taken up in water and this solu-

(6) Acknowledgment is made to Dr. Alfred Burger, of the Department of Chemistry of the University of Virginia, for suggesting the above change.

(7) J. S. Pierce, THIS JOURNAL, **50**, 241 (1928). Some β-monoallylaminoethanol prepared by the senior author fifteen years ago, as a possible intermediate for synthetic medicinals, had decomposed somewhat but, on vacuum distillation, yielded 85% of pure product.

(8) After most of this work was completed, β-monoethylaminoethanol and β-mono-*n*-butylaminoethanol appeared on the market.

TABLE I

ALKOXYBENZOIC ACID DERIVATIVES

Substituent	Alkoxybenzoates B. p. range, °C.	Mm.	Yield, %	Alkoxybenzoic acids B. p. range, °C.	Mm.	M. p., °C., uncor.	Yield, %	Alkoxybenzoyl chlorides B. p. range, °C.	Mm.	Yield, %
p-Methoxy								161–168[e]	38	93
p-Ethoxy								170–171[d]	35	90
p-*n*-Propoxy	189–191[a]	40	81			139–142[d,f,g]	99	175–178[d,f]	30	70
p-*n*-Butoxy	196–197.5[a]	31	77			145.5–147[f,g]	99	191–193[f]	33	75
p-*n*-Amyloxy	207–208[a,b]	30	69			118–121[h,i]	94	198–200	30	86
p-*n*-Hexyloxy	217–218[a]	30	79			105–106[h,i]	98	213–214	30	87
p-*n*-Heptyloxy	228–229[a]	30	86			90–92[h]	99	226–227	30	83
p-*n*-Dodecyloxy	290–301[a]	45	59			137[j]	85	251–261	2.5	95
p-*iso*-Propoxy	171–177[a]	30	70			163–165[d,]	94	177–181[f]	47	90
p-*iso*-Butoxy	192–198[a]	34	38			137–138[f,i,k]	90	181–187[f]	30	61
p-2-Octyloxy	226–229[a]	35	61	203–213[l,m]	2		62	224–229	40	87
p-Allyloxy	188–191[a]	37	72			160–162[d,f]	92	186–191	45	57
o-Ethoxy	167–179[c,d]	47	93	216–229[d]	90		63	172–184[d]	50	82
o-*n*-Propoxy	165–170[c,d,e]	40	64	205–207[d]	40		88	182–192[d]	50	85
o-*n*-Butoxy	184–190[c,e]	40	63	211–221[n]	35		82	189–205	47	91
o-*n*-Dodecyloxy	211–216[c]	2.5	64	234–242[o,p]	2.5		57	202–212	3	92
o-*iso*-Propoxy	182–190[c,d]	95	34	216–227[d]	93		81	174–189[d]	47	91
o-*iso*-Amyloxy	184–194[c,d]	40	50	239–246[d]	95		68	200–213[d]	50	89
m-Ethoxy	171–181[a,d]	37	65			131–135[d]	90	150–159[d]	30	97
m-*n*-Butoxy	192–198[a]	38	59			59– 61[q]	95	153–163	4	87
m-*n*-Amyloxy	200–206[a]	30	53			70– 71[r]	76	186–189	28	91

[a] Ethyl ester. [b] This crystallized as long needles, m. p. 29–33°, without further purification. [c] Methyl ester. [d] Also prepared by Cohen and Dudley, *J. Chem. Soc.*, 1732–1751 (1910). [e] Acknowledgment is made to Henry Heller and Henry Nakdimen for their assistance in the preparation of this compound. [f] Also prepared by Rohman and Scheurle, *Arch. Pharm.*, **274**, 110–116 (1936). [g] Also prepared by Bradfield and Jones, *J. Chem. Soc.*, 2660 (1929). [h] Also prepared by Jones, *ibid.*, 1874 (1935). [i] Also prepared by Lauer, Sanders, Leekley and Ungnade, THIS JOURNAL, **61**, 3050 (1939). [j] Also prepared by Bennett and Jones, *J. Chem. Soc.*, 420 (1939). [k] Also prepared by Bradfield and Jones, *ibid.*, 3073–3081 (1928). [l] This product, after one recrystallization from ethanol–water, melted at 58–62°. [m] Calcd. for $C_{15}H_{22}O_3$: neut. eq., 250.3. Found: neut. eq., 248.4, 247.4. [n] Calcd. for $C_{11}H_{14}O_3$: neut. eq., 194.2. Found: neut. eq., 190.4, 190.8. [o] This crystallized as fine needles, m. p. 43–47°, without further purification. [p] Calcd. for $C_{19}H_{30}O_3$: neut. eq., 306.4. Found: neut. eq., 319.5, 317.9. [q] Calcd. for $C_{11}H_{14}O_3$: neut. eq., 194.2. Found: neut. eq., 194.3, 194.2. [r] Calcd. for $C_{12}H_{16}O_3$: neut. eq., 208.2. Found: neut. eq., 208.0, 208.8. [s] Also prepared by Rossel, *Ann.*, **151**, 31 (1869).

TABLE II

β-MONOALKYLAMINOETHANOLS: $RNHCH_2CH_2OH$

R	B. p. range, °C., uncor.	Yield, %	Formula	Nitrogen, % Calcd.	Found
Ethyl[a]	164–169	35	$C_4H_{11}ON$	15.72	15.79
n-Propyl[a]	178–185	38	$C_5H_{13}ON$	13.58	13.24
n-Butyl[a]	195–205	53	$C_6H_{15}ON$	11.94	11.76
n-Amyl[a]	215–220	41	$C_7H_{17}ON$	10.68	10.51
n-Heptyl	248–251	42	$C_9H_{21}ON$	8.79	8.62
n-Dodecyl	188–198 (4.5 mm.)	16	$C_{14}H_{31}ON$	6.11	6.15
Isopropyl	172–174	23	$C_5H_{13}ON$	13.58	13.52
Isobutyl[a]	185–189	43	$C_6H_{15}ON$	11.95	11.92
Allyl[b]	89– 94 (3.5 mm.)	49	$C_5H_{11}ON$	13.85	13.66

[a] Also prepared by Goldberg and Whitmore, THIS JOURNAL, **59**, 2288 (1937). [b] Also prepared by Pierce, *ibid.*, **50**, 241 (1928).

tion was extracted with isopropyl ether or was filtered to remove acid insoluble material. The aqueous solution was made basic and was extracted with isopropyl ether. Hydrogen chloride was passed into this extract to precipitate the hydrochloride of the amino ester. Most of these compounds were purified by recrystallization. Table III lists these hydrochlorides.

Some of the β-monoalkylaminoethyl alkoxybenzoate hydrochlorides, on attempted recrystallization, came out of solution as gels. Others did not form crystalline products. Therefore, some of these products were not obtained in a pure condition. These hydrochlorides are listed below. They have the formula $ROC_6H_4COOCH_2CH_2NHR'\cdot HCl$, where R and R′ are, respectively, *p*-ethyl

TABLE III

β-MONOALKYLAMINOETHYL ALKOXYBENZOATE HYDROCHLORIDES: $ROC_6H_4COOCH_2CH_2NHR'\cdot HCl$

R	R'	M. p., °C. uncor.	Yield,[a] %	Formula	Chlorine, % Calcd.	Found
p-Methyl	*n*-Butyl[b]	127.5–129	36	$C_{14}H_{22}O_3NCl$	12.32	12.23
p-Ethyl	*n*-Butyl[b]	138 –140	41	$C_{15}H_{24}O_3NCl$	11.75	11.61
p-*n*-Propyl	*n*-Butyl[b]	136 –138	67	$C_{16}H_{26}O_3NCl$	11.23	11.27
p-*n*-Butyl	Ethyl[b]	135 –136	61	$C_{15}H_{24}O_3NCl$	11.75	11.80
p-*n*-Butyl	*n*-Propyl[c]	110.5–111.5	34	$C_{16}H_{26}O_3NCl$	11.23	11.08
p-*n*-Butyl	*n*-Butyl[b]	128 –130	61	$C_{17}H_{28}O_3NCl$	10.75	10.56
p-*n*-Butyl	*n*-Amyl[b]	123 –125	59	$C_{18}H_{30}O_3NCl$	10.31	10.23
p-*n*-Butyl	Isopropyl[b]	168 –170	40	$C_{16}H_{26}O_3NCl$	11.23	10.95
p-*n*-Butyl	Isobutyl[d]	171.5–172.5	52	$C_{17}H_{28}O_3NCl$	10.75	10.81
p-*n*-Butyl	Allyl[e]	94 – 97	44	$C_{16}H_{24}O_3NCl$	11.30	11.60
p-*n*-Amyl	*n*-Butyl[b]	124 –126	26	$C_{18}H_{30}O_3NCl$	10.31	10.18
p-*n*-Hexyl	Ethyl[b]	128 –129	54	$C_{17}H_{28}O_3NCl$	10.75	10.29
p-*n*-Hexyl	*n*-Butyl[b]	120 –123	17	$C_{19}H_{32}O_3NCl$	9.91	9.57
p-*n*-Heptyl	*n*-Butyl[c]	129.5–130.5	62	$C_{20}H_{34}O_3NCl$	9.53	9.60
p-*n*-Dodecyl	*n*-Butyl[b]	142 –143	50	$C_{25}H_{44}O_3NCl$	8.02	8.09
p-*iso*-Propyl	*n*-Butyl[e]	118 –120	54	$C_{16}H_{26}O_3NCl$	11.23	10.78
p-*iso*-Butyl	*n*-Butyl[b]	150 –152	67	$C_{17}H_{28}O_3NCl$	10.75	10.78
o-*n*-Propyl	*n*-Butyl[e]	135 –138	91	$C_{16}H_{26}O_3NCl$	11.23	11.44
o-*n*-Butyl	*n*-Butyl[e]	85.5– 87	39	$C_{17}H_{28}O_3NCl$	10.75	10.68
o-*n*-Butyl	Isopropyl[b]	107 –109	34	$C_{16}H_{26}O_3NCl$	11.23	11.25
o-*n*-Butyl	Isobutyl[c]	76 – 77	32	$C_{17}H_{28}O_3NCl$	10.75	11.05
o-*n*-Dodecyl	*n*-Butyl[b]	97 – 99	13	$C_{25}H_{44}O_3NCl$	8.02	8.00
m-*n*-Butyl	*n*-Butyl[e]	109 –110	46	$C_{17}H_{28}O_3NCl$	10.75	10.43

[a] Yields are based on one recrystallization. [b] Recrystallized from anhydrous acetone. [c] Recrystallized from anhydrous acetone–petroleum ether (b. p. 65–110°). [d] Recrystallized from anhydrous acetone–absolute ethanol. [e] Recrystallized from anhydrous acetone–anhydrous ether.

and *n*-heptyl, *p*-*n*-butyl and *n*-dodecyl, *p*-allyl and *n*-butyl, *p*-2-octyl and *n*-butyl, *o*-ethyl and *n*-butyl,[9] *o*-*n*-butyl and ethyl, *o*-*n*-butyl and *n*-propyl, *o*-*n*-butyl and *n*-dodecyl, *o*-isopropyl and *n*-butyl, *o*-isoamyl and *n*-butyl, *m*-ethyl and *n*-butyl, *m*-*n*-butyl and *n*-propyl, *m*-*n*-butyl and isobutyl, and *m*-*n*-amyl and *n*-butyl.

Since some of the monoalkylamino esters of alkoxybenzoates have been found to have high local anesthetic action, the work is being continued in this Laboratory with alkoxycinnamates and alkoxynaphthoates to see the effect of the variation of the aromatic nucleus on the anesthetic action.

Since Donleavy and English[10] found dialkylaminoethyl alkylthiobenzoates to have anesthetic action and to have low irritation, two β-monoalkylaminoethyl alkylthiobenzoates were prepared and tested for corneal anesthesia on a rabbit's eye. *o*-*n*-Butylthiobenzoyl chloride was prepared[11] as described by Donleavy and English.[10] This acid chloride was condensed with the hydrochlorides of β-mono-*n*-butylaminoethanol and β-mono-isobutylaminoethanol, as were the alkoxybenzoyl chlorides described in this paper. The butylaminoethyl *o*-*n*-butylthiobenzoates were isolated by the usual procedure and were recrystallized from anhydrous acetone.

β-Mono-*n*-butylaminoethyl *o*-butylthiobenzoate hydrochloride, m. p. 123.5–126°, was obtained in a 50% yield. Calcd. for $C_{17}H_{28}O_2NClS$: Cl, 10.27. Found: Cl, 9.97.

β-Mono-isobutylaminoethyl *o*-butylthiobenzoate hydrochloride, m. p. 83–84°, was obtained in an 82% yield. Calcd. for $C_{17}H_{28}O_2NClS$: Cl, 10.27. Found: Cl, 10.20.

Both of these products, in 1% aqueous solution, had a slight anesthetic action on a rabbit's cornea but were irritating.

(9) First prepared by David H. Miller.

(10) Donleavy and English, THIS JOURNAL, **62**, 220–222 (1940).

(11) Acknowledgment is made to Kenneth Garrison and O. G. Gilbert, Jr., for assistance in the preparation of *o*-*n*-butylthiobenzoic acid.

Summary

The hydrochlorides of a series of β-monoalkylaminoethyl alkoxybenzoates have been prepared and described.

RICHMOND, VIRGINIA RECEIVED SEPTEMBER 2, 1941

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

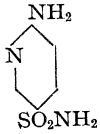
Substituted 2-Sulfonamido-5-aminopyridines

BY WILLIAM T. CALDWELL AND EDMUND C. KORNFELD[1a,1b]

Sulfanilamide and its numerous derivatives are all obtained from N-acetylsulfanilyl chloride or *p*-nitrobenzenesulfonyl chloride. In the hope of securing a group of compounds suited to comparative pharmacological studies and, of course, of obtaining products with superior therapeutic action, it seemed to us desirable to seek a new aromatic and isosteric sulfonyl chloride, *i. e.*, one which would serve as an intermediate for the preparation of a series of bactericides analogous to the many sulfanilamide derivatives already prepared.

The possible preparation of a *p*-aminopyridinesulfonamide, I or II, and its derivatives appeared


(I)


(II)

intriguing in view of the presence of the pyridine nucleus in such physiologically active substances as nicotinamide, vitamin B_6, and sulfapyridine, and also because of the solubility in water of pyridine itself. 2-Amino-5-sulfonamidopyridine II and several derivatives have been prepared and studied by investigators abroad.[2,3,4] Our work therefore centered about the isomer I, which now has been synthesized in this Laboratory. Six derivatives of this product also have been prepared according to the scheme shown in Fig. 1.

In this connection, it may be noted that 3-aminopyridine resembles aniline more closely than does either 2- or 4-aminopyridine; indeed, compounds with substituents in position 3 of the pyridine nucleus usually differ considerably in chemical behavior from isomers with these substituents in position 2 or 4. It should, therefore, be a matter of interest to compare, both chemically and pharmacologically, 2-sulfonamido-5-aminopyridine I, in which the sulfonamido group occupies the position of somewhat anomalous reactivity and the amino group is in the position characterized by closer adherence to type, with 5-sulfonamido-2-aminopyridine II where the substituent groups are interchanged. Anticipation of certain differences and even difficulties of a chemical nature has already proved to be not without foundation, as will appear from what follows.

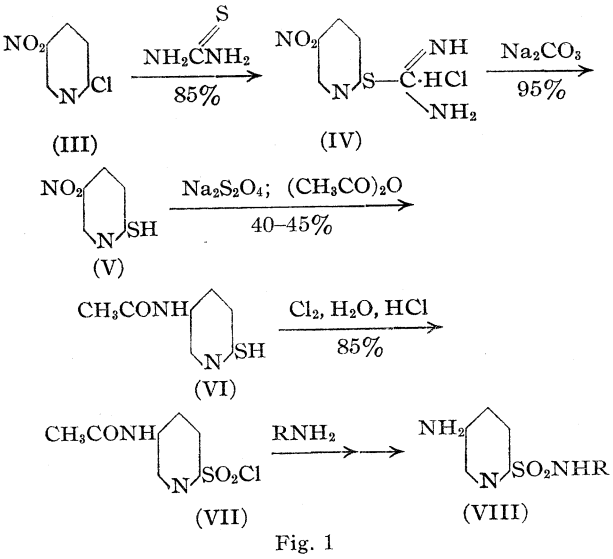
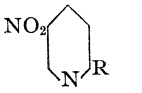


Fig. 1

The requisite intermediate for the preparation of the substituted sulfonamides VIII could be either 5-acetaminopyridine-2-sulfonyl chloride VII or a compound containing a nitro group in the 5 position. The latter possibility was abandoned when 2-thiol-5-nitropyridine V or 5,5′-dinitro-2,2′-dipyridyl disulfide could not be oxidized to the corresponding sulfonic acid in promising yield. Confirming and extending the work of Plazek,[5] we have found that oxidation of V with nitric acid, chromic acid, or potassium permanganate in acetone leads to the formation of 5-nitro-2-pyridone IX.



IX, R = OH
X, R = NH_2
XI, R = SO_3K
XII, R = OCH_3

Treatment of (V) with ammoniacal potassium permanganate yields 2-amino-5-nitropyridine X

(1a) Submitted in partial fulfillment of the requirements for the degree of Master of Arts.

(1b) Present address: Mallinckrodt Chemical Laboratory of Harvard University, Cambridge, Mass.

(2) Naegeli, Kündig and Brandenburger, *Helv. Chim. Acta*, **21**, 1746 (1938).

(3) Tchitchibabine and Vialatout, *Bull. soc. chim.*, [5] **6**, 736 (1939).

(4) Ewins, Phillips and Newbery, British Patent 516,288 (1939).

(5) Plazek, *Rocznicki Chem.*, **17**, 97 (1937); *Chem. Zentr.*, **108**, II, 73 (1937).

together with a little potassium-5-nitropyridine-2-sulfonate XI, while oxidation with chlorine results in 2-chloro-5-nitropyridine III. Oxidation of 5-nitro-2-pyridylpseudothiourea hydrochloride IV with chlorine also failed to produce the desired result. Obviously the 5-nitro group activates the 2-position to a remarkable extent. Most interesting of all, perhaps, is the fact that on treating 2-chloro-5-nitropyridine with sodium sulfite[6] in dilute methanol, 2-methoxy-5-nitropyridine XII is formed and not the desired sulfonic acid.

Therefore, to obviate the labilizing influence of the nitro group, 2-thiol-5-nitropyridine V was reductively acetylated in order to obtain 2-thiol-5-acetaminopyridine VI. This step was effected without difficulty by use of sodium hydrosulfite and acetic anhydride, and it was of particular moment to us to discover that this compound could be oxidized in excellent yield to the desired 5-acetamino-2-pyridinesulfonic acid with hydrogen peroxide (30%) in acetic acid. Nevertheless, all attempts to convert this acid to the sulfonyl chloride VII have been unsuccessful. In this connection, it is perhaps of interest to point out that King and Ware[7] were unable to obtain 4-pyridinesulfonyl chloride from 4-pyridinesulfonic acid.

Fortunately, however, 2-thiol-5-acetaminopyridine VI was found to be easily and directly convertible by the action of chlorine into the requisite intermediate, 5-acetamino-2-pyridinesulfonyl chloride VII, by the excellent method of Johnson, Sprague and Douglass.[8]

Condensations of this sulfonyl chloride with various amines have been found to be entirely analogous to those using N-acetylsulfanilyl chloride. We are reporting at this time the preparation of seven analogs of sulfanilamide and its derivatives, and the work will be continued if these show promise as therapeutic agents.

Pharmacological tests on these compounds are being made by Dr. A. E. Livingston and Dr. E. J. Fellows of the Department of Pharmacology, Temple University Medical School; the results will be published in detail elsewhere.

We wish to thank Mr. Furness Thompson of Smith, Kline and French, Inc., and Dr. James M. Sprague of Sharp and Dohme, Inc., for generous samples of some of the heterocyclic amines used in this work, and also to express our gratitude to the Temple University Committee on Research and Publication for a grant-in-aid.

(6) Erdman and Erdman, German Patent 65,240, prepared 2,4-dinitrobenzenesulfonic acid from 2,4-dinitrochlorobenzene by this method.

(7) King and Ware, *J. Chem. Soc.*, 873 (1939).

(8) Johnson, Sprague and Douglass, THIS JOURNAL, **58**, 1348 (1936); **59**, 1837, 2439 (1937); **60**, 1486 (1938); **61**, 176, 2548 (1939).

Experimental[9]

2-Chloro-5-nitropyridine, III.—This compound was prepared by a method similar to that of Phillips,[10] but the synthesis had been worked out independently in this Laboratory. It is based on the original work of Tchitchibabine.[11] 2-Aminopyridine (200 g., 2.13 moles) was added with efficient mechanical agitation to 800 ml. of concd. sulfuric acid while keeping the temperature below 50° by cooling in ice. Then 120 ml. (2.53 moles) of fuming nitric acid (d. 1.49) was run in below 40°. The solution was kept at 45° with occasional cooling in ice until the temperature no longer rose spontaneously above 45°, thus indicating that the rearrangement of 2-nitraminopyridine to 2-amino-3 or 5-nitropyridine was complete (three-quarters of an hour). The reaction mixture was kept at 45° for about one hour, allowed to stand at room temperature for several hours and was then neutralized by pouring cautiously into a mixture of concd. ammonia and ice. If it is desired to isolate 2-amino-3-nitropyridine, the mixture is steam distilled until about 18 liters are collected. This distillate on cooling deposits about 20–21 g. of 2-amino-3-nitropyridine; yield, 7%. The neutralized mixture, with or without steam distillation, was cooled, filtered, and the product washed with ice water. The crude 2-amino-5-nitropyridine was then dissolved in 1500 ml. of water containing 200 ml. of concd. sulfuric acid, decolorizing carbon was added, and the mixture filtered. A concentrated solution of 140 g. of sodium nitrite was then run in drop by drop at 10–15°. Very efficient mechanical stirring was essential. The thick mixture was then heated to boiling, cooled to 0°, and the product, 5-nitro-2-pyridone, filtered, washed with water, and dried; yield, 59% based on 2-aminopyridine. This may be used without further purification to prepare 2-chloro-5-nitropyridine using phosphorus pentachloride and phosphorus oxychloride[10]; yield, 90–95%. Recrystallization from methanol, using carbon, gave a product melting at 107–108°.

2-Methoxy-5-nitropyridine, XII.—To a solution of 7.9 g. (0.05 mole) of 2-chloro-5-nitropyridine in 200 ml. of hot methanol was added a solution of 10 g. (0.079 mole) of anhydrous sodium sulfite in 150 ml. of hot water.[6] The mixture was then refluxed for three hours, filtered hot, and the filtrate cooled. White needles separated which were recrystallized from dilute methanol, m. p. 108–108.5°. A mixed melting point with a sample of 2-methoxy-5-nitropyridine prepared from the silver salt of 5-nitro-2-pyridone and methyl iodide[12] was also 108–108.5°.

5-Nitro-2-pyridylpseudothiourea Hydrochloride, IV.—This was prepared by the method of Lindwall and Surrey[13]; yield, 85%.

2-Thiol-5-nitropyridine,[13] V.—The crude 5-nitro-2-pyridylpseudothiourea hydrochloride IV from 188 g. of 2-

(9) All melting points are corrected.

(10) Phillips, *J. Chem. Soc.*, 9 (1941).

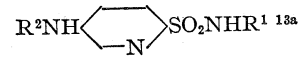
(11) Tchitchibabine, *J. Russ. Phys.-Chem. Soc.*, **46**, 1240 (1914); **47**, 1286 (1915); **50**, 471 (1918).

(12) Rath, *Ann.*, **484**, 52 (1930).

(13) Surrey and Lindwall, THIS JOURNAL, **62**, 1697 (1940).

TABLE I

PROPERTIES OF SUBSTITUTED 5-AMINOPYRIDINE-2-SULFONAMIDES



R^1	Solvent	M. p., °C., cor.	Formula R^2 = H-	Analyses, % Calcd.	Found	Nitrogen Calcd.	Found
H-	Water	184–185	$C_5H_7N_3O_2S$			24.26	23.75
C_5H_5N-	Dil. EtOH	205–206[a]	$C_{10}H_{10}N_4O_2S$			22.39	23.00[b]
C_6H_5-	Dil. EtOH	164–165	$C_{11}H_{11}N_3O_2S$			16.86	16.91[b]
CH_4N_3-	Water	220–221[a]	$C_6H_9N_5O_2S$			32.54	32.36[b]
C_3H_2NS-	Dil. EtOH	226–227[a]	$C_8H_8N_4O_2S_2$			21.86	21.64[b]
$C_4H_3N_2$-	Diox. H_2O[c]	283–285[a]	$C_9H_9N_5O_2S$			27.88	27.69[b]
C_5H_3NI	Dil. EtOH	219–220[a]	$C_{10}H_9N_4O_2IS$			I, 33.74	33.62
			R^2 = CH_3CO-	Carbon		Hydrogen	
H-	Water	232–233	$C_7H_9N_3O_3S$			N, 19.53	19.17
C_5H_5N-	*d*	231–232[a]	$C_{12}H_{12}N_4O_3S$	49.30	49.08[b]	4.14	4.34[b]
C_6H_5-	Dil. MeOH	213–214	$C_{13}H_{13}N_3O_3S$	53.59	53.64[b]	4.50	4.34[b]
CH_4N_3-	Water	228–229[a,e]	$C_8H_{11}N_5O_3S$	37.35	37.58[b]	4.31	4.55[b]
C_3H_2NS-	Dil. EtOH	234–235[a]	$C_{10}H_{10}N_4O_3S_2$	40.26	40.16[b]	3.38	3.57[b]
$C_4H_3N_2$-	Dil. MeOH	231–232[a]	$C_{11}H_{11}N_5O_3S$			S, 10.93	10.70
C_5H_3NI-	Dil. EtOH	225–226[a]	$C_{12}H_{11}N_4O_3IS$			I, 30.35	30.19

[a] Melts with decomposition. [b] Analyses by Carl Tiedcke. [c] Best purified by evaporating a solution of the compound in dilute ammonia. [d] Best purified by precipitation from alkaline solution by acid. [e] Dried at 150°.

chloro-5-nitropyridine III was suspended in 2 liters of water and 68 g. of sodium carbonate added with stirring. Agitation was continued for fifteen minutes, and then a solution containing 102 g. of sodium hydroxide was added to dissolve the product. The red-orange solution was then filtered to remove a small amount of 5,5′-dinitro-2,2′-dipyridyl sulfide and the filtrate acidified with concd. hydrochloric acid. The product was cooled, filtered, washed with water, and dried. The yield, based on 2-chloro-5-nitropyridine III, was 80–83%; m. p. 188–191° (d.).

2-Thiol-5-acetaminopyridine, VI.—2-Thiol-5-nitropyridine V (31.2 g., 0.2 mole) was suspended in 300 ml. of water, and 120 g. (0.69 mole) of sodium hydrosulfite was added with stirring, keeping the temperature below 50°. The mixture turned from orange to yellow, and all solids went into solution. Acetic anhydride (26 ml., 0.275 mole) was then added below 50°. The product, 2-thiol-5-acetaminopyridine, gradually separated from the warm solution. The mixture was stirred for one hour, cooled in ice, and the product filtered, washed with water, and dried; yield, 40–45% based on 2-thiol-5-nitropyridine. On recrystallization from water the bright yellow compound melted at 244–246°.

Anal. Calcd. for $C_7H_8N_2OS$: N, 16.66. Found: N, 16.78.

5,5′-Diacetamino-2,2′-dipyridyldisulfide.—2-Thiol-5-acetaminopyridine VI (0.84 g.) was dissolved in 20 ml. of warm water and a few drops of 30% hydrogen peroxide added. The white solid which separated immediately from the warm solution was cooled, filtered, washed with water, and dried; yield, 90%. Repeated crystallization from dilute ethanol gave a product melting at 240–241°.

Anal. Calcd. for $C_{14}H_{14}N_4O_2S_2$: N, 16.76. Found: N, 16.70.

5-Acetaminopyridine-2-sulfonic Acid.—To 37.5 g. (0.22 mole) of 2-thiol-5-acetaminopyridine VI suspended in 250 ml. of glacial acetic acid was added 78 ml. (0.76 mole) of 30% hydrogen peroxide keeping the temperature below 70° by cooling in ice. The solids dissolved, and the mixture became brown. When the temperature no longer rose spontaneously (one hour), the reaction mixture was allowed to stand overnight. Crystals of the sulfonic acid had deposited in 24 hours or less. These were cooled well in ice, filtered, washed with ethanol, and dried; yield, 82%. On recrystallization from water the acid melted at 302–303° (d.).

Anal. Calcd. for $C_7H_8N_2O_4S$: N, 12.96; S, 14.83; neut. equiv., 216.2. Found: N, 13.22; S, 14.75; neut. equiv., 215.3.

S-Benzylthiuronium Salt of 5-Acetaminopyridine-2-sulfonic Acid.—This compound was prepared by the method of Chambers and Watt[14]; m. p. after recrystallization from water, 93–95°.

Anal. Calcd. for $C_{15}H_{18}N_4O_4S_2 \cdot 2H_2O$: N, 14.35. Found: N, 14.37.

5-Acetamino-2-pyridone.—This was prepared to compare with 5-acetaminopyridine-2-sulfonic acid. To 1.4 g. of 5-nitro-2-pyridone in 20 ml. of water was added 6 g. of sodium hydrosulfite and then 1.3 ml. of acetic anhydride. Needles deposited on standing overnight; m. p. 232–233° after recrystallization from water.

Anal. Calcd. for $C_7H_8N_2O_2$: N, 18.41. Found: N, 18.14.

5-Acetamino-2-pyridinesulfonyl Chloride VII.—Attempts to prepare this compound from the corresponding sulfonic acid using chlorosulfonic acid, phosphorus pentachloride, thionyl chloride, sulfuryl chloride, sulfur chloride, or benzotrichloride[15] resulted only in unchanged sulfonic acid or dark, non-crystalline masses, which showed no properties of a sulfonyl chloride. The following procedure, however, gave the acid chloride in 85% yield. 2-Thiol-5-acetaminopyridine VI (60 g.) was dissolved in 450 ml. of

(13a) System based on that of Northey, *Chem. Rev.*, **27**, 85 (1940).

(14) Chambers and Watt, *J. Org. Chem.*, **6**, 376 (1941).

(15) Kranzlein and Hopff, German Patent 574,836.

cold, concd. hydrochloric acid, and then 100 ml. of ice water was added. Chlorine was bubbled into the solution, keeping the temperature below 10° throughout by external cooling. The solution became dark brown at first, and the chlorination was complete when the temperature no longer rose and when the color of the solution lightened (two and one-half hours). The solution was then diluted with 1200 g. of ice and water, keeping the temperature still below 10°. The product which separated was filtered, washed with ice water, dried *in vacuo* over phosphorus pentoxide, and recrystallized the same day from ethylene dichloride. The sulfonyl chloride should be dried and recrystallized rapidly to prevent decomposition to the sulfonic acid. An analytical sample melted at 165–166° (d.).

Anal. Calcd. for $C_7H_7ClN_2O_3S$: N, 11.94; Cl, 15.11. Found: N, 11.75; Cl, 14.97.

Substituted Acetaminopyridinesulfonamides.—2-Sulfonamido-5-acetaminopyridine was prepared by adding one part of the sulfonyl chloride to four parts of concd. ammonia (25%), and evaporating the excess ammonia on the steam-bath. The product crystallized out on cooling; yield, 86%. The guanidine derivative was made by the method of Marshall, Bratton, White and Litchfield[16]; yield, 51%. The derivatives of the cyclic amines were prepared in 62–98% yields by adding an equivalent of 5-acetaminopyridine-2-sulfonyl chloride to the cyclic amine dissolved in dry pyridine, the weight of the latter being equal to that of the total solids. Solution took place with evolution of heat and the reactions were completed by warming at 60° for one-half to one hour. The crude derivatives obtained by pouring the dark solutions into ice water were dissolved in one equivalent of aqueous sodium hydroxide, decolorized, and reprecipitated by addition of hydrochloric acid.

Hydrolysis of the N^4-Acetyl Group.—Six of the acetyl compounds were hydrolyzed by refluxing 0.5 to 1.0 molar solutions containing 2.5 equivalents of sodium hydroxide for two and one-half to three hours. The acetyl derivative of the guanidine condensation product was hydrolyzed with 6-molar hydrochloric acid by the method of Marshall, *et al.*[16]

(16) Marshall, Bratton, White and Litchfield, *Bull. Johns Hopkins Hosp.*, **67**, 163 (1940).

Summary

1. 5-Acetaminopyridine-2-sulfonyl chloride has been prepared and is available as an intermediate for the preparation of a new series of chemotherapeutic agents.

2. The preparation of seven new substituted 5-aminopyridine-2-sulfonamides and their acetyl derivatives is reported.

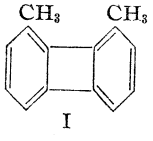
PHILADELPHIA, PA. RECEIVED APRIL 27, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF TRINITY COLLEGE]

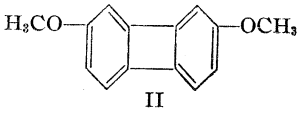
1,8-Dimethyl and 2,7-Dimethoxybiphenylene

BY WARREN C. LOTHROP

Continuing a line of investigation recently reported,[1] the present paper describes the preparation of two substituted biphenylenes. These new substances were obtained by following the procedure previously worked out for the parent substance, biphenylene, and have been assigned the structures



I



II

1,8-dimethylbiphenylene (I) and 2,7-dimethoxybiphenylene (II).

The hydrocarbon (I) was prepared with considerable difficulty and in very poor yield by the pyrolysis of 4,5-dimethylbiphenylene iodonium iodide with cuprous oxide. The over-all yield for the whole series of reactions starting with 100 g. of 2-amino-3-nitrotoluene was only 100 mg. of a pale yellow hydrocarbon crystallizing in plates from methanol. It melted at 79–80° and formed a picrate crystallizing in long crimson needles from ethanol and melting at 126°. It was lower melting and less highly colored than its isomer, 2,7-dimethylbiphenylene,[2] but otherwise similar.

For the preparation of II, a series of reactions previously reported[3] was followed but with variations in procedure materially improving the yields of all steps. Acetylation of *p*-anisidine (97%) followed by nitration with dilute nitric acid at room temperature (78%), and hydrolysis with alcoholic hydrochloric acid (95%) gave 3-nitro-*p*-anisidine[4] III. This when coupled by the procedure of Atkinson, *et al.*,[5] gave 2,2′-dinitro-*p*,*p*′-bianisole IV contaminated by a con-

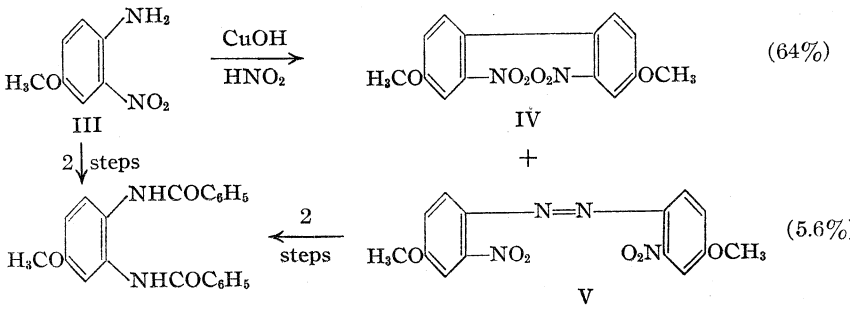
(1) Lothrop, THIS JOURNAL, **63**, 1187 (1941).

(2) Recrystallization and careful drying of the picrate of this compound gave needles (m. p. 110–111°) which were evidently free of the alcohol of crystallization previously reported.[1] *Anal.* Calcd. for $C_{14}H_{12}\cdot C_6H_3O_7N_3$: N, 10.27. Found: N, 9.90, 10.43.

(3) Hata, Tatematsu and Kubota, *Bull. Chem. Soc. Japan*, **10**, 425 (1935).

(4) *Cf.* Reverdin, *Ber.*, **29**, 2595 (1896).

(5) Atkinson, Lawler, Heath, Kimball and Read, THIS JOURNAL, **63**, 730 (1941).



siderable amount of orange material which was evidently 4,4′-azobis-3-nitroanisole V,[6] since on reduction and benzoylation it gave only 3,4-dibenzamidoanisole.

It is interesting to note that Atkinson's coupling procedure applied to 2-amino-3-nitrotoluene yields only 24% of 6,6′-dinitro-*o*,*o*′-bitolyl and 16% of 2,2′-azobis-3-nitrotoluene, possibly due to steric hindrance; the identity of the latter was proved by its conversion to 2,3-dibenzamidotoluene and comparison with an authentic sample.

Conversion of IV to the diamine and then to the iodonium iodide, followed by the usual pyrolysis, gave dimethoxybiphenylene in 2% yield, as glistening lemon yellow plates melting at 108° and forming a picrate crystallizing from alcohol in black needles melting at 125°. All attempts to convert II into dihydroxybiphenylene failed, since it was inert to alkaline reagents, as expected, and was rapidly cleaved by acids to give solutions of a deep purple color resembling permanganate, and from which only tar could be obtained. Experiments conducted in an atmosphere of nitrogen were identical with those performed in air.

This result may not be entirely unexpected since 2,7-dihydroxybiphenylene is seen to be an isomer of 4,4′-biphenylquinone which was found by Willstätter and Kolb[7] to be an unstable substance reacting even with warm water to give decomposition products.

Experimental Part

6,6′-Dinitro-*o*,*o*′-bitolyl was prepared in the manner of Wittig and Stichnoth[8] by the reaction of 2-iodo-3-nitrotoluene with copper. An attempt to obtain it directly from 2-amino-3-nitrotoluene (11 g.) by following exactly the procedure of Atkinson, *et al.*,[5] (called by them Method 2) gave a mixed product which was separated by extraction with 40 cc. of boiling alcohol. The alcoholic solution gave 2.4 g. of pale buff needles which after recrystallization melted at 107–108° and represented a 24% yield of dinitrobitolyl.

The alcohol-insoluble material was recrystallized from glacial acetic acid in bright orange needles weighing 1.8 g.; 16% yield; m. p. 199°. Reduction of this **2,2′-azobis-3-nitrotoluene** with zinc dust and boiling acetic acid and benzoylation of the water-soluble diamine by the Schotten–Baumann procedure gave **2,3-dibenzamidotoluene,** m. p. 228–229°, which crystallized from acetic acid in white needles. It was identical with the product obtained by reduction and benzoylation of 2-amino-3-nitrotoluene.

Anal. Calcd. for $C_{21}H_{18}O_2N_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.22; H, 5.58; N, 8.22.

6,6′-Diamino-*o*,*o*′-bitolyl was prepared as previously described[9] by reduction of the dinitro compound with stannous chloride and hydrochloric acid in acetic acid solution. The best yield obtainable was 55% of white plates, m. p. 132° after two crystallizations from alcohol.

When the above diamine was diazotized and treated with potassium iodide by the same procedure used for biphenylene iodonium iodide, a yield of 67% of crude **6,6′-diiodo-*o*,*o*′-bitolyl**[10] resulted. Since the product was completely soluble in dilute alcohol, it was apparent that no iodonium iodide had been formed in this case, doubtless due to the steric effects of the adjacent methyl groups.

1,8-Dimethylbiphenylene (I) resulted in very poor yield by pyrolysis of the above crude diiodide with cuprous oxide. It was isolated through its **picrate** which separated from alcohol in long, crimson needles; m. p. 126°.

Anal. Calcd. for $C_{14}H_{12}\cdot C_6H_3O_7N_3$: N, 10.27. Found: N, 10.27.

No trace of 4,5-dimethylphenazone could be found. This is in contrast to all other reaction series where the corresponding phenazone is present as an impurity.

Decomposition of the picrate with ether and ammonia gave a pale yellow hydrocarbon which crystallized from methanol in large, pearly plates, m. p. 79–80°, and had a slight odor reminiscent of biphenylene.

Anal. Calcd. for $C_{14}H_{12}$: C, 93.28; H, 6.72; mol. wt., 180. Found: C, 93.30; H, 7.04; mol. wt. (Rast micro), 182.

***p*-Acetamidoanisole** resulted in 97% yield by treatment of a solution of *p*-anisidine hydrochloride with sodium acetate in the presence of acetic anhydride.[11]

3-Nitro-*p*-acetamidoanisole[4] was prepared as follows: a sludge of 184 g. of acetaniside in 340 cc. of glacial acetic acid was mixed with a solution of 112 cc. of concentrated nitric acid in 615 cc. of water and allowed to stand at room temperature for one day. During this time the reaction warmed up to 60° spontaneously and all material went into solution while the product crystallized out on cooling in

(6) *Cf.* Saunders, "The Aromatic Diazo-compounds," Edward Arnold, London, 1936, p. 148.
(7) Willstätter and Kolb, *Ber.*, **38**, 1235 (1905).
(8) Wittig and Stichnoth, *ibid.*, **68**, 928 (1935).
(9) Meisenheimer and Horing, *ibid.*, **60**, 1425 (1927).
(10) Angeletti, *Gazz. chim. ital.*, **63**, 145 (1933).
(11) *Cf.* Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath Co., Boston, Mass., 1941, p. 165.

bright yellow needles; m. p. 115° (literature m. p. 117°); yield 183 g. or 78%.

3-Nitro-*p*-anisidine (III) was obtained when 243.5 g. of the acetyl derivative, after refluxing for six hours with 500 cc. of alcohol and 245 cc. of concentrated hydrochloric acid, was neutralized with 300 cc. of concentrated ammonia and cooled. The product separated in deep orange-red needles, m. p. 122° (literature 122°), weighing 183 g. (94%).

2,2′-Dinitro-*p,p′*-bianisole (IV) was prepared from the diazonium solution of the above nitroanisidine by the action of a solution of cuprous hydroxide. When 340 g. of the amine was treated by the procedure described under Method 2[5] a crude product not entirely soluble in acetic acid resulted. The soluble material crystallized from the solution and weighed 141.5 g. (64%), m. p. 131° and was identical with material prepared by heating 4-iodo-3-nitroanisole with copper powder.[3]

The insoluble material was crystallized from nitrobenzene in bright orange prisms, m. p. 259°, and was evidently **4,4′-azobis-3-nitroanisole** (V) since on reduction with zinc dust and boiling acetic acid followed by benzoylation of the water soluble diamine it gave 3,4-dibenzamidoanisole.[12]

This crystallized from acetic acid in white needles and gave no depression of the m. p. (250°) of an authentic sample.

Anal. Calcd. for $C_{14}H_{12}O_6N_4$ (V): N, 16.86. Found: N, 17.05.

2,2′-Diamino-*p,p′*-bianisole.[3]—When 89 g. of dinitrobianisole was reduced by the action of 297 g. of tin, 960 cc. of concentrated hydrochloric acid and 165 cc. of acetic acid, the diamine (m. p. 110°) crystallized from alcohol in pearly plates weighing 53 g. (74% yield).

2,7-Dimethoxybiphenylene iodonium iodide was obtained in a crude condition in 77% yield by treatment of the above diamine in the usual manner,[1] so that from 62.5 g. of the diamine, 92 g. of light brown powder resulted. This was not purified further but was subjected to pyrolysis with cuprous oxide.

2,7-Dimethoxybiphenylene (II).—When the crude product of the above pyrolysis was subjected to prolonged steam distillation, 6 g. of yellow crystals was isolated from the distillate (20 liters) by ether extraction. This was fractionally crystallized from alcohol yielding first of all 1.12 g. of pure white plates, m. p. 174°, which were identified as *p,p′*-bianisyl[13] by comparison with an authentic sample. From the mother liquor the desired product crystallized in lemon yellow plates. These were purified by conversion to the **picrate** which separated from its deep red alcoholic solution in thick needles of a red color so deep as to be almost black; m. p. 125°.

(12) Meldola and Eyre, *J. Chem. Soc.*, **81**, 991 (1902).
(13) Gillmeister, *Ber.*, **30**, 2849 (1897).

Anal. Calcd. for $C_{14}H_{12}O_2 \cdot C_6H_3O_7N_3$: N, 9.52. Found: N, 9.78.

Decomposition of the pure picrate with ammonia and ether gave 1 g. of pure dimethoxybiphenylene crystallizing in large, bright yellow, striated plates from ethanol; m. p. 107–108°.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.24; H, 5.70; mol. wt., 212. Found: C, 79.07, 79.51; H, 5.80, 5.95; mol. wt., 214 (Rast micro).

2,2′-Diiodo-*p,p′*-bianisyl.—The residue left from the above steam distillation was dissolved in hot glacial acetic acid, treated with norite and after filtration and cooling gave a deposit of pale buff prisms of unreacted diiodide (0.15 g.). Repeated crystallization failed to remove all color but the melting point stayed constant at 131°.

Anal. Calcd. for $C_{14}H_{12}O_2I_2$: I, 54.45. Found: I, 54.95.

2,7-Dimethoxyphenazone was recovered from the mother liquors as a gummy yellow precipitate which in acetone solution gave an orange **picrate**; m. p. 231–233°.

Anal. Calcd. for $C_{14}H_{12}O_2N_2 \cdot C_6H_3O_7N_3$: N, 14.92. Found: N, 15.14.

From this the pure dimethoxyphenazone was obtained in fine yellow needles from dilute acetic acid; m. p. 202–203° (literature 197°).[3]

2,7-Dihydroxybiphenylene.—Attempts to cleave dimethoxybiphenylene were uniformly unsuccessful, alcoholic alkali being without effect, while various acid reagents failed to give workable products. When the diether was treated in acetic acid solution with 48% hydrobromic acid or with concentrated hydrochloric acid, in air or under an atmosphere of nitrogen, a pink color appeared even at room temperature and rapidly turned to a deep purple, requiring about one minute on the steam-bath. From this solution a deep indigoid precipitate was obtained (m. p. above 360°) which was insoluble in alkali and all ordinary solvents and resisted attempts at acetylation. Parallel experiments with biphenylene showed that these effects were due to the methoxyl groups, since the hydrocarbon was untouched by such treatment.

An attempted cleavage in acetic anhydride solution gave a deep green solution and a gummy green precipitate which could not be crystallized.

Summary

Using methods previously employed for the preparation of biphenylene, 1,8-dimethylbiphenylene and 2,7-dimethoxybiphenylene have been prepared. Attempts to cleave the latter to form 2,7-dihydroxybiphenylene were unsuccessful.

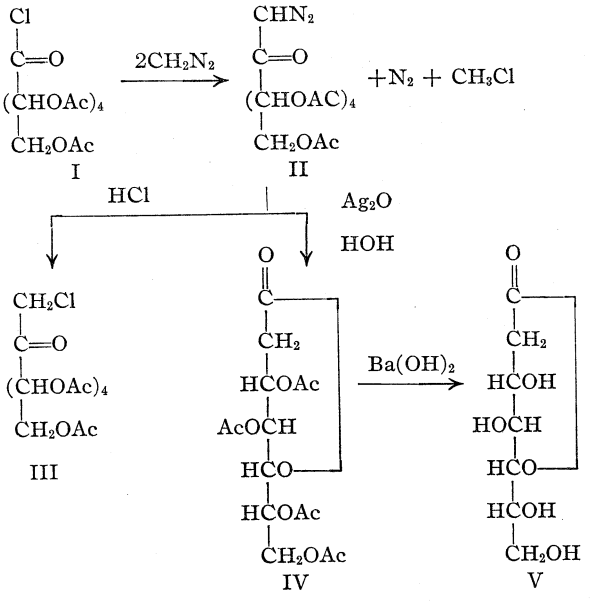
HARTFORD, CONN. RECEIVED MAY 6, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Action of Diazomethane upon Acyclic Sugar Derivatives.[1] II[2]

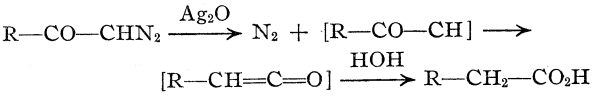
BY M. L. WOLFROM, S. W. WAISBROT AND ROBERT L. BROWN

In continuation of our work on the products obtained by the action of diazomethane upon the acid chlorides of fully acetylated sugar acids, we record the synthesis of 1-diazo-1-desoxy-*keto*-*d*-fructose tetraacetate from *d*-arabonyl chloride tetraacetate and diazomethane.

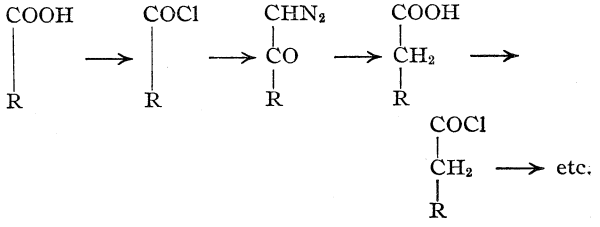


Treatment of the previously reported[2] 1-diazo-1-desoxy-*keto*-*d*-glucoheptulose pentaacetate (II) with ethereal solutions of dry hydrogen chloride and dry hydrogen bromide produced 1-chloro (III) and 1-bromo-*keto*-*d*-glucoheptulose pentaacetate, respectively. Similar treatment of 1-diazo-1-desoxy-*keto*-*d*-fructose tetraacetate produced 1-chloro and 1-bromo-*keto*-*d*-fructose tetraacetate. The chloro derivative III was the uncharacterized compound isolated in crude form from the mother liquors of our original preparations[2] of the diazomethyl ketone II. When the reaction was carried out under nearly anhydrous conditions, only traces of the chloro derivative were obtained. The 1-chloro-*keto*-*d*-fructose tetraacetate (m. p. 78°, spec. rot. +68°, $CHCl_3$) is isomeric with the chloro-*d*-fructose tetraacetate of Brauns[3] (m. p. 108°, spec. rot. +45°, $CHCl_3$,) to which the structural assignment of 6-chloro-*keto*-*d*-fructose has been made.[4]

In 1912 Wolff[5] described a characteristic rearrangement of diazoketones in their reaction with water or alcoholic ammonia in the presence of catalytic amounts of silver oxide.



It has not been until relatively recent years that the Wolff rearrangement has received any degree of attention. Arndt and co-workers[6] have developed the reaction as a general synthetic method for lengthening the carbon chain.



We have applied the Wolff rearrangement to the acetylated aldonic acids. Treatment of a suspension of II in hot water with catalytic amounts of silver oxide, followed by silver ion removal with hydrogen sulfide and concentration, yielded 2-desoxy-*d*-glucoheptono-δ-lactone tetraacetate (IV) of specific rotation +39.5° ($CHCl_3$). According to Lane and Wallis,[7] this rearrangement may take place with racemization provided that the terminal carbon of the migrating group R contains a hydrogen atom. This structural prerequisite is present in our compound and accordingly a mixture (not necessarily equimolecular) of 2-desoxy-*d*-glucoheptonic acid (or lactone) and 2-desoxy-*d*-mannoheptonic acid (or lactone) would be predictable. Only one product was isolated (*ca.* 70% yield). In the absence of any evidence for a second product, the 2-desoxy-*d*-glucoheptonolactone structure will be assigned provisionally to the substance isolated.

(1) An incomplete preliminary report of this work was published in THIS JOURNAL, **63**, 632 (1941). The work herein recorded was presented before the Division of Sugar Chemistry and Technology at the 101st Meeting of the American Chemical Society, St. Louis, Missouri, April 10, 1941.

(2) Previous publication in this series: M. L. Wolfrom, D. I. Weisblat, W. H. Zophy and S. W. Waisbrot, *ibid.*, **63**, 201 (1941).

(3) D. H. Brauns, *ibid.*, **42**, 1846 (1920).

(4) E. Pacsu and F. V. Rich, *ibid.*, **55**, 3018 (1933).

(5) L. Wolff, *Ann.*, **394**, 23 (1912).

(6) F. Arndt and B. Eistert, *Ber.*, **68**, 200 (1935).

(7) J. F. Lane and E. S. Wallis, *J. Org. Chem.*, **6**, 443 (1941).

Saponification of IV with barium hydrate, followed by removal of barium ion with sulfuric acid and concentration, yielded crystalline 2-desoxy-*d*-glucoheptonolactone (V) of specific rotation +20° (H_2O). The analytical data definitely indicate a lactone structure for IV and V. If, in accordance with the principles of Hudson's lactone rule, the rotations of these compounds are due almost in their entirety to the position of the lactone ring, then ring closure in IV and V must be on the right (as represented in the Fischer projection formula). The acceptance of such an hypothesis favors assignment to IV and V of a *delta* lactone structure, since carbon four in these structures is on the left. The *delta* lactones of the normal sugar acids are relatively unstable and exhibit moderately rapid hydrolysis. Further evidence for the 1,5 ring in IV, then, lies in the fact that it was found to be rapidly titratable to a stable end-point within a period of one and one-half minutes from the time of solution in acetone-water. It was found that V was too slowly soluble to allow rapid titration but was titratable to a stable end-point within four and one-half to five minutes. Contrary to expectation, IV exhibited no mutarotation in either methanol or aqueous acetone. V was too slowly soluble in water for early polarimetric readings in that medium; however, no mutarotation was observed after an initial rotation of +20° at twenty minutes. Attempts were made to follow lactonization of the free acid by the general method of Levene and Simms.[8] An initial reading at three minutes gave a specific rotation of +20°. Thereafter there was no observable mutarotation over a period of eighty hours.

Explanation of the apparently anomalous optical behavior of IV and V may lie in an effective increase in the rate of hydrolysis due to the influence of the 2-desoxy carbon. Again, the explanation may lie in an extraordinary similarity in rotation between the lactone and its acid, in the event of which Hudson's lactone rule would not be applicable. The expectation would be that in V *gamma* lactone formation would be sufficiently slow to be readily observable and an appreciable quantity of the *gamma* lactone in the equilibrium mixture should yield a more negative value. As more information is obtained concerning the little known group of 2-desoxy sugar acids, it may well be that their behavior will be found to differ markedly from that of the normal sugar acids. Thus, an abnormally high rate of hydrolysis has been found[9] for the glycopyranosides of the 2-desoxy sugars in comparison with the rate exhibited by the normal sugar pyranosides.

Further extension of these reactions is in progress in this Laboratory.

(8) P. A. Levene and H. S. Simms, *J. Biol. Chem.*, **65**, 31 (1925).

Experimental

1-Diazo-1-desoxy-*keto*-*d*-fructose Tetraacetate.—*d*-Arabonic acid tetraacetate[10] (7.1 g.), prepared according to the excellent method of Robbins and Upson,[11] was dissolved in 20 cc. of benzene and 3 cc. (2 moles) of thionyl chloride added. The solution was warmed until the evolution of hydrogen chloride ceased, as shown by ammonia test. The excess thionyl chloride was removed by solvent concentration under reduced pressure followed by repeated additions of benzene and subsequent removal in the same manner. The sirupy residue was dissolved in 50 cc. of anhydrous ether and the solution cooled to 0°. Two moles of diazomethane gas was then added and the solution allowed to stand overnight. At the end of this period, some separated polymethylenes were removed by filtration and the filtrate was concentrated with a stream of dry air until crystallization occurred. The cream-colored crystals were removed by filtration and washed with cold ether; yield 5.7 g.; m. p. 88.5–89°. Pure material was obtained on recrystallization from methanol–ether; yield 5 g.; m. p. 93–94°; spec. rot. −11° (23°, *c* 4, abs. $CHCl_3$).[12]

The purified substance possessed a slight cream color. It was soluble in alcohol, acetone and warm ether but was insoluble in petroleum ether and water. It reduced boiling Fehling solution.

Anal. Calcd. for $C_{14}H_{19}O_9N_2$: C, 46.93; H, 5.06; N, 7.82. Found: C, 46.93; H, 5.21; N, 7.67.

1-Chloro-*keto*-*d*-fructose Tetraacetate.—Two grams of 1-diazo-1-desoxy-*keto*-*d*-fructose tetraacetate was suspended in anhydrous ether and dry hydrogen chloride passed into the solution until the evolution of nitrogen ceased. The solution was cooled and an equal amount of petroleum ether was then added. The crystals which formed were removed by filtration and washed with ether–petroleum ether; yield 1.5 g.; m. p. 75–77°. Pure material was obtained on two further crystallizations from ether–petroleum ether; yield 1 g.; m. p. 77.5–78°; spec rot. +68° (22°, *c* 4, abs. $CHCl_3$).

The substance reduced boiling Fehling solution but no precipitate formed on boiling with alcoholic silver nitrate.

Anal. Calcd. for $C_{14}H_{19}O_9Cl$: C, 45.85; H, 5.22; Cl, 9.66. Found: C, 45.81; H, 5.40; Cl, 9.50.

1-Bromo-*keto*-*d*-fructose Tetraacetate.—1-Diazo-1-desoxy-*keto*-*d*-fructose tetraacetate (3.5 g.) was treated in the same manner as in the above-described synthesis of the corresponding 1-chloro derivative, using hydrogen bro-

(9) M. Bergmann and W. Breuers, *Ann.*, **470**, 38 (1929); P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, **88**, 791 (1930).

(10) C. D. Hurd and J. C. Sowden, THIS JOURNAL, **60**, 235 (1938).

(11) G. Robbins and F. Upson, *ibid.*, **62**, 1074 (1940); *cf.* J. M. Brakenbury and F. Upson, *ibid.*, **55**, 2512 (1933).

(12) All rotations are recorded to the D-line of sodium light, 23° is the temperature, *c* is the concentration in g. per 100 cc. of soln.

mide instead of hydrogen chloride. The product which crystallized was removed by filtration and washed with ether–petroleum ether; yield 3.4 g.; m. p. 67.5–68°. Pure material was obtained on crystallization from ether; yield 3 g.; m. p. 68°; spec. rot. +62.5° (26°, *c* 4, abs. $CHCl_3$).

The substance reduced boiling Fehling solution but no precipitate formed on boiling with alcoholic silver nitrate.

Anal. Calcd. for $C_{14}H_{19}O_9Br$: Br, 19.43. Found: Br, 19.12.

1-Chloro-*keto*-*d*-glucoheptulose Pentaacetate (III).—1-Diazo-1-desoxy-*d*-glucoheptulose pentaacetate[2] (1.0 g.) was suspended in anhydrous ether (15 cc.) and dry hydrogen chloride gas was passed into the solution until the compound was dissolved. The solution was then allowed to stand for two hours, after which the excess hydrogen chloride was removed by washing with aqueous sodium bicarbonate solution. An equal volume of petroleum ether was added to the dried (sodium sulfate) ethereal solution and the crystalline product which formed was removed by filtration and washed with petroleum ether; yield 0.6 g.; m. p. 100–101°; spec. rot. −5.5° (22°, *c* 5, abs. $CHCl_3$). These constants were unchanged on two further crystallizations from ether–petroleum ether.

The substance was soluble in the common solvents except petroleum ether and water. It reduced boiling Fehling solution. No precipitate was formed on boiling with alcoholic silver nitrate.

Anal. Calcd. for $C_{17}H_{23}O_{11}Cl$: C, 46.52; H, 5.28; Cl, 8.08. Found: C, 46.52; H, 5.28; Cl, 8.05.

This substance was the uncharacterized compound isolated in crude form from the mother liquors of our original preparations[2] of 1-diazo-1-desoxy-*d*-glucoheptulose pentaacetate (II). When the preparation of II was carried out under nearly anhydrous conditions only traces of the chloro compound were obtained.

1-Bromo-*keto*-*d*-glucoheptulose Pentaacetate.—1-Diazo-1-desoxy-*d*-glucoheptulose pentaacetate (3.5 g.) was treated in the same manner as in the synthesis of the corresponding 1-chloro derivative, using hydrogen bromide in place of hydrogen chloride. The product which crystallized was removed by filtration and washed with ether–petroleum ether; yield 3.3 g.; m. p. 80–82°. Pure material was obtained on three recrystallizations from ether–petroleum ether; m. p. 86–87°; spec. rot. −4° (24°, *c* 5, abs. $CHCl_3$).

This compound was slightly less soluble than the corresponding chloro derivative. It reduced boiling Fehling solution and yielded no precipitate on boiling with alcoholic silver nitrate.

Anal. Calcd. for $C_{17}H_{23}O_{11}Br$: Br, 16.54. Found: Br, 16.72.

2-Desoxy-*d*-glucoheptonolactone Tetraacetate (IV).—1-Diazo-1-desoxy-*d*-glucoheptulose pentaacetate (1 g.) was suspended in 40 cc. of water with 0.2 g. of silver oxide. The mixture was warmed to about 70° and 0.2 g. of silver oxide was added portionwise over a period of fifteen minutes. The mixture was then refluxed for fifteen minutes, after which the silver oxide was removed by filtration. The silver ion was removed with hydrogen sulfide, followed by filtration. The clear filtrate was then concentrated to about 15 cc. The fibrous crystals that formed were removed by filtration and washed with water; yield 0.5 g.; m. p. 129–130°, unchanged on further recrystallization from hot water; spec. rot. +40° (20°, *c* 4, abs. chloroform, no detectable mutarotation). The mother liquors on further concentration yielded 0.1 g. of additional material.

The substance did not reduce boiling Fehling solution.

Anal. Calcd. for $C_7H_8O_6(CH_3CO)_4$ (lactone tetraacetate): C, 50.00; H, 5.60; saponification value (five equivalents), 13.88 cc. 0.1 *N* sodium hydroxide per 100 mg. Calcd. for $C_7H_9O_7(CH_3CO)_5$ (acid pentaacetate): C, 48.57; H, 5.75; saponification value (six equivalents), 14.27 cc. Found: C, 49.76; H, 5.58; saponification value, 13.8 cc.

The analytical data indicate that in the course of the rearrangement one mole of acetic acid was lost, presumably by lactonization. In a study of the position of ring closure the following experiments were performed.

(*a*) 2-Desoxy-*d*-glucoheptonolactone tetraacetate (0.2766 g.) was dissolved in acetone (50 cc.). Boiled distilled water (100 cc.) was quickly added and the solution immediately titrated to a phenolphthalein end-point. Time elapsed from introduction of the acetone to complete neutralization was one minute and thirty seconds. A volume of 7.75 cc. of 0.1005 *N* sodium hydroxide which, less a blank of 0.15 cc., gives a volume of 7.60 cc. required for neutralization. The neutralization equivalent calculated therefrom is 362.1; theory for the lactone tetraacetate, 360.3. That the compound was instantaneously titratable is evidence in support of a *delta*-lactone structure.

(*b*) In absolute methanol solution there was no observable mutarotation (initial reading, four minutes) over a period of forty-five hours; spec. rot. +34° (22°, *c* 2.5).

(*c*) A sample of the lactone was dissolved in dry acetone (8 cc.) and made up to 15.00 cc. with water. There was no observable mutarotation (initial reading, six minutes) over a period of twenty hours; spec. rot. +35° (23°, *c* 4).

2-Desoxy-*d*-glucoheptonolactone (V).—2-Desoxy-*d*-glucoheptonolactone tetraacetate (5 g.) was treated with an equivalent amount of a saturated barium hydrate solution (10.95 g. of barium hydrate octahydrate) and allowed to stand at room temperature overnight. The barium ion was then removed with an equivalent amount of sulfuric acid (69.4 cc. *N*) and the barium sulfate removed by filtration. The clear filtrate was concentrated to about 10 cc. and on cooling crystallization ensued; yield 1 g.; m. p. 170°, unchanged on further recrystallizations effected by solution in water and subsequent concentration; spec. rot. +20° (26°, *c* 5, H_2O, no mutarotation).

The compound was soluble in warm water and insoluble in the common organic solvents except glacial acetic acid.

Anal. Calcd. for $C_7H_{12}O_6$ (lactone): C, 43.75; H, 6.29; sapon. equiv., 192. Calcd. for $C_7H_{14}O_7$ (acid): C, 40.00; H, 6.71; sapon. equiv., 210. Found: C, 43.44; H, 6.27; sapon. equiv., 196.

The lactone was too slowly soluble in water to allow early initial polarimetric readings in that medium. No mutarotation was observed after a reading of +20° at twenty minutes. Attempts were made to follow lactonization of the free acid, according to the general procedure of Levene and Simms.[8] The lactone (0.4717 g.) was suspended in water and 4.70 cc. of 0.5008 *N* sodium hydroxide was added. The compound went into solution slowly and

after about four minutes the alkaline color of phenolphthalein faded. Two additional drops (0.1 cc.) of base were required for complete neutralization (total 4.8 cc.). A further 0.2 cc. of alkali was added followed by the addition of an equivalent volume (5.00 cc.) of 0.5007 *N* hydrochloric acid. The solution was quickly made up to 15.00 cc. and the polarimetric reading taken (initial reading, three minutes); spec. rot. +20.1° (23°, *c* 3.1). Thereafter there was no observable mutarotation over a period of eighty hours.

We acknowledge the general assistance of Messrs. Percy McWain (N.Y.A. Project O.S.U. 170) and Clarence M. Clevenger.

Summary

1. 1-Diazo-1-desoxy-*keto*-*d*-fructose tetraacetate has been synthesized by the action of diazomethane upon *d*-arabonyl chloride tetraacetate.

2. The 1-chloro and the 1-bromo derivatives of the *keto*-forms of *d*-fructose and of *d*-glucoheptulose acetates have been synthesized by the action of the hydrogen halides upon the corresponding diazomethyl ketone acetates (II).

3. 1-Diazo-1-desoxy-*keto*-*d*-glucoheptulose pentaacetate (II) underwent the Wolff rearrangement to produce a lactone form of 2-desoxyglucoheptonic acid tetraacetate, from which 2-desoxyglucoheptonolactone was obtained by saponification.

4. The above 2-desoxyaldonolactone and its acetate exhibited anomalous properties.

5. The above reactions represent transformations from the aldose series to (*a*) the ketose series and to (*b*) the 2-desoxyaldonic acid series.

COLUMBUS, OHIO RECEIVED MAY 2, 1942

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

Anthochlor Pigments. III. The Pigments of *Cosmos Sulphureus*

BY T. A. GEISSMAN

Previous studies on the sap-soluble flower pigments of certain species of *Compositae* have shown that the petals of these species contain substances which form intensely red salts with alkalies. For convenience these pigments have been described by the term "anthochlor." The tetrahydroxychalcone butein (I) has been identified as one member of this class of pigments and has been isolated from *Dahlia variabilis*[1] and from two species of *Coreopsis*.[2]

It was noted in the paper describing the studies on *Coreopsis gigantea*[2b] that in this flower a second substance accompanies butein, and it was suggested on the basis of the analytical figures for its crystalline acetate that this substance was a pentahydroxychalcone hexoside. This compound has now been isolated from the ray florets of *Cosmos sulphureus* ("Orange Flare"). *C. sulphureus* is a garden annual whose bright orange rays and yellow disk florets give the anthochlor reaction with alkali. Ether extraction of the dried, powdered rays yielded the glycoside as a yellow amorphous powder which separated from the ether during the extraction. Further treatment of the ether-extracted rays by a somewhat more lengthy procedure yielded an additional amount of the pigment. It formed a white crystalline acetate identical with that of the pigment previously isolated from *Coreopsis gigantea*. It is proposed to call this pigment "coreopsin."

The previously reported analytical figures on the basis of which coreopsin was assumed to be a pentahydroxychalcone hexoside were somewhat in error since it has been found that the aglycone of the pigment is butein. Hydrolysis of coreopsin acetate (the acetate was chosen since it is readily crystallized while the pigment itself has been obtained only in an amorphous, although apparently homogeneous, condition), followed by acetylation of the ether-extractable products, yielded the triacetate of butin (II), the flavanone isomeric with butein. The formation of butin in the hydrolysis is undoubtedly due to the isomerization of the butein first produced from the glycoside. The isomerization of *o*-hydroxychalcones to the corresponding flavanones under these conditions is a well-known reaction[3] and the sample of butin triacetate used for purposes of comparison was synthesized by treating a sample of synthetic butein under conditions identical with those used for the hydrolysis of the glycoside. That coreopsin is a glycoside of butein and not of butin

(1) Price, *J. Chem. Soc.*, 1018 (1939).

(2) (a) Geissman, THIS JOURNAL, **63**, 656 (1941); (b) **63**, 2689 (1941).

(3) (a) Perkin and Hummel, *J. Chem. Soc.*, **85**, 1462 (1904); (b) Göschke and Tambor, *Ber.*, **45**, 186 (1912). These describe the preparation of butin.

is indicated by a number of considerations. The pigment is a bright yellow in color, while the corresponding flavanone and glycosides of similar flavanones are colorless substances; it dissolves instantly in cold, dilute aqueous alkali with the formation of a red color; it gives no color when reduced with magnesium and hydrochloric acid.

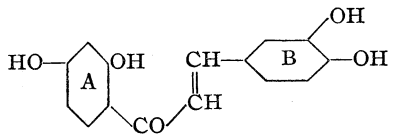
The aqueous solution from the hydrolysis of coreopsin acetate, after removal of the coloring matter, was found to reduce Fehling solution, but positive identification of the sugar has not yet been accomplished. On the basis of the analytical figures for coreopsin acetate it is probably a hexose. The position of attachment of the sugar has not yet been established, but it is very probable that it is attached to either the 2′ or 4′ position. The red color of alkaline solutions of coreopsin is similar to that shown by other chalcones hydroxylated in the 3,4-positions and is deeper than the colors of alkaline solutions of 4-hydroxy- or 4-hydroxy-3-methoxychalcones. Further, no naturally-occurring member of the large class of substances having the C_6–C_3–C_6 structure found in butein carries a sugar residue in the phenyl ring corresponding to the catechol nucleus of butein.

The study of the flowers of *Cosmos sulphureus* has been extended to include the remainder of the flower-head, consisting of the yellow disk-florets and the scarious involucral bracts. From this material there have been isolated a glycoside of quercetin, probably isoquercitrin, and (as the acetate)[4] luteolin (IV). Quercetin (III) was obtained in calculated amount from the hydrolysis of a weighed amount of the glycoside and identified by conversion to its acetate and comparison of this with an authentic sample. Although the disk-florets as well as the rays show the anthochlor reaction when touched with alkali, no pigment of this class was isolated from them except as a probable component of a crystalline acetate mixture which developed an intensely red solution when hydrolyzed with alcoholic alkali but which melted over a broad range.

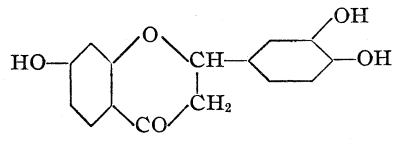
It appears likely that luteolin occurs as the free flavone since it was extracted from the flowers with ether and isolated without the use of any hydrolytic step.

(4) Since several thousand flower-heads yield an amount of dried material of the order of only a hundred grams, relatively small amounts of isolated substances have been available. For this reason it has proved convenient and often necessary to work up crude pigment fractions by acetylation, followed by purification of the readily crystallizable acetates. The pigments themselves are difficult to purify from the crude condition without considerable loss.

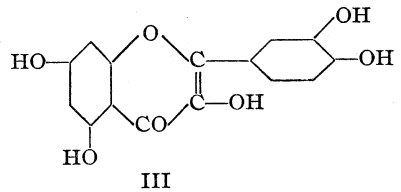
A comparison of the structures of the substances present in the flowers of *C. sulphureus* (I, III, and IV) adds an interesting example of a biogenetically and chemically related group of compounds to a number already recorded from studies on other plants.



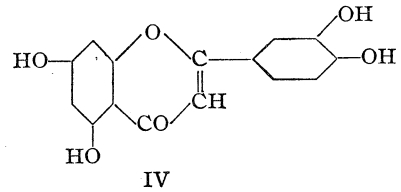
I



II



III



IV

All of these compounds have the $C_{6(A)}$–C_3–$C_{6(B)}$ carbon skeleton (*cf.* (I)) which is widespread in the plant kingdom and all of them contain the catechol nucleus as the $C_{6(B)}$ part of the molecule. They differ in the degree of oxidation in the $C_{6(A)}$–C_3 part of the molecule and in this respect bear to each other the same kind of relationship that exists between such related pairs of substances as pelargonidin and apigenin or pelargonidin and kampferol.

In view of the fact that all of the flowers so far known to belong to the anthochlor group, with the single recorded exception of the legume, *Butea frondosa*, are closely related taxonomically[5] a detailed study of their flower pigments should furnish a basis for evaluating in terms of the results obtained certain of the proposals that have been made concerning the biogenesis of plant materials, particularly those of the "flavone" (C_6–C_3–C_6) type.

(5) This close relationship is indicated by the fact that they have sometimes been classified as a sub-tribe *Coreopsidinae* of the tribe *Heliantheae*.

Experimental

All melting points are uncorrected.

Cosmos sulphureus was grown from commercially available seed. The flowers were collected at intervals, the rays separated immediately, and the rays and disk florets (with the involucral bracts) air-dried, ground to a powder and stored in stoppered containers.

Ray Flowers: Coreopsin.—Sixty grams of the dried, ground rays was extracted (Soxhlet) with petroleum ether (30–60°) until fresh portions of the solvent were no longer colored. The solution contained carotenoid pigments but no pigments of the anthochlor type. The powder was freed of petroleum ether and extracted with ether. The ether extract was greenish-yellow in color and contained a small amount of suspended solid. This was removed and dried. It weighed 0.130 g. It was a bright yellow substance, insoluble in ether, soluble in hot methanol, slightly soluble in hot water and gave an intense crimson solution in cold, dilute sodium hydroxide. Upon acidification of its alkaline solution, it separated as spherical globules of a glassy nature. The behavior of the crude material on melting indicated that it was not crystalline: it sintered at about 150° and decomposed at 190–195°.

Anal. Calcd. for $C_{21}H_{22}O_{10}\cdot 1.5H_2O$: C, 54.40; H, 5.39. Found: C, 54.50; H, 5.25.

From the ether solution was isolated by extraction with sodium carbonate solution, acidification and extraction with ether 40 mg. of a yellow-brown amorphous substance which could not be crystallized or converted into a crystalline acetate.

The ether-extracted petal-meal was dried and extracted with methanol. The filtered extract was evaporated, the sirupy residue dissolved in water and the solution washed with ether and clarified by filtration through Hyflo Supercel. To the deep red filtrate saturated lead acetate solution was added until no further precipitate was formed. The brick-red precipitate was removed and suspended in methanol and hydrogen sulfide passed into the suspension. The precipitated lead sulfide was removed and the deep orange-red solution evaporated under reduced pressure. The red-brown tar thus obtained was acetylated with acetic anhydride–sodium acetate and the tarry acetylation product separated into ether-soluble and ether-insoluble fractions by dissolving it in alcohol, adding ether and washing the resulting solution with water. The process was repeated with the tar which separated during the water washing. The nearly colorless ether solution finally resulting was evaporated and the gummy residue allowed to stand overnight with 20 ml. of 10% sodium hydroxide solution. The deep red alkaline solution resulting was decanted from some unchanged tarry material, washed with ether, acidified and the acidified solution saturated with ammonium sulfate. A yellow powdery solid separated on standing. It weighed 0.280 g. and was shown to be coreopsin by conversion into its crystalline acetate.

Coreopsin Acetate.—A portion of the pigment was acetylated with sodium acetate–acetic anhydride. The acetate formed soft, white needles; m. p. 171–172° after one recrystallization from alcohol. Mixed with a sample of the acetate, m. p. 171–2.5°, from *Coreopsis gigantea* no depression in melting point was observed. The two acetates gave identical colors when heated with alcoholic sodium hydroxide.

Anal. Calcd. for $C_{35}H_{36}O_{17}$: C, 57.67; H, 4.98. Found: C, 57.27, 57.22; H, 4.88, 4.79.

Hydrolysis of Coreopsin Acetate.—A suspension of 0.265 g. of coreopsin acetate (m. p. 171–172°) in a mixture of 50 ml. of 2% hydrochloric acid and 10 ml. of methanol was refluxed for four hours. The solid dissolved after about one hour and a pale yellow solution resulted. The solution was cooled and extracted with ether and the ether extract was dried and evaporated, leaving a red-yellow gum. This was acetylated by boiling it for about a minute with 2 ml. of acetic anhydride and 0.2 g. of sodium acetate. A nearly colorless solution resulted. After several hours ice and water and a few ml. of ether were added and upon standing colorless crystals (70 mg.) formed in the ether layer. After two recrystallizations from alcohol this material formed shining white leaflets, m. p. 120.5–121°. It was found to be butin triacetate by comparison with a sample prepared from synthetic butein by a procedure identical with that described above for the hydrolysis of coreopsin acetate. The melting points of both products and of a mixture of the two were identical, as were the colors produced by the magnesium and hydrochloric acid reduction test.

The behavior of butin triacetate when reduced with magnesium and hydrochloric acid in alcohol is noteworthy. The color produced is an intense red-violet to blue-violet (depending upon the concentration), and is markedly bluer than the colors shown by flavanones hydroxylated in the 5,7-positions, such as naringenin, eriodictyol and homoeriodictyol. This color test is the subject of another investigation now being carried on in this Laboratory. Butin triacetate has been previously reported to have a melting point of 123–125°[3a] and 123°.[3b] The sample from the hydrolysis of coreopsin acetate was analyzed.

Anal. Calcd. for $C_{21}H_{18}O_8$: C, 63.28; H, 4.57. Found: C, 63.01; H, 4.92.

The aqueous solution from which the butin had been removed was treated with lead carbonate and the lead removed with hydrogen sulfide. The solution reduced Fehling solution but no crystalline derivative of the sugar could be isolated in amount sufficient for identification.

Disk-florets and Involucral Bracts.—After a preliminary treatment with petroleum ether the powdered material was extracted with ether. The ether solution was washed with sodium carbonate solution and the deep red extract acidified and extracted with ether. The ether extract was dried and evaporated, leaving a brown, tarry residue which was induced to crystallize partially by adding small amounts of ether and allowing evaporation to proceed slowly between fresh additions. There was finally obtained 50 mg. of a yellow, powdery solid. An attempt to recrystallize this resulted in a product which did not melt below 250° but darkened from about 230°, and was obviously still impure. It was finally acetylated and yielded a white, crystalline acetate which after two recrystallizations from alcohol melted at 217–219°. It was similar in melting point and behavior to luteolin tetraacetate which has been reported by various investigators to melt at 213–

215°,[6] 223–226°,[7] 222–224°.[8] A sample of luteolin tetraacetate was synthesized according to the method of Kostanecki, Rozycki and Tambor,[8] starting with methyl veratrate and trimethoxyacetophenone. The synthetic material melted at 221–222° and a mixture of this and that from the natural source melted at 219–221°. In a repetition of the isolation from the florets and bracts there was obtained a product melting at 220–222°. The natural and synthetic samples gave identical red-orange colors when to their solutions in alcohol were added a fragment of magnesium and a drop of concentrated hydrochloric acid, and both samples dissolved in hot alcoholic sodium hydroxide to form yellow solutions. Unfortunately too little of the material from the natural source was obtained for satisfactory analytical figures. Each of the two samples described was analyzed.

Anal. Calcd. for $C_{23}H_{18}O_{10}$: C, 60.78; H, 4.00. Found: C, 61.74, 60.15, 60.29; H, 4.27, 4.04, 3.80.

It is felt, however, that the information from the melting point and color-test observations, coupled with the approximate agreement in the analyses is sufficient to establish the identity of the compound isolated.

From the oily mother liquor from which the crude luteolin separated was obtained a crystalline mixture of acetates; m. p. 130–190°. It formed a deep red solution in hot alcoholic alkali. Too little of it was obtained to permit of its separation into its components.

Isoquercitrin.—The alcohol extract of the ether-extracted meal (disk-florets and bracts) was diluted with water and concentrated to remove most of the alcohol. Saturated lead acetate was added in small portions and the brown precipitates which first appeared were discarded. The bright orange-yellow precipitate which then formed was removed, suspended in hot water and decomposed with hydrogen sulfide. The filtered solution was saturated with salt and extracted with ethyl acetate. Removal of the ethyl acetate left a yellow gum which on standing in alcohol–water solution deposited 60 mg. of a yellow powder. This crystallized from dilute alcohol as lemon-yellow needles; m. p. 217–219° after shrinking at about 115° (loss of water of hydration). It dissolved in alkali to a deep yellow solution, gave a deep olive-green color with aqueous-alcoholic ferric chloride and a rose-red solution when reduced in alcoholic solution with magnesium-hydrochloric acid. These observations are in agreement with those recorded for isoquercitrin (quercetin-3-glucoside); m. p. reported as 217–219°,[9] 218–220°,[10] 219°.[11]

Hydrolysis of 24.0 mg. of the glycoside with 6 ml. of 1 *N* sulfuric acid yielded 14.1 mg. of quercetin; calcd. for isoquercitrin, 14.4 mg. The product of the hydrolysis was converted into its acetate, m. p. 192–193°; no depression on mixing with an authentic sample, m. p. 193–194°, of quercetin pentaacetate.

Anal. Calcd. for quercetin pentaacetate, $C_{25}H_{20}O_{12}$: C, 58.58; H, 3.94. Found: C, 58.66; H, 3.99.

(6) Perkin, *J. Chem. Soc.*, **69**, 206 (1896).
(7) Herzig, *Ber.*, **29**, 1013 (1896).
(8) Kostanecki, Rozycki and Tambor, *ibid.*, **33**, 3416 (1900).

Summary

1. The flowers of *Cosmos sulphureus* ("Orange Flare") contain coreopsin (rays), luteolin and a quercetin glycoside which is probably isoquercitrin (disk-florets and involucral bracts).

2. Coreopsin has been found to be a butein glycoside. The nature and position of the sugar residue are as yet undetermined.

(9) Perkin, *J. Chem. Soc.*, **95**, 2190 (1909).
(10) Sando and Bartlett, *J. Biol. Chem.*, **54**, 640 (1922).
(11) Viehover, Chernoff and Johns, *J. Agr. Research*, **13**, 348 (1918).

LOS ANGELES, CALIFORNIA RECEIVED APRIL 22, 1942

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

The Catalysis of the Thermal Decomposition of Acetaldehyde by Hydrogen Sulfide

BY WALTER L. ROTH AND G. K. ROLLEFSON

In some previous work it has been shown that the acceleration of the rate of the thermal decomposition of acetaldehyde when iodine is added is due to a series of reactions in which the iodine reacts with the aldehyde and then is regenerated by reactions between the products of the first reaction.[1] In this paper we are presenting the results of some investigations of the nature of the action of hydrogen sulfide which has also been reported to accelerate the decomposition of acetaldehyde.[2]

Fromherz reported that the rate of the decomposition in the presence of hydrogen sulfide is dependent only on the pressure of the catalyst. In accordance with this statement the rate was constant throughout a considerable portion of any given run and the ratio of the time required for three-fourths completion to that required for half completion was approximately 1.5 as it should be if the rate were independent of the aldehyde pressure. On the other hand, if we utilize this linear character of the pressure–time curves to calculate the initial rates, we find continuous variation of the rate constants calculated on the assumption of independence of the aldehyde according to the

(1) Faull and Rollefson, THIS JOURNAL, **59**, 625 (1937).
(2) Fromherz, *Z. physik. Chem.*, **B25**, 301 (1934).

law $-d(CH_3CHO)/dt = k'(H_2S)$. The results for a series of aldehyde pressures are shown in Table I along with the times given by Fromherz for a pressure change one-half and three-fourths of the final value.

TABLE I

Temperature 510°, H_2S 20 mm.

CH_3CHO mm. initial	$t_{1/2}$, min.	$t_{3/4}$, min.	$t_{3/4}/t_{1/2}$	k', min.$^{-1}$
58	1.44	2.36	1.64	10.05
106.5	2.10	3.35	1.59	12.65
129	2.37	3.73	1.58	13.60
149	2.49	3.94	1.58	14.95
182.5	2.60	4.12	1.58	17.55
273	2.73	4.50	1.64	25.00
383	2.77	4.61	1.66	34.60

If the reaction were truly of the zero order with respect to the acetaldehyde the value in the fourth column should be 1.5 and the value in the fifth column should be constant. It is apparent that while the values of the ratios $t_{3/4}/t_{1/2}$ are approximately constant the value is too large and k' shows a marked trend with the initial pressure of the aldehyde. The experiments reported in this paper were designed to determine the true rate law for this reaction and to test several hypotheses concerning the mechanism of the catalysis.

Apparatus, Methods, and Materials.—The apparatus was of the type usually employed in the study of gaseous reactions in which the progress of the reaction can be followed by pressure measurements. The volume of the system was kept constant and the pressure measured by means of a click gage with the aid of a sulfuric acid manometer for the low pressures and a mercury manometer for the higher pressures. The reaction vessel was placed in a cylindrical electrical furnace, wired concentrically, and equipped with end heaters to eliminate temperature gradients. The furnace temperature was kept constant to 1° by manually controlled rheostats. Temperatures were measured with a chromel–alumel thermocouple which had been calibrated at the melting points of lead, tin and zinc. The thermocouple was placed in a well which extended to the center of the reaction vessel.

On account of the extreme sensitivity of the reaction to traces of air, all operations were carried out in a system which could be evacuated to a pressure of 10^{-6} mm. before starting an experiment. The sulfuric acid manometer was always separated from the reaction vessel by the click gage.

Experiments were performed with two Pyrex and one quartz reaction vessel. One of the Pyrex vessels was packed with glass tubing to increase the surface/volume ratio in some of the experiments. The surface/volume ratios were approximately unity in the unpacked vessels and 12 in the packed one. The volumes of the unpacked vessels ranged from 219 cc. to 379 cc. with a surface/volume ratio of *ca.* unity and the packed vessel had a free volume of 180 cc. with a surface/volume ratio of 12.

Acetaldehyde was purified by three different procedures. The only sample which was free from the effects which were found to be due to the presence of small amounts of air was one for which the entire preparation was carried out in a system which had been thoroughly evacuated. Merck paraldehyde which had been washed with sodium bicarbonate, dried over calcium chloride, and fractionated was depolymerized with a trace of concentrated sulfuric acid. The middle fraction was refluxed under vacuum, put in contact with recrystallized hydroquinone and calcium sulfate for twenty-four hours and fractionated, the middle fraction being saved for use. This sample was stored at 0° behind a mercury cutoff and small amounts distilled as needed into a second reservoir where it was given an additional degassing at −78° before using.

Some of the experiments were performed with hydrogen sulfide which had been obtained from the Ohio Chemical Company and had been degassed by repeated evacuations at −180°. The final results were obtained with a sample made from electrolytic hydrogen and sulfur.

Electrolytic hydrogen, free from oxygen, was supplied by Professor Giauque of this Laboratory.

The sulfur used was a sample prepared by Eastman and McGavock for heat capacity investigations.[3]

Carbonyl sulfide was prepared from ammonium thiocyanate and sulfuric acid.[4]

Nitric oxide which had been prepared by the method of Johnston and Giauque[5] was supplied by Dr. K. Atwood.

Eastman Kodak Company methyl mercaptan and Kahlbaum dimethyl sulfide were distilled and degassed in the vacuum system.

Distilled water was degassed thoroughly by boiling and distilling off the first half in the vacuum line.

The procedure followed in making a typical run and analysis was: The reaction vessel was first flushed with acetaldehyde, evacuated, and then hydrogen sulfide introduced and the pressure measured. Next the acetaldehyde was admitted and an electric clock started simultaneously. Pressure readings were taken at regular intervals, usually of one-half minute, during the initial stages of the reaction. The initial total pressure was determined by extrapolating the pressure–time curve to zero time.

When the pressure change indicated that the reaction had proceeded as far as was desired for that experiment the gases were drawn from the reaction vessel by means of a Toepler pump. Two spiral traps immersed in liquid air inserted between the vessel and the pump served to freeze out all of the condensable gases. The non-condensable gases were transferred to a gas buret and samples were analyzed by the micromethods which have been described by Blacet, Leighton, MacDonald and others.[6] The condensable gases were analyzed for hydrogen sulfide by treating them with a solution of lead nitrate and titrating the liberated acid with a solution of 0.01 *N* sodium hydroxide. Blank experiments showed that acetaldehyde and lead sulfide did not interfere with this analysis.

(3) Eastman and McGavock, THIS JOURNAL, **59**, 145 (1937).
(4) Kemp and Giauque, *ibid.*, **59**, 79 (1937).
(5) Johnston and Giauque, *ibid.*, **51**, 3194 (1929).
(6) (a) Blacet and Leighton, *Ind. Eng. Chem., Anal. Ed.*, **3**, 766 (1931); (b) Blacet, MacDonald and Leighton, *ibid.*, **5**, 272 (1933); (c) Blacet and MacDonald, *ibid.*, **6**, 334 (1934); (d) Blacet and Volman, *ibid.*, **9**, 44 (1937).

Results and Discussion.—Preliminary experiments showed that consistent results could not be obtained unless the reactants were carefully purified especially so as to eliminate oxygen. This observation is in agreement with that of Letort[7] who found that the thermal decomposition of acetaldehyde is accelerated by small amounts of oxygen. Furthermore with reactants which had not been carefully purified the reaction was found to be partially heterogeneous but it was immaterial whether the surface was quartz or Pyrex glass. With carefully purified reactants the reaction was found to be homogeneous as is shown by the data in Table II. The packed vessel had a surface/volume ratio twelve times that of the unpacked one. The remainder of this paper is concerned with this homogeneous reaction.

TABLE II

COMPARISON OF RATES IN QUARTZ AND PACKED PYREX REACTION VESSELS AT 713°K.

Initial pressure, cm. of mercury H_2S	CH_3CHO	Initial rate/(H_2S) cm./min.	Reaction vessel
3.68	18.79	0.324	Packed Pyrex
4.04	19.77	.296	Quartz
4.04	18.62	.268	Packed Pyrex
4.03	19.19	.265	Quartz
2.12	17.36	.821	Packed Pyrex
1.98	20.72	.824	Quartz

Analysis of the reaction mixture at various degrees of completion showed that the only products present in appreciable amounts were methane and carbon monoxide. Within the limits of accuracy of the methods used, the hydrogen sulfide was present in its original form throughout the course of the reaction. Some of the analytical results are shown in Table III. It follows from these observations that the pressure change at any time is a measure of the extent of the reaction.

Some typical pressure time curves are shown in Fig. 1. It is apparent that the curves are practically linear for the first half of the reaction or even more at high pressures but at low initial pressures and toward the end of the reaction the deviations from linearity are appreciable. These observations are in accord with those of Fromherz to the effect that over a wide range in any given run the rate is independent of the acetaldehyde pressure. However, the markedly different slopes of the three curves shown in Fig. 1 show that the initial rates are dependent on the aldehyde pressure. From a large number of initial rate measurements,

(7) Letort, *J. Phys. Chem.*, **34**, 355 (1937).

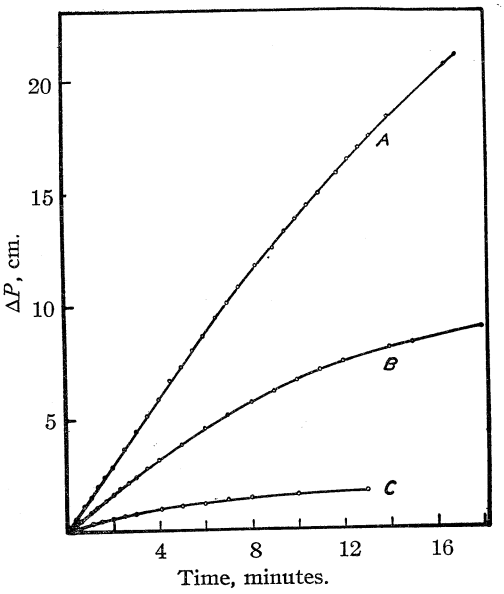


Fig. 1.—Pressure–time curves of the sensitized decomposition of acetaldehyde: 713°K.; H_2S, 4.00 cm.; CH_3CHO: A—31.70 cm., B—10.94 cm., C—2.01 cm.

the details of which are listed in Table V, it was found that the initial rates could be expressed by

$$-\mathrm{d}(CH_3CHO)/\mathrm{d}t = k_1(H_2S)(CH_3CHO) + k_2(H_2S)(CH_3CHO)/(1 + k_3(CH_3CHO))$$

in which the formulas in parentheses represent the initial pressures of aldehyde and hydrogen sulfide and the constants have the following values at 713°K.

$k_1 = 0.0081$ cm.$^{-1}$min.$^{-1}$ $= 1.82 \times 10^{-6}$mole^{-1}liter min.$^{-1}$
$k_2 = 0.0833$ cm.$^{-1}$min.$^{-1}$ $= 1.88 \times 10^{-5}$mole^{-1}liter min.$^{-1}$
$k_3 = 0.667$ cm.$^{-1}$ $= 1.50 \times 10^{-4}$mole^{-1}liter

It was found that the decomposition products, methane and carbon monoxide do not affect the rate. Furthermore, the addition of a fresh charge of aldehyde at the end of a run gave the same rate as if the aldehyde and hydrogen sulfide had been mixed directly, thus showing that the catalytic activity of the sulfide was not reduced by use. In Table III the last column gives the rate as calculated by the above equation. The rate during any given run could be fitted by a similar

TABLE III

ANALYTICAL RESULTS

Initial pressure, cm. of Hg. H_2S	CH_3CHO	% completion	Non-condensable gases, % CH_4	CO	H_2S found, %
1.94	9.61	7	50.2	49.8	97.2
1.95	13.40	36	50.3	49.4	98.7
23.99	5.00	80	49.7	50.3	..
55.95	0.90	100	49.3	49.2	..
2.58	7.20	100	51.0	49.0	98.7
1.94	6.13	100	49.9	49.8	99.4

equation but the value of k_2 would have to be much larger relative to k_1.

The effect of temperature on the rate is shown by the data in Table IV. In a simple reaction a corresponding change with temperature would be found if the activation energy were 36 kcal.

TABLE IV

RATES AT DIFFERENT TEMPERATURES

Temp., °K.	Initial pressure (cm. of mercury) H_2S	CH_3CHO	Initial rate cm./min.
713	2.00	20.00	0.556
728	2.05	20.67	1.07
744	1.96	20.72	1.63
760	1.98	20.48	2.65
772	2.00	19.98	4.13
776	2.03	21.15	4.57
786.5	2.00	21.10	5.98

Since the analyses failed to give any indication of the nature of the intermediary steps in the catalysis a number of experiments were performed with various substances which might be present in the reaction mixture in very minute amounts or which on the basis of structural similarity might be expected to have an effect similar to that of hydrogen sulfide. The results obtained, all at 713° K., were as follows:

Sulfur causes the aldehyde to decompose approximately five times as fast as in the presence of the corresponding amount of hydrogen sulfide. Within a few minutes the sulfur is converted into hydrogen sulfide, and the rate of decomposition becomes that determined by the latter substance.

If it is assumed that the hydrogen sulfide catalysis involves the hydrogen sulfide–sulfur equilibrium the addition of hydrogen to the reaction mixture should decrease the rate of the reaction. Actually it was found that the addition of 30.91 cm. of hydrogen decreased the rate only 14%. At intermediate pressures the effect was proportional to this value. The dependence of the rate on the aldehyde and hydrogen sulfide pressures was not altered by the addition of hydrogen. This result in itself tends to exclude the hypothesis of the sulfide–sulfur equilibrium. Additional ground for excluding that idea is supplied by the fact that the observed rate was 28 times that calculated from the data in the literature on the equilibrium and our observations on the effect of sulfur.

The effect of carbonyl sulfide on the rate was found to depend on the length of time the carbonyl sulfide was heated before the aldehyde was admitted to the reaction vessel. Extrapolation to zero preheating time indicated that the carbonyl sulfide had no appreciable effect on the rate. The observed behavior is attributed to the slow decomposition of the added substance into sulfur and carbon monoxide.

The addition of nitric oxide to the reaction mixture gave results of the type indicated in Table VI. It is apparent that the catalytic effect of a

TABLE V

RATE OF HYDROGEN SULFIDE SENSITIZED DECOMPOSITION OF ACETALDEHYDE

Quartz reaction vessel, heated volume 216 cc., dead space 3 cc., temperature 713°K.

Initial pressure, cm. H_2S	CH_3CHO	Initial rate, V_0 cm./min.	V_0/H_2S	V_0/H_2S, calcd.
3.99	1.24	0.21	0.053	0.066
4.05	1.40	.24	.059	.070
3.99	2.01	.29	.073	.086
4.03	2.79	.45	.112	.102
4.00	5.65	.56	.140	.144
4.02	8.75	.78	.194	.180
3.77	10.55	.79	.209	.195
4.04	10.94	.84	.208	.198
3.95	14.96	.98	.248	.234
3.97	16.96	1.02	.257	.251
4.11	20.36	1.18	.270	.281
4.01	20.65	1.15	.287	.284
3.88	20.75	1.20	.309	.285
3.89	21.63	1.11	.288	.292
3.98	22.47	1.24	.304	.299
4.03	23.67	1.33	.330	.309
3.95	31.70	1.47	.375	.376
3.99	35.28	1.65	.413	.405
3.98	36.59	1.67	.420	.416
3.80	42.64	1.83	.482	.465
3.92	45.55	1.90	.484	.488
3.98	47.15	2.06	.518	.502
3.98	54.53	2.20	.552	.563
3.84	57.13	2.14	.558	.582
3.92	58.54	2.40	.612	.595
3.97	61.41	2.49	.627	.618
0.63	21.02	0.15	.238	.286
0.75	20.59	.25	.333	.283
2.10	19.65	.66	.314	.275
2.75	20.54	.76	.276	.282
4.01	20.65	1.15	.287	.284
4.97	20.92	1.49	.300	.285
5.89	21.87	1.75	.297	.294
6.80	20.18	1.91	.281	.280
9.25	20.67	2.23	.241	.284
11.38	22.67	3.85	.338	.301
0.90	5.60	0.18	.200	.143
2.02	24.47	.65	.321	.316
2.14	33.63	.85	.397	.392
2.19	16.52	.56	.255	.247
2.62	5.20	.42	.160	.139
10.80	4.70	1.18	.109	.131
11.05	5.25	1.34	.121	.139
16.85	7.38	2.42	.144	.164

mixture of nitric oxide and hydrogen sulfide is greater than the sum of the effects of these gases taken separately.

TABLE VI

EFFECT OF NITRIC OXIDE AT 713°K.

Initial pressure, cm. of Hg			Initial rate
H_2S	NO	CH_3CHO	cm./min.
4.00	0	20.00	1.11
3.88	0.14	20.70	3.27
4.03	0.33	21.12	4.00
4.29	5.89	17.30	4.32
0	3.98	20.67	0.28

The effect of methyl mercaptan and dimethyl sulfide on the rate of decomposition of the aldehyde is of interest both because of the possibility that they are intermediates and because of their similarities in structure to hydrogen sulfide. The rates of decomposition of these substances were too great to study any specific effects due to them. It was noted, however, that the decomposition products catalyzed the aldehyde decomposition more than the corresponding amount of hydrogen sulfide. This may be an effect similar to that found with mixtures of nitric oxide and hydrogen sulfide or it may be due to the presence of some sulfur in the decomposition products of the mercaptan and sulfide added. An analysis of the gaseous products obtained from the complete decomposition of methyl mercaptan showed the composition in per cent. to be 29.2 methane, 7.1 ethane, 9.4 ethylene and 54.2 hydrogen sulfide. The non-gaseous products were not analyzed. The absence of ethane and ethylene in the products of the hydrogen sulfide catalyzed decomposition of the aldehyde indicates that the mercaptan is not an important intermediate.

Water had no appreciable effect on the rate of decomposition of acetaldehyde at 713°K.

The possibility that the reaction was caused by the dissociation of the hydrogen sulfide into hydrogen atoms and hydrosulfide radical followed by the reaction of these substances with the aldehyde to initiate a chain reaction was considered. The equilibrium concentration of the products of such a dissociation as calculated from data in the literature would be sufficient to account for the observed rates but the observed temperature coefficient seems to be too low to be compatible with such a mechanism. None of the mechanisms which we have considered will account for the results quantitatively so they will not be discussed in detail.

Summary

A study has been made of the catalysis of the thermal decomposition of acetaldehyde by hydrogen sulfide. The reaction results in the formation of equivalent amounts of methane and carbon monoxide with no net loss of hydrogen sulfide. The decomposition is homogeneous and the initial rates are given by $-d(CH_3CHO)/dt = k_1 \cdot (H_2S)(CH_3CHO) + (H_2S)(CH_3CHO)/(1 + k_3 \cdot (CH_3CHO))$. Values for the constants are given. The effect of temperature on the rate has been studied. The effects of adding hydrogen, sulfur, carbonyl sulfide, methyl mercaptan, dimethyl sulfide, and water to the reaction mixture have also been studied. The results indicate that none of these substances are of importance as intermediate in the hydrogen sulfide catalyzed reaction. Mixtures of nitric oxide and hydrogen sulfide were found to have a greater catalytic effect than the sum of the effects of these gases taken separately.

BERKELEY, CALIFORNIA RECEIVED MARCH 18, 1942

[COMMUNICATION NO. 852 FROM THE KODAK RESEARCH LABORATORIES]

Theory of Solutions of High Polymers[1]

BY MAURICE L. HUGGINS

Introduction

In recent years it has become increasingly evident that the large deviations from "ideal" behavior shown by solutions of long-chain molecules are due primarily to deviations from ideality of the *entropy* of mixing, rather than to any *heat* of mixing effect, such as is responsible for most deviations in solutions containing only small molecules.

The entropy of mixing of chain molecules with small molecules has been discussed qualitatively by Meyer.[2] Recently, Flory[3] and the writer[4] have, independently, treated the subject in a quantitative manner, with results which are essentially equivalent.

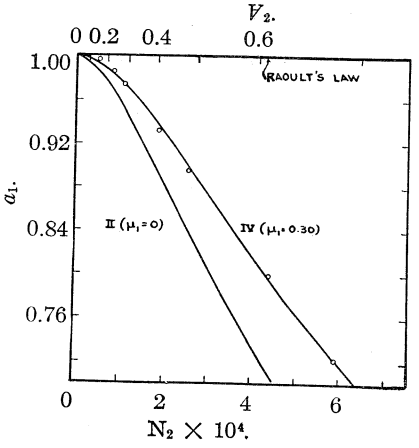


Fig. 1.—Activity as a function of mole fraction for the rubber–chloroform system at 25°. Vapor pressure data by Stamberger[5]; the curves correspond to Eq. 1; V_2/V_1 = 3644.

We consider a hypothetical solution consisting of N_1 spherical molecules (Type 1) and N_2 chain molecules (Type 2), each of the latter consisting of n submolecules of the same size as each Type 1 molecule. We assume that there is no volume change on mixing and that the intermolecular energy interactions are not such as to interfere with the randomness which would result if the heat of mixing were zero. We distribute the Type 1 molecules and Type 2 submolecules among $N_1 + nN_2$ sites, first adding the Type 2 molecules, one submolecule at a time, and then the Type 1 molecules. We count the number of different ways in which each can be added and then multiply these numbers together to obtain the total number of configurations. From the total number of *different* configurations possible, we proceed by well-known methods to the desired equations for the entropy of mixing and the activities of the components.

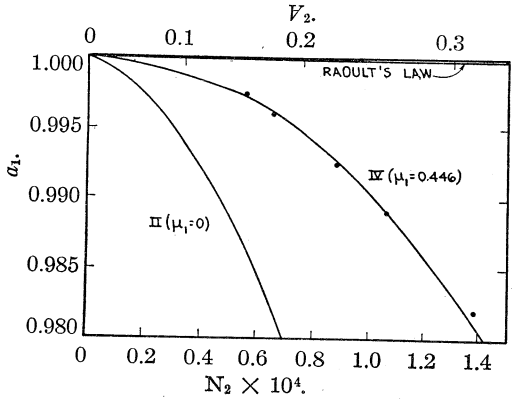


Fig. 2.—Activity *vs.* mole fraction for the rubber–benzene system at 15–20°. Swelling pressure data by Posnjak.[6] V_2/V_1 = 3307.

Equations for the Activities.—For the logarithms of the activities, we obtain the equations

$$\ln a_1 = \ln V_1 + \left(1 - \frac{\overline{V}_1}{\overline{V}_2}\right) V_2 + \mu_1 V_2^2 \qquad (1)$$

and

$$\ln a_2 = \ln V_2 + \left(1 - \frac{\overline{V}_2}{\overline{V}_1}\right) V_1 + \mu_2 V_1^2 \qquad (2)$$

with the empirical constants, μ_1 and μ_2, related by the equation

$$\mu_1 \overline{V}_2 = \mu_2 \overline{V}_1 \qquad (3)$$

V_1 and V_2 refer to the volume fractions[7] and $\overline{V}_1$ and $\overline{V}_2$ to the partial molal volumes of the two components. (With negligible error for our purpose we can assume the partial molal volumes to be equal to the actual molal volumes of the pure

(1) Presented before the Division of Paint, Varnish and Plastics Chemistry at the Memphis Meeting of the American Chemical Society, April 22, 1942.

(2) K. H. Meyer, *Z. physik. Chem.*, **B44**, 383 (1939); *Helv. Chim. Acta.*, **23**, 1063 (1940).

(3) P. J. Flory, *J. Chem. Phys.*, **9**, 660 (1941); **10**, 51 (1942).

(4) M. L. Huggins, *ibid.*, **9**, 440 (1941); *J. Phys. Chem.*, **46**, 151 (1942); *Ann. N. Y. Acad. Sciences*, **41**, 1 (1942).

(5) P. Stamberger, *J. Chem. Soc.*, 2318 (1929).

(6) E. Posnjak, *Kolloidchem. Beihefte*, **3**, 417 (1912).

(7) The new symbol, V, is introduced to replace N*, previously used by the writer[4] for volume fraction.

components.) The last term in each of Eqs. 1 and 2 takes care of the heat of mixing, deviations from complete randomness of mixing, and other factors.

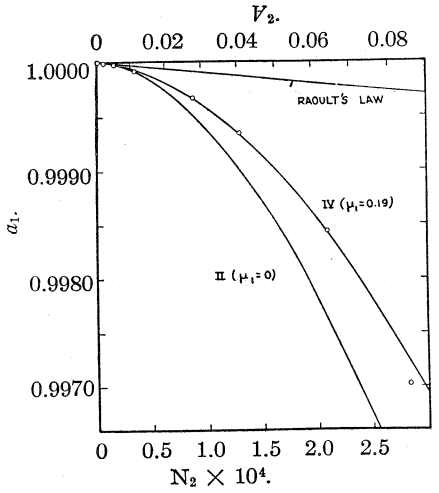


Fig. 3.—Activity *vs.* mole fraction for solutions of nitrocellulose in acetone at 20°: osmotic pressure data by Duclaux and Wollman[8]; $V_2/V_1 = 330$.

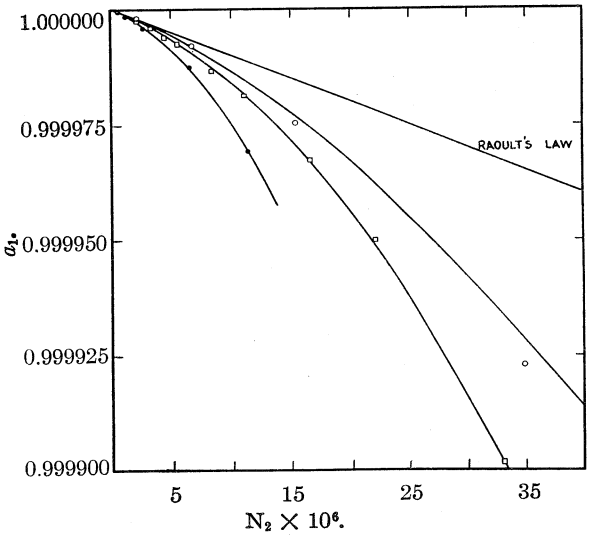


Fig. 4.—Activity *vs.* mole fraction for solutions of nitrocellulose in acetone: osmotic pressure data on three samples, differing with regard to the degree of nitration, the average chain length, and the temperature. Dots represent data by Dobry[9] ($\mu_1 = 0.265$; $V_2/V_1 = 793$; $t = 22°$). Squares represent data by Schulz[10] ($\mu_1 = 0.300$; $V_2/V_1 = 550$; $t = 27°$). Circles represent data by Duclaux and Wollman[8] ($\mu_1 = 0.19$; $V_2/V_1 = 330$; $t = 20°$).

For testing the equations just given, we may use activities calculated from vapor pressure, osmotic pressure, swelling pressure, boiling point elevation, or other measurements. A thorough survey of the pertinent data in the literature shows the agreement to be excellent, for both short- and long-chain molecules.[4] This agreement is exemplified by Figs. 1 to 8, in which the activity of the solvent is shown as a function of the mole fraction of the solute for solutions of various long-chain compounds in small-molecule solvents. In each of these figures the straight line represents Raoult's law; the other curves represent Eq. 1 with μ_1 equal to zero (curves II) or an empirical value (curves IV).

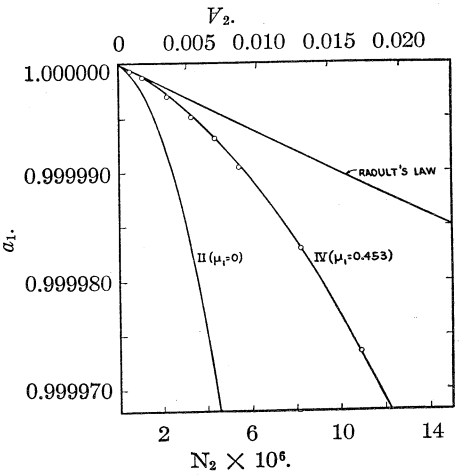


Fig. 5.—Activity *vs.* mole fraction for solutions of polyethylene oxide in water at 27°: osmotic pressure data by Schulz[10]; $V_2/V_1 = 1614$.

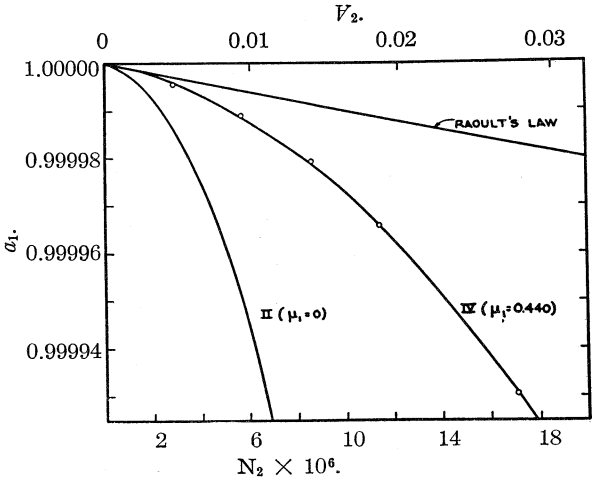


Fig. 6.—Activity *vs.* mole fraction for solutions of polystyrene in toluene at 27°: osmotic pressure data by Schulz[10]; $V_2/V_1 = 1667$.

Osmotic Pressure.—The osmotic pressure of a solution is related to the activity of the solvent by the equation

(8) J. Duclaux and E. Wollman, *Compt. rend.*, **152**, 1580 (1911).
(9) A. Dobry, *J. chim. phys.*, **32**, 50 (1935).
(10) G. V. Schulz, *Z. physik. Chem.*, **A176**, 317 (1936).

$$\Pi = -\frac{RT}{\bar{V}_1}\ln a_1 \qquad (4)$$

R is the gas law constant and T the absolute temperature. Combining this with equation (1), we obtain

$$\frac{\Pi}{V_2} + \frac{RT}{\bar{V}_1}\left(\frac{\ln V_1}{V_2} + 1\right) = \frac{RT}{\bar{V}_2} - \frac{RT\,\mu_1 V_2}{\bar{V}_1} \qquad (5)$$

Since

$$\ln V_1 = -V_2 - \frac{V_2^2}{2} - \frac{V_2^3}{3} - \cdots \qquad (6)$$

we can write, for dilute solutions (small V_2)

$$\frac{\Pi}{V_2} - \frac{RTV_2^2}{3\bar{V}_1} = \frac{RT}{\bar{V}_2} + \frac{RT}{\bar{V}_1}\left(\frac{1}{2} - \mu_1\right)V_2 \qquad (7)$$

For concentrations in weight fractions (W_2) or in grams of solute per cubic centimeter of solution (C_2), the corresponding equations are

$$\frac{\Pi}{W_2} - \frac{RT\,d_1^4 W_2^2}{3M_1 d_2^3} \approx \frac{RT\,d_1}{M_2} + \frac{RT\,d_1^3}{M_1 d_2^2}\left(\frac{1}{2} - \mu_1\right)W_2 \qquad (8)$$

and

$$\frac{\Pi}{C_2} - \frac{RT\,d_1 C_2^2}{3M_1 d_2^3} = \frac{RT}{M_2} + \frac{RT\,d_1}{M_1 d_2^2}\left(\frac{1}{2} - \mu_1\right)C_2 \qquad (9)$$

where d_1 and d_2 are the densities and M_1 and M_2 the molecular weights of the components.

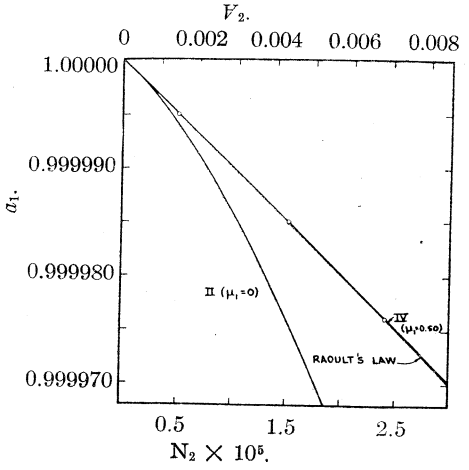


Fig. 7.—Activity *vs.* mole fraction for solutions of polyvinyl chloride in dioxane at 27°: osmotic pressure data by Staudinger and Schneiders[11]; $V_2/V_1 = 286$.

Given a set of accurate osmotic pressure values for different concentrations of a given solution, a plot of the quantity represented on the left side of one of these Eqs., 7, 8, or 9, against the concentration (V_2 or W_2 or C_2) should yield a straight line. From its intercept with the axis of ordinates (concentration = 0), one can obtain the molecular weight of the solute; from its slope one can compute μ_1.

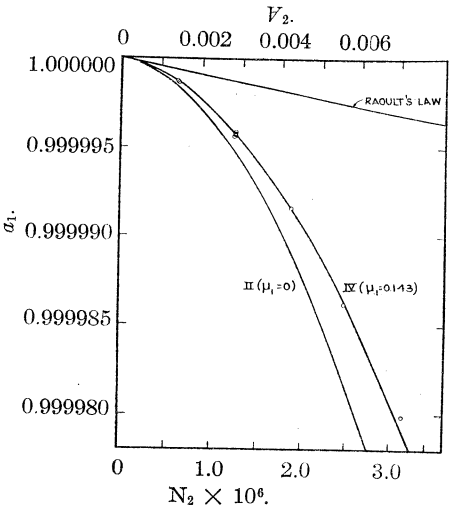


Fig. 8.—Activity *vs.* mole fraction for solutions of polyvinyl chloride in tetrahydrofuran at 27°: osmotic pressure data by Staudinger and Schneiders[11]; $V_2/V_1 = 2264$.

The second term on the left side of each of these equations is negligible at most concentrations at which osmotic pressure measurements of solutions of high molecular compounds are made. We thus have a theoretical basis for the well-known[12] rectilinear relationship between Π/C_2 and C_2 (or between Π/W_2 and W_2).

Since μ_1 should be independent of the chain length of the solute molecules—assumed to be alike in other respects—the slopes of the lines obtained for a series of fractions of a given type of polymer should all be equal. On the other hand, a change of either the solvent or the type of solute (*e. g.*, from a nitrocellulose of a certain degree of nitration to one with a different degree of nitration) should change the slope.

These conclusions are amply borne out by the experimental facts, as shown by Figs. 9 to 13.

Separation of Phases. Gels.—Assuming Eq. 1 to hold, the activity of the small-molecule component, in equilibrium with long-chain molecules having $\bar{V}_2/\bar{V}_1$ equal to 100 or ∞, varies with composition as shown in Figs. 14 and 15. If μ_1 is larger than a certain critical value, the calculated curve for activity *vs.* N_2 (or V_2 or W_2 or C_2) exhibits a minimum and a maximum, indicating a separation of the system into two phases. The critical value of μ_1 depends on the ratio of the partial molal volumes according to the equation

(11) H. Staudinger and J. Schneiders, *Ann.*, **541**, 151 (1939).

(12) *Cf.* H. Mark, "Physical Chemistry of High Polymeric Systems," Interscience Publishers, New York, N. Y., 1940, p. 240.

$$\mu_1 \text{ (crit.)} = \frac{1}{2}[1 + (\bar{V}_1/\bar{V}_2)^{1/2}]^2 \qquad (10)$$

This dependence is shown graphically in Fig. 16.

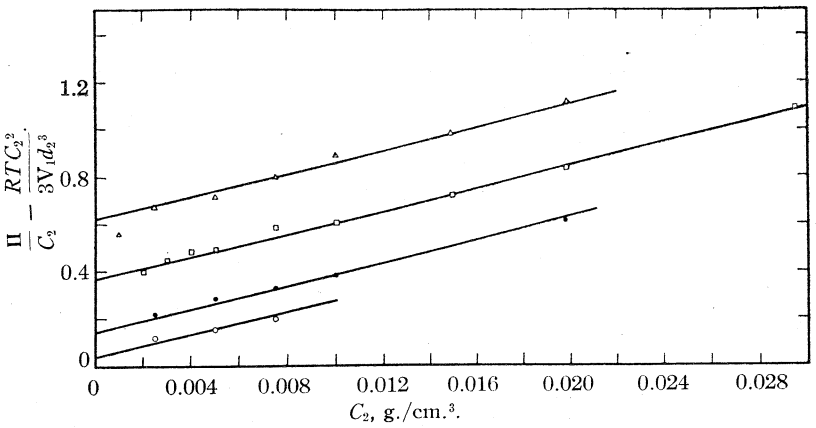


Fig. 9.—Osmotic pressure dependence on concentration for solutions of certain nitrocellulose fractions in acetone at 27°: data by Schulz.[10] The straight lines represent Eq. 9; $\mu_1 = 0.300$.

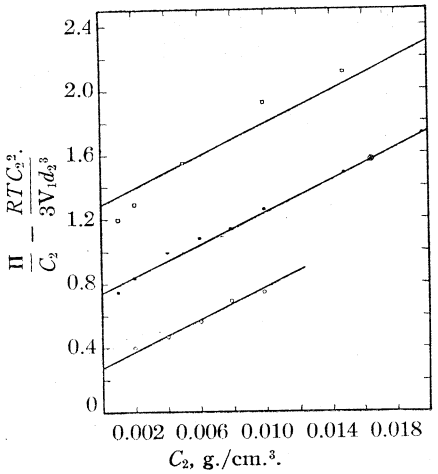


Fig. 10.—Osmotic pressure dependence on concentration for polyethylene oxide fractions in water at 27°: data by Schulz[10]; $\mu_1 = 0.453$.

For high molecular solutes, unless μ_1 is very near the critical value

$$a_1 \approx 1 \qquad (11)$$

for both phases. One phase is practically pure solvent, in agreement with the experimental findings of Brønsted and Volqvartz,[13] on the swelling of polystyrene in laurate esters. The composition of the other phase is related to μ_1 and the molal volume ratio according to the following equation, obtained by substituting Eq. 11 into Eq. 1.

$$\ln V_1 = \left(\frac{\bar{V}_1}{\bar{V}_2} - 1\right) V_2 - \mu_1 V_2^2 \qquad (12)$$

If the concentration and intermolecular attractions of the long-chain molecule component are such that the motion of each such molecule is greatly restricted by its neighbors, the solution will have a degree of rigidity—it will have the properties of a gel. The effective molecular weight and molecular volume will be very large, relative to the values for the small-molecule component. Hence

$$\ln V_1 = -V_2 - \mu_1 V_2^2 \qquad (13)$$

We should expect this equation to be applicable to gels in general, since the theoretical derivation of Eqs. 1 and 2 is such that they would be expected to hold as well for flexible *network* molecules as for *chain* molecules.

Figure 17 shows the solubility, as function of μ_1, of a small-molecule compound in a gel, for effective molal volume ratios ($\bar{V}_2/\bar{V}_1$) of 100 (Eq. 12) and ∞ (Eq. 13). It can be seen that the composition is very sensitive to the value of μ_1, but not to the relative sizes of the molecules—unless μ_1 is close to the critical value.

The data of Brønsted and Volqvartz on the swelling of polystyrene in alkyl laurates at different temperatures make it possible to determine the variation of μ_1 with temperature for each of

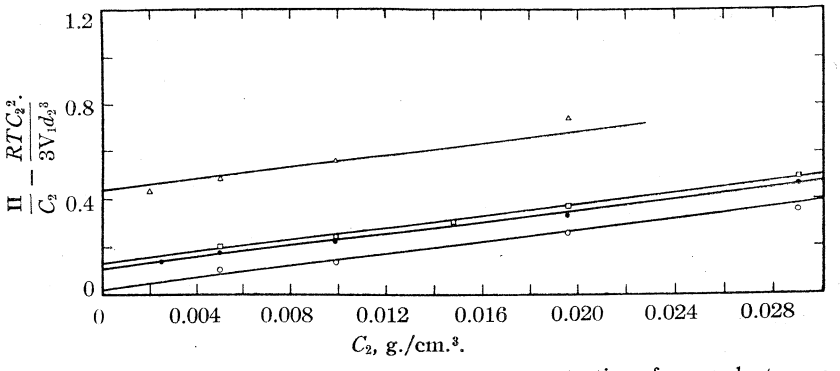


Fig. 11.—Osmotic pressure dependence on concentration for polystyrene fractions in toluene at 27°: data by Schulz[10]; $\mu_1 = 0.440$.

(13) J. N. Brønsted and K. Volqvartz, *Trans. Faraday Soc.*, **35**, 576 (1939).

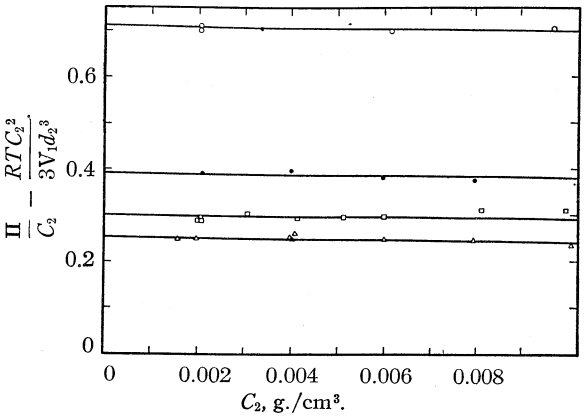


Fig. 12.—Osmotic pressure dependence on concentration for polyvinyl chloride fractions in dioxane at 27°: data by Staudinger and Schneiders[11]; $\mu_1 = 0.523$.

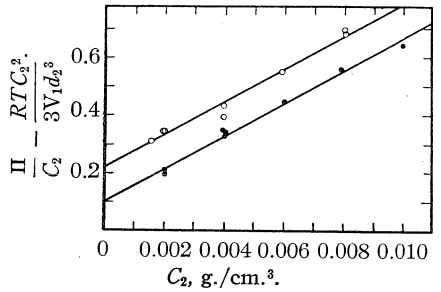


Fig. 13.—Osmotic pressure dependence on concentration for polyvinyl chloride fractions in tetrahydrofuran at 27°: data by Staudinger and Schneiders[11]; $\mu_1 = 0.143$.

the systems studied. As Fig. 18 shows, the relation

$$\mu_1 = \alpha_1 + \beta_1/T \qquad (14)$$

holds, within the probable experimental error. The straight lines in this figure are drawn for a constant value (−0.83) for α_1, with values of β_1

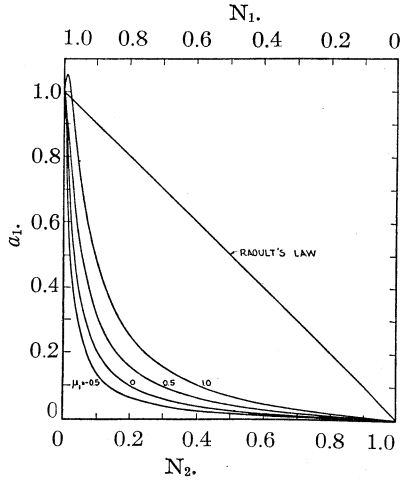


Fig. 14.—Activity *vs.* mole fraction, according to Eq. 1, for $V_2/V_1 = 100$, with certain values of μ_1.

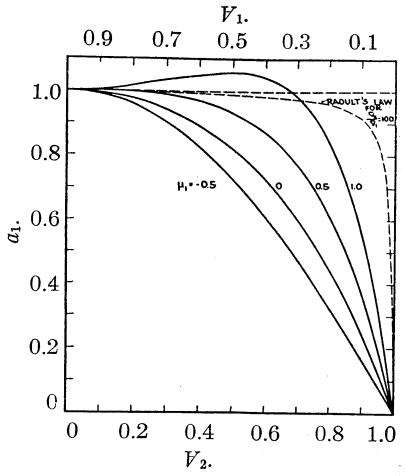


Fig. 15.—Activity *vs.* volume fraction, according to Eq. 1, for $V_2/V_1 = \infty$, with certain values of μ_1. The corresponding curves for finite values of the molal volume ratio are lower than those shown; for $V_2/V_1 \geqslant 100$ the difference is approximately the width of the lines, or less.

varying from 388 for ethyl laurate to 518 for isoamyl laurate. The experimental data, however, are insufficient to establish whether or not the α_1 values really are accurately the same for all of these systems.

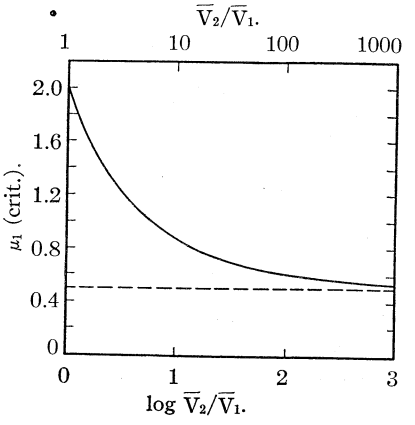


Fig. 16.—Dependence on the molal volume ratio of the critical value of μ_1 for separation of a solution into two phases, according to Eq. 10.

Probably the most important of the terms contributing to μ_1 is the heat of mixing term. From the work of van Laar,[14] Scatchard,[15] and Hildebrand,[16] this term would be expected to be approximately of the form $\overline{V}_1A_{12}/RT$, where A_{12} is a constant which measures the difference between the average cohesive energy density due to at-

(14) J. J. van Laar, *Z. physik. Chem.*, **A137**, 421 (1928).
(15) G. Scatchard, *Chem. Rev.*, **8**, 321 (1931).
(16) (a) J. H. Hildebrand, THIS JOURNAL, **57**, 866 (1935); (b) *Chem. Rev.*, **18**, 315 (1936); (c) "Solubility of Non-Electrolytes," second edition, Reinhold Publ. Corp., New York, N. Y., 1936, p. 73.

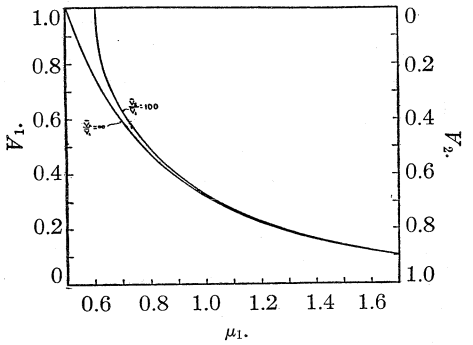


Fig. 17.—Dependence on μ_1 of the composition (volume fraction) of the polymer-rich phase in a two-phase system, for V_2/V_1 equal to ∞ and 100. Except for $\mu_1 \approx \mu_1$ (crit.), the curves agree with Eq. 12.

traction between *like* molecules and that due to attraction between *unlike* molecules. The greater the tendency of like molecules to cluster together, the larger is A_{12} and, in general, μ_1.

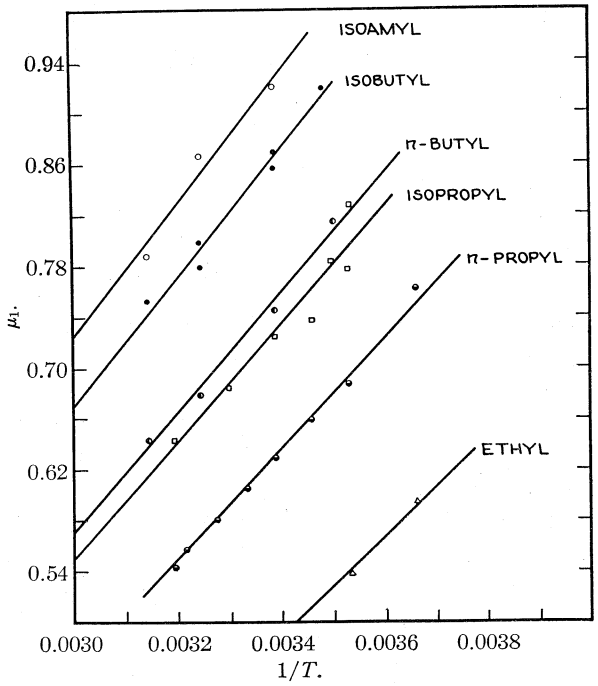


Fig. 18.—Variation of μ_1 with the reciprocal of the absolute temperature, for polystyrene swollen in alkyl laurates. The straight lines represent Eq. 14, with $\alpha_1 = -0.83$ in each case and β_1 equal to 388, 431, 460, 467, 500 and 518 for ethyl, *n*-propyl, . . . isoamyl laurates; data by Brønsted and Volqvartz.[13]

Figure 19 shows that for the alkyl laurates in polystyrene, β_1 is roughly proportional to V_1 (and so to $\overline{V}_1$). The inexactness of this proportionality is probably attributable in part to variation in A_{12} and in part to the existence of other terms contributing to μ_1.

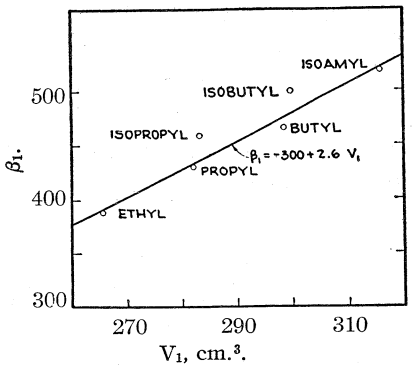


Fig. 19.—Relation between the constant β_1 of Eq. 14 and the molal volume of the small-molecule component, for polystyrene–alkyl laurate gels.[13]

Figure 20 shows the measure of agreement between the experimental polystyrene–laurate gel compositions and those computed from Eqs. (13) and (14).

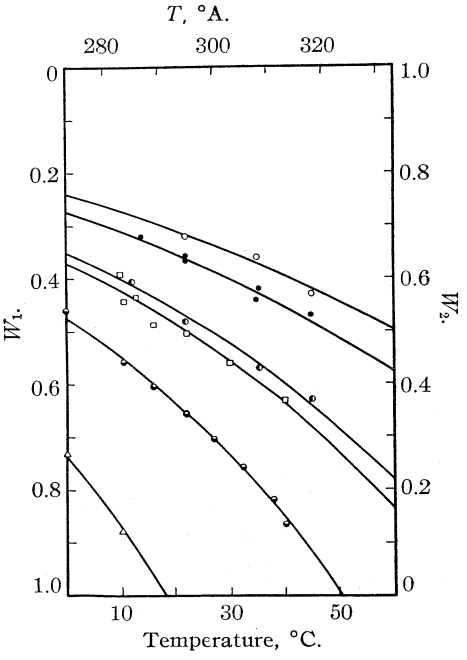


Fig. 20.—Comparison of experimental[13] compositions of polystyrene–alkyl laurate gels and the theoretical curves corresponding to Eqs. 12 and 14: ○, isoamyl; ●, isobutyl; ◐, *n*-butyl; □, isopropyl; ◒, *n*-propyl; △, ethyl.

Solubility of a Polymer in a Small-Molecule Liquid.—For equilibrium between a solid and its (saturated) solution in a liquid, the fugacity of the substance composing the solid must be the same in the two phases. Assuming the heat of fusion (ΔH_f) of the solid not to vary with the temperature between the temperature of the system and the melting point (T_f), the following

relation holds. (Compare Hildebrand's[17] treatment of ideal solutions.)

$$\ln a_2 = -\frac{\Delta H_f}{R}\left(\frac{T_f - T}{TT_f}\right) \quad (15)$$

Combining this equation with Eq. 2 and making the approximation that

$$\mu_2 = \frac{\bar{V}_2}{\bar{V}_1}\mu_1 = \frac{\bar{V}_2 B_{12}}{RT} \quad (16)$$

where B_{12} is a constant independent of temperature, we obtain

$$\ln V_2 = -\frac{\Delta H_f}{R}\left(\frac{T_f - T}{TT_f}\right) - \frac{\bar{V}_2 B_{12} V_1^2}{RT} + \left(\frac{\bar{V}_2}{\bar{V}_1} - 1\right)V_1 \quad (17)$$

This equation accounts quantitatively (Fig. 21) for the temperature dependence of the solubility of the normal paraffins, $C_{34}H_{70}$ and $C_{60}H_{122}$, in decalin (decahydronaphthalene, $C_{10}H_{18}$). In computing the theoretical curves for this figure, we have made use of the thermodynamic relation

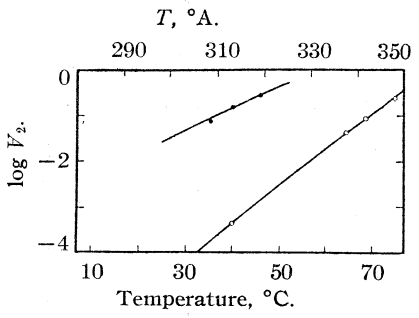


Fig. 21.—Solubility (volume fraction) of n-$C_{34}H_{70}$ and n-$C_{60}H_{122}$ in decalin, as a function of temperature. The curves correspond to Eq. 17, after substitution of Eqs. 18, 19, 20 and 21; experimental data by Meyer and van der Wyk[18]: ●, n-$C_{34}H_{70}$, B_{12} = 1.97; ○, n-$C_{60}H_{122}$, B_{12} = 2 66.

$$T_f = \Delta H_f/\Delta S_f \quad (18)$$

and the following empirical expressions:[19,20,21]

$$\Delta H_f = -1750 + 608.5n \quad (19)$$

$$\Delta S_f = 4.04 + 1.491n \quad (20)$$

$$\bar{V}_2 = V_2 = 26.96 + 16.49n + (29/n) \quad (21)$$

Here, n denotes the number of carbon atoms in the paraffin.

In these systems, the ratio V_2/V_1 is small (3.73 and 6.44), hence it is not surprising that the empirical values of B_{12} are slightly different (1.97 and 2.66) for the two systems. For very long chains which are similar in other respects, B_{12} would be expected to be independent of chain length.

For long chains in general we may make the approximations

$$\Delta H_f = nh_2 \quad (22)$$

$$\Delta S_f = ns_2 \quad (23)$$

and

$$V_2 = nv_2 \quad (24)$$

where h_2, s_2 and v_2 are heats of fusion, entropies of fusion, and volumes per "monomeric unit" of the chain compound. Then

$$\ln V_2 = -V_1 + n\left[\frac{s_2}{R} + \frac{v_2 V_1}{\bar{V}_1} - \frac{h_2}{RT} - \frac{v_2 B_{12} V_1^2}{RT}\right] \quad (25)$$

If the polymer is not very soluble, V_1 is approximately equal to unity. Then (provided the quantity in brackets in this equation is not close to zero)

$$\ln V_2 \approx n\left(\alpha - \frac{\beta}{T}\right) \quad (26)$$

and

$$V_2 \approx \exp\left[n\left(\alpha - \frac{\beta}{T}\right)\right] \quad (27)$$

where

$$\alpha = \frac{s_2}{R} + \frac{v_2}{\bar{V}_1} \quad (28)$$

and

$$\beta = \frac{h_2}{R} + \frac{v_2 B_{12}}{R} \quad (29)$$

These equations show the dependence of the solubility of a slightly soluble high polymer on the temperature and on other factors.

Further discussion and experimental tests of these solubility relations, together with a treatment of the solubility of polymers in mixed solvents, will be given at a later time.

The writer is glad to express here his indebtedness to Mrs. Dorothy Owen Davis for much help with the calculations and figures for this paper.

Summary

1. Theoretical equations derived for the activities of the components of a solution of chain molecules in a small-molecule solvent are in good agreement with experimental vapor pressure, osmotic pressure, swelling pressure and solubility measurements. A single constant, μ_1, partly but not entirely due to the heat of mixing effect, must be evaluated empirically.

2. Equations deduced for osmotic pressure as a function of composition account for the known straight-line relationship obtained when the ratio of osmotic pressure to concentration is plotted

(17) Ref. 16c, pp. 32–34.

(18) K. H. Meyer and A. van der Wyk, *Helv. Chim. Acta*, **20**, 1313 (1937).

(19) W. E. Garner, K. Van Bibber and A. M. King, *J. Chem. Soc.*, 1533 (1931).

(20) M. L. Huggins, *J. Phys. Chem.*, **43**, 1083 (1939).

(21) M. L. Huggins, THIS JOURNAL, **63**, 116 (1941).

against the concentration. For long chains the slope of this line depends on μ_1, but not on the chain length of the solute molecules.

3. The quantitative relationships derived for flexible chain molecules should also be applicable to flexible network molecules. For values of μ_1 greater than a critical value, the theoretical activity-composition curve indicates separation into two phases. One consists of the nearly pure small-molecule component. The other is usually a gel; its composition depends primarily on the value of μ_1. From experimental values of equilibrium compositions for polystyrene–alkyl laurate gels at different temperatures, μ_1 is a rectilinear function of V_1/T, the ratio of the molal volume of the small-molecule component to the absolute temperature.

4. An equation for the solubility of a solid chain compound in a small-molecule liquid is derived and found to be in agreement with measurements at various temperatures of the solubilities of n-$C_{34}H_{70}$ and n-$C_{60}H_{122}$ in decalin. Simplified solubility equations, applicable to long-chain polymers, are deduced.

ROCHESTER, N. Y. RECEIVED APRIL 28, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

Studies in Dehydrogenation.[1] II. Spirocyclopentane-1,1′-tetralin

BY MEYER LEVITZ[2] AND MARSTON TAYLOR BOGERT

The investigation of the rearrangement and dehydrogenation of spirocyclohexane-1,1′-indane[1] over a palladium on charcoal catalyst showed the importance of cautious postulation of structure based on the products obtained by dehydrogenation. Thus, a compound thought to be a hydrophenanthrene must be carefully examined if the only proof of its structure is dehydrogenation to phenanthrene, especially if its synthesis can theoretically yield isomeric spiranes.

When passed over Pd–C at 370–375°, spirocyclohexane-1,1′-indane was rearranged and dehydrogenated to phenanthrene while at 400–420° the main product was anthracene. This formation of both phenanthrene and anthracene from a tricyclic spirane has since been applied to the detection of spiranes.[3] It therefore appears important to study the action of other spiranes under similar dehydrogenation conditions. The closest isomer to the spirane previously studied is spirocyclopentane-1,1′-tetralin. This compound was therefore passed over the Pd–C catalyst in the vapor phase in a new apparatus especially designed to allow this repeated exposure of the hydrocarbon to the catalyst without the necessity of removing it from one end of the apparatus and reintroducing it at the other.

The heating element (A) was a brass tube 16 mm. in diameter and 75 cm. long, wound with nichrome wire. The closely fitting Pyrex dehydrogenation tube (B), inserted in the heating element, was closed at one end and had a stopcock sealed on the other end for the removal of samples during the dehydrogenation. The temperature inside this tube was checked beforehand with the temperature inside the thermometer well (C) enclosed by the heating coil. T-Tubes (D and D′) were sealed on the dehydrogenation tube 7 cm. from each end of the brass tube. Two 3-way stopcocks (E and E′) were connected to these T-tubes in such a way that either end of the dehydrogenation tube could be opened to the mercury trap (F) and a bubble counter (G), while the other end was opened to tube (H) leading to the supply of nitrogen or hydrogen. The palladium catalyst was prepared according to the method of Linstead and Thomas.[4] It was thoroughly mixed with twice its weight of asbestos and packed into the dehydrogenation tube with a space of 8 cm. left at each end as a preheating zone for the compound. The catalyst was changed for each run.

In operation the compound was pipetted into the dehydrogenation tube through (D) while the apparatus was tilted to prevent contact with the catalyst. Washed and dried nitrogen was passed into the apparatus through (H) to displace the air while the temperature was raised to the desired point. During this time stopcock (E) was open to (H) while stopcock (E′) led to the mercury trap.

(1) For the first paper in this series see Levitz, Perlman, and Bogert, *J. Org. Chem.*, **6**, 105 (1941).

(2) Visiting Scholar, Columbia University.

(3) Marvel and Walton, *J. Org. Chem.*, **7**, 88 (1942).

(4) Linstead and Thomas, *J. Chem. Soc.*, 1127 (1940).

The flow of nitrogen was then stopped and washed and dried hydrogen was admitted to displace the nitrogen. Stopcock (E) was then closed. The tube was tilted to allow the compound to flow slowly into the heated zone. After passing through, the compound condensed and collected in the cool portion. Stopcock (D′) was then closed and stopcock (D) was opened to the mercury trap. Any solid which had collected was melted by means of the radiant heat from an electric cigar lighter. The tube was tilted in the opposite direction and the compound was again passed over the catalyst. The process was repeated until dehydrogenation was complete.

The first run was made at 355–375° for six hours. The spirane was rearranged and dehydrogenated to phenanthrene. Another run was made at 420–430° to see whether anthracene would be produced as in the case of the spirocyclohexane-1,1′-indane. Phenanthrene was the only aromatic compound found in the product of this present dehydrogenation.

Experimental

Spirocyclopentane-1,1′-tetralin was prepared according to the method of Perlman, Davidson and Bogert.[5] Phenylpropyl bromide from phenylpropyl alcohol and phosphorus tribromide was put through a Grignard reaction with cyclopentanone. The resulting carbinol was cyclodehydrated by means of 85% sulfuric acid to the hydrocarbon; yield 32%, b. p. 135–137° (10 mm.), $n^{25}D$ 1.5539; previously reported[5]: yield 30%, b. p. 137–138° (10 mm.), $n^{25}D$ 1.5533.

Dehydrogenation at 355–375°.—The apparatus was charged with 8 g. of spirocyclopentane-1,1′-tetralin and the temperature was raised to 355°. Dehydrogenation started as soon as the hydrocarbon was passed over the catalyst, as evidenced by the rapid flow of hydrogen through the bubble counter. In twenty minutes all of the compound had passed completely over the catalyst and had condensed in the cool part of the tube. A considerable amount solidified as a low melting white solid. After one and one-half hours of continuous recirculation the rate of flow of hydrogen decreased materially. The temperature was raised to 365° and dehydrogenation was continued for three and one-half hours and finally at 375° for one hour, at the end of which time only solid collected. This was melted and removed from the apparatus. It weighed 6.5 g. and solidified at about 60°. It was crystallized by dissolving in petroleum ether (Skellysolve B) and chilling in a dry-ice–acetone bath. Recrystallization from ethyl alcohol produced phenanthrene melting at 98–99°, not depressed by an authentic sample. A picrate made with a saturated alcoholic solution of picric acid melted at 144–145°, not depressed by an authentic sample. No other aromatic compound could be isolated.

The catalyst was thoroughly washed with hot benzene. The highly fluorescent solution obtained yielded 0.6 g. of solid material when the benzene was evaporated. Purification produced only phenanthrene.

Dehydrogenation at 420–430°.—Six grams of spirocyclopentane-1,1′-tetralin was passed over the catalyst at 420–425° for ten hours. There was evidence that decomposition was taking place at this temperature. The product obtained showed a deep yellow-green fluorescence when liquid. Most of the product solidified at about 40° but 1 g. collected in the apparatus as a liquid. The liquid and solid were removed separately. Refluxing the liquid fraction with an alcoholic solution of picric acid yielded a picrate melting at 140–141° after recrystallization from hot ethyl alcohol. The melting point was not depressed by an authentic sample of phenanthrene picrate.

The solid, which weighed 3.7 g., was dissolved in petroleum ether and chilled in an ice–salt-bath. Filtration yielded 1.5 g. of solid melting at 90°. Recrystallization from ethyl alcohol gave phenanthrene, m. p. 98–99°, not depressed by an authentic sample of phenanthrene. The petroleum ether filtrate was chilled in a dry-ice–acetone bath and filtered. The 0.8 g. of solid melted at 94–95° and recrystallization from ethyl alcohol raised the melting point to 97–98°, not depressed by an authentic sample of phenanthrene.

The petroleum ether filtrate was still highly fluorescent. It was passed through an aluminum oxide adsorption column and developed with 4:1 petroleum ether–benzene. The non-fluorescent fraction which came through first was chilled in a dry-ice–acetone bath. White crystals of m. p. 93–94°, not depressed by an authentic sample of phenanthrene, were obtained. The fluorescent fraction turned out to be quite small when the solvent was evaporated. Refluxing with an alcoholic solution of picric acid gave no picrate on chilling. Picrates made from the phenanthrenes obtained above melted at 143–144°, not depressed by an authentic sample of phenanthrene picrate.

The catalyst was thoroughly digested with hot benzene. Evaporation of the benzene gave only dark carbonaceous material (0.4 g.), evidently the result of decomposition at the elevated temperature.

Summary

1. Spirocyclopentane-1,1′-tetralin was rearranged and dehydrogenated to phenanthrene when passed over palladium on charcoal at 355–375°.

2. Phenanthrene was the only aromatic compound produced when the reaction was carried out at 420–430°.

(5) Perlman, Davidson and Bogert, *J. Org. Chem.*, **1**, 300 (1936).

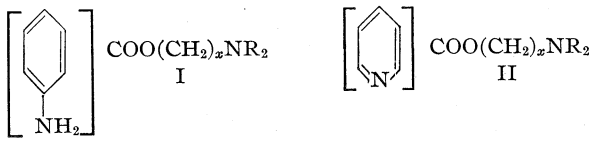
NEW YORK, N. Y. RECEIVED APRIL 11, 1942

[CONTRIBUTION FROM THE UNIVERSITY OF MICHIGAN COLLEGE OF PHARMACY]

Esters of Pyridinecarboxylic Acids as Local Anesthetics

BY F. F. BLICKE AND E. L. JENNER[1,2]

The nuclear amino group in dialkylaminoalkyl aminobenzoates (I)[3] contributes in some manner which is not understood to the local anesthetic activity of these compounds. It is a matter of interest to know the extent to which this activity would be affected by a shift of the nitrogen atom into the ring. Some information relative to this point could be gained by pharmacological examination of dialkylaminoalkyl esters of pyridinemonocarboxylic acids (II)[4]



It has been reported by Ingersoll and Robbins[5] that β-diethylaminoethyl and γ-diethylaminopropyl nicotinate are inactive as local anesthetics. They stated that these esters were prepared by them by interaction of the required basic alcohol with nicotinyl chloride; the "nicotinyl chloride" which was employed melted at 264–265° and was preserved over calcium chloride and paraffin. It has been shown by Meyer and Graf[6] that the true nicotinyl chloride melts at 15–16° and that it is so sensitive to moisture that it cannot be kept unchanged in a desiccator over alkali.

It seems that the material which Ingersoll and Robbins used as "nicotinyl chloride" was somewhat impure nicotinic acid hydrochloride; the latter, when pure, melts at 273–274°.[7]

We prepared nicotinyl chloride according to the procedure of Meyer and Graf and also by the method of Douglass and Forman.[8] In one instance the acid chloride was allowed to react with β-diethylaminoethanol and, in another, nicotinic acid was heated with β-diethylaminoethyl chloride in isopropyl alcohol. β-Diethylaminoethyl nicotinate hydrochloride was obtained in both cases but the properties of our ester hydrochloride were markedly different from those mentioned by Ingersoll and Robbins. When the ester salt was converted into the ester base, the latter was found to boil at a temperature which corresponds to that reported for this product by Knunyantz and Katznel'son.[9]

An examination of β-diethylaminoethyl nicotinate by L. W. Rowe, who tested all of our products in the Parke, Davis and Company Laboratories, showed that the base, as well as the hydrochloride, was practically inactive when applied to the rabbit's cornea. Local anesthesia was produced by injection of a 1–2% solution of the hydrochloride but the activity by this route of administration is greatly inferior to that of procaine or cocaine.

The fact that β-diethylaminoethyl nicotinate is soluble in about three parts of cold water, whereas bases of active esters are fairly insoluble, may account to some extent for its lack of action.

Although ethyl nicotinate has been known for some time, no statement relative to its effectiveness as a local anesthetic could be found. We submitted this ester for examination and it was shown to be practically inactive by topical application. Ethyl *p*-aminobenzoate is the well-known and widely used local anesthetic anesthesin (benzocaine).

Several other esters of nicotinic acid which we prepared are listed in Table I. Their potency is very slight.

In view of the fact that 1-alkyl 2-dialkylaminoalkyl 3-aminophthalates,[10] 1-dialkylaminoalkyl 2-alkyl 3-aminophthalates[11] and 1-alkyl 2-dialkylaminoalkyl 4-aminophthalates[12] are active local anesthetics it seemed desirable to prepare corre-

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by E. L. Jenner in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) Parke, Davis and Company Fellow.

(3) β-Diethylaminoethyl *p*-aminobenzoate is procaine. Corresponding esters of *o*- and *m*-aminobenzoic acids exhibit local anesthesia according to the German Patent 170,587 [*Frdl.*, **8**, 1002 (1906)].

(4) In the naphthalene series it has been found that β-diethylaminoethyl 4-amino-1-naphthoate is a strong local anesthetic [Blicke and Parke, THIS JOURNAL, **61**, 1200 (1939); Rowe, *J. Am. Pharm. Assoc.*, **29**, 241 (1940); Haury, Gruber and Drake, *J. Pharmacol. Exp. Therap.*, **70**, 315 (1940)]. We have been unable to find any reference with regard to the activity of dialkylaminoalkyl esters of quinoline-4-carboxylic acid, however, 2-alkyloxy derivatives of the latter are potent products [Wojahn, *Arch. Pharm.*, **269**, 422 (1931)].

(5) Ingersoll and Robbins, THIS JOURNAL, **48**, 2449 (1926).

(6) Meyer and Graf, *Ber.*, **61**, 2202 (1928).

(7) McElvain, "Organic Syntheses," Coll. Vol. I, p. 378.

(8) Douglass and Forman, THIS JOURNAL, **56**, 1609 (1934).

(9) Knunyantz and Katznel'son, Russian Patent, 35,836 [*C. A.* **29**, 8001 (1935)]. According to the abstract, the ester was made from the acid chloride and the basic alcohol; it was said to be of therapeutic value but it was not mentioned specifically that it exhibits local anesthetic action.

(10) Blicke and Otsuki, THIS JOURNAL, **63**, 1945 (1941).

(11) Blicke and Otsuki, *ibid.*, **63**, 2435 (1941).

(12) Blicke and Castro, *ibid.*, **63**, 2437 (1941).

sponding esters in the pyridine series. Accordingly, we synthesized a series of 2-alkyl 3-dialkylaminoalkyl quinolinates (Table III) in the following manner. 8-Hydroxyquinoline was oxidized to quinolinic acid (pyridine-2,3-dicarboxylic acid), the latter converted into quinoline anhydride and the anhydride heated with the required alkanol. The 2-alkyl acid quinolinates[13] obtained (Table II) were treated with a dialkylaminoalkyl chloride whereby the 2-alkyl 3-dialkylaminoalkyl esters were produced.

The local anesthetic activity of these esters, in comparison with those of the aminophthalic acid esters mentioned above, is relatively low. The most active product is 2-amyl 3-(γ-dibutylaminopropyl)-quinolinate.

Bis-(β-diethylaminoethyl) quinolinate dihydrobromide was found to be inactive, even in 4% solution, when applied to the rabbit's cornea.

Experimental Part

Dialkylaminoalkyl Nicotinate Hydrochlorides.—(A) To 0.05 mole of nicotinyl chloride, dissolved in 75 cc. of dry benzene, there was added 0.05 mole of the dialkylaminoalkanol dissolved in an equal amount of the same solvent. In some instances the product separated almost immediately as an oil or solid. After one to four days the precipitate was isolated and recrystallized.

(B)[14] A mixture of 0.05 mole of the dialkylaminoalkyl chloride and 0.05 mole of nicotinic acid in 50 cc. of dry isopropyl alcohol was refluxed on a steam-bath for twelve hours. After removal of the solvent under reduced pressure, the residue was triturated with anhydrous ether. In the event that the product remained oily, it was dissolved in water, the cold solution treated with Norit, filtered, the solution extracted with ether and the base liberated from the aqueous layer with concd. potassium carbonate solution. The oily base was extracted with ether and the solution dried over anhydrous magnesium sulfate. The solvent was removed and the base treated with the calculated amount of concentrated hydrobromic acid necessary for the formation of the hydrobromide. The material became crystalline when rubbed under dry ether.

Our β-diethylaminoethyl nicotinate hydrochloride melted at 128–129°, after recrystallization from acetone, was not hygroscopic, and could be recrystallized from ethyl or isopropyl alcohol. The "β-diethylaminoethyl nicotinate hydrochloride" described in the literature[5] melted at 140–160°, after recrystallization from acetone, was hygroscopic, and could not be recrystallized from the lower alcohols.

We found that the ester base is soluble in about three parts of cold water and precipitates upon the addition of solid potassium carbonate to the solution. It boiled at 120–125° (2 mm.); the boiling point 155–157° (10 mm.) has been reported.[9] The ester base produced a burning sensation when placed on the tip of the tongue but no anesthesia was experienced.

α-Phenyl-γ-diethylaminopropanol.—A solution of 24.2 g. of phenyl diethylaminoethyl ketone hydrochloride[15] in 50 cc. of water was treated with hydrogen under an initial pressure of three atmospheres in the presence of Raney nickel catalyst.[16] The calculated amount of hydrogen was absorbed in eight hours. The solution was filtered and the cold filtrate shaken with Norit, then with Filter-Cel, filtered again and the filtrate made strongly alkaline by addition of solid sodium hydroxide. After extraction of the product with ether the solution was dried over anhydrous magnesium sulfate. The product boiled at 122–124° (2 mm.).

When hydrogen chloride was passed into an ether solution of the basic alcohol, the hydrochloride precipitated as an oil. The latter was cooled and rubbed under dry ether whereupon it became crystalline; m. p. 84–86° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{13}H_{22}ONCl$: Cl, 14.54. Found: Cl, 14.57.

β-Dicyclohexylaminoethanol.—A mixture of 25.0 g. of ethylene bromohydrin and 72.4 g. of dicyclohexylamine[17] was heated for three days on a steam-bath, the precipitated dicyclohexylamine hydrobromide filtered and washed with toluene. From the filtrate there was obtained 28.0 g. (62%) of the desired ethanol; b. p. 131–134° (2 mm.).[18]

2-Alkyl Acidquinolinates.—The necessary quinolinic acid was obtained by oxidation of 8-hydroxyquinoline according to the procedure of Sucharda[19] but the purification of the acid was effected in the following manner. The residue of crude, moist quinolinic acid nitrate obtained from 250 g. of 8-hydroxyquinoline was pulverized, placed on a Jena funnel and washed thoroughly with five 20-cc. portions of 30% nitric acid. After recrystallization from 500 cc. of 40% acetic acid, 212 g. of dark orange product was obtained. The latter was dissolved in 2 liters of boiling water and treated successively with Norit and Filter-Cel. A large portion of the material separated from the cold solution and a further amount was obtained by concentration of the mother liquor; the total yield of nearly colorless acid was 178 g. (62%); m. p. 185–190° (decomp.).[20]

In order to convert quinolinic acid into quinolinic anhydride, a mixture of 100 g. of finely powdered acid and 200 cc. of acetic anhydride was maintained at 65° and fifteen 1-cc. portions of concd. hydrochloric acid[21] were added over a three hour period. The solution was poured into 2 liters of carbon tetrachloride and the precipitated, crystalline anhydride was recrystallized from 600 cc. of dry benzene; yield 64 g. (72%); m. p. 136–138°.[22]

(13) According to Kirpal [*Monatsh.*, **21**, 957 (1900)] the major product formed from quinolinic anhydride is the 2-alkyl ester and not the isomeric 3-alkyl compound.

(14) This general procedure was used originally by Horenstein and Pählicke [*Ber.*, **71**, 1644 (1938)] for the preparation of basic alkyl esters of hydroxy acids.

(15) Blicke and Burckhalter, THIS JOURNAL, **64**, 453 (1942).

(16) "Organic Syntheses," **21**, 15 (1941).

(17) The amine was dried for three days over stick sodium hydroxide prior to use; b. p. 129–134° (121 mm.).

(18) The boiling point reported is 135° (2 mm.) (German Patent 556,324). The method of preparation was not mentioned.

(19) Sucharda, *Ber.*, **58**, 1728 (1925).

(20) Skraup [*Monatsh.*, **2**, 148 (1881)] reported 190–195° (decomp.).

(21) German Patent, 442,221; *Frdl.*, **15**, 1632 (1927).

(22) Dox [THIS JOURNAL, **37**, 1948 (1915)] found 134°.

TABLE I

DIALKYLAMINOALKYL NICOTINATE HYDROCHLORIDES, C_5H_4N-COOR·HCl

	R	M. p., °C.[a]	Formula	Chlorine, % Calcd.	Chlorine, % Found
1	$CH_2CH_2N(C_2H_5)_2$	127–128[b]	$C_{12}H_{19}O_2N_2Cl$	13.71	13.77
2	$CH_2CH_2CH_2N(C_4H_9)_2$	104–105	$C_{17}H_{29}O_2N_2Cl$	10.78	10.79
3	$CH_2CH_2N(C_6H_{11})_2$[c]	163–165	$C_{20}H_{31}O_2N_2Cl$	9.66	9.75
4	$CH(C_6H_5)CH_2CH_2N(C_2H_5)_2$	145–146	$C_{19}H_{25}O_2N_2Cl$	10.16	10.20

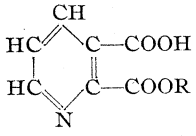
[a] Compound 1 was recrystallized from isopropyl alcohol; 2 from ethyl acetate; 3 and 4 from a mixture of absolute alcohol and ethyl acetate. [b] The melting point 140–160° has been reported (ref. 5). [c] C_6H_{11} = cyclohexyl.

2-Methyl acidquinolinate was obtained when a solution of 38 g. of quinolinic anhydride in 200 cc. of absolute methyl alcohol was refluxed for eight hours, the excess alcohol removed and the oily residue dissolved in 100 cc. of hot water. When the solution was cooled with ice, 39.8 g. of crude, crystalline ester separated. The latter was recrystallized from 40 cc. of water and then from 100 cc. of ethyl acetate; yield 19.1 g. (41%).

2-Amyl acidquinolinate was prepared by the same general procedure.

TABLE II

2-ALKYL ACIDQUINOLINATES



	R	M. p., °C.[a]	Formula	Neutralization equivalent Calcd.	Neutralization equivalent Found
1	CH_3	125–126[b]	$C_8H_7O_4N$	181.1	180.4
2	$CH_2(CH_2)_3CH_3$	110–111	$C_{12}H_{15}O_4N$	237.2	237.5
3	$CH_2(CH_2)_6CH_3$	104–105	$C_{15}H_{21}O_4N$	279.3	279.7
4	$CH_2(CH_2)_{10}CH_3$	106–107	$C_{19}H_{29}O_4N$	335.4	335.2
5	$CH_2CH_2C_6H_5$	139–140	$C_{15}H_{13}O_4N$	271.3	271.1

[a] Compounds 1, 3 and 4 were recrystallized from ethyl acetate; compounds 2 and 5 from water. [b] Kirpal [*Monatsh.*, **20**, 766 (1899)] reported 123°.

In the case of the 2-octyl, 2-lauryl and 2-β-phenylethyl esters, the calculated amount of the required alcohol was refluxed with the anhydride in dry toluene (50 cc. for 0.1 mole of anhydride). The crude esters were washed thoroughly with hot water before recrystallization.

2-Alkyl 3-Dialkylaminoalkyl Quinolinates.—These diesters were prepared from the dialkylaminoalkyl chloride and the 2-alkyl acidquinolinates by general procedure B, described under dialkylaminoalkyl nicotinate hydrochlorides.

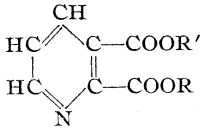
To obtain γ-dibutylaminopropyl chloride, the hydrochloride[23] of this compound obtained from 18.7 g. of γ-dibutylaminopropyl alcohol was dissolved in water, the solution made alkaline with solid potassium carbonate, the liberated base extracted with ether and the extract dried with anhydrous magnesium sulfate. Upon distillation there was obtained 16.4 g. (80%) of the basic alkyl halide; b. p. 73–75° (2 mm.).

Bis-(β-diethylaminoethyl) Quinolinate Dihydrobromide.—To 20.4 g. (0.10 mole) of quinolinyl chloride,[24] dissolved in dry benzene, there was added a benzene solution of 46.8 g. (0.40 mole) of β-diethylaminoethanol. The mixture refluxed vigorously during the addition of the ethanol and β-diethylaminoethanol hydrochloride precipitated. The mixture was warmed for eight hours on a steam-bath, the precipitate removed, the benzene solution shaken with water and then with a 10% sodium carbonate solution. The benzene solution was dried with anhydrous magnesium sulfate, the solvent removed and the base triturated with the amount of 48% hydrobromic acid required for the formation of the dihydrobromide. The product became crystalline when rubbed under anhydrous ether; m. p. 157–159° after recrystallization from alcohol.

Anal. Calcd. for $C_{19}H_{33}O_4N_3Br_2$: Br, 30.31. Found: Br, 30.28.

TABLE III

2-ALKYL 3-DIALKYLAMINOALKYL QUINOLINATE SALTS



	R	R′	M. p., °C.[a]	Formula	Halogen, % Calcd.	Halogen, % Found
1	CH_3	$CH_2CH_2N(C_2H_5)_2$	113–114	$C_{14}H_{21}O_4N_2Cl$	11.19	11.25
2	C_5H_{11}	$CH_2CH_2N(C_2H_5)_2$	98–101	$C_{18}H_{29}O_4N_2Br$	19.15	19.27
3	C_8H_{17}	$CH_2CH_2N(C_2H_5)_2$	59– 62[b]	$C_{21}H_{35}O_4N_2Br$	17.40	17.50
4	$C_{12}H_{23}$	$CH_2CH_2N(C_2H_5)_2$	72– 74	$C_{25}H_{43}O_4N_2Br$	15.50	15.60
5	$CH_2CH_2C_6H_5$	$CH_2CH_2N(C_2H_5)_2$	141–142	$C_{21}H_{27}O_4N_2Cl$	8.71	8.74
6	C_5H_{11}	$CH_2CH_2CH_2N(C_4H_9)_2$	oil	$C_{23}H_{39}O_4N_2Cl$	8.00	8.24

[a] Compounds 1 and 2 were recrystallized from isopropyl alcohol; 5 from ethyl alcohol; 4 from ethyl acetate; 3 from a mixture of acetone and petroleum ether (30–40°); 6 was washed repeatedly with dry ether. [b] Hygroscopic.

Summary

Dialkylaminoalkyl nicotinates, 2-alkyl acidquinolinates and 2-alkyl 3-dialkylaminoalkyl

(23) Blicke and Otsuki, THIS JOURNAL, **63**, 2435 (1941).

(24) Obtained in 84% yield by the method of Scheiber and Knothe [*Ber.*, **45**, 2256 (1912)].

quinolinates have been described. None of the esters possessed marked activity as a local anesthetic.

ANN ARBOR, MICHIGAN RECEIVED FEBRUARY 10, 1942

[COMMUNICATION NO. 853 FROM THE KODAK RESEARCH LABORATORIES]

The Reaction of β-Isodurylaldehyde Cyanohydrin with Phenylmagnesium Bromide[1]

BY A. WEISSBERGER AND DUDLEY B. GLASS

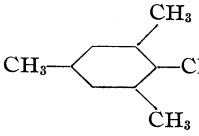
Benzoin and a number of substituted benzoins and other acyloins have been prepared by the reaction of aryl- or alkylmagnesium halides with the cyanohydrins of aryl aldehydes.[2,3] Omitting the reaction of the Grignard reagent with the active hydrogen of the cyanohydrin, and the acid used in decomposing the magnesium complex, the course of the reaction may be represented as

$$ArCHOHCN + RMgX \longrightarrow ArCHOHC(=NMgX)R \quad (1)$$

$$ArCHOHC(=NMgX)R + H_2O \longrightarrow ArCHOHC(=NH)R + Mg(OH)X \quad (2)$$

$$ArCHOHC(=NH)R + H_2O \longrightarrow ArCHOHCOR + NH_3 \quad (3)$$

The yields vary considerably, but no total failure of the reaction is reported in the literature. However, when β-isodurylaldehyde cyanohydrin,



—CHOHCN, was treated with phenylmagnesium bromide in an attempt to prepare 2,4,6-trimethylbenzoin for a study of its oxidation rate, the compound expected was not obtained. Instead, the product of the reaction was a nitrogen-containing substance with the properties of an α-aminoketone; the compound is a monohydric base, is oxidized by Fehling solution and by nitrosobenzene to 2,4,6-trimethylbenzil, and autoxidizes in alkaline solution.[4] The same substance was obtained by the following series of reactions

$$C_6H_3(CH_3)_3 + C_6H_5CH_2COCl \longrightarrow C_6H_2(CH_3)_3COCH_2C_6H_5 + HCl$$

$$C_6H_2(CH_3)_3COCH_2C_6H_5 + C_4H_9NO_2 \longrightarrow C_6H_2(CH_3)_3COC(=NOH)C_6H_5 + C_4H_9OH$$

$$C_6H_2(CH_3)_3COC(=NOH)C_6H_5 + 4H(SnCl_2) \longrightarrow C_6H_2(CH_3)_3COCHNH_2C_6H_5 + H_2O$$

I

This synthesis establishes the position of the oxygen and nitrogen atoms in respect to the mesitylene and benzene nuclei and identifies the compound as 2,4,6-trimethyldesylamine (I) or its tautomer (II).

If one considers the work of Kohler[5] and of Fuson,[6] who have shown that in compounds of the types $C_6H_2(CH_3)_3COCH=$ and $C_6H_2(CH_3)_3CH-OHC\equiv$ the mesitylene residue promotes the formation and enhances the stability of the enolic form $C_6H_2(CH_3)_3C(OH)=C<$, the anomalous course of the reaction of β-isodurylaldehyde cyanohydrin with phenylmagnesium bromide can be understood. With the mesitylene derivative, the imino compound, which ordinarily undergoes acid hydrolysis, eq. 3, is transformed by enolization into the amino compound II, eq. 4, which resists hydrolysis. This or the tautomeric amine I separates from the acid solution as the hydrochloride.

$$C_6H_2(CH_3)_3CHOHC(=NH)C_6H_5 \longrightarrow C_6H_2(CH_3)_3C(OH)=C(NH_2)C_6H_5 \quad (4)$$

II

The phase in the sequence of reactions in which the enolization occurs is indicated by the reaction of β-isoduraldehyde cyanohydrin with methylmagnesium iodide.[7] β-Isoduraldehyde cyanohydrin consumes two moles of the Grignard reagent and evolves one mole of methane. This agrees with the structure of the resulting complex as that of the imino derivative $ArCH(OMgBr)C(=N-MgBr)R$. The tautomeric enamino compound $ArC(OMgBr)=C(NHMgBr)—R$ should evolve another mole of methane. Hence, the amino compound is not formed before the hydrolysis of the Grignard complex.

The explanation of the anomalous reaction of β-isoduraldehyde cyanohydrin with phenylmag-

(1) This investigation was started in the Dyson-Perrins Laboratory, Oxford. I wish to express thanks to Sir R. Robinson for his hospitality and to Imperial Chemical Industries, Ltd. for financial assistance.—A. W.

(2) Gauthier, *Compt. rend.*, **152**, 1100, 1259 (1911); Tiffeneau and Levy, *Bull. soc. chim.*, **37**, 1247 (1925); Asahina and Terasaka, *J. Pharm. Soc.* (Japan), **494**, 219 (1923).

(3) Weissberger, Strasser, Mainz and Schwarze, *Ann.*, **478**, 112 (1930).

(4) *Cf.* James and Weissberger, THIS JOURNAL, **59**, 2040 (1937).

(5) Kohler and co-workers, *ibid.*, **57**, 2517 (1935); **58**, 2166 (1936); **59**, 887 (1937).

(6) Fuson and co-workers, *ibid.*, **58**, 1233 (1936), and succeeding papers.

(7) Kohler, Stone and Fuson, *ibid.*, **49**, 3181 (1927); Kohler and Richtmyer, *ibid.*, **52**, 3736 (1930). We wish to thank Dr. Alan Bell of these laboratories for the "Grignard Machine" analyses.

nesium bromide as given above is corroborated by the results of the hydrolysis of desylamine and of 2,4,6-trimethyldesylamine by heating with dilute hydrochloric acid. Under conditions that yield 40% of benzoin from desylamine, the 2,4,6-trimethyldesylamine remains unchanged. Under more drastic conditions a quantitative yield of benzoin is obtained while only about 20% of the 2,4,6-trimethyldesylamine is affected. Such results would be expected if the reaction mixture of the desylamine contains appreciable quantities of the imino compound, while the reaction mixture of the 2,4,6-trimethyldesylamine is composed almost exclusively of the enamine and/or the aminoketone.

On acetylation, trimethyldesylamine gives a monoacetate, and under very vigorous conditions, a triacetate. Formulation of these compounds as $(CH_3)_3C_6H_2C(OH)=C(NHCOCH_3)C_6H_5$ and $(CH_3)_3C_6H_2C(OCOCH_3)=CN(COCH_3)_2C_6H_5$ is in agreement with the solubility of the monoacetate in dilute and in concentrated hydrochloric acid, and the results of the "Grignard Machine" analysis. The monoacetate dissolves in a 1:1 mixture of alcohol and concentrated hydrochloric acid. Upon addition of more concentrated hydrochloric acid no precipitation occurs, while upon addition of water the acetate precipitates. The monoacetate shows two active hydrogen atoms and does not add methylmagnesium iodide. As in acetanilide, the acetyl group in the monoacetate is too tightly bound to be eliminated under the conditions of this analysis. The triacetate has no active hydrogen and uses up four moles of methylmagnesium iodide in splitting off two of the acetyl groups; from the reaction mixture the monoacetate can be recovered. The monoacetate of desylamine on the other hand reacts as $C_6H_5COCH(NHCOCH_3)C_6H_5$, showing only one active hydrogen, and using up one mole of methylmagnesium iodide, presumably in an addition to the carbonyl group. These results again demonstrate the difference between the derivative of benzene and of mesitylene, and the enolizing effect of the mesityl group.

The oxidation of trimethyldesylamine with molecular oxygen at a *p*H of 12.8 is about ten times faster than that of desylamine[8] under the same conditions. Since the reactive species of the α-aminoketone in this reaction is the enolate ion,[4] this result again indicates the higher tendency for enolization of the mesitylene derivative.

The reasons for this higher degree of enolization may be tentatively discussed. The stability of the enolic double bond depends on the degree of resonance between this double bond and the aromatic system. Several conditions might favor this resonance. A steric factor comes first to mind in connection with a compound of the marked stereochemical characteristics of mesitylene. For maximum degeneracy the resonating system must lie in one plane. It might, therefore, be suggested that the stability of the enolic double bond in mesitylene derivatives is increased because the double bond is forced into the plane formed by the aromatic system. However, a repulsion between the two methyl groups in the ortho positions and a group on the α-carbon atom would not produce such an effect. An attraction between the methyl groups and a group on the α-carbon atom would serve the purpose, but is, in itself, not likely to occur. A more probable reason for the increased stability of the aromatic-olefinic conjugated system in mesitylene derivatives lies in the high electron density in the mesitylene nucleus. The latter is indicated by the direction of the dipole moments of toluene and of *m*-xylene, and by the great reactivity of mesitylene with anionotropic reagents. It appears that the electron distribution of mesitylene, as compared with that of benzene, increases the degeneracy of the enolic-aromatic conjugation, and stabilizes the enolic double bond.

Experimental

β-Isodurylaldehyde was prepared from mesitylene, zinc cyanide, and hydrogen chloride by the method of Hinkel, Ayling and Morgan.[9] The yield of aldehyde was 75%. The aldehyde was purified by conversion to the anil, distillation and crystallization of the anil and, after hydrolysis of the anil, redistillation of the aldehyde. The yield of pure aldehyde was 60%, b. p. 113–115° (11 mm.), $n^{20}D$ 1.5505.

β-Isodurylaldehyde Cyanohydrin.—A solution of 44.4 g. (0.3 mole) of β-isodurylaldehyde in 240 cc. of petroleum ether was shaken vigorously for fifteen minutes with a solution of 52 g. (0.8 mole) of potassium cyanide and 44.4 g. (0.83 mole) of ammonium chloride in 135 cc. of water. The flask was closed tightly during the agitation. The resulting crystals were removed by filtration, washed with water and then petroleum ether, and dried in a vacuum desiccator over calcium chloride. There resulted 48 g. (91%) of cyanohydrin which melted at 106–107° (sealed tube) after recrystallization from two volumes of benzene.

(8) We are indebted to Mr. D. S. Thomas of these laboratories for the determination of the autoxidation rates.

(9) Hinkel, Ayling and Morgan, *J. Chem. Soc.*, 2793 (1932).

Anal. Calcd. for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.30; H, 7.50; N, 8.00.

2,4,6-Trimethyldesylamine Hydrochloride from β-Isodurylaldehyde Cyanohydrin and Phenylmagnesium Bromide.—To a Grignard solution prepared from one-half molar quantities of magnesium and bromobenzene in 375 cc. of ether, was added with stirring a solution of 17.5 g. (0.1 mole) of β-isodurylaldehyde cyanohydrin in 200 cc. of dry ether during a period of five minutes. The reaction mixture was heated under reflux on a steam-bath for fifteen minutes and then was poured onto a mixture of 1 kg. of ice and 200 cc. of concentrated hydrochloric acid. The mixture was stirred for a minute, the layers were separated, and the aqueous layer was extracted immediately with 200 cc. of ether and filtered. Then 200 cc. of concentrated hydrochloric was added. The flask was stoppered and allowed to stand for two days at 25±5°. The precipitate was removed by filtration, washed with water and ether, and dried in air. The yield was 16 g. (55%) of hydrochloride which melted at 287–289° (sealed tube). The substance was brought to analytical purity by dissolving in 150 cc. of 70% aqueous alcohol, filtering the solution and precipitating the hydrochloride with 300 cc. of concentrated hydrochloric acid. After cooling to around 15°, the hydrochloride was collected on a filter and recrystallized from 70% alcohol to which had been added 1% of hydrochloric acid; m. p. 290–291° (sealed tube).

Anal. Calcd. for $C_{17}H_{20}ONCl$: C, 70.45; H, 6.96; N, 4.83. Found: C, 70.10; H, 6.70; N, 4.88.

2,4,6-Trimethyldesoxybenzoin was prepared from mesitylene, phenylacetyl chloride and aluminum chloride in petroleum ether by the method of Klages.[10] There was obtained an 88% yield of ketone which boiled at 136–137° (0.5 mm.).

Isonitroso-2,4,6-trimethyldesoxybenzoin.—The 2,4,6-trimethyldesoxybenzoin was converted into the isonitroso derivative by a method similar to that used by Hartung and Munch[11] for the preparation of isonitrosopropiophenone. A solution of 88 g. (0.37 mole) of 2,4,6-trimethyldesoxybenzoin and 42 g. (0.41 mole) of redistilled butyl nitrite (b. p. 78–79°) in 275 cc. of ether was stirred, and dry hydrogen chloride was introduced at the rate of four to five bubbles per second for two and one-half hours. At the end of this time the flask was stoppered and allowed to stand overnight. Ether (300 cc.) was added and the oxime was extracted from the ethereal solution with one 450-cc. portion of 5% sodium hydroxide solution, and three 150-cc. portions of 3% sodium hydroxide solution. The alkaline extracts were combined, filtered and run into a mixture of ice and excess concentrated hydrochloric acid. The precipitate was removed by filtration and dried in air; yield 75 g. (76%); m. p. 152–153.5°. A sample recrystallized from alcohol melted at 156–156.5°.

2,4,6-Trimethyldesylamine Hydrochloride by the Reduction of Isonitroso-2,4,6-trimethyldesoxybenzoin.—A solution of 225 g. (1.0 mole) of stannous chloride in 500 cc. of concentrated hydrochloric acid was added rapidly to a solution of 53.4 g. (0.2 mole) of isonitroso-2,4,6-trimethyldesoxybenzoin in 500 cc. of alcohol. The reaction mixture was then heated under reflux on the steam-bath for one and one-half hours. After standing overnight at room temperature, the precipitate was removed by filtration and dried in air; yield 50 g. (86%). A sample was recrystallized from 60% alcohol to which had been added a little hydrochloric acid; m. p. 289–290° (sealed tube).

Anal. Calcd. for $C_{17}H_{20}ONCl$: N, 4.83. Found: N, 4.74.

Acetates of 2,4,6-Trimethyldesylamine: Monoacetate.—Ten grams of 2,4,6-trimethyldesylamine hydrochloride prepared by the Grignard method was added to a mixture of 100 cc. of acetic anhydride and 20 cc. of pyridine and the mixture was heated on the steam-bath for ten minutes. At the end of this time, the reaction mixture was poured onto ice and stirred until the anhydride had decomposed. The product was removed by filtration and crystallized from a benzene–ligroin mixture (1:2); m. p. 174.5–175°.

Anal. Calcd. for $C_{19}H_{21}O_2N$: C, 77.26; H, 7.17; N, 4.74; mol. wt., 295. Found: C, 77.50; H, 7.03; N, 4.76; mol. wt. (in benzene), 296, 300.

The 2,4,6-trimethyldesylamine hydrochloride prepared by the reduction method was carried through the same procedure. It acted in all ways identically with the amine hydrochloride prepared by the Grignard method. The acetates gave no depression in a mixed melting point test.

Triacetate.—Five grams of 2,4,6-trimethyldesylamine hydrochloride prepared by the Grignard method was added to a mixture of 50 cc. of acetic anhydride and 10 cc. of pyridine and the mixture was heated for seven hours on the steam-bath under a reflux condenser closed by a calcium chloride tube. After standing overnight, the reaction mixture was diluted with 250 cc. of warm (*ca.* 50°) water and stirred until the anhydride had decomposed. The precipitate was ground in a mortar with water and then recrystallized from 15 cc. of alcohol; m. p. 125–126°.

Anal. Calcd. for $C_{23}H_{25}O_2N$: C, 72.80; H, 6.64; N, 3.69; mol. wt., 379. Found: C, 73.01; H, 6.65; N, 3.71; mol. wt. (in benzene), 373, 368.

The 2,4,6-trimethyldesylamine hydrochloride prepared by reduction behaved identically with that prepared by the Grignard method. The triacetates gave no depression in a mixed melting point test.

Hydrolysis of Triacetate to Monoacetate.—One gram of triacetate was dissolved in 15 cc. of warm alcohol and 5 cc. of concentrated hydrochloric acid was added. The solution was boiled on the steam-bath for ten minutes, cooled and diluted with 50 cc. of water. The precipitate was removed by filtration and recrystallized from ligroin; m. p. 173–174°. On addition of known monoacetate, the melting point was unchanged.

Hydrolysis of Triacetate to Amine.—One gram of triacetate was added to a mixture of 10 cc. of alcohol and 10 cc. of concentrated hydrochloric acid and the solution boiled for five hours under reflux. The solution was cooled and allowed to stand in the ice box for two hours. The precipitate of 2,4,6-trimethyldesylamine hydrochloride was removed by filtration, washed with alcohol and dried in air; m. p. 283–285° (sealed tube). A small sample of the product was dissolved in 70% alcohol and allowed to stand in an unstoppered test-tube for one week. The precipitate was removed by filtration and dried in air; m. p. 134–135°. A mixed melting point with a known sample of 2,4,6-trimethylbenzil showed no depression.

(10) Klages, *Ber.*, **32**, 1564 (1899).

(11) Hartung and Munch, THIS JOURNAL, **51**, 2262 (1929).

Acetates of Desylamine. Monoacetate.—The monoacetate of desylamine[12] was prepared by the method used for the preparation of the monoacetate of 2,4,6-trimethyldesylamine; m. p. 135–136°.

Anal. Calcd. for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.12; H, 5.89; N, 5.51.

Triacetate.—Five grams of desylamine hydrochloride was heated on a steam-bath for eight hours with 50 cc. of acetic anhydride and 10 cc. of dry pyridine. At the end of this time 200 cc. of water was added and the mixture was stirred until the anhydride had decomposed. The aqueous portion was decanted and the gummy residue was washed with water. The gum was dissolved in 125 cc. of ligroin, and the solution was treated with Norit and filtered. After standing for twenty hours, the precipitate was collected on a filter and recrystallized from four volumes of methanol; m. p. 130–131°.

Anal. Calcd. for $C_{20}H_{19}O_4N$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.20; H, 5.62; N, 4.05.

RESULTS OF THE "GRIGNARD MACHINE" ANALYSES[7]

Compound	Reaction time	Active hydrogen	Addition
2,4,6-Trimethyldesylamine hydrochloride	10 min.[a]	3	0
2,4,6-Trimethyldesylamine monoacetate	1 hr.	2	0
2,4,6-Trimethyldesylamine triacetate[b]	1 hr.	0	4
β-Isodurylaldehyde cyanohydrin	10 min.	1	1
Desylamine monoacetate	1 hr.	1	1

[a] Upon prolonged heating the value of the active hydrogen approached 4. [b] The reaction mixture yielded the monoacetate upon being worked up.

(12) Davidson, Weiss and Jelling, *J. Org. Chem.*, **2**, 319 (1937).

Hydrolysis of 2,4,6-Trimethyldesylamine and of Desylamine.—(a) A mixture of 1 g. of the amine hydrochloride, 5 cc. of water, 5 cc. of concentrated hydrochloric acid, and 10 cc. of ethanol was heated at 95° in a sealed tube under nitrogen for twenty hours. Benzoin in a 40% yield separated and was collected on the filter. Under the same conditions 2,4,6-trimethyldesylamine was unaffected.

(b) Same as (a) except heated at 130° for twenty-four hours. Desylamine gave a quantitative yield of benzoin. 2,4,6-Trimethyldesylamine yielded 20% of a mixture of 2,4,6-trimethylbenzoin and 2,4,6-trimethylbenzil.

Summary

1. 2,4,6-Trimethyldesylamine has been prepared by the reaction of phenylmagnesium bromide with β-isodurylaldehyde cyanohydrin and also by the reduction of isonitroso-2,4,6-trimethyldesoxybenzoin.

2. The reactions of 2,4,6-trimethyldesylamine and desylamine with dilute hydrochloric acid were compared.

3. The autoxidation rate of 2,4,6-trimethyldesylamine was compared with that of desylamine.

4. The mono- and triacetate of 2,4,6-trimethyldesylamine were prepared and their reactions with dilute hydrochloric acid and with methylmagnesium iodide were studied.

5. The results obtained were ascribed to the propensity toward enolization shown by acetomesitylene derivatives.

ROCHESTER, NEW YORK RECEIVED APRIL 30, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Tri-*o*-tolyltin and the Instability of Organo-metallic Free Radicals

BY HUMBERT MORRIS, WARD BYERLY AND P. W. SELWOOD

Previous magnetic measurements on triphenylgermanium,[1] triphenyllead,[2] trimethyltin[3] and tricyclohexyllead[3] have shown that all these compounds exist in the diamagnetic or dimeric state. Molecular weight measurements by others have, on the contrary, consistently indicated partial or complete dissociation to the free radical. These results raise two questions: first, why do these compounds not exist as free radicals and, second, why do the magnetic measurements contradict the molecular weight measurements?

A possible answer to the first question is to be found in the much larger radius of the metal atoms as compared with carbon, as in triphenylmethyl. It has been suggested[3] that the increased radius leads to a much greater number of effective collisions leading to formation of the dimer, and that a compound such as tri-*o*-tolyltin, in which steric effects are large, might exist as a free radical. This hypothesis is tested in the work reported here.

An effort to answer the second question by repeating ebulliometric measurements on trimethyltin and on triphenyllead is also reported.

(1) Selwood, THIS JOURNAL, **61**, 3168 (1939).
(2) Preckel and Selwood, *ibid.*, **62**, 2765 (1940).
(3) Morris and Selwood, *ibid.*, **63**, 2509 (1941).

Experimental Part

Magnetic Measurements.—The magnetic susceptibilities were measured on the Gouy balance previously de-

scribed.[2] Measurements were made at 25 and 80°, benzene being used as the solvent. A field strength of about 13,100 oersteds was used throughout.

Ebulliometric Measurements.—These were made by means of a Swietoslawski differential ebulliometer.[4] The temperature differences were measured with an 8-junction thermocouple.

Preparation of Tri-*o*-tolyltin.—*o*-Bromotoluene was prepared from *o*-toluidine by diazotization and the Sandmeyer reaction.[5] Tetra-*o*-tolyltin was made by treating the Grignard reagent with stannic chloride. The Grignard reagent from 150 g. (0.88 mole) of *o*-bromotoluene and 21.5 g. of magnesium was refluxed with 33 g. (0.14 mole) of stannic chloride for twelve hours in ether. Water and dilute hydrochloric acid were added, and the ether evaporated off. The sludge was filtered dry and then refluxed in benzene to dissolve the tetra-*o*-tolyltin. The benzene solution was filtered and concentrated. White, powdery crystals were formed as the red-brown solution cooled. Two crops of crystals were obtained and recrystallized; yield, 15 g. ($^1/_{30}$ mole); melting point 200–215°. According to Krause and von Grosse[6] the melting point of tetra-*o*-tolyltin is 214–215°.

Tri-*o*-tolyltin bromide was prepared according to the method of Chambers and Scherer.[7] The tetra-*o*-tolyltin was dissolved in chloroform and treated with 6.5 g. of iodine. It was then shaken with 30% sodium hydroxide to convert it to the hydroxide and to remove di-*o*-tolyltin oxide, which is water-soluble. The water layer was separated, and the bromide was formed by shaking with dilute hydrobromic acid. The $(o\text{-tolyl})_3SnBr$ crystallizes with difficulty from chloroform, but it separates readily from petroleum ether; yield 1.5 g.; melting point 94–96°. The melting point is 97.5° according to Krause and von Grosse.[6]

The $(o\text{-tolyl})_3SnBr$ does not react with molecular silver; 0.1 g. of the halide was shaken with 0.1 g. of molecular silver for two hours. It was filtered and recrystallized from petroleum ether. The melting point of the product was 89–93°.

The halide was reacted with sodium in absolute alcohol, according to the method of Krause and Becker.[8] The halide in 18 cc. benzene was treated with 18 cc. of alcohol and 2 g. of sodium. Then it was shaken with water. The benzene layer was separated, washed, dried, concentrated, and cooled in snow. A fine white powder was obtained which melted at 208–212°. After recrystallization from petroleum ether, the melting point was 208–210°; yield, 0.25 g. It was dried in vacuum at 50°.

A molecular weight determination in freezing benzene gave the following results

Molality (as R_6Sn_2)	0.0175	0.0278	
Apparent mol. wt.	664	825	±30

The molecular weight calculated for $(o\text{-tolyl})_6Sn_2$ is 784. For reasons to be discussed below not much consideration should be given the molecular weight determination.

Analyses by T. S. Ma of the University of Chicago.

	Calculated for $(o\text{-tolyl})_6Sn_2$, %	Found, %	
Sn	30.4	29.73	29.95
H	5.4	5.19	5.20
C	64.4	63.27	63.16

This compound does not appear to have been previously reported.

Results

In order to treat the data it is necessary to know the diamagnetic susceptibility of hexa-*o*-tolylditin. The amount of this substance available was too small for direct measurement. The susceptibility was, therefore, calculated from Pascal's constants and the known susceptibility of hexamethylditin.[3] The susceptibility of this compound is -0.51×10^{-6} and the molar diamagnetism is -167×10^{-6}. The molar diamagnetism of quadricovalent tin is, therefore, nearer 39 than the usually accepted value of 30.[9]

For six phenylene groups plus six methyl groups the constants are $(6 \times 49.3) + (6 \times 14.85) \times 10^{-6} = 384.9 \times 10^{-6}$. Two quadricovalent tin atoms raise this to 462.9×10^{-6}. This number divided by the molecular weight gives -0.59×10^{-6} as the susceptibility of hexa-*o*-tolylditin per gram. Even if this value is as much as ten per cent in error it will not seriously affect the validity of the conclusions to be drawn from the work described here.

In the following table the susceptibilities of the solution are calculated for zero dissociation and for complete dissociation. These data are compared with the observed susceptibilities. Methods of calculation are given elsewhere.[2]

TABLE I

SUSCEPTIBILITY OF A 0.25 *M* SOLUTION OF TRI-*o*-TOLYLTIN IN BENZENE

Temp., °C.	Calcd. for zero diss. $\chi \cdot 10^6$	Calcd. for complete diss. $\chi \cdot 10^6$	Observed $\chi \cdot 10^6$
25	−0.700	−0.638	−0.7003
80	−0.701	−0.659	−0.705

It is clear from this table that the compound exists as hexa-*o*-tolylditin. At 25° as little as 2%, and at 80° as little as 4% dissociation could have been detected.

This work constitutes proof that steric considerations are in themselves insufficient to produce dissociation, although they may greatly modify

(4) Swietoslawski "Ebulliometry," Chemical Publishing Co. of New York, Inc., N. Y., 1937, p. 6.

(5) "Organic Syntheses," Collective Vol. 1, edited by Gilman, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 130.

(6) Krause and von Grosse, "Die Chemie der Metall-organischer Verbindungen," Gebrüder Borntraeger, Berlin, 1937, p. 320.

(7) Chambers and Scherer, THIS JOURNAL, **48**, 1054 (1926).

(8) Krause and Becker, *Ber.*, **53B**, 188 (1920).

(9) Stoner, "Magnetism and Matter," Methuen and Co.. Ltd., London, 1934, p. 470.

the degree of dissociation, as has been shown for the hexaarylethanes.[10,11] The work also increases the probability previously suggested[3] that no stable organo-metallic free radical has yet been prepared. The metal ketyls are, of course, dissociated, but the dissociation does not involve a metal-metal bond.

The question as to why organo-metallic free radicals are of such low stability remains unanswered. It is not simply a matter of relative sizes of metal and carbon atoms. It is apparently not a matter of relative electronegativities because tetraarylhydrazines are known to dissociate.[12] Whatever the underlying cause may be, it evidently inhibits the resonance, or other phenomenon, which is a necessary adjunct to free radical formation. The recent observation of Bauer and Beach [THIS JOURNAL, **64,** 1142 (1942)] on the structure of hexamethylethane suggests a clue to the instability of organo-metallic free radicals. They report a probable stretching of the central C–C bond to 1.58 ± 0.03 Å. It is possible that in hexaarylethanes still more stretching occurs with consequent weakening of the ethane bond. But in the cases of the organometallic compounds such as hexaphenylditin, the tin atoms are so large that no stretching of the Sn–Sn bond is necessary. There is, therefore, no weakening of the bond and no tendency to form free radicals. The same interpretation may be applied to the corresponding compounds of silicon, germanium and lead.

It may be worth noting that the known free radical forming elements are limited to carbon, nitrogen, oxygen, possibly sulfur, and chlorine. Thus paramagnetic molecules are formed by these elements, but the diboranes,[13] hexaaryldisilanes[14] and tetraaryldiarsines (*e. g.*, phenyl cacodyl),[15] which might be expected to dissociate, do not. Schönberg and Rupp[16] suggest that diphenylene disulfide may dissociate, while nothing is known of the tetraaryldiphosphines.

The remaining question is: why do the magnetic measurements contradict the molecular weight determinations? In this connection it should be pointed out that the dielectric measurements of Lewis, Oesper and Smyth[17] on triphenyllead exclude the remote possibility of an electrolytic type of dissociation.

Ebulliometric measurements were made on benzene solutions of trimethyltin and triphenyllead with the results given in Tables II and III.

TABLE II

BOILING POINT ELEVATION PRODUCED BY 0.9418 G. OF $(CH_3)_3Sn$ DISSOLVED IN 104 CC. OF BENZENE

Time in minutes after addition of solute	Boiling point elevation, °C.
10	0.076
15	.045
20	.045
35	.049
125	.023
305	.026
Calcd. elevation for the dimer	.089

TABLE III

BOILING POINT ELEVATION PRODUCED BY 1.0355 G. OF $(C_6H_5)_3Pb$ IN 104 CC. OF BENZENE

Time in minutes after addition of solute	Boiling point elevation, °C.
10	0.049
25	.027
55	.024
145	.008
Calcd. elevation for the dimer	.073

It is clear from these results that decomposition rapidly occurs, and that, even during the ten-minute interval necessary for the apparatus to come to equilibrium, considerable destruction of the compound must take place. In no case was the apparent molecular weight less than that of the dimer. During the test on triphenyllead a visible precipitate was formed during the first 30 minutes. It is, therefore, obvious that ebulliometric measurements are of as little value for the study of organo-metallic free radicals as they are for hexaarylethanes.[18] No attempt was made to determine the nature of the decomposition products from these compounds, but it is possible that they were similar to those reported by Calingaert, Soroos and Shapiro[19] as disproportionation products of R_6Pb_2 compounds.

Summary

Tri-*o*-tolyltin has been prepared and shown by magnetic measurements to be dimeric. Ebulliometric measurements on solutions of trimethyltin and of triphenyllead emphasize the unreliability of such methods for the study of free radicals.

EVANSTON, ILLINOIS RECEIVED MAY 15, 1942

(10) Roy and Marvel, THIS JOURNAL, **59,** 2622 (1937), *et seq.*
(11) Preckel and Selwood, *ibid.*, **63,** 3397 (1941).
(12) Weitz and Müller, *Ber.*, **68B,** 2306 (1935).
(13) Farkas and Sachsse, *Trans. Faraday Soc.*, **30,** 331 (1934).
(14) Schlenk, Renning and Racky, *Ber.*, **44,** 1178 (1911).
(15) Schlenk, *Ann.*, **394,** 216 (1912).
(16) Schönberg and Rupp, *Naturwiss.*, **21,** 561 (1933).
(17) Lewis, Oesper and Smyth, THIS JOURNAL, **62,** 3243 (1940).
(18) Preckel and Selwood, forthcoming publication.
(19) Calingaert, Soroos and Shapiro, THIS JOURNAL, **64,** 462 (1942).

NOTES

The Crystal Structure of Calcium Cyanamide

By M. A. Bredig*

When the reactivity of calcium carbide as a function of its crystal structure was studied by means of X-ray diffraction methods,[1] calcium cyanamide, product of its reaction with nitrogen, also was included. Very considerable discrepancies were observed between the positions of the X-ray lines obtained and those reported in a previous attempt to determine the structure by U. Dehlinger.[2] Recently, calcium cyanamide was listed among the first thousand substances of which X-ray data were assembled for use with the Hanawalt X-ray method of chemical analysis.[3] An examination of the figures given for calcium cyanamide indicated that the preparation used must have contained very little calcium cyanamide and that merely the X-ray interferences of calcium carbonate, of calcium hydroxide, and of graphite, major impurities and decomposition products of calcium cyanamide, were recorded. A reëxamination of the X-ray data of this industrially important compound appeared desirable.

A Debye–Scherrer–Hull powder diagram of a commercial grade, finely pulverized calcium cyanamide, containing approximately 70% calcium cyanamide, was obtained with copper K_α radiation in an X-ray camera of 57.5 mm. diameter. The sample was contained in a thin-walled Lindemann glass tube, and was not rotated during the exposure. The X-ray interferences of calcium hydroxide, principal impurity of this sample, were very easily distinguished from the dotted lines of calcium cyanamide, due to the much coarser grains of the latter. They were used as reference lines with which the data, for calcium hydroxide, of Hanawalt, Rinn and Frevel, and those of Landolt-Börnstein, Supplement Vol. IIb, were in perfect agreement, as the table shows. The interplanar distances of calcium cyanamide, as measured and as calculated with new rhombohedral lattice constants, $\alpha = 39°55'$ and $a_{rh} = 5.40$ Å., corresponding to a hexagonal lattice with the constants $c =$ 14.85 and $a = 3.67$ Å., are in very satisfactory agreement. The specific gravity becomes 2.29.

TABLE I

X-RAY POWDER DIAGRAM OF CALCIUM CYANAMIDE

Indices	$d_{exp.}$	$d_{calcd.}$	Intensities exp.	Intensities calcd.
111	4.92	4.95	m	140
C	3.39	3.38	v.w.	..
110	2.93	(2.93)	v.s.	370
$Ca(OH)_2$	2.63	2.63	s	..
211	2.422	(2.422)	m	80
221	2.170	2.180	m	110
$Ca(OH)_2$	1.928	1.93	s	..
$\bar{1}10$	1.853	1.840	m	82
$Ca(OH)_2$	1.786	1.79	m	..
322	1.753	1.760	w	62
102	1.723	1.725	w	35
$Ca(OH)_2$	1.685	1.690	w	..
333	1.637	1.650	v.w.	8
332	1.593	1.606	w	14
$\bar{1}11$		1.590		3
200	1.556	1.568	w-m	46
$Ca(OH)_2$	1.478	1.485	m	
220		1.470		17
$Ca(OH)_2$	1.442	1.450	w	..
$\bar{2}01$	1.447	1.455	v.w.	5

v.s. = very strong, s = strong, m = medium, w = weak, v.w. = very weak.

The rhombohedral lattice constants $\alpha = 43°50'$ and $a_{rh} = 5.11$ Å., and the hexagonal lattice constants $c = 14.1$ and $a = 3.91$, as given by Dehlinger, do not agree with his own experimental data, nor are they even compatible with each other. Dehlinger pointed to the agreement between the rhombohedral angle, calculated by him for the larger unit cell, containing four molecules of calcium cyanamide, with a figure (74°), determined on single crystals under the microscope by C. H. Warren.[4] However, two different angles were erroneously compared by Dehlinger, namely, the angle between the rhombohedral axes of the larger cell, calculated by him as 73°, and the cleavage angle of 74°, measured by Warren. Actually, 68°, as measured by Warren for the angle of the rhombohedral axes of the cleavage rhombohedron would have been the figure with which to compare Dehlinger's figure 73°, with no agreement to be observed. With Warren's figure 68°, however, the angle 68°15', as calculated from the data of the present investigation, agrees very well, and the

* Vanadium Corp. of America, New York, N. Y.

(1) H. H. Franck, M. A. Bredig, G. Hoffmann and Kin-Hsing Kou, *Z. anorg. allgem. Chem.*, **232**, 61, 75 (1937).

(2) U. Dehlinger, *Z. Krist.*, **65**, 286 (1927).

(3) J. D. Hanawalt, H. W. Rinn and L. K. Frevel, *Ind. Eng. Chem., Anal. Ed.*, **30**, 479 (1938).

(4) C. H. Warren, *Am. J. Science*, [5] **2**, 120 (1921).

same is true for the cleavage angle of 74°15′ (this paper) and 74° (Warren).

The structure of calcium cyanamide is entirely analogous to that of sodium azide, NaN_3, determined by S. B. Hendricks and L. Pauling[5] and confirmed recently by M. Bassière.[6] The cations occupy the positions 000, the carbon atoms the positions $\frac{1}{2}\frac{1}{2}\frac{1}{2}$, and the nitrogen atoms the positions ± (*uuu*). The parameter *u* was assumed by Dehlinger as 0.37. With this figure, the distance C–N was calculated by Dehlinger as 1.59 Å., while actually the calculation from his own data, $14.1\cdot(0.50 - 0.37)$, should have yielded 1.84 Å., an impossibly large value, compared with 1.17 Å. for the distance N–N, in sodium azide. A comparison of the intensities, as observed in the present investigation, with those calculated by using ionic scattering factors, as compiled by James and Brindley,[7] yields the parameter $u = 0.422 \pm 0.005$. The distance C–N becomes 1.16 ± 0.08 Å., and the distance Ca–N 2.49 ± 0.04 Å., which compares with 2.48 Å. for Na–N in sodium azide.

No attempt was made to refine the discussion of the X-ray intensities as much as to find the possible asymmetry in the position of the two nitrogen atoms, and to thereby determine whether the cyanamide anion has the carbodiimide structure —N=C=N— or the true cyanamide form =N—C≡N. The agreement between the values of the distances in the azide anion, in sodium azide, as obtained by M. Bassière[6] through a discussion of the X-ray intensities, 1.10 and 1.26 Å., and those previously determined for the azide radical in cyanogen azide $(CN)N_3$ by E. Knaggs,[8] 1.11 and 1.26 Å., and in methyl azide by Brockway and Pauling,[9] has not been supported by the former with sufficiently convincing proof. The asymmetry in the N_3^- ion is, in fact, highly improbable.[10] It also seems quite doubtful whether the accuracy of the method employed was sufficient to determine, from the agreement of the X-ray intensities, as observed and as calculated, the asymmetry in the distances C–O (1.13 Å.) and C–N (1.21 Å.),[11] in sodium isocyanate, NaNCO, another compound, isomorphous with calcium cyanamide.

The thanks of the author are due to Professor L. Thomassen for the permission to use the X-ray equipment of the Department of Chemical and Metallurgical Engineering of the University of Michigan.

(5) S. B. Hendricks and L. Pauling, THIS JOURNAL, **47**, 2904 (1925).

(6) M. Bassière, *Compt. rend.*, **208**, 659 (1939).

(7) "Internat. Tabl. Determ. Cryst. Struct.," **II**, 571 (1935).

(8) E. Knaggs, *Proc. Roy. Soc.* (London), **A150**, 576 (1935).

(9) Brockway and Pauling, *Proc. Nat. Acad. Sci.* (Wash.), **19**, 860 (1933).

(10) The author is indebted to Professor K. Fajans, University of Michigan, for the private communication that the polarization theory of chemical binding leads to a symmetrical structure for ions such as N_3^- and CN_2^{2-}, while asymmetry is expected in the group N_3 when connected by bonds of small polarity with other atoms or radicals, as in HN_3, $(CN)N_3$, or CH_3N_3.

(11) M. Bassière, *Compt. rend.*, **206**, 1309 (1938).

RECEIVED MARCH 30, 1942

Photoactivation of Adsorption of Hydrogen on Thorium Oxide[1]

BY A. LUYCKX,[2] J. BODART AND G. RENS

It is known[3] that activated adsorption of hydrogen requires an energy of activation. The hydrogen so adsorbed is supposed to be dissociated into atoms, this dissociation occurring on the surface of the catalyst during the adsorption. Confirmation of this assumption has been sought in the following experiments.

The temperature at which activated adsorption is observable is often several hundred degrees higher than the temperature of van der Waals adsorption, notably on oxide surfaces. We have sought to employ light instead of heat as the activating agent. In earlier work it has been found[4] that adsorption of certain solutes in solution could be photoactivated. Also, at 230°, the reaction between nitrous oxide and hydrogen in presence of boron nitride phosphors indicated a slight rise in reaction rate when irradiated with ultraviolet light. Other reactions on several catalysts and at different temperatures gave negative results.

We have studied the photo-activation of hydrogen adsorption on various catalysts with positive results which we shall illustrate with thorium oxide, prepared by calcination of the nitrate. The oxide so obtained was heated and evacuated in a quartz vessel at 700° for several hours. Electro-

(1) The original version of this Note was received from the authors on August 13, 1941, and was accepted by the Editorial Board subject to some revisions which were embodied in a revised manuscript kindly prepared by Professor Hugh S. Taylor, which was sent to the authors on November 13, 1941, for their approval. Since it has proved impossible to get any word from occupied Belgium where the authors reside, it has seemed wisest, in order to avoid any further delay, to publish this present version now, in spite of the fact that the authors have had no opportunity to express their approval or disapproval of it.—THE EDITOR

(2) Associé du Fonds National Belge de la Récherche Scientifique.

(3) See "Catalysis," by G. M. Schwab, H. S. Taylor and R. Spence, D. Van Nostrand Co., New York, N. Y., 1937.

(4) See A. Hedvall, *Nature*, **143**, 330 (1939).

lytic hydrogen was introduced to the cold adsorbent, to give a pressure of 2 mm. During the first seconds following the introduction of hydrogen a slight fall in pressure was observed owing to van der Waals adsorption.

Irradiation of the system, after the pressure becomes constant, with the light from a mercury lamp produces a regular and continuous decrease of pressure, which could be followed by means of a McLeod gage, during several hours. In favorable cases an irradiation of ten hours results in practically complete hydrogen adsorption. Further additions of hydrogen are adsorbed upon irradiation. Rates up to 1 cc. of hydrogen at 2.3 mm. pressure per minute, for 40 sq. cm. of irradiated surface and 18 g. of ThO_2, have been observed. In one case, more than 8 cc. of hydrogen at N. T. P. was taken up by 100 g. of thoria. Thermally activated adsorption on our thoria sample was observable at 420°.

Adsorption is only observable with the irradiation from a cold mercury lamp, which indicates that resonance radiation is involved and that it is atomic hydrogen which is taken up by the adsorbent. The formation of atomic hydrogen may occur in the gas phase by the Frank–Cario mechanism with excited mercury atoms. We can also imagine molecules adsorbed on the surface by van der Waals forces being dissociated by transference of energy from mercury atoms. We cannot yet decide between these alternatives. Comparison with the rate of reduction of tungstic oxide in the Frank–Cario experiment suggests a diffusion of atomic hydrogen to the surface.

At 20–30 mm. pressure no photoactivation is measurable. After subsequent lowering of the pressure to 2 mm., photoactivation is again observable, but at one-half to one-third the normal rate. We interpret this as due to an adsorbed molecular layer of hydrogen protecting the adsorption centers. Lowering the pressure does not uncover all such centers. Complete evacuation is necessary. When this is done the normal rate of photoactivated adsorption at 2 mm. pressure is found.

After many days of alternate irradiation and evacuation at 700° the rate of adsorption slowly decreases and falls to one-tenth of its initial value. If after evacuation at 700° air is introduced at atmospheric pressure and room temperature and then evacuated at room temperature, introduction of hydrogen at 2 mm. pressure followed by resonance irradiation restores the initial rate of hydrogen adsorption. The presence of oxygen on the surface of the catalyst is thus essential. This is confirmed by the observation that thoria samples heated in hydrogen to 700–800° and then evacuated at this temperature do not show hydrogen adsorption on irradiation unless oxygen is again introduced. Analysis of the gas desorbed after either thermal or photoactivated adsorption shows the presence of oxygen only.

We have found an increase in the rate of thermally activated adsorption of hydrogen by chromium oxide and by reduced nickel when a certain amount of oxygen was introduced to the adsorbent.

Hedvall uses the term photoactivation of adsorption when the light is absorbed by the crystals and their activity is changed by the irradiation. We must consider, however, the cases in which adsorbent and gas are both excited by irradiation or the gas alone. In practice it will not be easy to decide between the several processes. We use the general term photo-activation of adsorption when we can measure an adsorption of gas by a surface owing to light irradiation.

INSTITUT D'AREMBERG
UNIVERSITÉ DE LOUVAIN
LOUVAIN, BELGIUM

RECEIVED MAY 2, 1942

On the Structure of Fucosterol

BY H. B. MACPHILLAMY

Fucosterol was first isolated from the alga, *Fucus vesiculosus*, by Heilbron, Phipers and Wright.[1] These workers showed that the sterol had the empirical formula $C_{29}H_{48}O$ and that it was a bond isomer of stigmasterol. They further stated that both double bonds were situated in the nucleus, since treatment with ozone failed to give ethylisopropylacetaldehyde. Additional evidence indicated the absence of a conjugated system, while the ease with which stigmastanol was formed on hydrogenation showed the lack of any "inert" double bonds. Later it was proved that one of the ethylenic linkages occupied the 5-6 position.[2] In view of Sobotka's[3] suggestion that the second double bond might be located in the 11–12 position, which would render the sterol a suitable starting material for the synthesis of cortical

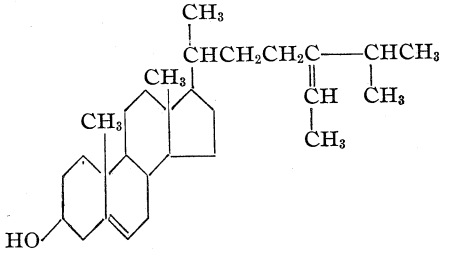
(1) I. M. Heilbron, R. F. Phipers and H. R. Wright, *Nature*, **133**, 419 (1934); *J. Chem. Soc.*, 1572 (1934).

(2) D. H. Coffey, I. M. Heilbron and F. S. Spring, *ibid.*, 738 (1936).

(3) H. Sobotka, "Chemistry of the Sterids," Williams and Wilkins Company, Baltimore, Md., 1938, p. 240.

hormones, the complete elucidation of its structure seemed desirable.

It was decided, first of all, to reinvestigate the ozonization reaction. The failure of Heilbron, *et al.*,[1] to isolate ethylisopropylacetaldehyde cannot be considered conclusive evidence for the lack of unsaturation in the side chain, since the later work of this author on zymosterol[4] has shown that side chain double bonds in sterols may occupy positions other than 22–23. The result of our study showed that fucosterol indeed presents a similar case. In two separate experiments acetaldehyde could be isolated as the *p*-nitrophenylhydrazone from the products of the ozonolysis. The yield of aldehyde was over 30% in both cases, which precludes the possibility that it may have been derived from an impurity or formed in a secondary reaction. Since position 24–28 for the double bond in question is the only one which would account for the formation of acetaldehyde by ozonolysis, is it suggested that the structure of fucosterol is best represented by the accompanying formula.



Experimental

Isolation of Fucosterol.—The material used for this work was obtained from a quantity of *Fucus vesiculosus* gathered along the New Jersey coast. About 22.5 kg. of the dried sea weed was ground and percolated thoroughly with ether. After evaporation of the solvent 650 g. of extracted material remained. The residue was saponified overnight at room temperature and on purification yielded 40 g. (0.18%) of sterol. Several recrystallizations from methanol gave pure fucosterol, the physical properties of which agreed quite closely with those given by Heilbron,[1] as shown in the following table

	MacPhillamy M. p., °C.	$[\alpha]_D$	Heilbron M. p., °C.	$[\alpha]_D$
Sterol	124	−41	124	−38.4
Acetate	118	−45	118–119	−43.8
Benzoate	121	−16	120	..

Ozonization of Fucosterol.—A finely divided suspension of 1.15 g. of fucosterol in 12 cc. of glacial acetic acid was ozonized for one-half hour at an ozone concentration of about 2%, the exit gases being led through 50 cc. of water. Over-ozonization had to be avoided as it results in low if not negligible yields. The reaction mixture, combined with the wash water, was distilled through an efficient fractionating column. After approximately 20 cc. of distillate had been collected, the receiver was removed, and a solution of 500 mg. of recrystallized *p*-nitrophenylhydrazine in 20 cc. of 50% acetic acid was gradually added. The hydrazone crystallized out immediately. It was filtered, washed with cold water, and after drying weighed 175 mg. (33.6%); m. p. 124–125°. After three recrystallizations from dilute alcohol the substance had a constant m. p. of 128–129°. The melting point of a mixture with authentic acetaldehyde *p*-nitrophenylhydrazone showed no depression.

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.58; H, 4.89; N, 23.69.

The author wishes to thank Dr. O. Wintersteiner for his interest and advice during this investigation.

THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH
DIVISION OF ORGANIC CHEMISTRY
NEW BRUNSWICK, N. J. RECEIVED MAY 20, 1942

(4) B. Heath-Brown, I. M. Heilbron and E. R. H. Jones, *J. Chem. Soc.*, 1482 (1940).

Olefin Rearrangements. The Equilibrium of Olefins from Pinacolyl Alcohol[1]

BY ROBERT KINSEL SMITH

The dehydration of saturated alcohols and the attendant rearrangement of olefins formed during the reaction have long been investigated experimentally. The mechanisms of these rearrangements have been studied intensively on the basis of experimental results. The absence of thermodynamical data has in general prevented the calculation of equilibrium constants for the ratios of different olefins obtained from a particular dehydration. Recently, thermal data have been published[2,3] concerning the heats of hydrogenation of 2,3-dimethyl-1-butene, 2,3-dimethyl-2-butene and 3,3-dimethyl-1-butene and the relative heat contents of 2,2-dimethylbutane and 2,3-dimethylbutane. These provide a basis for the calculation of the equilibrium mixture of these olefins produced in the dehydration of methyl-*t*-butylcarbinol. The equilibrium values for the ratios of the olefins obtained in this reaction are of importance because widely variant results are obtained through the use of different catalysts to effect the dehydration.

Meunier and Whitmore[4] dehydrated methyl-*t*-butylcarbinol with phosphoric acid on silica gel

(1) Original manuscript received August 7, 1941.

(2) (a) Dolliver, Gresham, Kistiakowsky and Vaughan, THIS JOURNAL, **59**, 831 (1937); (b) Kistiakowsky, Ruhoff, Smith and Vaughan, *ibid.*, **58**, 142 (1936).

(3) Rossini and Prosen, *ibid.*, **62**, 2250 (1940).

(4) Meunier and Whitmore, *ibid.*, **55**, 3721(1933).

at 350° and obtained 90% rearrangement. The products formed were 1.5% of *t*-butylethylene (I) which is the normal dehydration product, 34.5% of 2,3-dimethyl-1-butene (II) and 64% of 2,3-dimethyl-2-butene (III). Whitmore, Laughlin and Nash[5] passed (II) and (III) separately over the same catalyst and found 3% of (I), 31% of (II) and 61% of (III). This indicated that approximate equilibrium had been obtained.

Cramer and Glasebrook[6] dehydrated methyl-*t*-butylcarbinol over activated alumina at 350°. The results obtained by this procedure were greatly different from those obtained by Whitmore and co-workers with a more acidic catalyst.[4,5] Cramer and Glasebrook found alumina yielded 64.4% of (I), 27% of (II) and 8.6% of (III). When the more acidic aluminum sulfate was used as a catalyst, the proportions were 3.5% of (I), 34% of (II) and 62.5% of (III). These latter check closely with the results obtained with the phosphoric acid catalyst of Whitmore.[4,5]

Calculations.—The calculation of the equilibrium constant requires the experimental determination of the heat of reaction and the evaluation of the entropy change of the system.

The heats of hydrogenation and the heat of isomerization of the resulting saturated hydrocarbons as determined by the differences in their heat content provide a simple method for the evaluation of the heats of isomerization of the olefins. The values for the heats of hydrogenation of I, II and III have been found[2a,b] to be 30.341, 27.997 and 26.633 kcal./mole, respectively, at 355°K. The heat contents of 2,2-dimethylbutane and 2,3-dimethylbutane have been found[3] to be −2016 and −4095 cal., respectively, when compared to the heat content of normal hexane. In the subsequent calculations, the heat of isomerization has been assumed to remain essentially constant with change in temperature. This assumption is justified by the knowledge that the difference in the heat content of saturated isomeric hydrocarbons is little changed by temperature over the range involved here.

With these values, the complete calculation of the equilibrium constants is possible if the difference in entropy of the olefins is known. The entropies of (I) and (III) have been determined[7] through calorimetric measurements up to 298° K. The value for (II) was not found and thus estimations must be made to calculate the complete equilibria conditions.

The equation for the translational and rotational entropy of any molecule in the gas phase at a given temperature, T, and a pressure, P, may be expressed by

$$S = 8/2\,R \ln T - R \ln P + 3/2\,R \ln M + R/2 \ln ABC - R \ln \sigma + 265.35 \quad (1)$$

The products of the moments of inertia were calculated by the method of Eidinoff and Aston.[8] The ordinary atomic distances of C–H as 1.09 Å., C–C as 1.54 Å., and C=C as 1.33 Å. were used in the calculations with the angle C–C–C taken as 109°28′ and the C=C–C angle as 124°20′.

The entropy due to hindered rotation and internal rotation must be separately determined by Pitzer's method.[9] The expression which has been developed for the internal rotational entropy is

$$S_{i.r.} = R(-0.767 + 1/2 \ln T + 1/2 \ln I_r \times 10^{-40} - \ln n) - (S_f - S) \quad (2)$$

where I_r is the reduced moment of the two rotating groups, n is the number of potential minima and $(S_f - S)$ is determined by the potential barrier restricting rotation, the temperature, the reduced moment and n.

The potential barrier restricting rotation of a methyl group was assumed to be 3200 cal. except in the instances wherein a double bond was adjacent to the methyl group where the hindering potential was taken to be 2000 cal. The rotation of two alkyl groups about each other was assumed to have a potential barrier of 8500 cal. unless one of the carbons in the bond about which rotation was being considered has a double bond in which the potential was assumed to be 7500 cal.

The vibrational entropy involved has not been determined spectroscopically. A self-consistent method of approximating wave lengths was used and the results adjusted so that the final entropy of the compound agreed reasonably well with heat capacity data for the entropy of the gas at the boiling point. The approximations made are listed in Table I with values obtained for different molecular properties.

The entropy change from I to III is then 3.31 e. u. and the heat of isomerization is

$$-30{,}341 + 4095 - 2.016 + 26.633 = -1.629 \text{ kcal.} \quad (3)$$

(5) Whitmore, Laughlin and Nash, THIS JOURNAL, **56**, 1395 (1934).

(6) Cramer and Glasebrook, *ibid.*, **61**, 230 (1939).

(7) Parks, Shomate and Kennedy, *ibid.*, **60**, 1508 (1938).

(8) Eidinoff and Aston, *J. Chem. Phys.*, **3**, 379 (1935).

(9) Pitzer, *ibid.*, **5**, 46 (1937).

The free energy change is

$$\Delta F = -1629 - 3.31T \quad (4)$$
$$K_{623} = 20.1 \quad (4a)$$

The corresponding changes for II to III are

$$-27.997 + 26.633 = -1.664 \text{ kcal. and } -1.10 \text{ e. u.}$$
$$\Delta F = -1664 + 1.10 \quad (5)$$
$$K_{623} = 1.81 \quad (5a)$$

TABLE I

Assignment Compound	No.	Wave no. I	No.	Wave no. II	No.	Wave no. III
C—C—C	6	316	8	400	4	400
C—C=C	2	160	4	180	8	180
C—C—H	4	640	4	640		
C—C	4	950	4	900	4	900
At.....	315°K.				345°K.	
$S_{vib.}$	14.88				21.30	
$S_{int.\ rot.}$	5.75				5.60	
$S_{rot.\ trans.}$	63.13				61.10	
Total S	83.76				88.00	
Obs. S^a	83.92				88.00	
C_v (gas)$_{calcd.}$	34.7				32.3	
C_v (liq)$^b_{obs.}$	41.8				39.2	
At.....	673°K.		673°K.		673°K.	
$S_{vib.}$	31.59		35.88		37.86	
$S_{int.\ rot.}$	4.65		5.18		4.4	
$S_{trans.}$	68.58		68.22		65.92	
Total S	104.87		109.28		108.18	

[a] Observed entropies[7] extrapolated to boiling point by continuing C_v curves from 298°K. and adding 29.6 e. u.

[b] According to Kincaid and Eyring, *J. Chem. Phys.*, **6**, 620 (1938) the difference between C_v(liq.) and C_v(gas) is normally between 6 and 7 cal./mole deg. for complex materials. The differences observed here are 7.1 for I and 6.9 for III, which is quite reasonable. C_v(liq.) was found by using the value from entropy data[7] and subtracting an approximate factor obtained from the Landolt–Börnstein "Tabellen" in the following manner:

$$C_p - C_v = T\alpha^2 V/\beta = 3 \text{ cal./mole deg.}$$

The constant for the same reaction at 350° as calculated from the data of Whitmore and coworkers[5] was 20.3 for the ratio of III to I and 1.96 for the ratio of III to II. The results of Cramer and Glasebrook[6] were 18 and 1.81, respectively.

Discussion.—The results obtained by these methods cannot be regarded as final inasmuch as the calculations involving the vibrational entropy are not exact. However, assuming that the internal potential barriers for rotation are those assigned, little change in the relative entropy would be observed when the vibrational frequencies are consistently changed. The agreement of the calculated and observed entropy and the reasonable approximation of the specific heat of the perfect gas at the boiling point indicate that the assigned vibrations must be of the right order of magnitude.

Changes in the hindering potentials of the various groups by 500 cal. would change the difference in entropy by no more than 0.1 e. u. for I to III and even less for II to III.

The values for the vibrational frequencies were assigned by comparison of the molecules involved with similar olefins reported in Kohlrausch, "Der Smekal–Raman Effekt" and data in Hibben. The frequency assignments were made on the basis of similar work done on methylacetylene.[10]

Conclusion.—The rearrangement of these olefins using acidic materials as catalysts has been found to proceed in agreement with estimated thermodynamic values. The comparison of the dehydrations using acidic catalysts and those which do not furnish hydrogen ions indicates that the latter catalysts act merely in the removal of an equivalent of a water molecule with no effect upon the isomerization of the compounds formed. On the other hand, the catalytic action of hydrogen ion in the isomerization of olefins is definitely indicated.

The author wishes to thank Dr. F. C. Whitmore and Dr. J. G. Aston of the Pennsylvania State College and Dr. H. Eyring of this Laboratory for their assistance.

(10) Bryce Crawford, *J. Chem. Phys.*, **7**, 140, 555 (1939).

FRICK CHEMICAL LABORATORY
PRINCETON UNIVERSITY
PRINCETON, NEW JERSEY RECEIVED MARCH 16, 1942

The Utilization of Aliphatic Nitro Compounds. IV. Nitrodiols (Nitroglycols) Prepared from Simple Aldehydes[1]

BY C. AUSTIN SPRANG[2] WITH ED. F. DEGERING

In a recent paper[3] the authors discussed the condensation of nitroparaffins with aldehydes to form nitroalcohols. In a continuation of this work nitromethane has been condensed with aldehydes to form nitrodiols. Any primary nitroparaffin condenses with formaldehyde to form a nitrodiol,[4] but only nitromethane condenses with

(1) Presented before the Division of Organic Chemistry at the Memphis meeting of the American Chemical Society, in April, 1942. Abstracted from a thesis presented to the Faculty of the Graduate School of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, in June, 1941.

(2) Present address: Emery Industries, Inc., Cincinnati, Ohio.

(3) Sprang and Degering, THIS JOURNAL, **64**, 1063 (1942).

(4) Pauwels, *Rec. trav. chim.*, **17**, 27 (1898).

other aldehydes to form dihydric alcohols.[5,6] Sodium hydroxide is a suitable catalyst for condensations with formaldehyde but for other condensations the only catalysts which have been used successfully have been mild alkalies[7] such as calcium hydroxide or sodium or potassium carbonates. A large excess of the aldehyde is used to force the reaction as nearly to completion as possible and this is subsequently removed by low temperature distillation.

Procedure

4-Nitro-3,5-heptanediol.—The flask is charged with 61 g. (1 mole) of nitromethane, 50 ml. of 95% ethanol, and 3 g. of potassium carbonate. While stirring vigorousiy, 130 g. of propanal is added dropwise. External cooling is used to keep the temperature between 28–35°. A small amount of water is added to give a homogeneous solution which is left for four days at room temperature. The potassium carbonate is neutralized and the salt and aqueous layer removed. The solution is then stripped overnight with the water pump at room temperature to remove volatile substances. The salt, which precipitates, is removed by filtration and the stripping continued at room temperature at 1.5 mm. The residue is chilled to complete crystallization and then filtered (yield, about 50%) and finally recrystallized from a butanal–toluene mixture.

Unsymmetrical nitrodiols are prepared by first forming the nitroalcohol[2,6] from nitromethane and the more complex of the aldehydes and then treating this product with the second aldehyde in the presence of potassium carbonate as described above.

Nitrodiols are white, crystalline substances, soluble in water or alcohol, but insoluble in hydrocarbon solvents. Some data for three nitrodiols are listed in the table.

NITRODIOLS

Compound	Melting point, °C.	Empirical formula	Carbon or nitrogen, % Calcd.	Found
4-Nitro-3,5-heptanediol	97	$C_7H_{15}NO_4$	47.46	47.30[a]
3-Nitro-2,4-hexanediol	94	$C_6H_{13}NO_4$	8.58	8.47[b]
8-Nitro-7,9-pentadecanediol	66–67	$C_{15}H_{31}NO_4$	4.87	4.74[b]

[a] Percentage carbon by the "Wet Method," Pollard and Forsee, *Ind. Eng. Chem., Anal. Ed.*, **7**, 77 (1935).

[b] Percentage nitrogen by "Kjeldahl," Harte, *ibid.*, **7**, 432–3 (1935).

Because of the presence of three functional groups, these compounds are quite reactive and have unusual possibilities in organic synthesis.

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, INDIANA

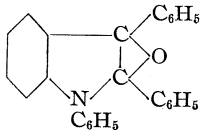
RECEIVED FEBRUARY 17, 1942

(5) Schmidt and Wilkendorf, *Ber.*, **55**, 316 (1922).
(6) Mousset, *Rec. trav. chim.*, **21**, 95 (1902).
(7) Hass and Vanderbilt, *Ind. Eng. Chem.*, **32**, 34 (1940).

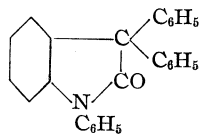
The Reaction of Phenylmagnesium Bromide with N-Phenylisatin

BY WARD C. SUMPTER

Stollé[1] obtained two products from the reaction of N-phenylisatin with excess phenylmagnesium bromide: a colorless compound melting at 161° and a yellow compound melting at 238°. Stollé described the colorless compound as 1,2,3-triphenylindole-oxide-2,3 (I). No formula was assigned to the yellow compound.

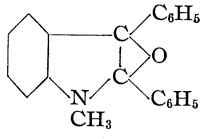


I

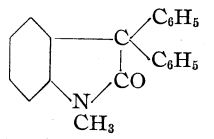


II

Myers and Lindwall[2] found that 2,3-diphenyl-1-methylindole-oxide-2,3 (III) is a yellow compound exhibiting greenish fluorescence and that a second colorless compound (IV) is obtained along with III when N-methylisatin reacts with excess phenylmagnesium bromide.



III



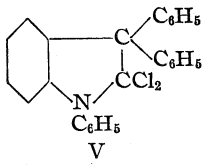
IV

In the light of these facts it seemed likely that Stollé's characterization was in error and that the colorless compound (m. p. 161°) was compound II and that the yellow compound (m. p. 238°) was in reality compound I.

To test this conclusion the experimental work of Stollé has been repeated. Analyses of both compounds are in agreement with the formula $C_{26}H_{19}ON$. That the colorless compound (m. p. 161°) is in reality 1,3,3-triphenyloxindole (II) was confirmed by its synthesis from 3,3-dichloro-1-phenyloxindole, benzene and aluminum chloride. The yellow compound exhibits green fluorescence in solution and is analogous in color and fluorescence to compound III of Myers and Lindwall. Accordingly it seems reasonable to assign structure I to the yellow compound (m. p. 238°).

Treatment of compound II with phosphorus pentachloride yields 2,2-dichloro-1,3,3-triphenyl-di-hydroindole (V).

(1) Stollé, Hecht and Becker, *J. prakt. Chem.*, **135**, 358 (1932).
(2) Myers and Lindwall, THIS JOURNAL, **60**, 2153 (1938).



V

Experimental Part

1,3,3-Triphenyloxindole (II) and 1,2,3-Triphenylindole-oxide-2,3 (I).—N-phenylisatin (0.025 mole) was added slowly, over a period of one hour, to a solution of phenylmagnesium bromide (0.125 mole) in 150 ml. of dry ether. After addition of the last portion the mixture was heated at the boiling temperature for one hour and then poured into a mixture of ice and concentrated sulfuric acid. The ether layer was separated, dried over anhydrous sodium sulfate and the ether removed under reduced pressure. The yellow mass which was obtained was crystallized from ethyl alcohol. Repeated crystallization yielded 5.75 g. of colorless plates; m. p. 161°, and a small yield of yellow crystalline powder, m. p. 238°. The yellow compound exhibited marked fluorescence in solution.

Anal. of compound m. p. 161° (II). Calcd. for $C_{26}H_{19}ON$: N, 3.87. Found: N, 3.84, 3.67. *Anal.* of compound m. p. 238° (I). Calcd. for $C_{26}H_{19}ON$: N, 3.87. Found: N, 3.87.

Compound II. By the Friedel–Crafts Reaction.—Powdered anhydrous aluminum chloride (0.05 mole) was added slowly to a solution of 3,3-dichloro-1-phenyloxindole (0.01 mole) in 40 ml. dry benzene and the reaction mixture heated for one hour at 60°. The benzene was removed under reduced pressure and the residue treated with ice and hydrochloric acid. The entire reaction mixture was then extracted with ether and the ether removed under reduced pressure after decolorizing with charcoal and drying over anhydrous sodium sulfate. The product was purified by crystallization from ethyl alcohol from which it separated as colorless plates, m. p. 161°. Mixed melting points with samples of the colorless compound from the Grignard reaction showed no depression.

2,2-Dichloro-1,3,3-triphenyl-di-hydroindole (V).—A mixture of 2 g. of 1,3,3-triphenyloxindole (II) with 10 g. of phosphorus pentachloride was heated for four hours at 150°, the mixture cooled and water added, the residue collected and crystallized from ethyl alcohol from which it separated as colorless prisms; m. p. 200°.

Anal. Calcd. for $C_{26}H_{19}NCl_2$: N, 3.36. Found: N, 3.36, 3.33.

This work has been supported by a research grant (A.A.A.S.) received through the Kentucky Academy of Science.

DEPARTMENT OF CHEMISTRY
WESTERN KENTUCKY STATE TEACHERS COLLEGE
BOWLING GREEN, KY. RECEIVED MAY 11, 1942

The Preparation of *m*-Hydroxybenzoic Acid

BY H. E. UNGNADE AND A. S. HENICK

m-Hydroxybenzoic acid has been prepared by fusion of *m*-chlorobenzoic acid with alkali,[1] by diazotization of *m*-aminophenol, subsequent replacement with the cyano group and hydrolysis,[2] by alkaline fusion of the sodium *m*-sulfonate of benzoic acid,[3] and by action of nitrous acid on *m*-aminobenzoic acid, followed by hydrolysis of the diazonium salt.[4]

It has been found in this Laboratory that the acid can be prepared conveniently from methyl *m*-aminobenzoate. The ester is used rather than the acid since methyl *m*-nitrobenzoate is readily obtained in a pure state, is easily reduced, and is an intermediate in the preparation of *m*-nitrobenzoic acid.[5]

The reduction of methyl *m*-nitrobenzoate may be carried out catalytically with Raney nickel either under low pressure or more rapidly under high pressure and at a slightly elevated temperature. The yields in the reduction are 93–95%.

Diazotization and hydrolysis of methyl *m*-aminobenzoate give *m*-hydroxybenzoic acid directly in yields of 80–87%.

Experimental

Methyl *m*-Aminobenzoate.—Methyl *m*-nitrobenzoate (20 g.)[6] in ethyl acetate (100 cc.) was reduced with hydrogen at 50 lb. in the presence of Raney nickel (3 g.). The theoretical amount of hydrogen was absorbed in twelve hours. A 100-g. sample of the nitro compound in 100 cc. of methanol could be reduced at 50° in two and one-half hours at 2000–3000 lb. with Raney nickel (3 g.). After removal of catalyst and solvent the product was dried in ether solution. The ether was distilled off and the residual oil distilled under reduced pressure. The pure methyl *m*-aminobenzoate boiled at 152–153° (11 mm.); f. p. 37° (from the cooling curve); yield 93–95%.

Acetyl Derivative.—The acetyl derivative was obtained by refluxing the amine for twenty minutes with acetic anhydride. It melted at 136–137° after crystallization from water.

Anal. Calcd. for $C_{10}H_{11}O_3N$: C, 62.17; H, 5.70. Found: C, 62.16; H, 5.87.[7]

***m*-Hydroxybenzoic Acid.**—Methyl *m*-aminobenzoate (50 g.) was dissolved in a solution of 75 cc. of concentrated sulfuric acid and 150 g. of ice. The solution was then treated with 100 g. of ice, cooled to 0° and diazotized by the addition of 25 g. of sodium nitrite in 60 cc. of water. The resulting diazonium salt solution was added all at once to a hot solution of 100 g. of anhydrous sodium sulfate and 40 cc. of concentrated sulfuric acid in 400 cc. of water. The mixture was refluxed for three hours. Then the reaction mixture was boiled with norite, filtered, and allowed

(1) Dembey, *Ann.*, **148**, 222 (1868).

(2) Ahrens, *Ber.*, **20**, 2953 (1887).

(3) Offermann, *Ann.*, **280**, 6 (1894); Graebe and Kraft, *Ber.*, **39**, 2512 (1906).

(4) Fischer, *Ann.*, **127**, 148 (1863); Bryd, *Roczniki Chem.*, **7**, 436 (1927); *Chem. Abs.*, **22**, 2372 (1928).

(5) "Org. Syntheses," Coll. Vol. I, 2nd ed., 392 (1941).

(6) "Org. Syntheses," Coll. Vol. I, 2nd ed., 372 (1941).

(7) Semi-microanalysis by E. Milberger.

to crystallize. The acid was filtered with suction and dried *in vacuo;* yield 37–41 g. Recrystallization from water gave a nearly white product melting at 199–200°.

CHEMISTRY DEPARTMENT
UNIVERSITY OF MISSOURI
COLUMBIA, MISSOURI

RECEIVED APRIL 15, 1942

Identification of Amides through the Mercury Derivatives

BY JONATHAN W. WILLIAMS, WILLIAM T. RAINEY, JR., AND ROBERT S. LEOPOLD

In characterizing amides the most general procedure is hydrolysis, followed by identification of the two products. With unsubstituted amides, solid derivatives may be prepared directly by reaction with phthalyl chloride.[1] Another procedure, the use of which obviates hydrolysis, is the preparation of the mercury derivative. This procedure is simple and gives satisfactory derivatives for a large number of unsubstituted amides.

The reaction represented by the equation

$$2R{-}\underset{\underset{O}{\|}}{C}{-}NH_2 + HgO \longrightarrow (R{-}\underset{\underset{O}{\|}}{C}{-}NH)_2Hg + H_2O$$

was first reported in 1852 by Dessaignes,[2] who prepared the mercury derivatives of benzamide and acetamide. Mercury derivatives of several other amides have since been described.[3]

Two general procedures were investigated for the preparation of these mercury compounds. Procedure 1, patterned after the work of Dessaignes,[2] consisted of bringing a mixture of yellow mercuric oxide and excess amide to the melting point of the amide, maintaining that temperature and adding more mercuric oxide in small portions until no further reaction occurred, and then purifying the product by recrystallization from ethanol or by leaching with hot ethanol. This process is the more generally applicable one, and the one that must be used with aliphatic amides. Procedure 2, based on the process described by Mann and Saunders,[4] consisted of refluxing about 0.04 mole of amide with excess (around 0.025 mole) yellow mercuric oxide in 50 ml. of 95% ethanol for one hour, filtering while hot, cooling, removing the crystalline mercury derivative, and purifying by recrystallization or leaching.

(1) Evans and Dehn, THIS JOURNAL, **51**, 3651 (1929).

(2) Dessaignes, *Ann.*, **82**, 231 (1852).

(3) For summary and complete references, see Whitmore, "Organic Compounds of Mercury," Chemical Catalog Company (Reinhold Publishing Corporation), New York, N. Y., 1921, pp. 159–161.

(4) Mann and Saunders, "Practical Organic Chemistry," Longmans, Green and Company, London, 1938, p. 79.

In Table I are listed the melting points and mercury analyses[5–7] of the compounds successfully prepared. Due to low solubility in boiling ethanol, the purification of the mercury derivatives of *p*-anisamide and *m*-chlorobenzamide must be accomplished by leaching.

TABLE I

Amide	M. p., °C. (uncor.)	M. p. of mercury derivative, °C. (uncor.)	Mercury, % Calcd.	Found	
Acetamide	82	196–197	..	..	..
Propionamide	79	201	58.2	57.8	58.5
Butyramide	115	222–224	53.8	53.3	53.4
Benzamide	128	222	45.5	45.1	45.2
m-Chlorobenzamide	134	245	39.2	39.0	38.6
p-Chlorobenzamide	178	258	39.2	38.9	39.1
o-Bromobenzamide	155	242	33.5	33.5	..
m-Bromobenzamide	155	235	33.5	33.2	33.2
p-Bromobenzamide	191	266	33.5	33.1	33.5
o-Toluamide	158	196	42.6	42.4	42.5
m-Toluamide	94	200	42.6	43.1	42.3
p-Toluamide	166	260	42.6	42.5	..
o-Anisamide	128	241	40.1	39.8	40.3
p-Anisamide	167	222	40.1	39.9	40.3
Salicylamide	139	190	42.4	42.7	..

Unsuccessful attempts were made to prepare the mercury derivatives of isovaleramide, stearamide, *m*-anisamide and benzenesulfonamide. In the first two cases, decomposition occurred at the temperature used, making isolation of the mercury derivative impossible. With the latter two substances, reaction occurred readily, but the products obtained could not be rendered analytically pure.

Experimental

Procedure 1.—In a test-tube were placed 1.5 g. of the amide and 0.5 g. of yellow mercuric oxide. Using a small flame, the mixture was heated at the melting point of the amide until all mercuric oxide had reacted (disappearance of color) and the water vapor had been dispelled. More mercuric oxide was then added in small portions until no more would react. If an excess of mercuric oxide was obtained, enough of the amide to react with it was added and the yellow color removed completely. The melt was cooled somewhat, then taken up in the minimum amount of boiling ethanol and allowed to cool. The crystals were filtered and washed with cold ethanol or ether. Considerable variations were found in the solubilities of the mercury derivatives in alcohol. The derivatives of aliphatic amides were quite soluble, even in cold ethanol. On the other hand, the derivatives of *p*-anisamide, *m*-chlorobenzamide and benzenesulfonamide were quite insoluble in

(5) Rauscher, *Ind. Eng. Chem., Anal. Ed.*, **10**, 331 (1938).

(6) Shriner, "Quantitative Analysis of Organic Compounds," Edwards Brothers, Ann Arbor, Mich., 1938, p. 31.

(7) Shukis and Tallman, *Ind. Eng. Chem., Anal. Ed.*, **12**, 123 (1940).

boiling ethanol, and were best purified by leaching out the unreacted amide with boiling ethanol.

Procedure 2.—This process was found to be satisfactory for amides whose mercury derivatives were soluble in hot ethanol, insoluble in cold. It was used successfully with benzamide, *p*-chlorobenzamide, the bromobenzamides, the toluamides, *o*-anisamide and salicylamide. Five grams of yellow mercuric oxide and 4 g. of amide were added to 50 ml. of 95% ethanol, the mixture refluxed for one hour, filtered while hot through a fluted filter, chilled in an ice-bath, and the crystals removed by suction. Purification, where necessary, was accomplished as in Procedure 1.

VENABLE CHEMICAL LABORATORY
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, N. C. RECEIVED APRIL 23, 1942

Crystalline Xylitol

BY M. L. WOLFROM AND E. J. KOHN

Fischer[1] and Bertrand[2] prepared xylitol as a sirup in 1891 by the sodium amalgam reduction of *d*-xylose. Xylitol has been prepared subsequently by other investigators but, to our knowledge, no record of its crystallization has appeared in the literature. We wish to report that the crystallization of xylitol now has been effected in this Laboratory. The xylitol was prepared by the high-pressure catalytic reduction of highly purified *d*-xylose and the crystalline reduction product was characterized by elementary analysis, behavior with periodate and by the preparation of two known crystalline derivatives. The crystals were anhydrous, low-melting (61°) and hygroscopic.

Experimental

A solution of 300 g. of highly purified *d*-xylose in 750 cc. of water containing 60 g. of a nickel catalyst supported on kieselguhr was reduced in a steel shaking autoclave (American Instrument Company) at an initial hydrogen pressure of 1700 lb. per sq. in. (113 atm.) at 30°. A maximum temperature of 150° at a pressure of 2400 lb. per sq. in. (160 atm.) was attained in one hour and maintained for an additional four hours. The catalyst was removed from the cooled solution by filtration followed by treatment with an excess of hydrogen sulfide and by heating at 55° with decolorizing charcoal. The clear sirup obtained on solvent removal below 50° under reduced pressure, crystallized on standing for some weeks under absolute ethanol and at icebox temperature; yield 255 g. Pure material was obtained on recrystallization from anhydrous methanol; m. p. 61–61.5° (cor.), optically inactive (H_2O, D line of sodium). The hygroscopic, crystalline product was very soluble in water and was fairly soluble in hot methanol. It did not reduce boiling Fehling solution.

Anal. Calcd. for $C_5H_{12}O_5$: C, 39.47; H, 7.95. Found: C, 39.43; H, 7.85. Sodium periodate analysis[3]: moles periodate consumed, 4.0 (calcd., 4); moles formic acid formed, 2.8 (calcd., 3); moles formaldehyde formed,[4] 1.8 (calcd., 2).

The crystalline substance was further characterized by the preparation of two previously known crystalline derivatives, the pentaacetate[5] (m. p. 62.5–63°, cor.) and the dibenzylidene derivative[6] (m. p. 187.5–188°, cor.). Hockett and Hudson[5] record 61.5–62.5° (cor.) as the melting point of xylitol pentaacetate. Lobry de Bruyn and Alberda van Ekenstein[6] record 175° as the melting point of dibenzylidene-xylitol but previous experience in this Laboratory with sirupy xylitol preparations has indicated the higher melting point of 187.5–188° (cor.).

(1) E. Fischer and R. Stahel, *Ber.*, **24**, 538 (1891).
(2) G. Bertrand, *Bull. soc. chim.*, [3] **5**, 554 (1891).
(3) R. M. Hann, W. D. Maclay and C. S. Hudson, THIS JOURNAL, **61**, 2432 (1939).
(4) Determined by the dimedon method as per D. Vorländer, *Z. anal. Chem.*, **77**, 321 (1929).
(5) R. C. Hockett and C. S. Hudson, THIS JOURNAL, **57**, 1753 (1935).
(6) C. A. Lobry de Bruyn and W. Alberda van Ekenstein, *Rec. trav. chim.*, **18**, 151 (1899).

CHEMICAL LABORATORY
THE OHIO STATE UNIVERSITY
COLUMBUS, OHIO RECEIVED APRIL 3, 1942

Nitrovinylnaphthalene

BY DAVID E. WORRALL AND ABRAHAM TATILBAUM

Since α,β-unsaturated compounds containing a naphthalene group have not as yet been described, it appeared worth while to prepare 2-(α-nitrovinyl)-naphthalene and some of its derivatives.

2-(α-Nitrovinyl)-naphthalene.—A condensation of 0.1 g. mole each of β-naphthaldehyde and nitromethane in the presence of alcoholic sodium hydroxide yielded 16 g. of the crude product, which, when recrystallized from alcohol, gave yellow needles, m. p. 120.5–122°.

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.4; H, 4.5. Found: C, 72.3; H, 4.8.

Aliphatic amines instead of alkali proved unsuitable for promoting the reaction because of the formation of polymers. Thus, using amylamine, considerable amounts of an amorphous, tan-colored substance relatively insoluble in common solvents was obtained, which, after digestion with hot nitric acid, washing with alcohol and drying, melted indefinitely with decomposition at about 253°.

Anal. Calcd. for $(C_{12}H_9NO_2)_x$: C, 72.4; H, 4.5. Found: C, 72.2; H, 4.6.

2-(α-Bromo-α-nitrovinyl)-naphthalene.—The dibromide of the original compound was prepared by the action of bromine on a chloroform solution of the unsaturated substance. The bromination which did not go smoothly gave best results on long standing at room temperature in sunlight. Spontaneous evaporation left a crystalline residue which after washing with cold alcohol to remove oily impurities, crystallized from alcohol as white needles, m. p. 125–126°. Warm alcoholic potassium acetate converted

it into the vinyl derivative, yellow needles from alcohol, m. p. 107–108°.

Anal. Calcd. for $C_{12}H_8BrNO_2$: Br, 28.7. Found: Br, 28.8.

Attempts to prepare addition products with aniline, phenylhydrazine, etc., were fruitless. Using fuming nitric acid a yellow amorphous substance, apparently containing two added nitro groups, was isolated.

PEARSON MEMORIAL LABORATORY
TUFTS COLLEGE
MEDFORD, MASSACHUSETTS RECEIVED APRIL 28, 1942

Anhydrous Tantalum Tribromide

BY RALPH C. YOUNG AND THOMAS J. HASTINGS, JR.

If tantalum pentabromide vapor and hydrogen are passed through a tube at 700°, reduction of the compound occurs and lower bromides are produced prior to the formation of tantalum metal.[1] Complete reduction to the metal occurs, however, if the reaction at 700° is continued for a long enough time.

By the employment of the St. Claire-Déville principle it has been found possible to obtain the anhydrous tribromide of tantalum by a process analogous to that by which the tribromide[2] of titanium and the tribromide[3] of zirconium were formed. A Pyrex tube 27 mm. in diameter and 100 cm. long was used as the reaction tube and the middle section (33 cm. in length) was heated in an electric furnace at 700°. Into the forward end which held the tantalum pentabromide[4] was passed pure dry hydrogen at a rate of 24 liters per hour. During this interval 18 g. of tantalum pentabromide was volatilized and carried with the hydrogen into the heated zone. The reduction product and unchanged pentabromide collected on the surface of an inner tube through which water at 0° flowed. This inner tube extended to within 15 cm. of the forward end of the furnace.

At the conclusion of the experiment the apparatus was cooled to room temperature and dry carbon dioxide substituted for the hydrogen. The apparatus was so constructed that the products of the reaction could be directed into an arm sealed to the lower side of the reaction tube about 20 cm. from the end. After the arm had been sealed off from the apparatus, the outer end which was provided with a stopcock was sealed directly to a high vacuum system and the excess tantalum pentabromide was removed from the reduced product by sublimation at 1×10^{-5} mm. pressure at a temperature of 160°. The residue, which weighed 1 g., was a grayish-green powder which under a lens appeared uniform. *Anal.* Calcd. for $TaBr_3$: Ta, 43.0; Br, 57.0. Found: Ta, 43.4, 45.5; Br, 59.5, 58.3, 55.5.

The analyses indicate the formation of the tribromide, mixed with higher and lower bromides.

The tribromide reacts with water and alkali. Hydrogen is evolved and in the absence of air in an amount that corresponds to a change of the tantalum from an oxidation state of 3 to 4. In accord with this fact a brown tetravalent oxide was formed, the composition of which corresponded to $TaO_2 \cdot 2H_2O$ after it had been washed with water, alcohol, and ether and dried at a pressure of 0.05 mm. for ten minutes. The dioxide is slowly oxidized in the air at room temperature and rapidly at elevated temperatures to the white Ta_2O_5. The latter is quickly formed from the tribromide and dioxide by the action of strong oxidizing agents such as nitric, permanganic and dichromic acids.

CONTRIBUTION NO. 91
RESEARCH LABORATORY OF INORGANIC CHEMISTRY
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE, MASS. RECEIVED MAY 11, 1942

d-Allulose and Some Methylated Derivatives

BY F. W. ZERBAN AND LOUIS SATTLER

In the industrial fermentation of cane molasses to produce ethyl alcohol, part of the sugar remains unfermented, and we have shown[1] that the unfermentable residue of a molasses distillery contains a ketohexose whose osazone is identical with the osazones of *d*-allose and *d*-altrose. Consequently the ketose must be *d*-psicose. Because of

HC=O	HC=O	H_2COH
HCOH	HOCH	C=O
HCOH	HCOH	HCOH
HCOH	HCOH	HCOH
HCOH	HCOH	HCOH
H_2COH	H_2COH	H_2COH
d-Allose	*d*-Altrose	*d*-Allulose

(1) Van Haagen, THIS JOURNAL, **32**, 729 (1910).
(2) Young with Schumb, *ibid.*, **52**, 4233 (1930).
(3) Young, *ibid.*, **53**, 2148 (1931).
(4) Tantalum pentabromide was prepared by the action of bromine on a mixture of sugar charcoal (2 moles) and tantalum oxide (0.1 mole). This mixture was first heated in a silica tube at 700° in a current of nitrogen to remove water. Subsequently the reaction tube was raised to 860°. The sublimate was resublimed at 0.05 mm. pressure and at a temperature of 400°; yield 80%.

(1) Presented at the Atlantic City meeting of the American Chemical Society, Sept., 1941.

the relationship of the ketose to the two aldoses, we prefer the name *allulose* proposed by Professor William Lloyd Evans.

From commercial distillery residues we have now obtained *d*-allulose by way of its diacetone derivative. This compound when heated with dilute acetic acid decomposes to form the free sugar. The sirup thus prepared was dissolved in water and read in a saccharimeter.

$$[\alpha]^{20}D = \frac{+0.05°S \times 100}{1.2044 \times 0.5} \times 0.3462 = +2.9°$$

Steiger and Reichstein[2] reported $[\alpha]^{20}D$ +3.1°.

Methylation of the crude allulose concentrate followed by a high-vacuum distillation of the product yielded 1,3,4,6-tetramethyl ($\alpha \rightleftarrows \beta$) methyl *d*-alluloside which distilled as a thick oil from a bath temperature of 105–140° at a pressure of 8×10^{-5} mm.

Anal. Calcd. for $C_{11}H_{22}O_6$: C, 52.77; H, 8.86; OCH_3, 62.00. Found: C, 53.00; H, 9.24; OCH_3, 59.70; $n^{21.5}D$ 1.4572.

When 0.3199 g. of the tetramethyl methyl alluloside was dissolved in 25 ml. of methyl alcohol containing four drops of concentrated hydrochloric acid and heated in a pressure bottle for two hours at 100°, the product (probably an equilibrium mixture of tetramethyl methyl allulosides) had a specific rotation in sodium light of +36° at 20°.

Further work with allulose derivatives is in progress.

(2) Steiger and Reichstein, *Helv. Chim. Acta*, **19**, 187 (1936).

THE NEW YORK SUGAR TRADE LABORATORY
BROOKLYN COLLEGE
BROOKLYN, N. Y.

RECEIVED APRIL 24, 1942

NEW COMPOUNDS

N,N′-Piperazinium Bis-(2-methyl-5-isopropylbenzenesulfonate)

Smith and Pollard[1] have prepared a number of N,N′-piperazinium bis-(arylsulfonates) and found them moderately soluble in cold water, and quite soluble in hot water. McKee and Bahner[2] found that, while the benzenesulfonate and 2,4-dimethylbenzenesulfonate salts of ethylenediamine and also the 2-methyl-5-isopropylbenzenesulfonate salts of diethylenetriamine and triethylenetetramine are all relatively soluble in water at room temperature, the 2-methyl-5-isopropylbenzenesulfonate salt of ethylenediamine is only slightly soluble. This property was used to separate ethylenediamine from mixtures.

We have prepared N,N′-piperazinium bis-(2-methyl-5-isopropylbenzenesulfonate) and have found that, while it is readily soluble in hot water, it is only slightly more soluble at room temperature than the corresponding salt of ethylenediamine. It is soluble only to the extent of 1 part in 80 of water at 30° or 1 part in 200 at 0°.

The salt was prepared by mixing aqueous solutions of recrystallized sodium 2-methyl-5-isopropylbenzenesulfonate and N,N′-piperazinium dichloride, the former being in excess at all times.[3] The product, obtained in almost the theoretical yield, consisted of small, white leaflets which did not melt below 300°. After recrystallization from water and drying at 110° it was analyzed by the Kjeldahl method.

Anal. Calcd. for $C_{24}H_{38}N_2O_6S_2$: N, 5.45. Found: N, 5.47, 5.58, 5.64.

(1) Smith and Pollard, THIS JOURNAL, **63**, 631 (1941).

(2) McKee and Bahner, U. S. Patent 2,164,587, July 4 1939.

(3) We are indebted to Carbide and Carbon Chemicals Corporation for piperazine hexahydrate and to Professor Ralph H. McKee for technical sodium cymenesulfonate used as raw materials for this preparation.

(4) Present address: Alabama Ordnance Works, Sylacauga, Ala.

CHEMISTRY DEPARTMENT
CARSON-NEWMAN COLLEGE
JEFFERSON CITY, TENNESSEE
CARL T. BAHNER
DANIEL HAMILTON[4]

RECEIVED MARCH 25, 1942

N-Substituted Piperonylamides

These compounds were prepared by treating a benzene solution of piperonoyl chloride with slightly more than two equivalents of the appropriate amine in the same solvent and heating the solution under reflux for thirty minutes. The mixture was treated with water to dissolve the hydrochloride of the amine and the benzene was removed by distillation under reduced pressure with a water pump. The remaining aqueous solution containing the amide in suspension was filtered and the amide washed with water. This procedure was found preferable to distilling separately the benzene solution of the amide as some amides tended to separate from this solvent as an oil. The yield of crude amide was 90% or more in all cases. Purification of the amide was effected by recrystallization from dilute alcohol. The nitrogen determinations were made by the Kjeldahl method.

Name	Formula	M. p., °C. (cor.)	Nitrogen, % Calcd.	Found
N-Phenylpiperonylamide	$C_{14}H_{11}NO_3$	146 –147	5.81	5.83
N-(*o*-Chlorophenyl)-piperonylamide	$C_{14}H_{10}ClNO_3$	107 –108	5.08	5.27
N-(*p*-Chlorophenyl)-piperonylamide	$C_{14}H_{10}ClNO_3$	206.5–207.5	5.08	5.16
N-*o*-Tolylpiperonylamide	$C_{15}H_{13}NO_3$	137.5–138.5	5.49	5.44
N-*m*-Tolylpiperonylamide	$C_{15}H_{13}NO_3$	121 –122	5.49	5.46
N-*p*-Tolylpiperonylamide	$C_{15}H_{13}NO_3$	149 –149.5	5.49	5.46
N-(1-Naphthyl)-piperonylamide	$C_{18}H_{13}NO_3$	192.5–193	4.81	4.82
N-(2-Naphthyl)-piperonylamide	$C_{18}H_{13}NO_3$	156.5–157.5	4.81	4.60
N-Benzylpiperonylamide	$C_{15}H_{13}NO_3$	126.5–127.5	5.49	5.46
N-Cyclohexylpiperonylamide	$C_{14}H_{17}NO_3$	167.5–168.5	5.67	5.61

BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE
U. S. DEPT. OF AGRICULTURE
WASHINGTON, D. C.
S. I. GERTLER
H. L. HALLER

RECEIVED MARCH 9, 1942

Selenium Tetracysteine

To an aqueous solution of 0.01 mole of cysteine hydrochloride an aqueous solution of 0.0025 mole of sodium selenite was added. On cooling, a white granular material separated. It was removed by filtration, washed with water, and recrystallized from hot water. The yield was 80–85% of the theoretical amount. Under the microscope, the crystals had the form of clusters of small rods. The substance began to darken at 164–165° and decomposed at 195–196°. The analysis of the substance indicated that it was apparently identical with selenium tetracysteine.

	C	H	N	Se	N:Se
Found	25.41	4.38	9.87	14.00	4:1
Calcd. for $Se(SC_3O_2NH_6)_4$	25.73	4.29	10.01	14.16	

Selenium tetracysteine is moderately soluble in cold water, readily soluble in hot water. It is soluble in dilute mineral acids, but decomposes on heating the acid solution to yield what appears to be elementary selenium (brick-red in color, characteristic odor, gives intense codeine test). It readily decomposes in cold dilute alkali yielding elementary selenium. An aqueous solution of selenium tetracysteine gives a negative test for free SH— with nitroprusside and ammonia. On treatment with sodium cyanide, the nitroprusside test becomes positive.

The ready reactivity of the selenite toward cysteine is analogous to that of arsenious acid toward cysteine to give arsenious tricysteine. The latter compound was prepared by Johnson and Voegtlin[1] using arsenious trichloride. We found in unpublished studies that arsenious acid also reacts with cysteine to give the tricysteine in 90% yields.

The cysteine derivatives of selenium and arsenic are of interest in connection with the selenium poisoning in animals, and the well-known inactivation of certain enzymes by arsenious acid and the selenite.

(1) J. M. Johnson and C. Voegtlin, *J. Biol. Chem.*, **89**, 27 (1930).

VANDERBILT UNIVERSITY SCHOOL OF MEDICINE
DEPARTMENT OF BIOCHEMISTRY
NASHVILLE, TENNESSEE JAKOB A. STEKOL

RECEIVED MAY 4, 1942

COMMUNICATION TO THE EDITOR

SOME X-RAY DIFFRACTION MEASUREMENTS ON BIOTIN

Sir:

About one milligram of free biotin, $C_{10}H_{16}O_3N_2S$, was made available to the writer through the courtesy of Dr. Vincent du Vigneaud, of the Cornell Medical School. Repeated micro-recrystallizations produced a few crystals large enough for single crystal X-ray studies.

Biotin crystallizes in long thin needles. Under the polarizing microscope, the extinction is straight, the fast vibration direction, α, being along the length. The needle cross-section is approximately a rhombus, the acute angle of which is about 55°. This value could not as usual be determined accurately by the use of optical reflections, as the prism faces were not perfect enough. The intermediate vibration direction, β, is the obtuse angle bisector, and γ the acute. Optically the crystal is negative. These data suggested that the crystal was orthorhombic, a choice confirmed by the subsequent X-ray work. The a, b and c axes were taken to coincide with the corresponding principal optic directions α, β and γ.

Oscillation films about all three crystallographic axes were made as well as "a" axis Weissenberg films of the equator, first and second layers. The only systematic absences found were the extinctions of the odd orders of the (h00), (0k0), and (00l) reflections. The space group is therefore $P2_12_12_1$. This space group has four general positions.

The lengths of the a, b and c axes were found to be 5.25, 10.35 and 21.0 Å., respectively. If the molecules are asymmetric and identical, then there would be four molecules per unit cell. The density of the crystals as measured by immersion in a mixture of carbon tetrachloride and methylene dichloride was 1.41. The X-ray molecular weight, computed from these data, is 245 ± 6. The molecular weight computed from the chemical formula is 244.

Some idea as to the possible character of the molecule may be obtained from the X-ray data without making a detailed analysis. The short "a" axis and the fact that it is parallel to the fast vibration direction, α, suggests a flattish molecule lying approximately in the bc plane. The width would be approximately in the "b" direction and the length in the "c" direction. The molecules will almost certainly deviate somewhat from be-

ing parallel with the crystallographic directions but nevertheless a molecule about 5 × 5.5 × 10.5 Å. in size is indicated.

The equatorial "*a*" axis Weissenberg shows an interesting pseudo-halving of the (0*kl*) reflections; *i. e.*, the (0*kl*) reflections for *k* odd are generally weak. A possible explanation can be given in terms of a pseudo-symmetry of the biotin molecule. A molecule which in projection is approximately symmetrical to a plane normal to the "*c*" axis could result in such an intensity distribution.

Another interesting systematic pseudo-halving exists which was not noticed until a Patterson synthesis of the (0*kl*) reflections was made. The two largest peaks (excluding of course the identity peak at 0,0) were found at $^1/_2$, 0 and $^1/_4$,$^1/_2$. The first of these peaks is merely the expression of the first mentioned pseudo-halving. The peak at $^1/_4$,$^1/_2$ can be traced to the second pseudo-halving; (0*kl*) reflections, where *k* is even and $k/2 + l$ is odd, were generally weak. This suggests that the flattish molecules are packed approximately side by side, neighbors being related to one another by a two-fold screw axis. In the direction of their lengths the packing would be imbricated. The one sulfur atom per molecule of biotin should be fairly near the central bisecting pseudo-plane of symmetry.

It should be emphasized that much of the foregoing note is highly speculative; indeed only the great interest in biotin could warrant its publication in its present form. The actual X-ray cell determinations are probably accurate to within about 1%. The picture of the molecular size and shape, however, is merely a reasonably plausible explanation of some of the X-ray and optic data. A more complete study of the X-ray data is now under way.

Much of the experimental work was done while the writer was National Research Fellow in Protein Chemistry at the Massachusetts Institute of Technology.

ANDERSON INSTITUTE FOR BIOLOGICAL RESEARCH
RED WING, MINN., AND
DEPARTMENT OF PHYSIOLOGY, UNIVERSITY OF MINNESOTA
MINNEAPOLIS, MINN. I. FANKUCHEN

RECEIVED JUNE 3, 1942

NEW BOOKS

Anhydrous Aluminum Chloride in Organic Chemistry. By CHARLES ALLEN THOMAS, Central Research Director, Monsanto Chemical Company, in collaboration with MARY BALUK MOSHIER, HERBERT E. MORRIS and ROSS W. MOSHIER, Thomas and Hochwalt Laboratories, Monsanto Chemical Company. (A. C. S. Monograph Series.) Reinhold Publishing Corporation, 330 West 42nd St., New York, N. Y., 1941. xiii + 972 pp. 15.5 × 23.5 cm. Price, $15.00.

This is truly a monumental work, 878 pages of text, an author index of some 7000 names, a subject index of over 20,000 entries and a patent index with 594 U. S. patents and more from other countries.

The book opens with an historical sketch of Friedel and Crafts. This is followed by a chapter on the physical and chemical properties of aluminum chloride and its many combinations and one on the mechanisms of the reactions catalyzed by it. The manufacture, handling and storage of this material are also cared for. The main portion of the book, 656 pp., is a well-ordered, comprehensive and detailed presentation of the reactions of aromatics with alkyl halides, olefins, acyl halides, anhydrides and the like, with their numerous modifications. This is what every organic chemist knows, only a great deal more of it. Three chapters, 107 pages, are given to the new, tremendously important applications of aluminum chloride to aliphatic compounds. This section with its thousand references, largely patents, covers among other things the isomerization of hydrocarbons and the addition of olefins to paraffins to make high octane gasoline, the production of ethyl chloride from ethylene and hydrogen chloride, the polymerization of olefins to lubricants, high molecular weight, semi-solid products and resins and the cracking and refining of petroleum products.

The enormous amount of information is concisely yet clearly presented and should be of great service to organic chemists whether interested in pure chemistry or in its applications.

E. EMMET REID

A Treatise on Physical Chemistry. Third Edition—In Five Volumes. Volume One. **Atomistics and Thermodynamics.** Edited by HUGH S. TAYLOR, David B. Jones Professor of Chemistry, Princeton University, and SAMUEL GLASSTONE, Professor of Chemistry, The University of Oklahoma. D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N. Y., 1942. vii + 679 pp. Illustrated. 15.5 × 23.5 cm. Net price, $7.50; $6.50 on order for set.

If Mr. Gallup were to poll the country's middle-aged physical chemists for the book that had the greatest in-

fluence on their professional training the returns would very likely show Nernst's "Theoretical Chemistry" to be it, although the younger generation seems to be hardly better acquainted with this book than they are with the Bible! But beginning with the early 'twenties the rapidly expanding science demanded, and got, a whole set of working-textbook-reference books individually addressed by very competent authors to special fields, which in some cases involved a developing body of knowledge treated by Nernst in only a few pages or a few chapters, and which in other cases involved facts and approaches not even hinted at or dreamed of before 1920 by Nernst or anybody else.

The persistent and very proper demand for a summarizing story of how we stand in certain special fields as explained to us by a few persons who are gifted with the power to swallow a field whole, digest it, and come up with a clear, logical and interesting account of it, has brought to American chemists a really excellent review-service and colloquium-service, as well as our special-field book service.

Professor Hugh Taylor and the nineteen authorities who collaborated with him in writing the various summarizing chapters of "A Treatise on Physical Chemistry" (first edition—October, 1924, second edition—December 1930) did a great service to American chemistry. All who have used these two volumes are much interested to know what the third edition, now expanded to five volumes, will be like. The first volume is off the press, March, 1942. Professor Taylor and Professor Samuel Glasstone have combined forces as editors of the enlarged Treatise.

Volume I, labelled Atomistics and Thermodynamics, contains four chapters, an appendix (Values of Physical Constants) and a subject index.

Its Chapter I, The Atomic Concept of Matter, by Hugh S. Taylor, runs 1–117 pages as compared with 1–34 pages in the second edition. It carries extensive revisions and many additions of new material including more comprehensive treatments of radioactivity and the mass spectrograph and very helpful sections on separation of isotopes, nuclear structure, nuclear fission, nuclear processes, and a most useful table of induced radioactivities. In this chapter one can get a brief but excellent and well-balanced picture of how we stand at present with respect to the nucleus.

Chapter II, Quantum Theory of Atomic Spectra and Atomic Structure, is written by Saul Dushman in his incomparably fine manner of exposition. The chapter runs from page 119 to 436, as compared with 276 pages in the second edition. Dr. Dushman's treatment runs the whole gamut of the quantum effects of interest to chemists, including sections on: Quantum Phenomena, Photoelectric Effect, Inverse Photoelectric Effect, Compton Effect, Raman Effect, Quantum Theory of Radiation, Matter Waves, Corpuscles and Waves, The Bohr–Sommerfeld Theory of Electronic Orbits, The Wave Mechanics Treatment of the Hydrogen Atom, Inner Quantum Number and Electron Spin, Effect of Magnetic and Electrostatic Fields on Spectral Terms, Electron Configuration in Atoms and Periodic System of the Elements, Quantum Numbers for Inner Electrons, Multiplet Levels in Optical Spectra, Intensities of Spectral Lines, Magnetic Properties of Atoms and Ions in Relation to Spectral Type, Hyperfine Structure of Spectral Lines, Quantum Theory of Valence.

Chapter III, First and Second Laws of Thermodynamics, by Hugh S. Taylor, follows along for about one-half its length very much the same pattern of the chapter "The Energetics of Chemical Change" in the second edition, with some changes and additions, and then treats Partial Molal Quantities, The Activity Function, Thermodynamics and Statistics. The last section gives a very nice discussion of partition functions.

Chapter IV, The Third Law of Thermodynamics and Statistical Mechanics, is a beautifully written treatment by John G. Aston, a professor of *organic* chemistry (let it be noted) and a new addition to the staff of contributing authors. Seventy-five listed topics are organized under section headings as follows: The Third Law of Thermodynamics; Statistical Mechanics; Nuclear Spin Effects; Gases; The Third Law and Statistical Mechanics; Heat Content, Free Energy and Equilibrium Constants; Solids; Magnetic Cooling; and several valuable appendices. Throughout the chapter *entropy* is naturally Professor Aston's most absorbing theme.

Many chemists will be looking forward with freshly aroused interest to the other four volumes. The authors of the forthcoming chapters will indeed have to exert themselves to rival the excellent performance of their colleagues in this first volume. The publishers, too, have done a piece of first-class book manufacture.

EDWARD MACK, JR.

Advances in Enzymology and Related Subjects. Edited by F. F. NORD, Fordham University, New York, N. Y., and C. H. WERKMAN, Iowa State College, Ames, Iowa. Volume II. Interscience Publishers, Inc., 215 Fourth Avenue, New York, N. Y., 1942. viii + 374 pp. 23 illustrations. 15.5 × 23.5 cm. Price, $5.50.

The second volume of "Advances in Enzymology" is characterized by a breadth of interest far transcending its chosen field of enzyme chemistry or "Enzymology" as the editors have so unhappily chosen to express it. In accordance with this, we find a comprehensive report "Vitamin K, its Chemistry and Physiology," by Henrik Dam, once of Copenhagen, now of Rochester. A few years ago the inclusion of such vitamin chemistry in a treatise on enzymes would seem incongruous indeed. With the striking developments in biological oxidations where riboflavin, thiamin and nicotinic acid, once identified as vitamins, have now been shown to be the prosthetic groups of many important enzyme systems, vitamin K appears to "belong." Perhaps this foreshadows the development of a role for vitamin K among the enzymes of the body. Typical also of the all-inclusive nature of this volume are the reviews "The Adrenal Cortical Hormones" by J. J. Pfiffner and "Bacterial Viruses (Bacteriophages)" by Max Delbrück.

Dealing with the purely hydrolytic enzymes, there are three papers of very great value. The first of these, "The Kinetics of Hydrolytic Enzymes and Their Bearing on Methods for Measuring Enzyme Activity," by Donald D. Van Slyke, should be carefully studied by any investigator in this field. In it the author analyzes the kinetic behavior of simple hydrolyses of this type, develops the mathematical treatment of such reactions and then shows how the

experimental conditions should be chosen and interpreted so that valid and significant results may be obtained. Undoubtedly many false and misleading reports which now find publication could be transformed into valuable contributions by strict observance of the rules as Dr. Van Slyke has elaborated them. There are, then, two reviews of proteolytic enzymes, "A Classification of Proteolytic Enzymes," by Max Bergmann, and "The Enzymatic Properties of Peptidases," by M. J. Johnson and J. Berger. These are in many ways complementary. The latter authors, restricting their attention to the "peptidases," summarize the occurrence of these enzymes in nature, with emphasis on the varied nature of the same type of enzyme from different sources. For instance, there are really many different kinds of enzymes which split leucyl peptides; there is no justification to consider them all a single enzyme, "leucyl peptidase," and far less to label them "amino peptidase" or "peptidase" as some authors have a tendency to do. Dr. Bergmann's attention is focussed on the recent work from his Laboratory at the Rockefeller Institute. He presents a new working classification of the proteolytic enzymes, in which peptidases and proteinases, as groups, are discarded in favor of endopeptidases and exopeptidases. Again, emphasis is placed on the like and unlike characteristics of enzymes from different sources in nature. Thus, there are enzymes in beef spleen, beef kidney, swine kidney, cattle pancreas (trypsin), and the papaya which split benzoyl-*l*-arginineamide and benzoyl-*l*-lysineamide at proportionate rates, but which differ strikingly in other properties such as their *p*H requirements and dependence upon activators. The accumulated evidence suggests that such proteolytic enzymes are composed of several determinant groupings of amino acid or other residues—one common to them all which controls the specificity of the family as a whole, and others peculiar to each member, which influence the *p*H and activation requirements. It is likely that when normal conditions return, striking advances will be made in this direction.

There is also a group of reports dealing more or less with carbohydrate metabolism, "Heterotrophic Assimilation of Carbon Dioxide" by C. H. Werkman and H. G. Wood, "Cellulose Decomposition by Microorganisms," by A. G. Norman and W. H. Fuller, and "A Unified Hypothesis of the Reciprocal Integration of Carbohydrate and Fat Catabolism" by E. J. Witzemann. "Diamin–Oxydase" by E. A. Zeller, "The Chemistry of Tea Fermentation," by E. A. Houghton Roberts and a paper on the respiration and metabolism of Aspergillus[1] by Hiroshi Tamiya complete the contents.

(1) "Atmung, Gärung und die sich daran beteiligenden Enzyme von Aspergillus."

W. F. ROSS

The Spectrochemical Analysis of Metals and Alloys. By F. TWYMAN, F.R.S., Managing Director, Adam Hilger, Ltd. Chemical Publishing Company, Inc., 234 King Street, Brooklyn, New York, 1941. vii + 355 pp. 61 figs. 14.5 × 22 cm. Price, $8.50.

As managing director of Adam Hilger, Ltd., Mr. Twyman has had a great deal to do with the instrumental design of spectrographs and accessory apparatus, and also with the general furtherance of spectrochemical analysis. He is thus in a position to write an authoritative book on the subject. In the preface the author states that he had three classes of readers in mind when writing the book, namely, "(1) teachers and students of metallurgy who wish to acquaint themselves with the scope and nature of spectrochemical analysis as carried out in industrial laboratories; (2) metallurgists already engaged in industry to whom it may fall to introduce the method for routine control or research; (3) those already engaged in this field of analysis." To these he might well have added directors of research or heads of analytical laboratories who may be considering the application of spectrochemical analysis to their own particular problems.

Chapter I, The History of the Development of Spectrochemical Analysis, is based on a similar chapter in Kayser's "Handbuch der Spektroskopie." Chapter II, The Elements of Atomic Spectrum Theory, is a revised version of the section of the same title that A. C. Candler contributed to "Spectrochemical Analysis in 1938." Chapter III deals with Spectrographs and Accessory Apparatus. In this chapter the author discusses both grating and prism types of instruments, with a distinct preference for the latter. It is interesting to note that two commercial grating instruments of American manufacture have been joined by the "Technal" grating spectrograph for metallurgical analysis, which was put on the market by Adam Hilger, Ltd., in 1940. Chapter IV, The Microphotometer, is one of the most readable yet concise discussions the reviewer has seen. It is a pity that the visual comparator type of instrument was not discussed in this chapter.

Part II opens with Chapter V, Methods of Exciting Emission Spectra. This is a comprehensive survey of the various methods and the apparatus required for each. Chapter VI deals with the Taking of Spectrograms, Measuring Wavelengths, and Identifying Elements: Books and Tables. Chapter VII covers the Techniques of Spectrochemical Analysis, which the author defines as the proper selection of apparatus, mode of excitation of the spectrum, and the evaluation of the photographic plate applied to a particular analytical problem. In this chapter the logarithmic sector, the step sector and the step diaphragm, etc., are discussed. Chapter VIII, Types of Problem to which Spectrochemical Analysis is Applicable, should be read by every research director who may not know either the advantages or disadvantages of this mode of analysis. From the purely practical standpoint, the practising spectrochemical analyst will probably get the most out of Chapter IX, dealing as it does with the Practice of Spectrochemical Analysis of Metals and Alloys. The commercial analysis of Aluminum and its Alloys, Cadmium, Gold, Iron, Steel and Ferrous Alloys, Lead and its Alloys, Magnesium and its Alloys, the Platinum Metals, Silver, Tin, Zinc and Zinc-base Alloys, are all discussed. Chapter X, The Analysis of Substances not in Metallic Form including Gases, concludes the text. This is followed by two appendices, the first on Units and Definitions, and the second Additional Notes on methods.

The style of the book is very simple and readable. References are to paragraph numbers throughout the book, and literature references are made by the authors' names

followed by the year in which the paper appeared. These are all listed at the end of the book under the heading Bibliography and Author Index. Without a doubt this book is the best exposition of the principles and practice of emission spectrum analysis that has appeared in English. It is a "must own" book for the library of every analyst who has anything to do with spectrochemical analysis.

Since the American edition was undoubtedly printed from the British plates (or perhaps the printed forms were imported into the United States) it is a pity that a better quality of paper was not used. The paper quality in the American edition is worse than that in the British. The American publisher did not even see fit to print the spectrum plates, such as the frontispiece, on glazed paper. In view of these things, it is strange that the American edition should be priced at $8.50, which seems exorbitant in comparison to the British price of one guinea. After all, the cost of the plates would be absorbed in the British publisher's cost, and even allowing for an import duty, the American cost is exorbitant.

LOUIS WALDBAUER

BOOKS RECEIVED

May 10, 1942–June 10, 1942

A. A. BENEDETTI-PICHLER. "Introduction to the Microtechnique of Inorganic Analysis." John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y. 302 pp. $3.50.

PETER GABRIEL BERGMANN. "Introduction to the Theory of Relativity." Prentice-Hall, Inc., 70 Fifth Avenue, New York, N. Y. 287 pp. $4.50.

J. C. COLBERT. "A Shorter Course in Organic Chemistry." Second edition. D. Appleton–Century Company, Inc., 35 West 32nd Street, New York, N. Y. 355 pp. $3.75.

LOUIS J. CURTMAN. "Introduction to Semimicro Qualitative Chemical Analysis." The Macmillan Company, 60 Fifth Avenue, New York, N. Y. 377 pp. $2.75.

ED. F. DEGERING AND COLLABORATORS. "An Outline of Organic Nitrogen Compounds." John S. Swift Co., 5 East Third Street, Cincinnati, Ohio. 381 pp. $6.00.

HORACE G. DEMING AND CLIFFORD HENDRICKS. "Introductory College Chemistry. A Course for Beginners." Second edition. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y. 521 pp. $3.00.

JOHN C. HOGG AND CHARLES L. BICKEL. "Laboratory Manual to Elementary General Chemistry." D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N. Y. 283 pp. $1.60.

FOREST RAY MOULTON, Editor. "Liebig and after Liebig. A Century of Progress in Agricultural Chemistry." American Association for the Advancement of Science, Smithsonian Institution Building, Washington, D. C. 111 pp.

LEON B. RICHARDSON AND ANDREW J. SCARLETT. "Brief College Chemistry." Henry Holt and Company, Inc., 257 Fourth Avenue, New York, N. Y. 385 pp. $3.00.

H. R. ROSENBERG. "Chemistry and Physiology of the Vitamins." Interscience Publishers, Inc., 215 Fourth Avenue, New York, N. Y. 674 pp. $12.00.

PAUL VON STEIN. "Organic Reagents in Inorganic Analysis." Chemical Publishing Company, Inc., 234 King Street, Brooklyn, N. Y. 242 pp. $4.50.

J. D. STRANATHAN. "The 'Particles' of Modern Physics." The Blakiston Company, 1012 Walnut Street, Philadelphia, Pa. 571 pp. $4.00.

F. P. TREADWELL AND WILLIAM T. HALL. "Analytical Chemistry. Volume II. Quantitative Analysis." Ninth English Edition. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y. 806 pp. $6.00.

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

VOLUME 64 AUGUST 10, 1942 NUMBER 8

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Heats of Organic Reactions. XIII. Heats of Hydrolysis of Some Acid Anhydrides

BY JOHN B. CONN, G. B. KISTIAKOWSKY, RICHARD M. ROBERTS AND ELGENE A. SMITH

For the purpose of quantitative estimation of the effect of substitution on the stability of cyclic structures, it would be of interest to compare the heats of hydrolysis of straight-chain acid anhydrides with those of cyclic acid anhydrides. It is necessary to obtain the heat of the reaction

$$\text{Anhydride (g)} + H_2O\text{ (g)} = \text{Acid (g)} + \Delta H \quad (1)$$

since only in the gas phase, where entropy changes would be very nearly the same for a series of reactions of the type contemplated here, would the ΔH values be a fair measure of stability. Unfortunately no cyclic anhydrides are of sufficient volatility, and no acid anhydrides, whether cyclic or straight-chain, are reactive enough with water to permit application of the technique of gas calorimetry. Nevertheless, as the first step toward obtaining heats of the above reaction 1, we have carried out calorimetric measurements in solution which allow calculation of heats of the following type of reaction

$$\text{Anhydride (s or l)} + H_2O\text{ (l)} = \text{Acid (s or l)} + \Delta H \quad (2)$$

Some of the heats of reaction 2 which we report here can be computed from existing heats of combustion; however, our data cover a wider range of compounds, and we believe that our direct measurements are of greater accuracy than the heats of hydrolysis obtainable from these older combustion data.

Experimental Procedure

The calorimeter used in these measurements has been described in a previous paper of this series.[1] It was used in this work as a single calorimeter. The chemical reaction was carried out in one calorimeter; the other calorimeter was filled with water and allowed to attain its equilibrium temperature due to stirring, thus serving as a reference bath for the main thermel.

An electrical calibration of the calorimeter preceded and followed each chemical run. The procedure was as follows.

The calorimeter was filled and was brought by electrical heating to a suitable temperature somewhat below that of the bath. After waiting fifteen minutes for the attainment of a steady state, observations on the main thermel were made every five minutes for half an hour. A current of approximately 0.4 ampere was then passed through the calorimeter heater for about five minutes. The time interval was measured with an error of less than 0.1% by a chronograph connected with the heater switch. Measurements of the potential across the calorimeter heater and across a 0.1 ohm standard resistance in series with the heater were made frequently during the heating period. Current from the batteries was allowed to pass through a ballast coil of the same resistance as the calorimeter heater for at least half an hour before making a run, and was thrown directly from the ballast coil to the heater. Following the heating period, readings on the main thermel were made frequently until a steady state was reached, then every five minutes for half an hour. From the readings of the half-hour periods before and after the heating period the equilibrium temperature and the cooling constant of the calorimeter and contents were determined. The effective microvolt rise due to electrical heating was then calculated by logarithmic extrapolation of the two cooling curves to the middle of the heating period. The effective microvolt rise, together with the potential readings across the heater and standard resistance gave the calibration constant of the calorimeter and contents in calories per microvolt. In this paper 1 cal. = 4.1833 int. joule. The electrical calibrations before and after the chemical run differed by less than 0.1%.

The method of making the chemical run will now be de-

(1) Conn, Kistiakowsky and Roberts, THIS JOURNAL, **62**, 1895 (1940).

scribed. After purification, the various compounds were packed in previously weighed thin-walled soft glass sample bulbs whose outside dimensions were about 5 × 80 mm. Solid compounds were introduced into the sample bulbs in a dry box and sealed off immediately after filling. Sample bulbs were filled with liquid compounds in the absence of air by distillation into special receivers (described below) holding the sample bulbs. The sample bulbs for liquids had capillary tips, and were quickly sealed off after filling and removing from the receiver. The sample bulb was held in place in the calorimeter by four stainless steel strips wired at the bottom, forming a cage for the bulb. At the top the strips were fastened to a stainless steel truncated cone ground to fit the truncated conical sample aperture in the top of the calorimeter.[2] The cone had a threaded hole in its center, into which was screwed a threaded stainless steel rod terminating in a sharp conical tip at its lower end. The upper end of the threaded rod was above the thermostat bath, and was attached to a small reversible motor making it possible to screw the rod up or down. When a sample tube was in place, upon screwing the rod downward the sharp tip on the lower end of the rod drove into the sample bulb and shattered it, allowing the sample to dissolve and react with the alkali. The heat of breaking the sample bulb was determined and was taken into account in calculating the results of the chemical run.

At the beginning of the chemical run the sample bulb was broken, and main thermel readings were made every thirty seconds while the heat evolution was rapid, later at longer intervals, until the cooling constant resumed its normal value. Correction for heat loss during the reaction period was made by numerical computation of the area under a plot of cooling constant × thermal head against time.

Direct measurement of the heat of hydrolysis of the acid anhydrides in pure water was first attempted, with fair success in the case of acetic anhydride, but the rate of hydrolysis of propionic anhydride proved too slow. The plan was therefore revised, and the hydrolysis was carried out in a slight excess of alkali, so that the sum of the heat of hydrolysis and the heat of neutralization of the acid was measured. Under these conditions the reaction was complete in most cases in about an hour. Heats of neutralization of the acids were subsequently measured. To increase the solubility of some of the compounds studied, the reaction was carried out in a dioxane-water mixture. Heats of dilution of these mixtures were determined.

Preparation of Compounds

Acetic Acid and Anhydride.—Merck Blue Label acetic acid was purified first by partial freezing and then carefully fractionated through Column B.[3] In this and subsequent distillations, the receiver which was to contain the calorimetric sample was specially designed so as to carry within it six previously weighed bulbs. At the conclusion of the distillation, the bulbs were filled by pumping out the receiver and then admitting dry air; as soon as they were full, they were removed and immediately sealed and reweighed. The calorimetric sample was taken in the middle of the distillation after the head thermometer had been registering a constant temperature for some time (usually an hour). The acetic acid fraction used for calorimetric measurement boiled at 118.03 ± 0.01° (770 mm.)[4] Merck Blue Label acetic anhydride was similarly distilled; the fraction used boiled at 138.70 ± 0.01° (770 mm.).

Propionic Acid and Anhydride.—Eastman Kodak Co. best grade materials were distilled through Column B. The acid boiled at 141.28 ± 0.01° (766 mm.). The anhydride boiled at 166.94 ± 0.04° (777 mm.).

Isobutyric Acid and Anhydride.—Commercial isobutyl alcohol was oxidized to the acid as described by Pierre and Puchot.[5] After preliminary purification, a precision distillation yielded a calorimetric sample boiling at 154.68 ± 0.02° (767 mm.). Isobutyryl chloride was made from the acid by distillation with benzoyl chloride;[6] yield 91%; b. p. 92.8–92.9° (765 mm.). Isobutyric anhydride, prepared from the above chloride and sodium isobutyrate (67% yield), gave a calorimetric sample boiling at 92.41 ± 0.04° (34.1 mm.). It froze at −56.37° with a drift of 0.065° to the point where jamming of the stirrer by solid made thermocouple readings unreliable.

Trimethylacetic Acid and Anhydride.—A quantity of trimethylacetic acid was kindly furnished us by Professor P. D. Bartlett of these Laboratories; a further amount was obtained from Eastman Kodak Co. The portion reserved for the calorimeter boiled at 164.18 ± 0.01° (763 mm.). Conversion to the chloride as previously described gave a 96% yield of material boiling at 104.8–105.0° (762 mm.). The anhydride was prepared from the chloride and the dry sodium salt[7]; yield, 78%. The calorimetric sample boiled at 95.00 ± 0.01° (28 mm.) and froze at −4.24° with a drift of 0.03° to jamming of the stirrer.

Succinic Acid and Anhydride.—Mallinckrodt Analytical Reagent succinic acid was used for the neutralization measurements. The anhydride was prepared from this acid by phosphorus oxychloride dehydration[8]; yield, 92%. The product was recrystallized from acetyl chloride (m. p. 119–120°), and then sublimed *in vacuo* at 91°. The sublimator is of all-metal construction; vaporization takes place on a circular plate through the center of which the condenser tube runs. Condensation occurs below the plate; the solid is removed by a rotary scraper, and falls into a series of glass cups carried on a movable tray. The sublimator bell and plate are heated electrically; glass windows in the bell and receiver carriage permit observation of the process. The sublimate, which was in the form of an almost impalpable powder, was preserved in a desiccator over phosphorus pentoxide until transferred to the bulbs.

Maleic Acid and Anhydride.—Eastman Kodak Co. best grade maleic anhydride was recrystallized from acetyl chloride. The best material was sublimed *in vacuo;* f. p. 52.27° with 0.08° drift to jamming of the stirrer. Some of the best anhydride was hydrolyzed to the acid.

(2) See ref. 1 for a diagram of the calorimeter.

(3) Column B is described by Kistiakowsky, Ruhoff, Smith and Vaughan, THIS JOURNAL, **57**, 877 (1935).

(4) This value may be in error in absolute magnitude, inasmuch as the only correction applied to it was for barometric fluctuation. The deviation includes the uncertainty in reading the thermometer used plus the magnitude of the random fluctuations.

(5) Pierre and Puchot, *Ann. Chim.*, (4) **28**, 366 (1873).

(6) Brown, THIS JOURNAL, **60**, 1325 (1938).

(7) Butlerow, *Ann.*, **173**, 374 (1874).

(8) "Organic Syntheses," Vol. XII, 1932, p. 66.

After two recrystallizations from water, the m. p. was 130–131°, with some decomposition.

Methylenesuccinic (Itaconic) Acid and Anhydride.—Mallinckrodt Analytical Reagent citric acid was converted to methylenesuccinic anhydride as described in "Organic Syntheses."[9] The yield of crude acid anhydride mixture from 4400 g. of citric acid was 45%. The solid acid which separated on standing was systematically recrystallized from water until no further alteration in melting behavior occurred, then twice more; m. p. 162–166°, dec. Some of the best acid was converted to the anhydride by means of acetyl chloride[10]; yield 79%; m. p. 67–68°. It was then sublimed *in vacuo* at 90°.[11]

Methylmaleic (Citraconic) Acid and Anhydride.—Methylmaleic anhydride was prepared by distillation of crude itaconic anhydride[12]; yield 80%; b. p. 119–120° (37 mm.). Precise fractionation through Column B yielded a calorimetric sample with b. p. 110.35±0.01° (28.8 mm.) and f. p. +6.03°, drift, 0.04° to jamming of the stirrer. A sample of the best anhydride was hydrated with a slight excess of water.[12] After prolonged drying in a vacuum desiccator over phosphorus pentoxide, the acid melted at 91–92°.

Methylsuccinic Acid and Anhydride.—Methyl cyanosuccinic ester was prepared from purified ethyl α-bromopropionate (b. p. 80.0–80.1° at 46 mm.) and ethyl cyanoacetate (b. p. 103.0–103.1° at 17.5 mm.).[13] Condensation was carried out in 3.75 mole lots; yield of product boiling flatly at 162.7° (22 mm.), 67%. Hydrolysis of the cyanosuccinic ester (2.5 liters of concentrated hydrochloric acid suffices for 1 kg. of ester) gave 84% yield of methylsuccinic acid; m. p. 112–112.5° after recrystallization from water and absolute ether. The acid was converted to the anhydride by means of phosphorus oxychloride; yield 67%. The calorimetric sample boiled at 135.78±0.02° (24 mm.). The anhydride crystallizes very sluggishly and will remain in the supercooled state almost indefinitely unless it is seeded or strongly cooled in dry-ice.

***dl*- and *meso*-α,β-Dimethylsuccinic Acid; *trans*- and *cis*-α,β-Dimethylsuccinic Anhydride.**—Much confusion exists in the literature as to the configuration of these two acids, and the impression seems to be prevalent that neither of them has ever been resolved,[14] although the resolution of the low melting isomer was carried out by Werner and Basyrin in 1913,[15] and confirmed by Ott in 1928.[16] Thus the "*anti*" acid of Bischoff and Voit[17] and the "*cis*" acid of Bone and W. H. Perkin, Jr.,[18] and of Bone and Sprankling[13] is the *dl*- form and will be so described here; while the "*para*" or "*trans*" acid is *meso*-. The correctness of the configurations assigned is further indicated by the fact that the lower-melting acid gives the higher-melting anhydride, which would be expected in view of its greater symmetry.

Diethyl α-methyl α′-cyanosuccinate was methylated with purified methyl iodide[13] in 2.5 mole lots. An excess of both sodium and methyl iodide was employed so as to insure completeness of the process; this is necessary since the two esters boil within a few degrees of each other. The yield of product boiling flatly at 161.1° (21 mm.) was 85%. Hydrolysis was effected with concentrated hydrochloric acid (3 liters of acid for 968 g. of ester). The *meso*-acid, which crystallized on cooling, was repeatedly recrystallized from water with intervening treatments with cold acetyl chloride as recommended by Bone and Sprankling.[13] The melting point attained the value 209° given by these workers only on very rapid heating, inasmuch as decomposition to the anhydride is noticeable around 180°, and becomes rapid at 190°. The mother liquor from the *meso*-acid was evaporated to dryness and extracted with boiling acetone, giving the racemic acid contaminated with some of the *meso*- acid (total recovery, 83%). The dry extract was converted to the *trans*-anhydride by refluxing with acetyl chloride and distilling (b. p. 232–233°)[19]; yield, 84%. The *trans*-anhydride was recrystallized from benzene–absolute ether mixture and then sublimed *in vacuo;* m. p. 87–88°. The corresponding *cis*-anhydride was prepared from some of the best *meso*-acid by means of acetyl chloride and subsequent recrystallization from this solvent; m. p. 42°. Owing to its lability when heated, sublimation was not attempted.

Hydration of the best *trans*-anhydride yielded a calorimetric sample of *dl*-acid, m. p. 126°, with some decomposition. The behavior of both the *meso*-α,β-dimethylsuccinic acid and the corresponding *cis*-anhydride in the calorimeter was abnormal; a secondary reaction was indicated by a failure of the calorimeter to return to its normal cooling rate. The only side reaction which would seem to be possible is that of epimerization. The following test was carried out: 1 g. of the best *meso*-acid was dissolved in an excess of C. P. base at room temperature and allowed to stand for nineteen hours. At the end of this time the solution was acidified with C. P. hydrochloric acid, taken to dryness at room temperature *in vacuo* and the residue extracted with C. P. anhydrous ether in a Soxhlet apparatus. The dry extract melted over a wide range of temperature, becoming completely fluid at 184°. Epimerization would thus seem to be established.

α,α-Dimethylsuccinic Acid and Anhydride.—The procedure of Vogel[20] was adopted; the yield of ethyl α-cyanodimethacrylate boiling at 122.9–123.0° (20 mm.) was 52%. Treatment of this ester with sodium cyanide and subsequent hydrolysis with concentrated hydrochloric acid gave a 62% yield of α,α-dimethylsuccinic acid. After three recrystallizations from water the m. p. was 141–142° (dec.). Conversion to the anhydride with acetyl chloride gave an 82% yield; b. p. 222–223°. A precision distillation was unsuccessful because the anhydride solidified in the condenser; likewise sublimation failed because the material condensed as liquid, then froze and jammed the scraper.

(9) "Organic Syntheses," Vol. XI, 1931, p. 70.

(10) Anschütz and Petri, *Ber.*, **13**, 1539 (1880).

(11) The alkaline hydrolysis of methylenesuccinic anhydride pursued an abnormal course, as was shown by the failure of the calorimeter to return to its normal cooling rate after the main reaction was over. The calorimeter liquid was also brownish in color. The abnormality was not observed during neutralization of the acid, nor during hydrolysis of the isomeric methylmaleic anhydride.

(12) "Organic Syntheses," Vol. XI, 1931, p. 28.

(13) Bone and Sprankling, *J. Chem. Soc.*, 839 (1899).

(14) *Cf.* for instance, Whitmore, "Organic Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1937, p. 462.

(15) Werner and Basyrin, *Ber.*, **46**, 3229 (1913).

(16) Ott, *ibid.*, **61**, 2134 (1928).

(17) Bischoff and Voit, *ibid.*, **22**, 390 (1889).

(18) Bone and Perkin, Jr., *J. Chem. Soc.*, **69**, 253 (1896).

(19) Any *cis*-anhydride present is converted to the *trans*-form by this process (*cf.* ref. 18).

(20) Vogel, *J. Chem. Soc.*, 2010 (1928).

It was finally recrystallized from a mixture of anhydrous ether and ligroin.

Tetramethylsuccinic Acid and Anhydride.—As starting material, commercial phorone was used. Neither repeated fractionation through our tall columns nor partial freezing sufficed to obtain a flat boiling fraction.[21] The best sample (1065 g. from 1 gallon) boiled at 103.0–104.2° (35 mm.), began to freeze at 23.4°, and had $n^{20}D$ 1.4912. Following the synthesis of Francis and Willson,[22] the steps were: (1) phorone to phorone tetrabromide, yield, 50%; (2) phorone tetrabromide to dibromophorone, yield, 67%; (3) dibromophorone to 2,2,3,3-tetramethyl-4-bromo-5-hydroxy-Δ^4-cyclopentenone-1, yield of crude product, nearly quantitative; (4) oxidation to α-ketotetramethylglutaric acid, yield, 86%; (5) keto-acid to tetramethylsuccinic acid, quantitative. The crude acid was dissolved in excess acetyl chloride and distilled. The anhydride, b. p. 218–220°, formed a white powder which quickly became sticky and reverted to a waxy mass. That this is not due to hydration has been shown by Auwers and Meyer.[23]

Successive calorimetric runs on this material showed a steadily diminishing heat of hydrolysis. Since this seemed to be due to alteration in crystal form, a portion of the anhydride was left for two weeks in contact with a saturated ether solution of the material, the ether being allowed to evaporate slowly. Large waxy crystals were deposited which underwent no change on standing. This presumably stable form of the solid was used in the calorimeter.

A portion of the best anhydride was dissolved in sodium hydroxide solution, and the acid recovered by acidification. It melted at 200–201° with decomposition (bath preheated to 190°).

Results and Discussion

The experimental results to be presented here are heats of three types of reaction. For the straight-chain anhydrides the three reactions are

$$1\text{ Anhydride (l)} + H_2O\text{ (dioxane-water)} + 2NaOH\text{ (d - w)} = 2NaA\text{ (d - w)} + 2H_2O\text{ (d - w)} + \Delta H_1 \quad (3)$$

$$1HA\text{ (s or l)} + 1NaOH\text{ (d - w)} = 1NaA\text{ (d - w)} + 1H_2O\text{ (d - w)} + \Delta H_2 \quad (4)$$

$$1H_2O\text{ (l)} = 1H_2O\text{ (d - w)} + \Delta H_3 \quad (5)$$

In Eqs. 3 and 4 A represents the acid radical. Taking (3) − (2 × (4)) + (5), one obtains

$$1\text{ Anhydride (l)} + 1H_2O\text{ (l)} = 2HA\text{ (s or l)} + \Delta H_1 - 2\Delta H_2 + \Delta H_3 \quad (6)$$

Equation (6) is identical with Eq. 2, in which the heat of hydrolysis is

$$\Delta H = \Delta H_1 - 2\Delta H_2 + \Delta H_3 \quad (7)$$

For the cyclic anhydrides the equation corresponding to (6) is

$$1\text{ Anhydride (s or l)} + 1H_2O\text{ (l)} = H_2A\text{ (s or l)} + \Delta H_1 - \Delta H_2 + \Delta H_3 \quad (8)$$

where ΔH_2 is now the heat of neutralization of one mole of the dicarboxylic acid by two moles of sodium hydroxide.

Table I consists of the heats of hydrolysis and neutralization of the anhydrides. The letters A, B and C in the column headed "Solution" refer to the compositions of the solutions in which the reactions were carried out; these compositions are given in Table III along with the heats of dilution. Table II contains heats of neutralization of the acids. Heats of neutralization are given for some acids for which the heats of hydrolysis and neutralization of the corresponding anhydrides could not be obtained, due to side reactions. These cases were discussed in the section on preparation of materials. In Tables I and II the mean temperatures listed refer to the temperature of the thermostat bath during the reaction. This temperature was measured with a five-junction thermel, one end of which was immersed in ice. This thermel was previously calibrated against a platinum resistance thermometer. The temperature of the calorimeter during reaction in no case differed by more than one degree from that of the bath.

TABLE I

HEATS OF HYDROLYSIS AND NEUTRALIZATION, $-\Delta H_1$

Anhydride	State	Soln.	Mean temp., °C.	$-\Delta H_1$, cal. per mole	$-\Delta H_1$, mean, cal. per mole
Acetic	l	A	30.46	40174	40174
Propionic	l	B	30.44	38703	
		B	30.44	38815	38754
Isobutyric	l	A	30.44	38904	
		A	30.44	38931	38918
Trimethylacetic	l	A	30.45	37048	
		A	30.45	36924	
		A	30.45	37104	37025
Maleic	s	A	30.45	30326	
		A	30.45	30333	
		A	30.63	30310	30323
Methylmaleic	l	A	30.45	31483	
		A	30.45	31430	31457
Succinic	s	A	30.44	30183	
		A	30.44	30202	30192
Methylsuccinic	l	A	31.04	34035	
		A	31.04	33992	34013
α,α-Dimethylsuccinic	l	A	50.12	32442	
		A	50.12	32456	32449
trans-α,β-Dimethylsuccinic	s	C	50.13	29105	
		C	50.24	29118	29112
Tetramethylsuccinic	s	A	50.12	27737	
		A	50.12	27869	27803

It was hoped that the heat of reaction of equation 1 could be obtained by conversion of the

(21) *Cf.* Auwers and Eisenlohr, *J. prakt. Chem., N. F.*, **84**, 77 (1911).

(22) Francis and Willson, *J. Chem. Soc.*, **103**, 2238 (1913).

(23) Auwers and Meyer, *Ber.*, **23**, 293 (1890).

TABLE II

HEATS OF NEUTRALIZATION, $-\Delta H_2$

Acid	State	Soln.	Mean temp., °C.	$-\Delta H_1$, cal. per mole	$-\Delta H_1$, mean, cal. per mole
Acetic	l	A	30.46	13171	13171
Propionic	l	B	30.44	12655	
		B	30.44	12643	12649
Isobutyric	l	A	30.44	12229	
		A	30.44	12235	
		A	30.44	12232	12232
		A	40.09	12085	12085
Trimethylacetic	s	A	40.03	10882	
		A	40.03	10864	10873
Maleic	s	A	30.44	22159	
		A	30.44	22107	22133
Methylmaleic	s	A	30.44	23488	
		A	30.44	23435	23462
Succinic	s	A	30.45	19143	
		A	30.45	19127	19135
Methylsuccinic	s	A	30.64	21056	
		A	30.81	21008	21032
Methylene-succinic	s	A	30.45	19485	
		A	30.45	19487	19486
α,α-Dimethyl-succinic	s	A	50.12	18899	
		A	50.12	18954	18927
meso-α,β-Di-methylsuccinic	s	A	30.55	22342	
		A	30.55	22319	22330
dl-α,β-Dimethyl-succinic	s	C	50.12	22077	
		C	50.12	22319	22061
		C	30.70	23242	
		C	30.70	23234	23238
Tetramethyl-succinic	s	A	50.12	19492	
		A	50.12	19487	19489

TABLE III

HEATS OF DILUTION, $-\Delta H_3$

Solution	Composition, % dioxane	Temp., °C.	$-\Delta H_3$, cal. per mole
A	45.5	30	136
		50	117
B	30	30	58
C	0	50	1

data of Table IV to the gaseous state by determining heats of vaporization and sublimation. A static all-glass vapor pressure apparatus was constructed which permitted accurate vapor pressure measurements in the range 0.01 to 100 mm. With this equipment measurements on many of the compounds listed in the above tables were made over a range of temperatures, with good results for liquids but with indifferent success in the case of solids. The solid compounds showed extraordinary delays in the establishment of constant vapor pressure. Furthermore, the solid dicarboxylic acids were recrystallized from solvents, and in order to free them from traces of these impurities, sublimation *in vacuo* into the vapor pressure apparatus was attempted. It was found, however, that at temperatures at which sublimation could be effected with reasonable speed, some decomposition, attended by formation of water, occurred. This work was therefore abandoned and the incomplete data will not be reported here, since no use can be made of them in the following discussion.[24]

Our failure to reduce the data to a common and readily interpretable standard state destroys much of the force of the conclusions to be drawn from Table IV. Nevertheless, some interesting qualitative points can be brought out. In this discussion more weight will be given to values obtained in this investigation than to those determined from heats of combustion, also given in Table IV. The justifications for this choice are: (a) carefully purified materials used by us, and (b) formation of our data of Table IV as rather large differences of relatively small directly determined heat values. We are unable, however, to explain in detail the causes of the discrepancies of the two sets of data of Table IV. It will be noted first of all that methyl substitution in acetic acid has substantially no effect on the heats of hydrolysis of the corresponding anhydrides. The trimethylacetic anhydride is no exception since the heat of fusion of the acid is probably of the order of 1 to 2 kcal.,[25] thus making the heat of the liquid to liquid reaction about 13 to 14 kcal. This is in marked contrast to the well-known effect of methyl groups on the acid strength, demonstrated also by the series of the heats of neutralization given in Table II.

In the series of cyclic anhydrides of Table IV, however, methyl substitution has a very marked and systematic effect. If one allows again 1 to 2 kcal. for the heats of fusion and computes all reactions to the same state of aggregation, one sees that *unsymmetrical* methyl substitution invariably increases the heat of hydrolysis while symmetrical substitution decreases it still more markedly. Even the comparison of the *trans*-α,β-dimethylsuccinic and the tetramethylsuccinic anhydrides bears out this conclusion. Although we are unable to account for these effects even semiquanti-

(24) The work of F. H. MacDougall on acetic and propionic acids [THIS JOURNAL, **58**, 2585 (1936); **63**, 3420 (1941)] indicates that the very considerable association of the vapors of these acids even at low pressures seriously impairs the calculation of heats of vaporization from vapor pressures of the carboxylic acids.

(25) The heat of fusion of trimethylacetic acid is not recorded in the literature. The heats of fusion of propionic and isobutyric acids are 1.8 and 1.2 kcal., respectively.

TABLE IV

HEATS OF HYDROLYSIS, $-\Delta H$

Anhydride	Present investigation: State Anhydride	Acid	$-\Delta H$, kcal. per mole	From heats of combustion: State Anhydride	Acid	$-\Delta H$, kcal. per mole
Acetic	l	l	13.96			
Propionic	l	l	13.52			
Isobutyric	l	l	14.59			
Trimethylacetic	l	s	15.12			
Maleic	s	s	8.33			
Methylmaleic	l	s	8.13			
Succinic	s	s	11.20	s	s	12.5[b]
Methylsuccinic	l	s	13.11	l	s	14.6[b]
α,α-Dimethylsuccinic[a]	l	s	13.63	s	s	12.1[b]
trans-α,β-Dimethylsuccinic[a]	s	s	7.06	s	s	7.7[b]
Tetramethylsuccinic[a]	s	s	8.43	s	s	3.1[b]

[a] Reaction carried out at 50°; all others at 30°. [b] From heat of combustion at 15° given by Verkade and Hartman, *Rec. trav. chim.*, **52**, 945 (1933).

tatively, it is more than probable that interactions are here involved similar to those which show themselves in the heats of hydrogenation of some five-membered carbon ring compounds[26] and which have been interpreted as "steric hindrance" between hydrogen atoms on adjacent carbons. In line with this conclusion is also the difference in the heats of hydrolysis of maleic and of succinic anhydrides, while the conventional view would take maleic anhydride for the more strained of the two five-membered rings, the data actually indicate the reverse, in line with the above-mentioned data on the cyclopentene–cyclopentane relationship.[27]

Finally, the absence of methyl substitution effects in straight-chain anhydrides, where complete freedom of orientation exists, points again to "steric hindrance" as the main if not the sole cause of the observed variations of the heats of hydrolysis. It may be noted in passing that these effects seem to bear no relation to the heats of ionization of the corresponding acids, for which Table II gives a series of relative values.

Without knowledge of the entropy changes concerned, it is rather futile to discuss in detail the relation of the thermal data obtained to the thermodynamic stability of the anhydrides and acids. It may be noted, however, that the increased stability of cyclic, as against the straight-chain, acid anhydrides, can be accounted for by their generally lower heats of hydrolysis and a probably less positive entropy change caused by a loss of mole numbers in their reaction with water. On the other hand, it is not at all probable that the increasing stability in the series succinic to tetramethylsuccinic anhydrides[28] can be so explained. Possibly some purely rate factors are here of more importance.

The authors wish to thank the Rockefeller Foundation for the grant under which this investigation was carried out.

Summary

Heats of the hydrolytic reaction: Anhydride (s or l) + H_2O (l) = Acid (s or l) computed from heats of reaction in solution are reported here for a number of straight-chain and cyclic (five-membered ring) acid anhydrides.

Acetic, propionic, isobutyric and trimethylacetic anhydrides were found to have the same heat of hydrolysis, showing no effect due to methyl substitution.

Methyl substitution in the ring compounds markedly alters the heat of hydrolysis. Unsymmetrical substitution of methyl groups in succinic anhydride increases the heat of hydrolysis, while symmetrical substitution decreases it. The presence of a double bond in the ring also decreases the heat of hydrolysis.

These effects are qualitatively discussed, and similarities to the trend of heats of hydrogenation of five-membered carbon ring compounds are pointed out.

CAMBRIDGE, MASS. RECEIVED MARCH 10, 1942

(26) Dolliver, Gresham, Kistiakowsky and Vaughan, THIS JOURNAL, **59**, 839 (1937).

(27) Some resonance interactions in maleic anhydride are not excluded, although they are unlikely in view of previous results on the heats of hydrogenation of the system —C=C—CO—O—, *cf.* Dolliver, Gresham, Kistiakowsky, Smith and Vaughan, *ibid.*, **60**, 448 (1938).

(28) Verkade, *Rec. trav. chim.*, **40**, 199 (1921).

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 878]

The Electron Diffraction Investigation of Propargyl Chloride, Bromide, and Iodide

BY LINUS PAULING, WALTER GORDY,[1] AND JOHN H. SAYLOR

The surprising discovery that the carbon–carbon single-bond distance in methylacetylene[2] and some related substances[2c] is less than the normal value suggested that the study of the propargyl halides would be of interest. We have carried out this study, and have found that the carbon–carbon triple-bond and single-bond distances are the same in these molecules as in methylacetylene, and that the carbon–halogen bond distances are somewhat larger than normal.

Experimental Methods

The propargyl halides were prepared in these Laboratories by Mr. Allan Grossberg from α-chloroallyl alcohol ($H_2C{=}CClCH_2OH$) kindly furnished by the Shell Development Company. This substance was converted into propargyl alcohol by the method described by Henry.[3] Propargyl chloride and propargyl bromide were then prepared by treating the alcohol with phosphorus trichloride and phosphorus tribromide, respectively.[4] Propargyl iodide was prepared from propargyl bromide and sodium iodide.[5]

The electron diffraction photographs were made in the usual way, with film distance 10.85 cm. and electron wave length 0.0613 Å. For each substance the ring diameters were measured separately by two observers on about ten photographs and the resultant values of $q_{obs} = 40 (\sin \theta/2)/\lambda$ were averaged. Estimates were made of the intensities of the apparent maxima and minima, and in addition curves were sketched reproducing the appearance of the photographs.

Radial distribution curves were calculated by the equation

$$lD(l) = \sum_k C_k \sin \frac{\pi}{10} q_k l$$

with use of coefficients C_k obtained from the estimated intensities by multiplication by the damping factor e^{-aq^2}.

(1) National Research Fellow in Physics.

(2) (a) G. Herzberg, F. Patat, and H. Verleger, *J. Phys. Chem.*, **41**, 123 (1937); (b) R. M. Badger and S. H. Bauer, *J. Chem. Phys.*, **5**, 599 (1937); (c) L. Pauling, H. D. Springall, and K. J. Palmer, THIS JOURNAL, **61**, 927 (1939).

(3) L. Henry, *Ber.*, **5**, 453, 569 (1872); **6**, 729 (1873).

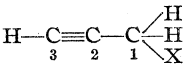
(4) L. Henry, *ibid.*, **7**, 761 (1874); **8**, 398 (1875); A. Kirsmann, *Bull. soc. chim.* [iv], **39**, 698 (1926).

(5) L. Henry, *Ber.*, **17**, 1132 (1884).

The simplified theoretical intensity curves were calculated by the equation

$$I(q) = \sum_i \sum_j (\psi_i \psi_j / l_{ij}) \sin \frac{\pi}{10} q l_{ij}$$

The scattering powers ψ were taken proportional to the atomic numbers of the atoms. The values C_3—H = 1.06 Å. and C_1—H = 1.09 Å. were assumed, and as the bond angle C_2–C_1–X was varied the other five angles of C_1 were kept equal in value. The atoms $HC_3C_2C_1$ were assumed to be collinear, as indicated by the bonds in the model



All calculations were made with use of punched cards and International Business Machines.

Interpretation of the Data

Propargyl Chloride.—The photographs of propargyl chloride, showing about thirteen maxima and thirteen minima, have the appearance indicated by curve Chloride Obs. in Fig. 2. The radial distribution curve calculated from the data of Table I is given in Fig. 1. The peaks of this curve are at 1.18, 1.48, 1.81, 2.72, and 3.72 Å. The same values, to within 0.01 Å., were found for the three principal peaks for other curves calculated with somewhat changed values of the coefficients C. These distances correspond, respectively, to C_3—C_2, C_2—C_1, C_1—Cl, C_2—Cl (plus C_3—C_1), and C_3—Cl.

We make the following assumptions: 1. The distance C_3—C_2 has the triple-bond value 1.20 Å. 2. The carbon chain is linear. 3. The three carbon–chlorine distances have approximately (to within about 0.02 Å.) the values 1.81, 2.72, and 3.72 Å. given by the three principal peaks of the radial distribution curve.

These assumptions determine the structure completely, except for the uncertainty resulting from the possible small deviations from the radial distribution values. The bond angle $\alpha = C_2$–C_1–Cl is indicated to be near 112°. If the distance C_2–C_1 were equal to 1.47 or 1.48 Å., as indicated by the radial distribution curve and by the values for methylacetylene and related molecules, and the three carbon–chlorine distances were to

TABLE I
ELECTRON DIFFRACTION DATA FOR PROPARGYL CHLORIDE

Max.	Min.	I	C	q_{obs}	q_B	q_B/q_{obs}
	1	−2	−20	7.83	8.9	(1.14)
1		+0.5	+ 5	10.66	11.4	(1.07)
	2	−2.5	−23	13.81	13.9	1.007
2		+7	+63	16.97	17.1	1.007
	3	−6	−51	20.25	20.2	0.997
3		+7	+57	23.55	23.7	1.006
	4[a]	0	0	28.53	29.9	...
4		+3	+20	32.42	33.6	(1.036)
	5	0	0	35.61	35.6	1.000
5		+6	+34	38.69	38.5	0.995
	6	−7	−35	42.38	42.0	0.991
6		+7	+32	45.43	45.6	1.003
	7	−2	− 8	50.19	51.3	1.022
7		+5	+16	54.03	55.2	1.021
	8	0	0	57.33	57.5	1.003
8		+5	+12	60.09	59.9	0.997
	9	−7	−14	63.93	63.9	1.000
9		+7	+12	68.50	69.7	1.017
10		+4.5	+ 5	75.18	76.3	1.015
11		+6	+ 4	81.48	82.4	1.011
12		+6	+ 3	88.17	91.3	(1.023)
					Average	1.006
					Average deviation	0.008

[a] A small apparent maximum could be seen between maxima 3 and 4.

show the minimum deviations from the above values, the bond angle would be 111°.

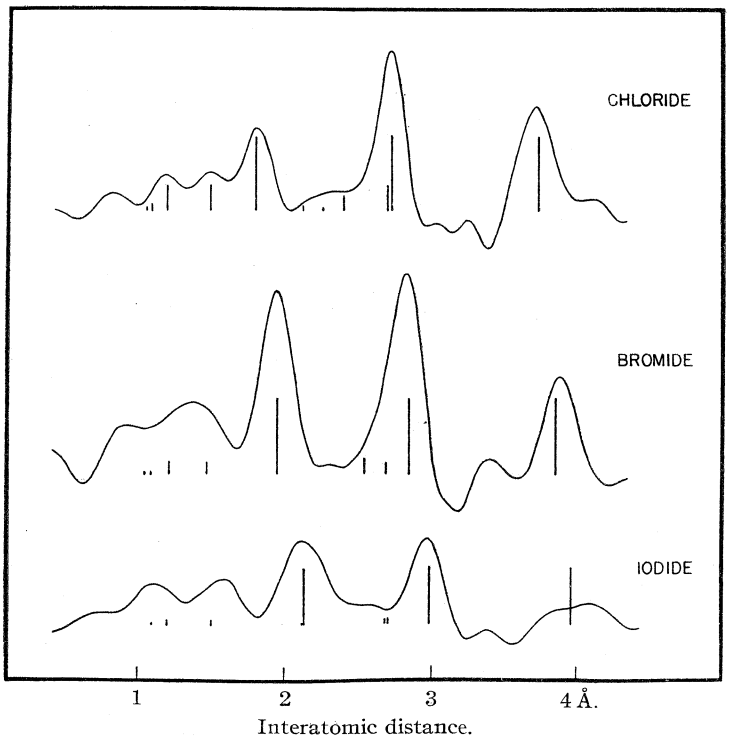


Fig. 1.—Radial distribution curves for the propargyl halides. The vertical lines correspond to the finally accepted structures.

In Fig. 2 calculated intensity curves are given for models with $\alpha = 109° 30'$, 111°, and 112° 30′ and with the above assumptions satisfied (Table IV). These curves, A, B, and C, agree well with the appearance of the photographs; the agreement is best for the curve with $\alpha = 111°$, in particular with respect to the relative intensities of maxima 7 and 8, and we accept the value of this angle as $\alpha = 111° \pm 2°$.

Curves for various other models for which interatomic distances differ from those for this model by as much as 0.03 Å., such as those for models D and E (Fig. 2, Table IV), were found to be less satisfactory, and those for models with larger deviations were unsatisfactory.

The quantitative comparison of values of q_{ob} and q_{calcd} for model B given in Table I leads to the average ratio $q_B/q_{obs} = 1.006$. Giving equal weight to this and the radial distribution values, we accept as the final values for propargyl chloride the following: $C_3—C_2 = 1.20$ Å. (not varied), $C_2—C_1 = 1.48 \pm 0.02$ Å, $C_1—Cl = 1.82 \pm 0.02$ Å., angle $C_2—C_1—Cl = 111 \pm 2°$, $C_2—Cl = 2.72 \pm 0.03$ Å., $C_3—Cl = 3.73 \pm 0.03$ Å.

Propargyl Bromide.—The data for propargyl bromide given in Table II lead to a radial distribution curve (Fig. 1) with the two carbon–carbon peaks unresolved and with well-defined carbon–bromine peaks at 1.95, 2.84, and 3.85 Å. The three intensity curves F, G, and H of Fig. 2 are calculated for the assumed values $C_3—C_2 = 1.20$ and $C_1—Br = 1.95$ Å., the angle α and $C_2—C_1$ distance being varied in such a way as to give the longer carbon-bromine distances approximately the radial distribution values. It is seen that all three curves are in good agreement with the appearance of the photographs as represented by the curve shown in Fig. 2; the $C_1—C_2$ distance and bond angle accordingly cannot be determined directly. We assume that the $C_1—C_2$ distance has the value 1.47 Å., the average of those found in methylacetylene (1.46 Å.) and the chloride (1.48 ± 0.02 Å.); the corresponding curve, G, is a little better than the other two, of which F makes the 8th maximum too weak and H makes the 5th too weak.

TABLE II

ELECTRON DIFFRACTION DATA FOR PROPARGYL BROMIDE

Max.	Min.	I	C	q_{obs}	q_G	q_G/q_{obs}
1		+ 1.3	+10	10.35	11.0	(1.06)
	2	− 3	−26	13.23	13.8	(1.04)
2		+ 8	+60	16.55	16.4	0.991
	3	−10	−68	19.45	19.1	0.982
3		+12	+75	22.45	22.8	1.015
	4	− 8	−48	27.20	28.0	(1.029)
4		+ 6	+30	30.85	32.3	(1.046)
	5	− 1.5	− 7	33.75	35.2	(1.043)
5		+ 4	+15	37.04	37.0	0.999
	6	− 6.5	−20	40.54	39.9	0.984
6		+10	+25	43.19	43.3	1.003
	7	− 6.5	−12	48.22	47.5	0.985
7		+ 5	+ 7	51.82	53.1	1.024
	8	− 2	− 2	54.1	55.7	1.029
8		+ 4	+ 4	57.1	57.7	1.011
9		+ 7	+ 4	63.6	64.1	1.008
10		+ 7	+ 2	70.6	73.4	(1.039)
					Average	1.003
					Average deviation	0.003

Various other models were found to be unsatisfactory; for example, models I and J (Fig. 2), with C_1—Br given the value 1.91 equal to the sum of the single bond radii and the C—C—Cl angle chosen so as to make the long C—Br distances close to the radial distribution values, fail to give the observed relative intensities of maxima 6, 7, and 8.

The quantitative comparison of q_{obs} and q_{calcd} for model G leads to the average ratio q_G/q_{obs} = 1.003 (omitting values which seem less reliable than the others). We accept the following parameter values: C_3—C_2 = 1.20 Å., C_2—C_1 = 1.47 ± 0.02 Å., C_1—Br = 1.95 ± 0.02 Å., angle C_2—C_1—Br = 112° ± 2°, C_2—Br = 2.85 ± 0.03 Å., C_3—Br = 3.85 ± 0.03 Å.

TABLE III

ELECTRON DIFFRACTION DATA FOR PROPARGYL IODIDE

Max.	Min.	I	C	q_{obs}	q_{calcd}	q_{calcd}/q_{obs}
1		+ 3	+28	9.80	10.8	(1.10)
	2	− 4	−40	12.47	13.6	(1.09)
2		+ 2	+16	15.83	15.9	1.004
	3	− 6	−46	18.51	18.2	0.983
3		+11	+77	21.49	21.5	1.000
	4	− 8	−48	25.56	25.0	0.978
4		+ 7	+35	29.60	30.7	(1.037)
	5	− 6	−26	32.93	34.1	(1.035)
5		+ 2	+ 7	36.45	36.5	1.001
	6	− 3	−10	37.85	38.0	1.003
6[a]		+ 9	+25	40.55	41.1	1.013
	7	− 9	−18	46.29	44.5	(0.962)
7		+ 9	+14	49.07	48.3	0.984
8		+ 6	+ 6	54.8	56.0	1.022
9		+ 6	+ 3	62.4	61.4	0.984
					Average	0.997
					Average deviation	0.012

[a] A shelf at q = 44.7 could be seen on the outer edge of this ring.

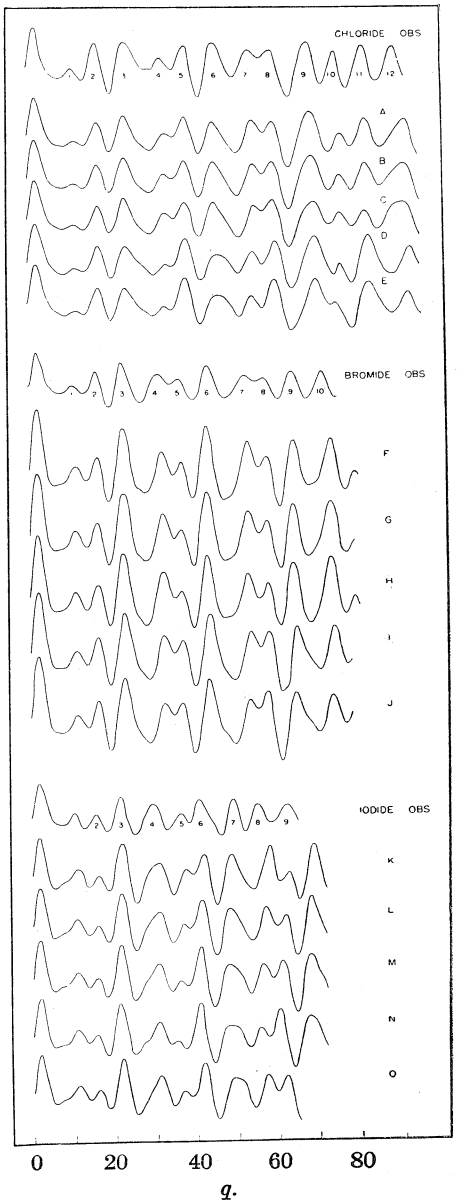


Fig. 2.—Curves (marked Chloride Obs., Bromide Obs., Iodide Obs.) drawn to represent the appearance of electron diffraction photographs, and calculated intensity curves for the propargyl halides.

Propargyl Iodide.—The photographs of propargyl iodide were not so good as those of the bromide, which were themselves inferior to those of the chloride. The radial distribution curve of Fig. 1, corresponding to the data in Table III, has well-defined maxima at 2.13 and 2.96 Å., and poorer ones at 1.2, 1.5, and 4.1 Å.

TABLE IV

DISTANCES AND BOND ANGLES FOR PROPARGYL HALIDE MODELS

Model X = Cl	C_1-X	C_3-C_2	C_2-C_1	Angle α	C_2-Cl	C_3-Cl
A	1.81	1.20	1.50	109°30′	2.71	3.72
B	1.81	1.20	1.47	111°	2.71	3.72
C	1.81	1.20	1.44	112°30′	2.72	3.72
D	1.81	1.20	1.50	111°	2.69	3.72
E	1.76	1.20	1.47	113°40′	2.71	3.72
X = Br						
F	1.95	1.20	1.52	110°	2.85	3.85
G	1.95	1.20	1.47	112°	2.85	3.85
H	1.95	1.20	1.42	114°	2.84	3.85
I	1.91	1.20	1.47	112°	2.81	3.82
J	1.91	1.20	1.47	115°	2.86	3.88
X = I						
K	2.13	1.20	1.47	108°	2.95	3.90
L	2.13	1.20	1.47	110°	2.98	3.95
M	2.13	1.20	1.47	112°	3.01	4.00
N	2.13	1.20	1.47	114°	3.05	4.05
O	2.10	1.20	1.47	110°30′	2.95	3.94

There is no possibility of evaluating the carbon-carbon distances from the data. We assume the values C_1–C_2 = 1.47 Å. and C_2–C_3 = 1.20 Å. With these, the two C–I distances 2.13 and 2.96 Å. lead to the value 109° for the C—C—I bond angle. Curves K, L, M, and N of Fig. 2 are calculated for models with C—I = 2.13 Å. and with bond angle 108, 110, 112, and 114°, respectively (Table IV); of these K and N are unsatisfactory, especially with respect to the intensities of maxima 8 and 9. The best agreement is obtained for the curve interpolated between L and M; because of the poor quality of the photographs, however, this cannot be given much significance. Various other models also give unsatisfactory curves, such as that for model O (with C_1–I = 2.10 Å., angle 110°30′) shown in Fig. 2.

The quantitative comparison in Table III is for the model with angle 111°, intermediate between L and M. It leads to the ratio q_{calcd}/q_{obs} = 0.997. We accept for this molecule the values C_3–C_2 = 1.20 Å., C_2–C_1 = 1.47 Å., C_1–I = 2.13 ± 0.03 Å., angle C_2–C_1–I = 111° ± 3°, C_2–I = 3.00 ± 0.05 A., C_3–I = 3.98 ± 0.07 Å.

Discussion of the Structures

There is only one surprising feature of the structures found for these molecules; this is that the carbon–halogen bond distances are larger than those usually observed. Each of the values found, C–Cl = 1.83 Å., C–Br = 1.95 Å., and C–I = 2.13 Å., exceeds the normal single-bond value (1.76, 1.91, and 2.10 Å., respectively) by a significant amount, the difference being largest (0.07 Å.) for the chloride and smallest for the iodide.

A plausible *ad hoc* explanation for this is that there occurs resonance between the normal structure H—C≡C—CH_2–:$\ddot{X}$: and an ionic structure H—C^+=C=CH_2 :$\ddot{X}$:$^-$ (in addition to the usual ionic structure H—C≡C—$\overset{+}{C}H_2$:$\ddot{X}$:$^-$ which confers ionic character on the C–Cl bond). This explanation accounts for the decrease in magnitude of the deviation in the sequence chloride, bromide, iodide, for which the electronegativity of the halogen decreases.[6]

A much greater deviation, about 0.30 Å., of nitrogen–halogen interatomic distances from the single-bond values was observed for nitrosyl chloride and nitrosyl bromide by Ketelaar and Palmer,[7] who offered a similar explanation, based on resonance with the ionic structure :O$^+$≡N: :$\ddot{X}$:$^-$.

We are indebted to Dr. V. Schomaker for valuable help in this work.

Summary

The electron diffraction investigation of the propargyl halides has been carried out, leading to the interatomic distances C≡C = 1.20 Å. (assumed), C–C = 1.47 ± 0.02 Å., C–Cl = 1.82 ± 0.02 Å., C–Br = 1.95 ± 0.02 Å., and C–I = 2.13 ± 0.03 Å. and the angles C–C–Cl = 111 ± 2°, C–C–Br = 112 ± 2°, and C–C–I = 111 ± 3°.

PASADENA, CALIFORNIA RECEIVED MAY 1, 1942

(6) It was suggested by Dr. S. Winstein [Dissertation, California Institute of Technology (1939)] that the large values of the mole refraction of the allyl halides could be explained as resulting from large polarizabilities of the molecules due to resonance of the type discussed in the text above. This would lead to large values of the mole refraction for the propargyl halides also.

(7) J. A. A. Ketelaar and K. J. Palmer, THIS JOURNAL, **59**, 2629 (1937).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Cyanates and Thiocyanates of Phosphorus, Arsenic and Antimony

BY HERBERT H. ANDERSON

Forbes and Anderson[1] recently isolated cyanates or isocyanates, or both, of silicon, phosphorus and boron by the action of silver (iso)cyanate upon the corresponding chlorides. In the present report similar halogenoid derivatives have been prepared from $POCl_3$, $AsCl_3$ and $SbCl_3$, and some interesting transformations have been noted in the compounds thus obtained. Thiocyanates, $PO(SCN)_3$ and $As(SCN)_3$, have been prepared also.

Phosphoryl Isocyanate and Cyanate

Preparation.—The preparation was made in two sections, each of which gave about the same yield of product. A total of 300 g. of powdered silver (iso)cyanate and 200 g. of phosphoryl chloride in 225 ml. of pure benzene was used in a forty-four hour reflux, with occasional shaking. Filtration removed silver chloride and phosphoryl cyanate, $PO(OCN)_3$, a hydrolyzable yellowish compound (from the thermal transformation of soluble liquid into insoluble solid). After removal of benzene, there remained 12.5 g. of a colorless liquid; an 11% yield of isocyanate. Formation of the insoluble cyanate was the chief reason for the low yield. Lead cyanate reacted extremely slowly with phosphoryl chloride under similar conditions. Vacuum distillation of $PO(NCO)_3$ was necessary. *Analysis* of the purified material: a weighed sample was hydrolyzed in a large excess of 3 *N* sodium hydroxide, and then heated in 6 *N* nitric acid for an hour; ammonium phosphomolybdate was precipitated from a volume of 100 ml., 2 *N* in nitric acid. $PO(NCO)_3$: phosphorus found 17.4, 17.7%, average 17.6%; calculated 17.90%. The molecular weights were determined by the Dumas method, with determination and subtraction of the weight of phosphoryl-cyanate, non-volatile, from thermal transformation of the isocyanate during the experiment. Found: 171.4, 169.9, average 170.7; calculated 173.04.

Properties.—The m. p. was 5.0 ± 0.5°. Density measurements were obtained by the delivery from a pipet; the index of refraction was obtained at 20° using an Abbé refractometer, with thermostated prism. Boiling points at various pressures were obtained via the dynamic method in an all glass apparatus, with a calibrated thermometer. A slight uncertainty exists, because of a non-volatile form, $PO(OCN)_3$ possibly having a slight solubility; this cyanate is produced very slowly by heating the isocyanate above 100°.

A summary of the data obtained: colorless compound; b. p. (760 mm.) 193.1 ± 2°; m. p. 5.0 ± 0.5°; vapor pressure, $\log_{10} p$ (mm.) = $9.1682 - 2931/T$; λ_v = 13,410 cal.; λ_v/T = 28.8 cal./deg.; density, 1.570 ± 0.003 g./cc.; refractive index 1.4804; vapor pressure at 25°, calculated 0.2 mm. As a lachrymator it is much weaker than phosphoryl chloride.

(1) Forbes and Anderson, THIS JOURNAL, **62**, 761 (1940).

Non-volatile Form; Phosphoryl Cyanate.—This form was prepared from pure phosphoryl isocyanate by heating at 156° for five hours, and then removing unchanged $PO(NCO)_3$ in a high vacuum. Analysis for phosphorus, 17.6%; calculated 17.90%. This cyanate was a light yellow powder without evident crystalline structure. A gas was evolved when the substance was treated with acid. About 2% of the isocyanate was converted into an insoluble form in twenty hours at 100°. This cyanate darkened when warmed in a high vacuum, and was non-volatile. It has been previously[1] shown that phosphorus triisocyanate and its insoluble product are in equilibrium; one form can be converted into another—high temperatures favor the liquid form.

Phosphoryl Thiocyanate[2]

Preparation.—The preparation was made with benzene as solvent, to preclude loss of any low-boiling isothiocyanate. One hundred and ten grams of powdered silver thiocyanate, 80 g. of phosphoryl chloride, and 130 ml. of pure benzene were heated forty hours on a steam-bath, with shaking. Twenty grams of product was obtained by fractional distillation at diminished pressure. The middle fraction was redistilled and the new middle fraction taken for measurements.

Analysis.—A weighed sample was hydrolyzed in 6 *N* nitric acid—since the hydrolysis in water alone would have been very slow. $PO(SCN)_3 + 3H_2O = H_3PO_4 + 3HSCN$. Nitric acid, especially hot concentrated acid, converts thiocyanic acid into ammonium acid sulfate and hydrocyanic acid. The solution was kept at 100° for a half hour, to ensure presence of phosphorus at its highest oxidation level. Ammonium phosphomolybdate was precipitated in a volume of 100 ml., 2 *N* in nitric acid. Phosphorus found 13.9, 13.5, 14.2%, average 13.9%; calculated 14.00%. Molecular weights were obtained from the freezing point lowering of benzene; found 222, 232, average 227; calculated 221.2.

Properties.—The purest liquid when freshly prepared was colorless, although old samples tended to become orange colored. This liquid supercooled below 0° before freezing; m. p. 13.8 ± 1.0°; boiling point 300.1 ± 2°; slight decomposition and darkening set in during vapor pressure determinations, especially at temperatures over 250°. Vapor pressure equation: $\log_{10} P = 8.5330 - 3240/T$; λ_v = 14.820 cal.; λ_v/T = 25.8 cal./deg.; density 1.484 g./cc.; isomeric changes, none. Thiocyanate test on 0.01 ml. of pure fresh liquid, with acidified ferric nitrate was very strong. Vapor pressure at 25°: calculated 0.005 mm.; no lachrymatory properties.

Arsenic Tricyanate

Preparation.—The analog of phosphorus tricyanate[1] was prepared by reaction of 45 g. of silver (iso)cyanate and 17 g. of arsenic trichloride in 100 ml. of benzene (all operations

(2) Previously prepared in solution, only; Dixon, *J. Chem. Soc.*, **79**, 541 (1901).

were carried out under a hood, with special precautions to avoid inhalation or physical contact with poisonous arsenic compounds). The reaction was complete after thirty minutes of reflux on a steam-bath, with much shaking. Filtration yielded a very pale yellow solution; evaporation of the solution under diminished pressure resulted in a white solid of only moderate solubility in benzene at 30°. Upon warming the solid melted. Attempts to distil the liquid were made at various pressures: at 1 atmosphere, little distillation, product isomerizing from $As(NCO)_3$ into non-volatile $As(OCN)_3$ as shown later; at 150 mm., in an all-glass system, 10–11 g. or 60% distillation; at 73 mm. and 150.7°, about 80% distillation. Two products were obtained, volatile $As(NCO)_3$, and non-volatile $As(OCN)_3$; both liberated carbon dioxide with water or acid.

Analysis was accomplished by hydrolysis of weighed pellets in hydrochloric acid. $As(NCO)_3 + 3HCl = AsCl_3 + 3HNCO$. Then $3HNCO + 3H_2O + 3HCl = 3NH_4Cl + 3CO_2$. The solution was made alkaline, then acid, and finally a large excess of sodium bicarbonate was added. Arsenic was determined by titration with standard iodine solution, with addition of starch indicator near the end-point. Found, arsenic 37.28, 37.20%, average 37.24; calcd. 37.28%. This end-point is quite sharp at room temperature.

Properties.—Because of the poisonous nature of the arsenic compound and because of its instability, only limited observations were made. A boiling point at 760 mm., 224.0 ± 2°, was obtained by rapid comparison with that of naphthalene under similar conditions, and with the same thermometer; m. p. 97.1 ± 1°. Color was pure white; crystalline form, long needles. Vapor pressure equation, from 73 and 760 mm. points: $\log_{10} P = 8.7638 - 2924/T$. At room temperature the vapor pressure of the solid is estimated at 0.05 mm. Needles were obtained by cooling a saturated benzene solution. Approximately: $\lambda_v = 14{,}800$ cal.; $\lambda_v/T = 26.9$ cal./deg.

Non-volatile Form; Arsenic Cyanate.—This was prepared by refluxing $As(NCO)_3$ at about 230°, with fairly rapid production of the solid form; excess $As(NCO)_3$ was removed in a high vacuum. Heating of the solid form, presumably $As(OCN)_3$, at 0.001 mm. pressure resulted only in darkening, without volatilization.

Arsenic Thiocyanate

Miquel[3] thought he had volatilized a few centigrams of this compound when he heated arsenic trichloride with lead thiocyanate. He may have obtained a mixture of arsenic trioxide with some diluent. A reaction of arsenic trichloride with silver thiocyanate, in benzene as solvent, did produce a substance containing arsenic and thiocyanate. This supposed arsenious thiocyanate was soluble in benzene, but did not crystallize from benzene. Upon heating in a molecular still (tested with mercury) the substance did not distil or sublime; there was no melting point, and the solid merely darkened. Color, yellow to orange-yellow, perhaps due to free thiocyanic acid.

Antimony Cyanates

Preparation.—Twenty-seven grams of distilled antimony trichloride was dissolved in 150 ml. of pure benzene, and 60 g. (an excess) of powdered silver cyanate was added, with shaking. After ten minutes on a steam-bath the reaction started, with extremely vigorous boiling of the solvent. After thirty minutes, with shaking and addition of more benzene, the solution was filtered hot. Some $Sb(NCO)_3$ deposited as needles from the solution upon cooling. Three hundred ml. of hot benzene was used in washing the solid mixture, but the major fraction of the antimony isocyanate remained undissolved; the solubility of this isocyanate is much less than (2 g./100 ml.) of benzene at 30°. Upon careful evaporation of all the benzene, the solid was transferred to a molecular still, and partially sublimed—P = 0.001 mm. approximately; temperatures, upper bath −78°, lower bath 175°; distance between surfaces about 25 mm.

Analysis for antimony (*cf.* arsenic isocyanate): found 48.9, 49.2%; calculated 49.13% Sb.

Properties.—The color was pure white; small crystals in sublimation; larger crystals from a benzene solution. The vapor pressure was roughly 0.002 mm. at 125°. At 160° this $Sb(NCO)_3$ isomerizes, with considerable swelling, to $Sb(OCN)_3$, even with gradual elevation of temperature. The calculated m. p., 196°, is above the isomerization point.

Non-volatile Form; Antimony Cyanate.—The outstanding features of the supposed $Sb(OCN)_3$ are: its non-volatility at 0.001 mm.; the swelling at 160°, during its production from $Sb(NCO)_3$; lastly, evolution of gas when the cyanate is hydrolyzed in water.

Discussion of Results

Outside of the fifth group of the periodic table, the only available boiling points were $Si(SCN)_4$, b. p. 314.2°,[4] $Si(NCO)_4$, b. p. 185.6°,[1] and $Si(OCN)_4$, b. p. 247.2°.[1] The cyanate and isocyanate isomers were obtained in a definite ratio in several experiments; no evidence has been obtained indicating transformation of one isomer into the other.

In the fifth group definite trends have been observed. Isomeric changes are: $P(NCO)_3 \underset{100°}{\overset{\text{slowly}}{\rightleftharpoons}} P(OCN)_3$.[1] As shown above, $PO(NCO)_3 \xrightarrow{\text{heat}} PO(OCN)_3$. $As(NCO)_3 \xrightarrow{\text{heat}} As(OCN)_3$. $Sb(NCO)_3 \xrightarrow{\text{heat}} Sb(OCN)_3$. The evidence with the thiocyanates is not so clear-cut. Miquel[3] said his $P(SCN)_3$ boiled between 260 and 270° (average 265); Dixon[2] described $P(SCN)_3$ as follows, "A reddish-yellow, clear, dense oil . . . at 170° . . . suddenly changed to a sticky black solid which presently became hard and brittle." $PO(SCN)_3$ shows no marked isomeric changes. The behavior of $As(SCN)_3$ seems intermediate, between $P(SCN)_3$ and $PO(SCN)_3$: upon expulsion of the last trace of solvent at reduced pressure, the liquid turned into a yellowish solid which was not volatile—not even in a molecular still.

(3) Miquel, *Ann. chim. phys.*, [V] **II**, 343 (1877).

(4) Reynolds, *J. Chem. Soc.*, **89**, 397 (1906).

Regularity of Boiling Points.—A comparison of the boiling points of isocyanates with those of the corresponding chlorides shows interesting regularities. The difference between the boiling points of PCl_3 and $P(NCO)_3$ divided by the number of halogenoid groups is 31.9° − (169.3 − 73.5)/3. When $PO(NCO)_3$, $As(NCO)_3$, and $Si(NCO)_4$ are included, the average increment is 31.0°. The only volatile *cyanate*, $Si(OCN)_4$, yields a higher increment, 47.4°.

Upon comparing the *thiocyanate* series with the corresponding chlorides, the increment is also found identical; $P(SCN)_3$, $PO(SCN)_3$, and $Si(SCN)_4$ yield an average increment of 64.1°. All of these three thiocyanates have been shown to be thiocyanates, not isothiocyanates.

Further work in this field is planned. The author is much indebted to Professor George S. Forbes, of this Laboratory, for valuable suggestions during the experimental work.

Summary

1. Phosphoryl isocyanate, $PO(NCO)_3$, arsenic isocyanate, $As(NCO)_3$, and antimony isocyanate, $Sb(NCO)_3$, have been prepared by the action of silver (iso)cyanate with the appropriate chloride.

2. Thermal transformations of these volatile isocyanates into the corresponding non-volatile cyanates have been observed.

3. Phosphoryl thiocyanate has been isolated; arsenic thiocyanate, provisionally reported by Miquel, has been found non-volatile.

4. Various physical properties have been investigated quantitatively and an apparent regularity of boiling points has been observed.

CAMBRIDGE, MASSACHUSETTS RECEIVED MARCH 24, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF MICHIGAN]

The Preparation and Properties of Potassium Oxalatostannate[1]

BY HOBART H. WILLARD AND TAFT Y. TORIBARA[2]

Previous workers[3] prepared and studied the complex oxalatostannates. Pechard[3b] claimed to have isolated a complex oxalatostannic acid, but he made no investigation of it. Hausmann and Löwenthal[3a] and Rosenheim and Platsch[3c] found that such an acid of constant composition could not be obtained.

Pechard prepared a potassium salt by dissolving stannic acid in potassium bioxalate solution and reported a formula $K_2SnO(C_2O_4)_2 \cdot 7H_2O$. Rosenheim and Platsch repeated Pechard's work but got entirely different results and reported a formula $K_6Sn_2(C_2O_4)_7 \cdot 5H_2O$. They state that the usual qualitative reactions for stannic tin and for oxalic acid are completely concealed and attribute this to the formation of a complex.

In connection with some proposed studies on oxalatothiostannates, further studies were made on the oxalatostannates.

Experimental

Preparation of Oxalatostannates.—The previous use of stannic acid in preparing solutions of oxalatostannates was tedious as well as undesirable because of the introduction of adsorbed impurities. For this reason a scheme was devised for preparing a solution of stannic tin in excess of oxalic acid only. Attempts to isolate an oxalatostannic acid proved unsuccessful as previous workers had found. The potassium salt was prepared and studied.

A mixture of 25 g. of metallic tin (30-mesh) and 125 g. of oxalic acid in 800 ml. of distilled water was cooled in an ice–salt-bath to about 5°. With continuous mechanical stirring, 150 ml. of 30% hydrogen peroxide (superoxol) was gradually added, and the reaction mixture was kept cool until all the tin had dissolved. Such a procedure required six hours or more. The excess of hydrogen peroxide was decomposed by adding 40 mg. of finely divided platinum black, and the solution was kept cool in an ice–salt bath during this procedure to prevent hydrolysis of the tin. The platinum was removed by filtration and the filtrate was the desired solution of oxalatostannic acid in excess of oxalic acid.

To prepare the potassium salt, the solution was analyzed for total oxalate and for tin. Allowing two moles of oxalate per mole of tin, the excess oxalic acid was neutralized by adding the calculated quantity of solid potassium bicarbonate. The solution was cooled to 0°, and the solid was filtered off. To recrystallize the salt obtained, it was dissolved in the smallest amount of water at 60°, allowed to cool to room temperature and then cooled to 0°. This salt was found to be very stable, and the air-dried solid gave a very definite composition, $K_6Sn_2(C_2O_4)_7 \cdot 4H_2O$. The potassium was determined gravimetrically as the perchlorate after first removing the tin by dropping hydrobromic acid into a boiling perchloric acid solution. The tin was determined gravimetrically as stannic oxide, using

(1) From a dissertation submitted by Taft Y. Toribara in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan, 1942.

(2) Florence Fenwick Memorial Fellow, 1939–1942.

(3) (a) Hausmann and Löwenthal, *Ann.*, **89**, 104 (1854); (b) Pechard, *Compt. rend.*, **116**, 1513 (1893); (c) Rosenheim and Platsch, *Z. anorg. Chem.*, **20**, 308 (1899).

ammonium hydroxide to precipitate the tin after the oxalate had been removed with concentrated sulfuric acid. The quantity of stannic oxide after ignition was determined by difference, using solid ammonium iodide in the second ignition. The amount of oxalate present was determined gravimetrically by oxidizing it to carbon dioxide with permanganate and absorbing the gas on ascarite.

Anal. Calcd.: K, 20.22; Sn, 20.46; C_2O_4, 53.11; H_2O, 6.21. Found: K, 20.23, 20.18; Sn, 20.41, 20.46, 20.51; C_2O_4, 53.13, 53.16, 53.20; H_2O, 6.21, 6.21.

It will be noticed that the formula obtained is identical with that of Rosenheim and Platsch[3c] with the exception of the water of hydration. In this work the water of hydration was determined directly by driving it off by heat and absorbing it on dehydrite. Previous workers determined the amount of water by difference. In order to make certain that the tetrahydrate was the solid phase in equilibrium with a saturated solution at 25°, a solution of the salt was evaporated at that temperature until the solid precipitated out. This solid was then centrifuged and analyzed immediately for water. Analyses gave 6.27% and 6.24% of water as compared to 6.21% theoretical for a tetrahydrate.

Titration of $K_6Sn_2(C_2O_4)_7$ by Alkali.—It was noticed in preparing the salt that the *p*H was low even after the calculated quantity of potassium bicarbonate had been added. A water solution of the pure compound gave the same acidic solution. Standard potassium hydroxide was added, and the *p*H change was followed with a glass electrode. The titration curve is shown in Fig. 1.

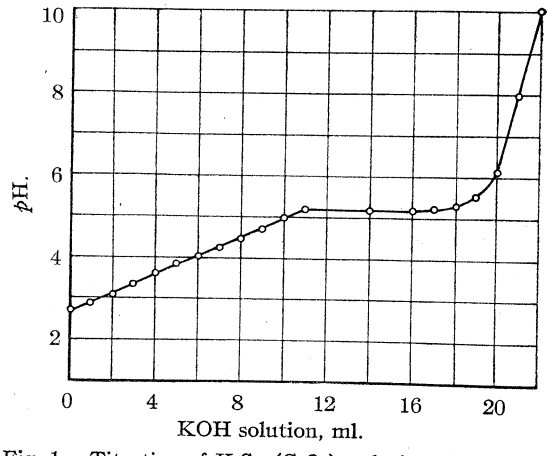


Fig. 1.—Titration of $K_6Sn_2(C_2O_4)_7$ solution with alkali.

The *p*H increased uniformly with the addition of the base until a value of 5.2 was attained. At the point where the solution became turbid from the precipitation of stannic hydroxide, the ratio $KOH/K_6Sn_2(C_2O_4)_7$ was 4.0. The *p*H remained constant until nearly all the tin had been precipitated and then increased rapidly. At the point where the steep rise in the curve occurs, the ratio $KOH/K_6Sn_2(C_2O_4)_7$ is 8.0, or just enough potassium hydroxide to precipitate all the tin in the compound as stannic hydroxide. The low value of the *p*H of a water solution of the compound may be explained on the basis of the hydrolysis of the tin.

The System $K_2C_2O_4$–$Sn(C_2O_4)_2$–H_2O.—The compound $K_6Sn_2(C_2O_4)_7 \cdot 4H_2O$ may be considered as composed of $3K_2C_2O_4$, $2Sn(C_2O_4)_2$ and $4H_2O$. Rosenheim and Platsch[3c] reported the composition of the barium salt as $Ba_2Sn(C_2O_4)_4 \cdot 8H_2O$. For these reasons it appeared as if a complex might result from other combinations of $K_2C_2O_4$, $Sn(C_2O_4)_2$ and H_2O.

The system was studied at 25°. In order to obtain true equilibrium between the solid phase and the saturated liquid phase, the solid was caused to precipitate out of the liquid phase at the temperature desired by slow evaporation. This was accomplished by the use of an isothermal evaporator constructed by attaching a number of side-arms just below the neck of a one-liter round-bottom flask. Rubber stoppers were placed on the side-arms so that 8-inch test-tubes containing the solutions could be attached. Sulfuric acid was placed in the flask as the desiccant, and the system was evacuated to hasten evaporation.

The solutions were made by adding appropriate quantities of potassium oxalate to a properly neutralized oxalatostannate solution with an oxalate to tin ratio of 2.9 and to a nearly saturated solution of potassium oxalatostannate. When a sufficient amount of solid phase had been deposited, the tubes were removed from the evaporator and allowed to stand a few days in the thermostat to ensure equilibrium between the solid and liquid phases. Samples of the solution were measured in weight pipets and the wet solid in weighing bottles. Both solution and solid were analyzed for total oxalate and tin; the water was determined by difference. The composition of the solid in equilibrium with the liquid was determined by the well-known residue method of F. A. H. Schreinemakers.[4]

The data in Table I are shown plotted on triangular coördinates in Fig. 2.

(4) Schreinemakers, *Z. physik. Chem.*, **11**, 75–109 (1893).

TABLE I

THE SYSTEM $K_2C_2O_4$–$Sn(C_2O_4)_2$–H_2O AT 25°

Wt. in liquid phase $K_2C_2O_4$	Wt. in liquid phase $Sn(C_2O_4)_2$	Wt. in wet residue $K_2C_2O_4$	Wt. in wet residue $Sn(C_2O_4)_2$
1.90	5.54	24.06	37.84
1.80	2.14	24.91	29.32
4.11	0.79	28.31	33.04
7.44	0.72	30.99	34.79
13.64	1.41	36.53	40.19
22.37	0.79	38.57	38.81
27.25	2.81	69.94	2.82
27.80	1.25	71.20	0.29
27.21	0.54	68.16	0.47
27.12	0.00	$K_2C_2O_4 \cdot H_2O$	

The tie lines indicate that only two solid phases, $K_6Sn_2(C_2O_4)_7 \cdot 4H_2O$ and $K_2C_2O_4 \cdot H_2O$, were found in the region of oxalate to tin ratio greater than 3.5, showing that tin does not form any complex with potassium oxalate in which the oxalate to tin ratio is greater than this. Since the purified product obtained from a neutralized oxalatostannate solution with an oxalate to tin ratio less than 3 was $K_6Sn_2(C_2O_4)_7 \cdot 4H_2O$, there is reason to believe that it is the only compound formed from a combination of the three components.

That point on the isotherm representing the solubility of pure potassium oxalatostannate in water, was determined from both under- and super-saturation; equilibrium was reached very slowly from the latter direction, but the results obtained were in close agreement, giving an average of 3.94% of the anhydrous salt as the solubility. The aqueous solubility of potassium oxalate at 25° here reported, 27.12% (averaged from 6 determinations ranging between 27.09 and 27.15), differs somewhat from previous values: 27.40,[5] 27.36,[6] 27.2,[7] 27.40.[8] Equilibrium in this work was approached from both sides. The disagreement may result from the difference in analytical methods: whereas previous workers used the permanganate titration, oxalate was here determined gravimetrically as already described. Because of the absence of interferences and because larger samples may be used, the precision of the gravimetric method is greater than that of the volumetric method, which must be carried out under carefully controlled conditions. The density 25°/4° of the potassium oxalate solution, 1.2135, agrees with Rivett and O'Conner's value, 1.215.

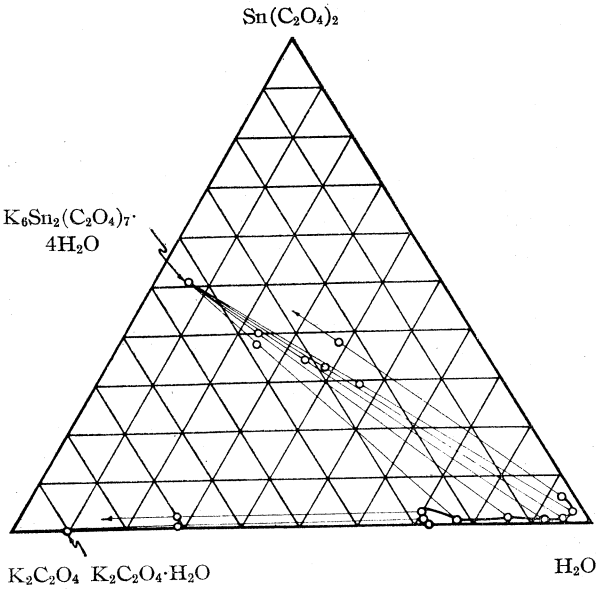


Fig. 2.—The system $K_2C_2O_4$–$Sn(C_2O_4)$–H_2O at 25°.

(5) Foote and Andrew, *Am. Chem. J.*, **34**, 153 (1905).
(6) Hartley, Drugman, Vlieland and Bourdillon, *J. Chem. Soc.*, **103**, 1747 (1913).
(7) Rivett and O'Conner, *ibid.*, **115**, 1346 (1919).
(8) Woskressenskaja, *Z. anorg. allgem. Chem.*, **155**, 115 (1926).

Summary

1. Tin was dissolved directly in oxalic acid, using hydrogen peroxide as an oxidizing agent.

2. Crystallized potassium oxalatostannate was shown to have the formula $K_6Sn_2(C_2O_4)_7 \cdot 4H_2O$.

3. The titration of a solution of potassium oxalatostannate was followed by *p*H measurements.

4. The solubility relations in the system, $K_2C_2O_4$–$Sn(C_2O_4)_2$–H_2O at 25° were determined, and the only solid phases present in the region of oxalate to tin ratio greater than 3.5 were $K_6Sn_2(C_2O_4)_7 \cdot 4H_2O$ and $K_2C_2O_4 \cdot H_2O$.

ANN ARBOR, MICHIGAN RECEIVED FEBRUARY 12, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF MICHIGAN]

A Study of Complex Dioxalatothiometastannates[1a]

BY HOBART H. WILLARD AND TAFT Y. TORIBARA[1b]

F. W. Clarke[1c] first noticed the unusual phenomenon that hydrogen sulfide will not precipitate stannic tin from an oxalic acid solution. This fact was used as the basis of a separation of tin from arsenic, antimony, molybdenum, lead, bismuth, copper and cadmium by a number of later investigators. Among them Thompson[2] was the first to recognize that hydrogen sulfide was actually absorbed by the solution of the oxalate of tin, and he suggested that a sulfostannate might be formed. Wheeler[3] found that under proper conditions one mole of sulfur was absorbed for every mole of tin present. He was interested in its application as a volumetric method for tin and made no attempt to study the complex. It was the purpose of this work to isolate this complex and to study its properties.

Experimental

Preparation of Dioxalatothiometastannates.—Tin was dissolved in oxalic acid using hydrogen peroxide[4] as the oxidizing agent. To the solution of oxalatostannic acid, an additional quantity of oxalic acid was added to increase the oxalate to tin ratio to a value greater than 10, following Wheeler's directions, to prevent precipitation of stannic sulfide in the next step. Hydrogen sulfide to saturation was passed into the solution near the boiling temperature. At room temperature, continued passage of hydrogen sulfide caused precipitation of stannic sulfide even from these high oxalate ratios, before the complex apparently could be formed. The excess of the gas was swept out of the cooled solution by passing carbon dioxide or nitrogen through it. By cooling this solution to 0°, a large part of the free oxalic acid but none of the dioxalatothiometastannic acid was precipitated. Attempts to isolate this acid proved unsuccessful because of its instability. Cautious evaporations to deposit a solid phase removed all the hydrogen sulfide along with the water. A number of other schemes were tried in an attempt to precipitate out either the desired acid or oxalic acid, but the properties of the two were found to be quite parallel.

The subsequent studies were made on the potassium salt, which was chosen because it was much less soluble than the impurity of potassium oxalate, and this made separation by crystallization a simple matter. The dipotassium dioxalatothiometastannate was prepared by neutralizing the excess of oxalic acid in much the same manner as in preparing potassium oxalatostannate. Allowing the one atom of sulfur and one mole of oxalate for each atom of tin, the excess of oxalic acid was neutralized with potassium bicarbonate.

At this stage it is very important that hydrogen sulfide be passed in long enough to give a 1:1 ratio between sulfide and tin. If the ratio is less than unity, part of the tin will be in the form of the more insoluble potassium oxalatostannate. It is also important that the *p*H after neutralization be high enough to convert all the excess oxalic acid to the neutral oxalate but still low enough to ensure that all the carbonate be present as undissociated carbonic acid. A consideration of the ionization constants of oxalic acid and carbonic acid shows that a *p*H of 6 will give a ratio $C_2O_4^{=}/HC_2O_4^{-}$ of 61, whereas the same *p*H will give a ratio H_2CO_3/HCO_3^{-} of 30. The most favorable *p*H is, therefore, somewhat under 6. In one experiment in which a quantity of potassium bicarbonate calculated from the analysis of the solution was gradually added, the *p*H during the process was followed with a glass electrode. The final *p*H obtained was 5.64, which agrees with that calculated to be the most favorable.

In order to obtain a good separation by fractional crystallization, it is important that the impurities be more soluble substances. Both potassium oxalatostannate and potassium bioxalate are much less soluble than the desired salt, but potassium oxalate is much more soluble.

An oxalatostannic acid solution was prepared as previously described,[4] and an additional 100 g. of oxalic acid was added to the solution. After heating the solution to about 80°, hydrogen sulfide was passed into the hot solution for 1.5 hours. The excess of hydrogen sulfide was swept out at room temperature by passing nitrogen or carbon dioxide through the solution for forty minutes. A sample of the solution was taken at this point and titrated with iodine to determine the sulfide content in order to ensure the equality of the tin and sulfur present. When this had been established, the solution was cooled to 0° to freeze out most of the excess of oxalic acid. After removing this oxalic acid, the solution was allowed to warm up to room temperature. Solid potassium bicarbonate was added cautiously until a *p*H of 5.6 was attained. Upon cooling this solution to 0°, it was found that most of the salt crystallized out in pure form. It was recrystallized from water by dissolving the solid at 50–60° and cooling to 0°. Prolonged standing at the higher temperature was avoided because of the relative instability of the salt. The solid was filtered off and vacuum-dried over sulfuric acid, then kept in a desiccator in an atmosphere of nitrogen. Of a theoretical quantity of 93 g., a total of 81 g. of the recrystallized salt was obtained, a yield of 87%.

It was found much more convenient to use concentrated solutions of oxalatostannic acid for the preparation because the relative losses due to solubility at 0° were small. Although concentration of a dilute solution is not possible,

(1a) From a dissertation submitted by Taft Y. Toribara in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan, 1939. The material in this paper was presented before the Division of Physical and Inorganic Chemistry at the Memphis meeting of the American Chemical Society, April, 1942.

(1b) Florence Fenwick Memorial Fellow, 1939–1942.

(1c) Clarke, *Am. J. Sci.*, **49**, 48–51 (1870).

(2) Thompson, *J. Soc. Chem. Ind.*, **15**, 179–181 (1896).

(3) Wheeler, *Analyst*, **63**, 883–4 (1938).

(4) Willard and Toribara, THIS JOURNAL, **64**, 1759 (1942).

it is still possible to obtain almost complete recovery by adding 3 volumes of ethyl alcohol to precipitate the solids in solution. Alcohol also precipitates all the potassium oxalate, but this can be removed by fractional crystallization. The use of more dilute solutions necessitates an extra recrystallization to obtain a very pure salt.

Since the compound was dried immediately after preparation to prevent decomposition, the amount of water of hydration varied with the time of drying. For this reason the samples for the analyses of the several constituents were all weighed at one time and after a short period of drying to remove surface moisture. The analyses gave the ratio of the components in the compound.

Anal. Found (moles $\times 10^3$ per gram): K, 4.532, 4.528; Sn, 2.265, 2.270; S, 2.265, 2.267; C_2O_4, 4.537, 4.531; H_2O (by difference), 4.50. Indicated formula: $K_2SnS(C_2O_4)_2 \cdot 2H_2O$.

Hydration and Stability of Dipotassium Dioxalatothiometastannate.—Water was determined directly on a salt which had been crystallized by cooling a solution saturated slightly above room temperature and which had been centrifuged at 1600 r. p. m. for thirty minutes. Analysis showed 9.11% of water, including surface moisture, or 2.25 moles of water per mole of salt. Some of this salt was dried at 95° for four hours without any decomposition. An analysis showed 8.30% of water, or 2.03 moles of water of crystallization. Continued drying at 60° for two weeks left only 0.6 molecule of water. Continued desiccation over sulfuric acid in a vacuum was also found to remove most of the water. A drastic process of desiccation, using the best vacuum obtainable from a Cenco Megavac pump and phosphorus pentoxide as the desiccant at a temperature of 60° for ten days, was found to remove all the water of hydration. No odor of hydrogen sulfide was evident when the flask was opened; such was not the case when the compound was decomposed by strong heating. The results indicate that the dihydrate is the phase which crystallized out of the solution and that it is quite stable. The stability of the compound to drastic drying was quite unexpected, especially in view of its behavior when wet.

The wet compound and the compound in solution were found to be unstable for two reasons: because of hydrolysis and because of atmospheric oxidation of the sulfide. A saturated solution of the compound remained clear for several weeks; a 0.1 *M* solution became tinged with yellow stannic sulfide within a few days; and more dilute solutions became tinged in even shorter periods of time. Boiling a solution of the compound caused separation of stannic sulfide, and prolonged heating at somewhat lower temperatures had the same effect. For this reason the process of recrystallization was accomplished in the shortest time possible. If the wet solid were allowed to remain in contact with air for any appreciable length of time, the sulfide was partially oxidized to free sulfur. When the compound had been dried, contact with air had no deleterious effects.

Reduction of the pressure above a solution of the salt at room temperature caused the liberation of hydrogen sulfide sufficient to precipitate stannic sulfide, making it impossible to use a low pressure evaporation to recover the salt. Complete removal of the water by such a process did not remove all the sulfur as in the case of the dioxalatothiometastannic acid.

Solubility of Dipotassium Dioxalatothiometastannate in Water.—The solubility of the salt at 25° was determined by saturating a solution at a slightly higher temperature in contact with the solid and then allowing it to come to equilibrium in the thermostat at the desired temperature. The average values obtained (based on oxalate, tin and sulfur analyses; the first two as already described[4] and sulfur by a titration with iodine) were: at 0°, 2.87% (±0.015); at 25°, 10.31% (±0.01); at 50°, about 30%, no exact determination being possible because of the instability of the solution.

***p*H of Water Solutions.**—A solution 0.1 *M* in dipotassium dioxalatothiometastannate, kept free from oxygen, was prepared, and the first *p*H was determined with a glass electrode as soon after solution as possible. It was found that the *p*H of this solution did not change definitely in a period of one week, the readings varying in the range of 3.38 to 3.31. After two days the solution started to take on a tinge of yellow from small amounts of stannic sulfide. The quantity of stannic sulfide formed was sufficient to impart a yellowish tint to the solution but was not an appreciable quantity. This seems to indicate that all the time-change of *p*H must have occurred in the first few minutes while the solid was being dissolved.

The 0.1 *M* solution was then diluted to make solutions approximately 0.025 *M* and 0.01 *M*. The initial *p*H for the 0.025 *M* solution was 3.48, dropping to 2.38 in twenty-five minutes and returning to 3.48 as a steady value. For the 0.01 *M* solution, the initial *p*H was 3.40, dropping to 2.33 in fifteen minutes and increasing to 3.52 on long standing. Noticeable formation of colloidal stannic sulfide took place during these changes. It appears from these results that an equilibrium *p*H between 3.3 and 3.5 exists for solutions of dipotassium dioxalatothiometastannate. The fact that the neutral salt gives an acid solution indicates hydrolysis of the tin. The decrease in *p*H with dilution suggests a dissociation of the complex with further hydrolysis of the tin, and the subsequent rise in *p*H with the precipitation of stannic sulfide a reversal of the hydrolysis.

Reactions in Solution.—Different cations were added to an approximately 0.1 *M* solution of dipotassium dioxalatothiometastannate. The metals giving sulfide precipitates in acid solution with hydrogen sulfide gave an interesting set of reactions. The metals forming the more insoluble sulfides as silver, bivalent copper, bismuth, pentavalent antimony and bivalent mercury precipitated immediately as sulfides when added to the solution of dipotassium dioxalatothiometastannate. Bivalent lead and cadmium produced white precipitates which gave a test for sulfur, indicating that oxalatothiometastannate precipitates of those metals were formed. Zinc gave no precipitate. From these data a rather qualitative estimation may be made of the concentration of the sulfide ion. Lead and cadmium did not give sulfide precipitates, but it may be reasoned that this might be caused by the lesser solubilities of their oxalatothiometastannates. In the case of zinc, the fact that no precipitate was formed may serve as a limit for the concentration of sulfide ion, for zinc can be completely precipitated by hydrogen sulfide from a solution in which the *p*H is between 2 and 3. Although zinc forms a complex in an oxalate solution, the introduction of hydro-

gen sulfide in such a solution (pH about 3) causes precipitation of zinc sulfide.

The alkaline earths gave precipitates of a complex oxalatothiometastannate in all cases when the concentration of dipotassium dioxalatothiometastannate was made sufficiently large. The qualitative order of decreasing solubility was found to be magnesium, strontium, calcium and barium. In the case of magnesium, it was necessary to use a saturated solution of the potassium salt and allow it to stand for some time after solid magnesium chloride had been dissolved in it. The strontium and calcium precipitates formed rather slowly. Solid lithium chloride and solid sodium sulfate were added to saturated solutions of the potassium salt. The lithium salt dissolved and then gave a dense precipitate of an oxalatothiometastannate salt, but the sodium salt caused no precipitation.

E. m. f. Measurements with Silver–Silver Sulfide Electrodes.—An attempt was made to determine the sulfide ion concentration by means of e. m. f. measurements, using a Ag–Ag_2S electrode. The silver–silver sulfide electrodes were prepared according to Noyes and Freed,[5] but the value of E did not agree with their value. Several other sets of electrodes were prepared in an attempt to check their value, but no two identical sets of electrodes could be prepared. It was found that consistent results could be obtained by using the same electrodes in different solutions of the same strength. For this reason one set of electrodes was used for all the measurements.

The standard potential, E_0, of this electrode was determined on the cell

Ag, Ag_2S, H_2S (0.0685) HCl (0.1) || satd. calomel electrode,

using the apparatus shown in Fig. 1. This cell gave 0.0780 v. for E at 25°, based on the value 0.2448 v. for the calomel electrode. Calculating the sulfide ion activity through the usual ionization constants for hydrogen sulfide (7.4×10^{-8} for K_1 and 1.2×10^{-15} for K_2), E_0 was then derived through the Nernst equation

$$E = E_0 - \frac{RT}{2F} \ln \frac{1}{a_{S^=}}$$

giving $E_0 = 0.7051$ v.

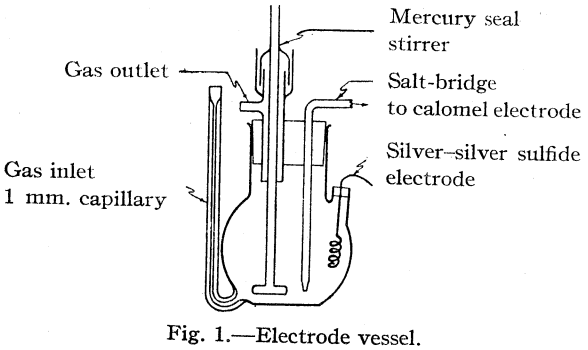


Fig. 1.—Electrode vessel.

Having found the value for E_0, e. m. f. measurements on solutions of different concentrations of dipotassium dioxalatothiometastannate were made. The solutions were made with water which had been freed of dissolved air by bubbling through it nitrogen for a sufficient length of time. After removing air from the apparatus, both the gas inlet and outlet were closed off. The results obtained are shown in Table I.

TABLE I

SULFIDE ACTIVITIES BY E. M. F. MEASUREMENTS AT 25°

$K_2SnS(C_2O_4)_2$ concn., M	E, volt	$a_{S^=}$, moles per liter
0.2458	0.0692	3.1×10^{-22}
.2189	.0698	3.2×10^{-22}
.0914	.1014	3.8×10^{-21}
.0906[a]	.0936	2.1×10^{-21}
.1000	.0889	1.4×10^{-21}
.0466[a]	.1110	8.0×10^{-21}

In the results marked a the maximum value of the e. m. f. was used. The e. m. f. was found to rise to a maximum and then to decrease. The solutions were examined and found to be colored with a yellow tinge from colloidal stannic sulfide. The other e. m. f. values were all steady, indicating equilibrium conditions, and the solutions were not colored by colloidal stannic sulfide. Equilibrium as evidenced by steady readings for eight hours or more was reached in about twelve hours.

The behavior of the solutions which showed the maximum e. m. f. values may be explained by stating that the hydrolysis of the salt proceeded to the point where the sulfide ion concentration built up sufficiently to produce a stannic sulfide precipitate. Since the electrode followed the concentration of the sulfide ion, the e. m. f. would rise to this point and then start to diminish as precipitation removed the sulfide ions. This point is probably the same point as that indicated by the minimum pH value noticed in the study of the pH of solutions of different concentrations.

The sulfide ion concentrations of the solutions of dipotassium dioxalatothiometastannate are in accord with the more qualitative observations on the addition of different metallic ions. In a solution of pH 2, the sulfide ion concentration in a saturated hydrogen sulfide solution would be approximately 6×10^{-20}. This is about the lower limit of pH at which zinc can be precipitated. Comparing this value with that of an approximately 0.1 M solution of dipotassium dioxalatothiometastannate as shown in Table I, it can be seen readily why zinc does not precipitate as a sulfide when added to a solution of the salt. Both lead and cadmium can be precipitated as

(5) Noyes and Freed, THIS JOURNAL, **42**, 476 (1920).

sulfides in a solution with such a sulfide ion concentration, but the complexes are precipitated instead probably because of their greater insolubility.

Summary

1. Dipotassium dioxalatothiometastannate was isolated for the first time and proved to have the formula $K_2SnS(C_2O_4)_2 \cdot 2H_2O$.

2. The compound was stable enough to permit removal of all of the water of hydration.

3. The solubilities of dipotassium dioxalatothiometastannate in water at 25 and 0° were determined.

4. The *p*H of water solutions of varying concentrations of dipotassium dioxalatothiometastannate was studied.

5. The reactions of a water solution of dipotassium dioxalatothiometastannate with various cations were studied.

6. E. m. f. measurements in solutions of dipotassium dioxalatothiometastannate with a silver–silver sulfide electrode were made in an attempt to determine the concentration of the sulfide ion.

ANN ARBOR, MICHIGAN RECEIVED FEBRUARY 12, 1942

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

The Reduction of Unsaturated Hydrocarbons at the Dropping Mercury Electrode. I. Phenyl Substituted Olefins and Acetylenes

BY H. A. LAITINEN AND S. WAWZONEK

Isolated ethylenic and acetylenic linkages are not reducible at the dropping mercury electrode. However, double bonds which are either conjugated with carbonyl groups or present in heterocyclic nuclei like pyridine and quinoline can be reduced.[1] We have found that other types of unsaturated linkage are electroreducible. In the present paper the results of a polarographic study of phenyl substituted olefins and acetylenes are reported. The reduction of other types of unsaturated hydrocarbons will be described in forthcoming publications.

Experimental

Dioxane–water mixtures containing 75% dioxane were used as a solvent, with 0.175 *M* tetrabutylammonium iodide as a supporting electrolyte. Since the half-wave potentials were unaffected by the *p*H of the solution (v. i.) unbuffered solutions were suitable for the measurements. Dioxane was found to be superior to acetone, isopropanol or methanol as a solvent in permitting the attainment of very negative potentials. In 50 to 85% dioxane solutions, using tetrabutylammonium iodide as the supporting electrolyte, the decomposition potential of the solvent was essentially constant at about −2.9 volts (*vs.* saturated calomel electrode), showing that the negative potential limit is determined by the discharge of the cation. Tetrabutylammonium salts were found to be superior to tetramethylammonium salts in having a more negative discharge potential.

The dropping mercury electrode had the following characteristics. At a pressure of 46.5 cm. of mercury, the drop time in the solvent used was 3.34 seconds (open circuit). The value of m was 2.05 mg. sec.$^{-1}$, with a calculated value of $m^{2/3}t^{1/6}$ of 1.973 mg.$^{2/3}$ sec.$^{-1/2}$ (open circuit). Values of $m^{2/3}t^{1/6}$ at various potentials are given in Table II.

The electrolysis cell had a simple cylindrical shape with a mercury pool anode, and was provided with side arms for anode connection and for admission of nitrogen for the removal of dissolved oxygen. The anode potential was measured against a saturated calomel electrode (S. C. E.) by using a sintered glass salt bridge of the type described by Laitinen.[2] Its value was found to be reproducible at −0.452 volt in solutions of constant electrolyte concentration.

The current–voltage curves were determined with a Model XI Heyrovsky Polarograph having a current scale calibrated in microamperes. Data for the logarithmic analyses of the curves were obtained with a Fisher Elecdropode having specially calibrated current and voltage scales. The average resistance of the electrolytic cell was determined by the conventional Wheatstone bridge method, and found to be 2000 ohms. The half-wave potentials given in Table I are corrected for iR drop. All experiments were carried out at 25° in a water thermostat regulated to ±0.1°.

Materials.—The tetrabutylammonium iodide was prepared by a slight modification of the method used by Cox, Kraus and Fuoss.[3] Tri-*n*-butylamine (200 ml.) and *n*-butyl iodide (100 ml.) were heated together on a steam-bath for sixty-five hours. The resulting solid was filtered, washed with a small amount of ethyl acetate and then dissolved in the least amount of cold ethanol. The resulting solution was mixed with an equal volume of 10% potassium hydroxide in ethanol and poured into water. Removal of part of the alcohol under reduced pressure gave a crystalline precipitate of tetrabutylammonium iodide

(1) I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, New York, N. Y., 1941.

(2) H. A. Laitinen, *Ind. Eng. Chem., Anal. Ed.*, **13**, 393 (1941).

(3) N. L. Cox, C. A. Kraus and R. M. Fuoss, *Trans. Faraday Soc.*, **31**, 749 (1935).

which, after three recrystallizations from anhydrous ethyl acetate, melted at 141–142°; yield 150 g.

The dioxane was purified by refluxing with sodium for ten hours and distilling.

Stilbene, triphenylethylene, diphenylbutadiene, heptyne-1, *o*-allylanisole, and phenylacetylene were obtained from stock and were purified before using. The styrene was first treated with K_2HgI_4 and then freshly distilled.

1,1-Diphenylethylene,[4] β-methylstyrene[5] and tetraphenylethylene[6] were prepared by appropriate methods given in the literature.

Diphenylacetylene was prepared by a modification of the method used by Limpricht and Schwanert.[7] Stilbene dibromide was refluxed with 200 ml. of 30% potassium hydroxide in methanol for twelve hours. The potassium bromide formed was filtered off while hot and washed with ether. Water was next added to the filtrate, the methanol removed by distillation and the resulting solution extracted with ether. Removal of the ether followed by distillation under reduced pressure gave 14.6 g. of diphenylacetylene; b. p. 111–112° (1 mm.).

Results

All of the hydrocarbons investigated showed a single well-defined reduction wave. Tracings of typical polarograms are shown in Fig. 1 for styrene and in Fig. 2 for triphenylethylene. Only a slight tendency toward the appearance of maxima was observed. With low concentrations of hydrocarbons no maxima were found, whereas slight maxima were obtained in most cases with increasing hydrocarbon concentration. The most prominent maxima are shown in Fig. 2, and never were found to interfere with diffusion current measurements. The maxima were not suppressed by methyl red. Hence half-wave potential measurements were made only on curves having no maxima.

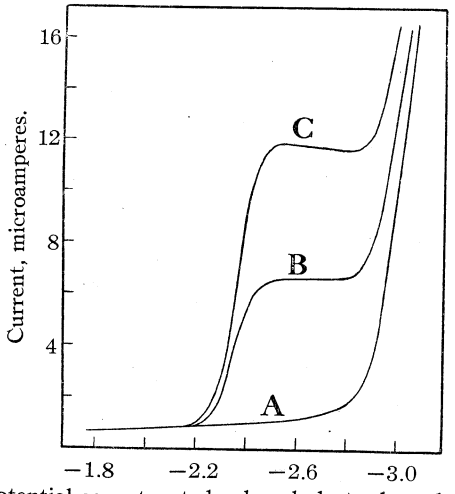


Fig. 1.—Polarogram of styrene in 75% dioxane, 0.175 *M*, tetrabutylammonium iodide: Curve A, residual current; curve B, 1.095 × 10^{-3} *M* styrene; curve C, 2.19 × 10^{-3} *M* styrene.

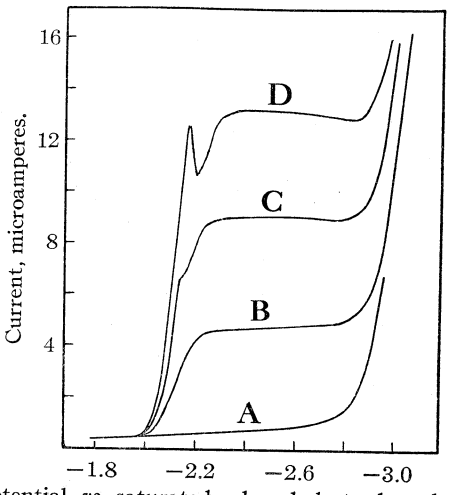


Fig. 2.—Polarogram of triphenylethylene in 75% dioxane, 0.175 *M* tetrabutylammonium iodide: Curve A, residual current; curve B, 1.178 × 10^{-3} *M*; curve C, 2.36 × 10^{-3} *M*; curve D, 3.54 × 10^{-3} *M* triphenylethylene.

TABLE I

HALF-WAVE POTENTIALS AND DIFFUSION CURRENT CONSTANTS OF VARIOUS COMPOUNDS IN 0.175 *M* TETRABUTYLAMMONIUM IODIDE, 75% DIOXANE

Compound	$\pi_{1/2}$ *vs.* S. C. E., volts	i_d, microamperes	*C*, millimoles/liter	i_d/C, microamperes/millimole/liter
$C_6H_5CH{=}CH_2$ (I)	2.343	5.63	1.095	5.25
	2.351	11.00	2.190	5.03
$C_6H_5CH{=}CHCH_3$ (II)	2.537	5.26	1.176	4.48
	2.539	13.00	2.940	4.42
$(C_6H_5)_2C{=}CH_2$ (III)	2.258	3.62	0.947	3.82
	2.270	9.03	2.365	3.98
$C_6H_5CH{=}CHC_6H_5$ (IV)	2.140	2.38	0.597	3.99
	2.137	4.83	1.194	4.05
	2.157	7.20	1.790	4.02
	2.136[a]	4.60[a]	1.127[a]	4.08[a]
$C_6H_5{-}CH{=}CH{-}CH{=}CHC_6H_5$ (V)	1.981	3.18	0.810	3.92
	1.978	6.40	1.620	3.85
$(C_6H_5)_2C{=}CHC_6H_5$ (VI)	2.118	4.19	1.178	3.56
	2.113	8.68	2.36	3.53
	...[b]	12.83	3.54	3.62
$(C_6H_5)_2C{=}C(C_6H_5)_2$ (VII)	2.046	6.87	1.95	3.52
$C_6H_5C{\equiv}CH$ (VIII)	2.370	12.85	1.395	9.20
	...[b]	25.12	2.790	9.00
$C_6H_5C{\equiv}CC_6H_5$ (IX)	2.195	12.10	1.595	7.59
	...[b]	23.88	3.190	7.48

[a] In 0.175 *M* tetrabutylammonium iodide, 0.052 *M* tetrabutylammonium hydroxide; anode potential −0.440 volt (*vs.* S. C. E.). [b] Slight maximum, half-wave potential not determined.

(4) C. F. H. Allen and S. Converse, "Organic Syntheses," Collective Vol. I, 2nd ed., p. 226.

(5) J. Levy and M. Dvoleitzka-Gombinska, *Bull. soc. chim.*, **49**, 1765 (1931).

(6) J. F. Norris, R. Thomas and B. M. Brown, *Ber.*, **43**, 2958 (1910).

(7) H. Limpricht and H. Schwanert, *Ann.*, **145**, 347 (1868).

Table I shows a summary of the observed half-wave potentials and diffusion current constants.

The half-wave potential was found quite generally to be independent of the concentration of hydrocarbon even in unbuffered solution. Since the solution at the electrode surface becomes more alkaline at the half-wave point with increasing hydrocarbon concentration it may be inferred that the half-wave potential is independent of the *p*H of the solution. Actually it was shown (Table I) that stilbene has the same half-wave potential in alkaline solution as in neutral solution when proper correction for anode potential is made.

The diffusion current showed a proportionality with concentration in every case studied. It is evident that the polarographic method offers a possible quantitative procedure for the determination of these hydrocarbons in the absence of more readily reducible substances.

A comparison of the half-wave potentials of the series of phenyl ethylenes (I, III, IV, VI, VII in Table I) shows the increasing ease of electroreduction with increasing substitution. The comparison between stilbene and 1,1-diphenylethylene (compounds III and IV) clearly demonstrates the increased activation of the double bond in stilbene. Styrene (I) was found to be distinctly more readily reduced than β-methylstyrene (II).

1,4-Diphenylbutadiene-1,3 (V) was shown to undergo a 1,4-reduction, because a comparison of its diffusion current constant with those of ethylenic hydrocarbons of similar molecular weight (III and IV) showed that only two electrons per molecule are involved in the reduction. No indication of a second reduction step was found.

Phenylacetylene (VIII) and diphenylacetylene (IX) were found to have slightly more negative half-wave potentials than the corresponding ethylenic compounds (I and IV). A complete reduction involving four electrons per molecule, giving rise to a single polarographic wave, was found in each case by a comparison of the observed diffusion current constants.

Heptyne-1 and *o*-allylanisole did not give polarographic waves under these conditions, showing that isolated double or triple bonds are not electroreducible.

Mechanism of the Reduction.—Logarithmic analyses of the reduction waves of stilbene and diphenylacetylene were made by plotting the quantity log $i/(i_d - i)$ against the potential. The results are shown in Fig. 3. In each case a straight line was obtained. The slopes of the lines were 0.062 and 0.069 volt for stilbene and diphenylacetylene, respectively. These results are in essential agreement with the theoretical slope of 0.059 volt (25°) for a reversible, potential-determining reaction involving one electron.

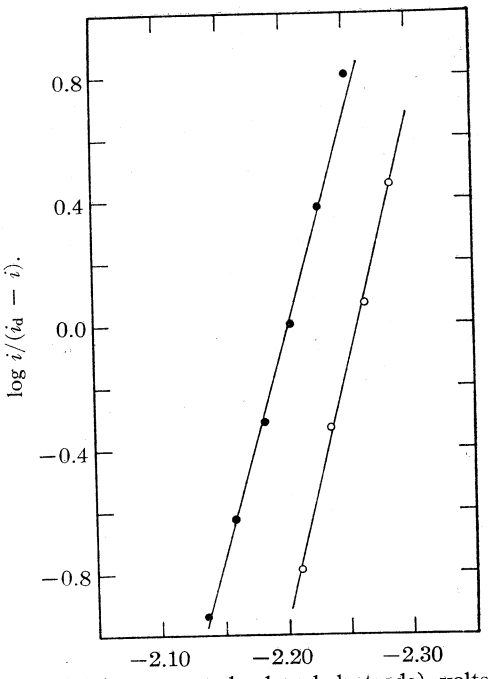


Fig. 3.—Analysis of current–voltage curves: O, $C_6H_5CH{=}CHC_6H_5$; ●, $C_6H_5C{\equiv}CC_6H_5$; in 75% dioxane, 0.175 *M* tetrabutylammonium iodide.

Considering the fact that the half-wave potential is independent of the *p*H, the following mechanism is suggested for the electroreduction of olefins in neutral or alkaline solution.

$$R + e^- \rightleftarrows R^- \text{ (reversible, potential determining)} \quad (1)$$

$$R^- + e^- \longrightarrow R^= \text{ (irreversible)} \quad (2)$$

$$R^= + 2H_2O \longrightarrow RH_2 + 2OH^- \text{ (irreversible, rapid)} \quad (3)$$

The first reversible reaction would yield a univalent negative ion, the surface concentration of which would be proportional to the current, i. The concentration of the original hydrocarbon is porportional to the quantity $i_d - i$, where i_d is the diffusion current. The potential π would be determined by the ratio $C^0_R/C^0_{R^-}$ of the surface concentrations of R and R^-. Then

$$\pi = \text{const} + \frac{RT}{F} \ln \frac{C^0_R}{C^0_{R^-}} = \pi_{1/2} + \frac{RT}{F} \ln \frac{i_d - i}{i} \quad (4)$$

Equation 4 is the observed current–voltage relationship, with the theoretical slope of the logarithmic plot equal to 0.059 volt at 25°.

The second step of the reduction cannot involve the addition of a proton to form a free radical RH unless the rate of the reaction $R^- + H_2O \rightarrow RH + OH^-$ would be independent of the pH, because the surface concentration $C^0_{R^-}$, and hence the half-wave potential, would be a function of the pH. Hence the simplest assumption is made, namely, that the second step involves the irreversible addition of a second electron to form a divalent negative ion of the type postulated as a product of sodium addition to unsaturated hydrocarbons in liquid ammonia.[8] The subsequent addition of two protons to the divalent ion could not affect the concentration of the potential-determining system; hence the reduction potential would not depend on the pH.

For acetylenic hydrocarbons, a similar two-step electron addition is postulated as the first stage. Since the half-wave potential of an acetylenic hydrocarbon is in general more negative than that of the corresponding ethylenic compound, it is readily understood that a single reduction wave must be obtained. The reduction potential, according to the proposed mechanism, is determined by the ease of addition of the first electron. The corresponding ethylenic compound at this potential would be rapidly reduced completely to the substituted ethane.

Diffusion Coefficients.—A knowledge of the relative diffusion coefficients of organic compounds as a function of the molecular weight is helpful in determining the number of electrons involved per molecule in the electrode reaction. For an accurate calculation it is necessary to correct the observed values of the diffusion current constants for the change of drop time with potential, particularly at extremely negative values of the potential.[9] At potentials more negative than −2 volts (*vs.* S. C. E.) the drop time becomes so small that a direct measurement no longer is convenient. Hence the relative value of $m^{2/3}t^{1/6}$ as a function of potential was measured by determining the diffusion current of nitrobenzene over a wide range of potentials (−1.4 to −2.8 volts). From the relative values, the absolute values of $m^{2/3}t^{1/6}$ were easily calulated.

Table II gives the values of $m^{2/3}t^{1/6}$ at the potentials, π_d, at which the diffusion currents were measured, together with the relative values of the diffusion coefficient taking that of styrene as unity. The absolute values in the last column were calculated from the Ilkovic equation,[1,10] using average values of the diffusion current constants from Table I. The decrease in the diffusion coefficients with increasing molecular weight is evident. Although there may be some question as to the accuracy of the Ilkovic equation at very negative potentials because of the rapid drop rate, the results given are certainly sufficiently exact to be useful in interpreting diffusion current data in 75% dioxane in unknown cases.

TABLE II

COMPARISON OF DIFFUSION COEFFICIENTS OF HYDROCARBONS IN 75% DIOXANE

Compound	π_d	$m^{2/3}t^{1/6}$, mg.$^{2/3}$sec.$^{-1/2}$	D, rel.	D_1 cm.^{2} sec.$^{-1}$ × 10^5
I	2.51	1.792	1.000	0.562
II	2.75	1.702	0.832	.468
III	2.45	1.800	.579	.325
IV	2.31	1.828	.593	.333
V	2.15	1.869	.526	.296
VI	2.28	1.836	.461	.260
VII	2.21	1.852	.440	.248
VIII	2.55	1.782	.793	.440
IX	2.35	1.820	.521	.293

Summary

The polarographic reduction of a series of phenyl substituted olefins and acetylenes has been studied. The most suitable solvent medium was found to be a dioxane–water mixture containing 75% dioxane, with tetrabutylammonium iodide as a supporting electrolyte.

Each compound was found to give a single reduction wave in neutral or alkaline medium with a half-wave potential which is independent of the pH. The diffusion current was found to be proportional to the hydrocarbon concentration. The polarographic method has been shown to be useful in the detection and determination of olefins and acetylenes with activated double or triple bonds.

The half-wave potential is suggested as a measure of the relative activation of ethylenic and acetylenic linkages by substituent groups.

The equations of the rising portions of the waves have been determined for an olefin and an acetylenic hydrocarbon, and a reduction mechanism is suggested.

The diffusion coefficients of the hydrocarbons have been calculated from diffusion current data.

URBANA, ILL. RECEIVED MAY 13, 1942

(8) W. C. Fernelius and G. W. Watt, *Chem. Rev.*, **20**, 216 (1937).

(9) I. M. Kolthoff and E. F. Orlemann, THIS JOURNAL, **63**, 2085 (1941).

(10) D. Ilkovic, *Coll. Czech. Chem. Commun.*, **6**, 498 (1934).

[CONTRIBUTION FROM THE METALLURGICAL FUNDAMENTALS SECTION, METALLURGICAL DIVISION, BUREAU OF MINES, UNITED STATES DEPARTMENT OF THE INTERIOR]

High-temperature Heat Content of Mn_3O_4, $MnSiO_3$ and Mn_3C[1]

BY J. C. SOUTHARD[2] AND G. E. MOORE[3]

This paper is a report of part of a program of study of the thermodynamic properties of manganese compounds that is being conducted at the Pacific Experiment Station of the Bureau of Mines, U. S. Department of the Interior. Entropies of Mn_3O_4,[4] $MnSiO_3$[5] and Mn_3C[6] have been determined previously. Heats of formation of these substances are given in standard reference tables, so that high-temperature heat contents are the only additional quantities required for the calculation of their free energies at high temperatures. These calculations will not be presented here, however, because present values of the heats of formation are not considered satisfactorily accurate and a redetermination of them is in progress.

Apparatus and Materials

The high-temperature heat contents were determined in an apparatus previously described.[7] The apparatus was calibrated electrically, using the relation 1 calorie = 4.1833 Int. Joules. During the measurements Mn_3O_4 was contained in an unsealed platinum-alloy capsule, $MnSiO_3$ in a sealed platinum-alloy capsule, and Mn_3C in an evacuated and sealed silica-glass capsule.

Mn_3O_4 was prepared by roasting a high-purity sample of $MnSO_4$ in air at about 1000°. Analysis for active oxygen by titration with ferrous sulfate and potassium permangate gave 7.01 and 7.03% before the measurements and 6.96% afterward (calcd. 6.99%). Manganese was determined to be 71.89 and 71.92% (calcd. 72.02%). The sample was sintered at 1200° before use. Description of the preparation and analysis of the $MnSiO_3$ sample has been given by Kelley.[5] Mn_3C was prepared by F. S. Boericke from ground electrolytic manganese and high-purity, degassed carbon black by heating three days at 850°. Analysis showed that the sample contained about 98.8% Mn_3C and 1.2% free manganese. No correction will be made for this impurity, since it would be of the order of 0.1%.

(1) Published by permission of the Director, Bureau of Mines, U. S. Department of the Interior. Not subject to copyright.

(2) Formerly Chemist, Metallurgical Division, Bureau of Mines; present address, Titanium Alloy Mfg. Co., Niagara Falls, N. Y.

(3) Associate Physical Chemist, Metallurgical Division, Bureau of Mines.

(4) R. W. Millar, THIS JOURNAL, **50**, 1875 (1928).

(5) K. K. Kelley, *ibid.*, **63**, 2750 (1941).

(6) K. K. Kelley and G. E. Moore, unpublished.

(7) J. C. Southard, THIS JOURNAL, **63**, 3142 (1941).

Results

The experimentally determined heat contents above 298.1° K. of Mn_3O_4, $MnSiO_3$ and Mn_3C are given in Tables I, II, and III in the order in which they were taken. Graphs of the data show transitions in Mn_3O_4 at 1445 ± 40° K. amounting to 4500 cal./g. f. w., and in Mn_3C at 1310 ± 2° K. amounting to 3140 cal./g. f. w. The heat-content curve of $MnSiO_3$ shows no discontinuities. No previous high-temperature heat-content data for these substances appear in the literature.

TABLE I

HIGH-TEMPERATURE HEAT CONTENT OF Mn_3O_4
(g. f. w. = 228.79)

Temp., °K.	$H_T - H_{298.1}$ cal./g. f. w.
1290.9	42,180
1429.9	49,680
1421.1	49,050
985.6	28,020
984.3	27,890
1510.2	57,840
1476.0	56,520
1547.5	60,040
1448.6	55,110
1431.4	49,870
1441.4	50,370
763.0	18,480
760.2	18,340
498.9	7,560
498.3	7,520
1188.6	37,110
1768.8	71,200
1761.1	70,830
666.1	9,290
664.9	9,240
1245.0	26,190
1245.7	26,270
488.5	4,470
502.5	4,880
1365.6	30,050
1451.8	32,710
1508.7	34,550

TABLE II

HIGH-TEMPERATURE HEAT CONTENT OF $MnSiO_3$
(g. f. w. = 130.99)

Temp., °K.	$H_T - H_{298.1}$ cal./g. f. w.
1058.0	20,670
1060.1	20,640
845.6	14,400
844.4	14,320

TABLE III

HIGH-TEMPERATURE HEAT CONTENT OF Mn_3C
(g. f. w. = 176.80)

Temp., °K.	$H_T - H_{298.1}$ cal./g. f. w.
871.0	15,370
872.3	15,390
668.3	9,640
670.8	9,660
470.7	4,250
1071.6	21,500
1069.9	21,420
1176.3	24,840
1321.0	33,050
1252.8	27,410
1292.0	28,810
1371.1	34,940
2d series	
1268.5	28,070
1393.3	35,690
1309.1	30,360
1307.9	29,950
1295.3	29,350
1420.4	36,830

Table IV is a summary at even 100° intervals of their heat contents and entropies above 298.1° K.

TABLE IV

HEAT CONTENTS AND ENTROPIES ABOVE 298.1° K. IN CAL./G. F. W. AT 100° INTERVALS

Temp., °K.	Mn_3O_4 $H_T - H_{298.1}$	Mn_3O_4 $S_T - S_{298.1}$	Mn_3C $H_T - H_{298.1}$	Mn_3C $S_T - S_{298.1}$	$MnSiO_3$ $H_T - H_{298.1}$	$MnSiO_3$ $S_T - S_{298.1}$
400	3,700	10.60	2,450	7.07	2,320	6.66
500	7,590	19.26	5,020	12.79	4,800	12.19
600	11,590	26.54	7,700	17.67	7,430	16.98
700	15,760	32.96	10,490	21.96	10,200	21.24
800	19,980	38.59	13,350	25.78	13,080	25.09
900	24,230	43.59	16,300	29.25	15,980	28.50
1000	28,620	48.22	19,300	32.41	18,890	31.56
1100	33,130	52.52	22,400	35.36	21,830	34.37
1200	37,740	56.53	25,650	38.19	24,900	37.04
1300	42,620	60.43	29,200	41.03	27,950	39.45
1310			α29,550	41.30		
1310			β32,690	43.70		
1400	47,960	64.39	36,040	46.17	31,090	41.77
1445	α50.460	66.15				
1445	β54,960	69.26				
1500	57,700	71.12	39,840	48.79	34,300	43.99
1600	62,700	74.38				
1700	67,740	77.40				
1800	72,820	80.31				

This table, in combination with similar tables for oxygen, carbon, and silicon, permits ready calculation of free energies at these temperatures from whatever values of the heat of formation an investigator may select.

Summary

The heat contents of Mn_3O_4, $MnSiO_3$ and Mn_3C from room temperature to temperatures between 1140 and 1500° have been determined. These determinations have disclosed transitions of Mn_3O_4 at 1172° and Mn_3C at 1037°.

A table summarizing the increments in the heat contents and entropies of these substances above room temperature at 100° intervals has been prepared from these data and others in the literature.

NIAGARA FALLS, N. Y. RECEIVED APRIL 6, 1942

[CONTRIBUTION FROM THE METALLURGICAL FUNDAMENTALS SECTION, METALLURGICAL DIVISION, BUREAU OF MINES, UNITED STATES DEPARTMENT OF THE INTERIOR]

Heat of Formation and High-temperature Heat Content of Manganous Oxide and Manganous Sulfate. High-temperature Heat Content of Manganese[1]

BY J. C. SOUTHARD[2] AND C. HOWARD SHOMATE[3]

The free energy of formation of manganous oxide at high temperatures has been uncertain because of the lack of satisfactory high-temperature heat content data. Further, the heat of formation of manganous oxide has been based almost entirely on heats of combustion. The combustion of manganese metal with oxygen in the bomb calorimeter does not proceed according to any definite reaction but yields a mixture of oxides assumed to be manganous oxide and manganomanganic oxide.[4,5] The mixture consists of 10 to 50 per cent. manganous oxide. The heat of formation of manganous oxide therefore has depended on the combustion of manganous oxide to manganomanganic oxide. This requires the use of paraffin oil and also yields a product of varying composition. Under these conditions the heat of reaction is only 5 per cent. of the total heat measured.[5] The heat of reaction also seemed to depend on whether the fraction converted to manganomanganic oxide was determined by increase in weight or by actual analysis.[4] Determination of the heat of formation of manganous oxide by a completely independent, more direct, method appears advantageous.

The thermodynamic properties of manganese sulfate have been studied and entropies of the substances involved already have been determined, as well as the high-temperature heat-content data, with the exception of manganous sulfate. The heat of formation of manganous sulfate has not been determined since the days of Thomsen and Berthelot, at which time pure manganese was not available.

Methods and Materials

The high-temperature heat contents were determined in an apparatus previously described.[6] The apparatus was calibrated electrically, using the relation 1 calorie = 4.1833 Int. joules. During the measurements manganous oxide and manganous sulfate were contained in a sealed platinum-alloy capsule and manganese metal in an evacuated and sealed silica-glass capsule. The heats of formation of manganous oxide and manganous sulfate

(1) Published by permission of the Director, Bureau of Mines, U. S. Department of the Interior. Not subject to copyright.

(2) Formerly Chemist, Metallurgical Division, Bureau of Mines; present address, Titanium Alloy Mfg. Co., Niagara Falls, N. Y.

(3) Assistant Chemist, Metallurgical Division, Bureau of Mines.

(4) W. A. Roth, *Z. angew. Chem.*, **42**, 981 (1929).

(5) H. Siemonsen, *Z. Elektrochem.*, **45**, 637 (1939).

(6) J. C. Southard, THIS JOURNAL, **63**, 3142 (1941).

TABLE I

HEAT OF SOLUTION OF MANGANESE, MANGANOUS OXIDE AND MANGANOUS SULFATE IN 1.006 *N* SULFURIC ACID

1 G. F. W. IN 100.27 KG. ACID AT 298.1° K.

	Manganese sample A, cal./g. f. w.	MnO, cal./g. f. w.	$MnSO_4$, cal./g. f. w.	Manganese "quenched," sample B, cal./g. f. w.
	−54,023	−30,607	−11,621	−54,081
	−54,041	−30,643	−11,644	−54,111
	−54,008	−30,653	−11,623	−54,089
				−54,075
Mean	−54,024 ± 11	−30,634 ± 18	−11,629 ± 10	−54,089 ± 11
Corrn. for evap. of water	−332			−332
Corrn. for diln. by water		2		
Corrected mean	−54,356	−30,632	−11,629	−54,421

were determined by the solution of manganese, manganous oxide and manganous sulfate in 1.006 *N* sulfuric acid solution in a calorimeter also described previously.[7] The time of solution was about twelve minutes for manganese and manganous sulfate and about twenty to thirty minutes for manganous oxide.

The manganese metal was an electrolytic product at least 99.9 per cent. pure. It was degassed by heating to 850° in a vacuum corresponding to 10^{-5} mm. and allowed to cool slowly (sample A). A portion of this sample was quenched from 800° in the high-temperature calorimeter (sample B) for use in certain heat-of-solution measurements. The metal was sized by passing through a 20- onto a 28-mesh screen. The manganous oxide was prepared by Millar[8] by reduction of higher oxides with hydrogen at 1100°. It was further purified for this work by removing visible particles of silica by flotation with tetrabromomethane, followed by drying in a high vacuum up to 250°. Analysis showed that it contained less than 0.04% silica and 77.42, 77.45% Mn (calcd. 77.44%). Manganese sulfate was prepared from a hydrated "C. P." preparation. It was found to contain 36.33% Mn by analysis (calcd. 36.38%). It was dried to constant weight in the capsule and bulbs at 400° before being weighed and sealed.

Results

Heat of Formation.—The heats of solution of manganese, manganous oxide, and manganous sulfate are summarized in Table I. Determinations were made at the dilution of 1 gram-atom of manganese to 100.27 kg. of acid solution. Correction for the vaporization of water by evolved hydrogen was made on the assumption that none of the hydrogen remained in solution by the time equilibrium was attained, and that it was saturated with water vapor when it left the solution. The partial pressure of water vapor over the acid solution was taken to be 23.34 mm. at 25° with a temperature coefficient of 0.14 mm. per degree. The heat of vaporization of water from 1 *N* sulfuric acid was taken to be 10,501 cal./g. f. w. at 25°. The final temperature lay between 25.0 and 25.2° in every case.

The heat of formation of manganous oxide, according to Eq. 5, is calculated from the heats of the following reactions, all at 298.1° K.

$$Mn_\alpha + 49.05\ H_2SO_4 \cdot 5299\ H_2O(soln.) \longrightarrow MnSO_4 \cdot 48.05\ H_2SO_4 \cdot 5299\ H_2O(soln.) + H_2(g) \quad (1)$$

$$MnO(s) + 49.05\ H_2SO_4 \cdot 5299\ H_2O(soln.) \longrightarrow MnSO_4 \cdot 48.05\ H_2SO_4 \cdot 5300\ H_2O(soln.) \quad (2)$$

$$MnSO_4 \cdot 48.05\ H_2SO_4 \cdot 5299\ H_2O(soln.) + H_2O(l) \longrightarrow MnSO_4 \cdot 48.05\ H_2SO_4 \cdot 5300\ H_2O(soln.) \quad (3)$$

$$H_2(g) + {}^1/_2O_2(g) \longrightarrow H_2O(l) \quad (4)$$

$$Mn_\alpha + {}^1/_2O_2(g) \longrightarrow MnO(s) \quad (5)$$

$$\Delta H_5 = \Delta H_1 + \Delta H_4 - \Delta H_2 + \Delta H_3$$

The heats of reactions (1), (2) and (3) are given in Table I. The heat of reaction (4) was determined by Rossini[9] as −68,318 ± 9 cal./g. f. w. The heat of formation of manganous oxide from the elements at 298.1° K. is thus computed to be −92,040 ± 110 cal./g. f. w. The limits of error are estimated as the sum of the average deviations from the mean of the heats of solution of manganese and manganous oxide, plus 0.05% of the total energy measured, plus 10% of the correction for vaporization of water plus 9 calories uncertainty in the heat of formation of water. The value computed here allows the maximum correction for vaporization of water by the evolved hydrogen. Any other assumption would decrease the magnitude of the heat of formation. A comparison of the present value of the heat of formation of manganous oxide with those previously determined is given in Table II. Virtually all previous data were obtained by combustion methods from Le Chatelier's day on.

The value determined here by solution methods is believed to be more trustworthy than that obtained by combustion methods, for two reasons. (1) The combustion process does not proceed ac-

(7) J. C. Southard, *Ind. Eng. Chem.*, **32**, 442 (1940).

(8) R. W. Millar, THIS JOURNAL, **50**, 1875 (1928).

(9) F. D. Rossini, *Bur. Standards J. Res.*, **22**, 407 (1939).

TABLE II
HEAT OF FORMATION OF MANGANOUS OXIDE

	Year	Method	$\Delta H_{298.1}$ cal./g. f. w.
Le Chatelier[10]	1896	Combustion with oyxgen and charcoal	−90,900
Guntz[11]	1896	Not stated	−98,200
Roth[4]	1929	Combustion with oxygen and oil	−96,200
Siemonsen[5]	1939	Combustion with oxygen and oil	−93,100
This work	1942	Solution in 1 *N* sulfuric acid	−92,040 ± 110

cording to any definite reaction, while the initial and final states in the solution method are well-defined. (2) The total amount of heat per g. f. w. of manganous oxide measured in the combustion method is 5 to 7 times that measured by the solution method. The agreement between the present work and that of Siemonsen is evidence of extremely careful calorimetry on his part. The result of Roth and Müller is higher because they used a sample contaminated by silicon and aluminum and probably because it contained hydrogen.

The heat of formation of manganous sulfate from the elements (Eq. 8) is calculated from Eq. (1) above, in combination with the following reactions, all at 298.1° K.

$$H_2 + S(rh) + 2O_2 + MnSO_4\cdot 48.05\ H_2SO_4\cdot 5299\ H_2O(soln.) \longrightarrow MnSO_4\cdot 49.05\ H_2SO_4\cdot 5299\ H_2O(soln.) \quad (6)$$

$$MnSO_4(s) + 49.05\ H_2SO_4\cdot 5299\ H_2O(soln.) \longrightarrow MnSO_4\cdot 49.05\ H_2SO_4\cdot 5299\ H_2O(soln.) \quad (7)$$

$$Mn_\alpha + S(rh) + 2O_2(g) \longrightarrow MnSO_4(s) \quad (8)$$

$$\Delta H_8 = \Delta H_1 + \Delta H_6 - \Delta H_7$$

The heat of reaction (7) is given in Table I. ΔH_6 is calculated from the heats of the reactions

$$H_2(g) + S(rh) + 2O_2(g) \longrightarrow H_2SO_4(l) \quad (9)$$

$$H_2SO_4(l) + 49.05\ H_2SO_4\cdot 5299\ H_2O(soln.) \longrightarrow 50.05\ H_2SO_4\cdot 5299\ H_2O(soln.) \quad (10)$$

$$H_2(g) + S(rh) + 2O_2(g) + 49.05\ H_2SO_4\cdot 5299\ H_2O(soln.) \longrightarrow 50.05\ H_2SO_4\cdot 5299\ H_2O(soln.) \quad (11)$$

$$\Delta H_{11} = \Delta H_9 + \Delta H_{10}$$

The heat of reaction 9 was calculated to be −194,100 ± 100 cal./g. f. w. from the heat of formation of sulfur dioxide of Eckmann and Rossini[12] and the heat of oxidation of sulfur dioxide and heats of solution of sulfur dioxide, sulfur trioxide and sulfuric acid obtained by Roth, Grau and Meichsner.[13] It was necessary to correct some of the data to 25°. The limits of error are those set by Roth. The heat of reaction (10) has been calculated from the data of Grau and Roth[14] at about 290° K. as −17,350 calories. No correction was made to 298.1° K., and the error is estimated at ±50 cal. The heat of reaction (11) must necessarily be assumed the same as that of reaction (6) but little error can arise from this source because the ionic strengths of the solutions are the same. The heat of formation of manganous sulfate from the elements is thus calculated to be −254,180 ± 250 cal./g. f. w. at 298.1° K. The limits of error are estimated as the sum of the average deviations from the mean of the heats of solution of manganese and manganous sulfate, plus 0.05% of the total energy measured, plus 10% of the correction for vaporization of water by the hydrogen in Eq. 1, plus 100 calories in the heat of formation of sulfuric acid plus 50 calories for the heat of reaction (10).

Previous determinations of the heat of formation of manganous sulfate at room temperature by Thomsen (ΔH = −249,730) and Berthelot (ΔH = −249,400) are discussed by Kelley.[15] Maier[16] has calculated a value of $\Delta H_{298.1}$ = −250,700 from the dissociation pressure measurements of Marchal.[17] This value is not changed much by using the present high-temperature heat-content data, but may be changed by the proposed investigation of the heat of formation of manganomanganic oxide. However, Marchal's data lead to an abnormally high entropy of manganous sulfate so that not much weight can be given to values of the heat of formation calculated from them.

The difference in the heats of solution of annealed and "quenched" manganese is computed from Table I to be 65 calories per g. f. w. This heat is required for the calculation of heat contents of manganese above the transition at 1012° K.

High-temperature Heat Contents.—The measurements of the heat content at T° K., minus the heat content at 298.1° K. for manganese, manganous oxide, and manganese sulfate, are given in Tables III, IV and V. Manganous oxide and manganous sulfate show no transitions. Manganese metal shows a transition at 1012° K. Known transitions at higher temperatures could not be investigated in this work because of devitrification of the silica-glass capsule and reaction of the manganese with it. The correction of 65 cal./g. f. w. must be applied to the data of Table III above 1012° K. because the manganese did

(10) H. Le Chatelier, *Compt. rend.*, **122**, 80 (1896).
(11) Guntz, *ibid.*, **122**, 465 (1896).
(12) J. D. Eckmann and F. D. Rossini, *Bur. Standards J. Res.*, **3**, 597 (1929).
(13) W. A. Roth, R. Grau and A. Meichsner, *Z. anorg. Chem.*, **193**, 169 (1930).
(14) R. Grau and W. A. Roth, *ibid.*, **188**, 195 (1930).
(15) K. K. Kelley, *Bur. Mines Bull.*, **406**, 101 (1937).
(16) C. G. Maier, *Bur. Mines Inf. Circ.* 6769, 68 (1934)
(17) G. Marchal, *J. chim. phys.*, **22**, 559 (1925).

not come to the same final state in the calorimeter when dropped from temperatures above this as when dropped from temperatures below it. It is not supposed that this quantity represents the difference in heat content between α and β manganese at 298.1° K. but merely that it is a correction that must be applied to the calorimetric heat obtained when the capsule was dropped from the temperature range in which β manganese is stable.

TABLE III

HIGH-TEMPERATUTE HEAT CONTENT OF MANGANESE

(g. f. w. = 54.93)

T, ° K.	$H_T - H_{298.1}$ cal./g. f. w.
963.8	5030
962.8	4987
925.6	4686
669.0	2622
669.3	2626
486.4	1264
481.7	1206
880.7	4307
879.2	4298
962.5	5016
1003.9	5361
977.6	5134
1027.1	6103
1071.8	6395
1075.4	6431
1013.0	5988
2d series	
855.5	4116
1153.0	7221
1161.6	7331
1260.1	8246
1264.5	8276
1307.3	8666
1307.3	8640
1105.8	6737
1379.1	9505

TABLE IV

HIGH-TEMPERATURE HEAT CONTENT OF MANGANOUS OXIDE

(g. f. w. = 70.93)

T, ° K.	$H_T - H_{298.1}$ cal./g. f. w.
1268.6	12,050
1270.1	12,080
1041.6	8,980
1043.5	8,980
774.6	5,600
774.6	5,572
519.8	2,517
518.9	2,503
1519.0	15,490
1511.0	15,310
1153.8	10,440
1258.5	11,850
1773.4	18,980

TABLE V

HIGH-TEMPERATURE HEAT CONTENT OF MANGANESE SULFATE

(g. f. w. = 150.99)

T, ° K.	$H_T - H_{298.1}$ cal./g. f. w.
870.3	18,180
873.5	18,250
681.5	11,620
679.9	11,480
497.0	5,520
483.3	5,070
1083.6	26,140
1082.3	26,060

The heat of transition $\alpha \rightarrow \beta$ manganese is calculated from the heat-content data to be 615 calories per g. f. w. at 1012° K. This includes the above-mentioned 65 calories. Gaylor[18] reported the transition as occurring at 1013 ± 2° K., with distilled manganese. Umino[19] observed that this transition occurred at 1108° K., accompanied by a heat effect of but 68 calories per g. f. w. Other investigators of the high-temperature heat content observed none at all. There was no evidence in the present work of a transition reported by Gaylor at 943° K.

Previous measurements on the high-temperature heat content of manganese have been surveyed by Kelley.[20] The present work lies between that of Umino and that of Wüst, Meuthen and Durrer[21] and not far from that of Laemmel.[22] The present work is believed to be more reliable because it was done with a higher-purity sample of manganese, completely protected from oxidation, and with a higher-precision calorimeter than was previous work.

No previous determinations have been reported on the heat content of manganous oxide and manganous sulfate at high temperatures.

Table VI is a summary at 100° intervals of the heat content and entropy above 298.1° K. of manganese, manganous oxide and manganous sulfate. The 65-cal. correction to the heat content of manganese in the β range has been applied. Table VI also includes values of the free energy of formation of manganous oxide from gaseous oxygen and the form of manganese stable at the stated temperature. The present value of −92,040 cal./g. f. w. for the heat of formation of manganous oxide is used in conjunction with the values 7.61, 24.52 and 14.4 for the entropies of manganese, $^1/_2$ oxygen and manganous oxide, respectively,[23] to calculate a free energy of formation of manganous oxide of −86,760 cal./g. f. w. at 298.1° K. Values at higher temperatures were calculated with the aid of the present high-temperature heat-content data on manganese and manganous oxide and the tables of free energy of oxygen given by Johnston and Walker.[24] Comparison may be made with the experimental data of Aoyama and Oka[25] for the reaction $Mn + H_2O(g) \rightleftarrows MnO + H_2(g)$. They made five determinations in the temperature range 1,048 to 1,460° K. Their data were recalculated to the reaction $Mn + {}^1/_2O_2 \rightarrow MnO$ by adding the free energy of formation of water vapor, which was calculated from the tables of A. R. Gordon[26] and W. F. Giauque,[27] and the free energy of formation of water vapor at 298.1° K.

(18) M. L. V. Gaylor, *J. Iron Steel Inst.*, **115**, No. 1, 393 (1927).
(19) S. Umino, *Sci. Repts. Tôhoku Imp. Univ.*, **16**, 775 (1927).
(20) K. K. Kelley, *U. S. Bur. Mines Bull.*, **No. 371**, p. 34 (1934).
(21) F. Wüst, A. Meuthen and R. Durrer, *Forsch. Arb. Ver. deut. Ing.*, **No. 204** (1918).
(22) R. Laemmel, *Ann. Physik*, **16**, 551 (1905).
(23) K. K. Kelley, *Bur. Mines Bull.* **434**, 115 (1941).
(24) H. L. Johnston and M. K. Walker, THIS JOURNAL, **55**, 183 (1933).
(25) S. Aoyama and Y. Oka, *Sci. Repts. Tôhoku Imp. Univ.*, **22**, 824 (1933).
(26) A. R. Gordon, *J. Chem. Phys.*, **2**, 65 (1934).
(27) W. F. Giauque, THIS JOURNAL, **52**, 4816 (1930).

TABLE VI

HEAT CONTENTS AND ENTROPIES OF MANGANESE AND MANGANOUS OXIDE ABOVE 298.1° K. AND THE FREE ENERGY OF FORMATION OF MANGANOUS OXIDE AT 100° INTERVALS

	Mn		MnO			$MnSO_4$	
T, ° K.	$H_T - H_{298.1}$, cal./g. f. w.	$S_T - S_{298.1}$, cal./deg. g. f. w.	$H_T - H_{298.1}$, cal./g. f. w.	$S_T - S_{298.1}$, cal./deg. g. f. w.	ΔF of formation, cal./g. f. w.	$H_T - H_{298.1}$, cal./g. f. w.	$S_T - S_{298.1}$, cal./deg. g. f. w.
298.1					−86,760		
400	660	1.89	1130	3.26	−84,970	2680	7.70
500	1364	3.46	2280	5.82	−83,240	5630	14.28
600	2100	4.80	3470	7.99	−81,520	8850	20.14
700	2874	5.99	4680	9.85	−79,820	12210	25.32
800	3668	7.05	5900	11.48	−78,120	15710	29.99
900	4480	8.00	7150	12.95	−76,430	19280	34.18
1000	5328	8.90	8430	14.30	−74,730	22970	38.07
1012α	5438	9.01					
1012β	6053	9.62					
1100	6750	10.26	9750	15.56	−73,000	26730	41.65
1200	7734	11.11	11100	16.73	−71,260		
1300	8672	11.86	12470	17.82	−69,500		
1340β	9040	12.14					
1340γ	(9220)	(12.28)					
1400	(9770)	(12.69)	13840	18.84	−67,740		
1500	(10690)	(13.33)	15210	19.79	−65,980		

given by Rossini.[9] The three lowest of Aoyama and Oka's points lie within a few hundred calories of values interpolated from Table VI, which may be said to be in good agreement. In general, however, their data give a larger ΔH and ΔS for the reaction than may be calculated from the third law.

Summary

The heat of formation of manganous oxide has been determined to be −92,040 ± 110 calories per g. f. w. and of manganous sulfate to be −254,180 ± 250 calories per g. f. w. at 25°.

The heat contents of manganese, manganous oxide, and manganous sulfate from room temperature to temperatures between 811 and 1500° have been determined. These observations have disclosed a transition in manganese at 739°.

A table summarizing increments of heat contents, entropies and free energies at 100° intervals has been prepared from these data and others in the literature.

NIAGARA FALLS, N. Y. RECEIVED APRIL 6, 1942

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

Isomers of Crystal Violet Ion. Their Absorption and Re-emission of Light

BY GILBERT N. LEWIS, THEODORE T. MAGEL AND DAVID LIPKIN

The possibility of a new type of isomerism in such substances as triphenylmethyl and its ions was pointed out recently.[1] An extensive investigation of the light absorption of the free radicals has not given us positive evidence of such isomerism.[2] On the other hand, in the derivatives of triphenylmethyl ion we have sought, and believe to have found, these isomers.

It is often observed that the absorption curve of what is apparently a single substance, such as the ion of crystal violet (tris-(dimethyl-*p*-aminophenyl)-methyl ion, Fig. 6) as it exists in neutral or alkaline solution, has a shoulder as seen in Fig. 1. This shoulder suggests the superposition of two neighboring bands, which might result from (1) a partial resolution of the vibrational structure belonging to a single electronic level, which, according to the work of Dr. Goldschmid,[2] seems to be the explanation of a similar shoulder in the adsorption curve of methylene blue, or (2) two neigh-

(1) Lewis and Calvin, *Chem. Rev.*, **25**, 273 (1939).

(2) The two absorption bands of triphenylmethyl in the visible which were obtained by Meyer and Wieland [*Ber.*, **44**, 2557 (1911)] and which were resolved into three bands by Anderson [THIS JOURNAL, **57**, 1673 (1935)] were shown by Dr. O. Goldschmid [Ph.D. Thesis, University of California (1939)] to be vibrational bands belonging to a single electronic band. This was shown by comparison of the absorption and fluorescence spectra of triphenylmethyl. We have further confirmed his results, but with a very high resolution we have found a much more intricate structure. This will be discussed in another place.

boring electronic levels, or finally (3) two isomers in rapid equilibrium with one another. We shall find that it is the last of these theories which accounts for the crystal violet spectrum. In the experimental work that has led to this conclusion several perplexing phenomena have appeared which will be dealt with in their turn, and about 200 absorption curves have been obtained, of which only a few can be shown.

When we study the light absorption of crystal violet in a variety of solvents the curves fall roughly into three classes, exemplified by the solid curves in Figs. 1, 2 and 3. In each curve the ordinates (α) are proportional to the molar extinction coefficient, ϵ, the proportionality factor

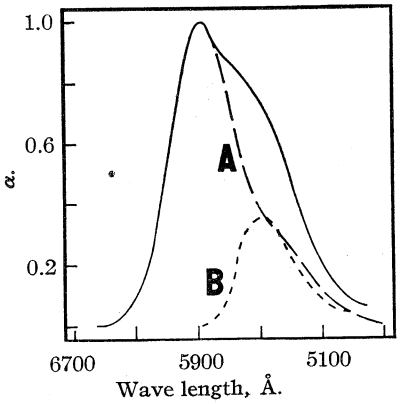


Fig. 1.—Relative extinction coefficient of 10^{-6} M crystal violet (chloride) in absolute ethanol at 293°K. (solid curve). Curve A (dashed line) is the curve of malachite green in ethanol, displaced horizontally to coincide with solid curve at maximum. This is also assumed to be the A band of crystal violet. Curve B (dotted) obtained from the two other curves by subtraction.

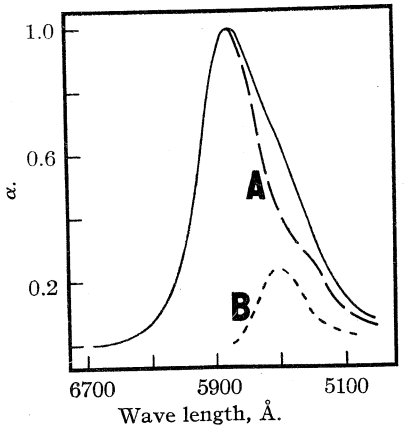


Fig. 2.—Relative extinction coefficient of 5×10^{-7} M crystal violet (chloride) in chloroform at 293°K. Curve A, malachite green curve in chloroform, displaced. Curve B obtained as in Fig. 1.

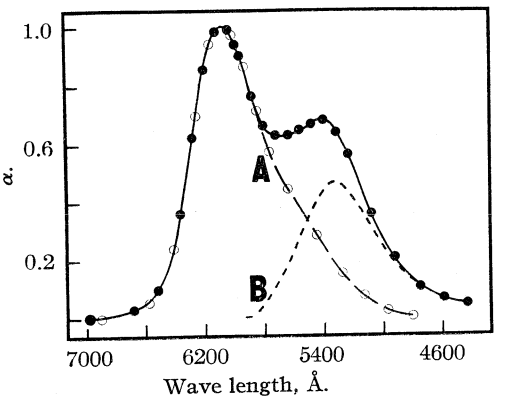


Fig. 3.—Relative extinction coefficient of 10^{-6} M crystal violet (chloride) in toluene containing 0.1% β-naphthol at 293°K. Curve A is malachite green curve in same solvent, displaced. Curve B obtained as in Fig. 1. In this case the actual experimental points are shown.

being so chosen that in each case $\alpha_{max.}$ is unity.[3]

In order to show that in all three cases the absorption curve is a summation of two bands which differ in position and relative height, we may use a crude but apparently effective mode of analysis. We have noticed that the absorption curve of malachite green, which shows no pronounced shoulder, if displaced horizontally to bring the maximum into coincidence with that of the crystal violet curve, coincides with the latter in the whole left-hand portion. This is shown in Fig. 3 where the open circles represent experimental points for malachite green and the black circles those for crystal violet. If we assume now that this coincidence would continue all the way for the first (A) band of crystal violet, then we may construct the other (B) band by subtracting the dashed from the solid curve. When this is done we obtain the dotted curve which is marked B. Similarly, using the malachite green curve for the corresponding solvent we have obtained the A and B bands in Figs. 1 and 2.

It seems that in spite of the different appearance of the three solid curves of Figs. 1–3, they differ chiefly in the positions and the relative intensities of the A and B bands.

All of the solvents which we have studied can be classified roughly according to the resemblance of the absorption curves of crystal violet in the several solvents to the curves of Figs. 1, 2 and 3.

(3) We have chosen this method of representation best to display the shapes of the several curves. Furthermore, our determinations of relative extinction are far more accurate than our absolute values. The values of $\epsilon_{max.}$ that we actually obtained for these three curves were 8.1×10^4 in absolute ethanol, 8.5×10^4 in chloroform and about 7×10^4 in toluene.

Class I comprises all the solvents that we have examined of high, or moderately high, dielectric constant: namely, ethanol, methanol, *t*-butanol, water, glycol, glycerol, glucose (supercooled), ethylene chlorohydrin, methyl cyanide, acetone, acetaldehyde, glacial acetic acid, pyridine, and aniline. In all of these $\lambda_{max.}$ (A) lies between 5830 and 5940 Å., except that aniline gave 5990 Å.

Class II comprises chloroform,[4] *trans*-dichloroethylene, methyl iodide, chlorobenzene and a saturated solution of chloral hydrate in water. For all of these $\lambda_{max.}$ (A) lies between 5780 and 5800 Å., except for chlorobenzene, 5940 Å. It will be noted that all of these solvents of Group II contain halogen and therefore have, if not for the molecule as a whole, at least for some part of it, a considerable dipole moment.

On the other hand, the tetrahedrally symmetrical carbon tetrachloride and the linearly symmetrical carbon bisulfide, both with high bond moments, fall into our third class, which also contains toluene, hexane, dioxane, isopentane, ether, methylal, carbon tetrachloride and carbon bisulfide. Here $\lambda_{max.}$ (A) varies widely from 5930 Å. for methylal to 6140 Å. for carbon bisulfide. In all of these solvents small amounts of phenol, β-naphthol or ethanol were added to make the crystal violet chloride soluble. It seems to make no difference in the absorption curve which is used or at what concentration, provided that it does not exceed 1 or 2%.

The observation by Lewis and Seaborg[5] that crystal violet can be made to dissolve freely in toluene by the addition of a small amount of a substance with labile hydrogen seemed to show "that crystal violet in toluene forms complexes with alcohols and acids, and the stability of these compounds reaches a maximum in the case of phenol." At first it seemed likely that such complexes, formed by hydrogen bonds at the nitrogen atoms, might account for the peculiarities in the absorption curve of Fig. 3. However, it was later found that other salts of crystal violet (perchlorate, iodide, acetate) are of themselves soluble in toluene, and in one experiment pure, dry crystal violet acetate was dissolved in very dry toluene. The absorption curve was identical with that of Fig. 3.

(4) Mr. J. Biegeleisen, to whom we are indebted for several of our absorption curves, has measured the absorption of crystal violet in mixtures of chloroform and ethanol. The curves change continuously from one pure solvent to the other, the main difference being in the height of the B band which, relative to that of the A band, is 0.22, 0.35, 0.38, 0.40 and 0.40 with 0, 25, 50, 75, and 100% ethanol.

(5) Lewis and Seaborg, THIS JOURNAL, **61**, 1894 (1939).

Absorption Spectra in Alcohol and Other Solvents of Class I.—Solutions in solvents of Class I are the only ones, as we shall see, in which we have the isolated ion of crystal violet. In these solvents the absorption curve proves extremely insensitive to any isothermal change.[6] In alcohol identical curves were obtained at 10^{-4} and 10^{-6} M, and in less exact measurements over a still wider range. Moreover, the curve was in no way affected by the nature of the anion (chloride, bromide, acetate or perchlorate). Even when large amounts of sodium chloride or bromide were added (10^{-2} M) the absorption curve was not altered.

Even the change from one to another solvent of Class I has, as we have seen, very little effect upon the absorption spectrum. The formation of complexes through hydrogen bonds,[7] which we have just shown to have no effect upon the spectrum in toluene, appears also to have very little effect in solvents of Class I. From cases where these complexes should be prominent, such as glacial acetic acid and ethanol containing considerable amounts of phenol, to cases such as acetone and pyridine, where such complexes must be absent, there is an increase in $\lambda_{max.}$ of only about 50 Å.

When the temperature of the alcoholic solution is lowered, beginning at room temperature, there is a gradual but readily noticeable change in the character of the absorption curve. The shoulder (B band) becomes less marked and nearly disappears as we approach the temperature of liquid air. This phenomenon occurs in methanol and ethanol. We have studied most carefully ethanol containing 5% water,[8] the curves being shown in Fig. 4. Here again we have made $\alpha_{max.} = 1$ for each curve. As we go to lower temperatures there is the usual slight steepening of the curve at the left. The value of $\epsilon_{max.}$, allowance having

(6) It is true that in water at very high concentration (2×10^{-3} M) a new absorption band at about 5400 A. was found by Holmes [*Ind. Eng. Chem.*, **16**, 35 (1924)] which probably is due to a dimeric ion such as has recently been studied experimentally and theoretically in the case of the thionine dyes by Rabinowitch and Epstein [THIS JOURNAL, **63**, 69 (1941)].

(7) It was noted by Lewis and Seaborg[5] that the trinitrotriphenylmethide ion seems to form complexes with substances like alcohol, phenol or acetic acid by attachment through hydrogen to the nitro groups, without causing any marked change in color. However, when hydrogen ion was similarly attached to a nitro group the color changed from blue to orange. In our present case the production of various solvates may be considered to produce slight shifts in the absorption band while the addition of hydrogen ion or other strong acid, such as stannic chloride [Lewis, *J. Franklin Institute*, **226**, 293 (1938)], produces an altogether new absorption band. Evidently what has become known as the hydrogen bond differs not only in degree but in kind from a true chemical bond.

(8) It has been shown by Prietzschk [*Z. Physik*, **117**, 482 (1941)] that a small amount of water greatly inhibits the crystallization of alcohol at low temperatures.

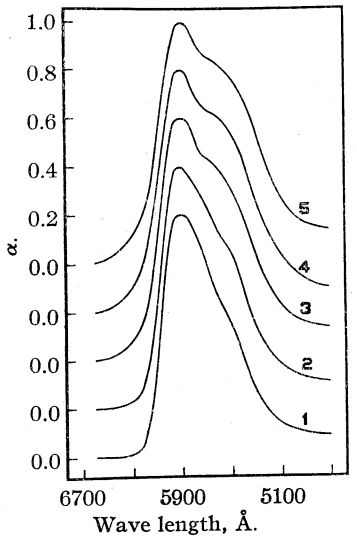


Fig. 4.—Relative extinction coefficient of 10^{-6} M crystal violet (chloride) in 95% ethanol at (1) 114°, (2) 162°, (3) 193°, (4) 240° and (5) 294°K.

been made for thermal contraction, increases 16 per cent. in going from 294° to 114°K. Some such increase is to be expected if we assume that much of the B isomer existing at room temperature has gone over to the A isomer at low temperature.

That the two bands are actually to be ascribed to two isomers is made nearly certain by a simple analysis of the absorption curves.[9] If we subtract from the other curves of Fig. 4 the one obtained at 114°K. we obtain a set of curves given in Fig. 5 (the scale is twice that of Fig. 4). Although in this subtraction of curves the errors are exaggerated,

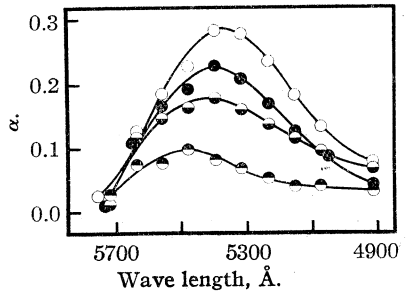


Fig. 5.—Curves obtained by subtracting successively Curve 1 from each of the other curves of Fig. 4. Since in this subtraction the experimental errors are greatly magnified the actual experimental data are shown.

(9) A previous detection of isomers by spectrophotometric methods occurred in the study of the infrared vibrational spectrum of *o*-chlorophenol. Two neighboring vibrational bands were found by Wulf and Liddel [THIS JOURNAL, **57**, 1464 (1935)] and attributed by Pauling [*ibid.*, **58**, 94 (1936)] to *cis* and *trans* forms. This interpretation has been confirmed by Davies [*Trans. Faraday Soc.*, **34**, 1427 (1938)] and more quantitatively by Zumwalt and Badger [THIS JOURNAL, **62**, 305 (1940)].

it is evident that the experimental points fall on curves which are essentially the same except for height. Even at 114°K. there must be some of the B isomer. Assuming the correctness of our calculation of the height of the B band at room temperature in Fig. 1, namely, $\alpha_{max.}$ (B) = 0.36, we obtain the following values for $\alpha_{max.}$ (B) at the several temperatures by adding 0.08 to the maximum values at the several temperatures shown in Fig. 5.

T, °K.	114	162	193	240	294
$\alpha_{max.}$ (B)	0.08	0.17	0.26	0.30	0.36

These values should be proportional to the ratio of the amount of B isomer to the amount of A isomer at each temperature. If we plot the logarithms of these values against $1/T$, all but the point at 193°K. lie on a straight line, from which we may conclude that we are dealing with an equilibrium between two substances. From the slope of the line we find that the B isomer has the greater energy by about 580 cal., while a similar but less exact set of measurements in pure ethanol gave 500 cal. On the other hand, the two isomers in their electronically excited states differ much more in energy. From $\lambda_{max.}$ (A) and $\lambda_{max.}$ (B) we find that the difference in energy is increased by 3300 cal.

The Nature of the A and B Isomers

We shall attempt to visualize the two isomers A and B with the aid of Fig. 6, which shows approximately the atomic distances in the crystal violet ion. Of the hydrogen atoms only the six in the ortho positions of the rings are shown. If the rings and the six ortho hydrogens were all to be in a plane, two adjacent hydrogens such as 2 and 6″ would be only about 0.5 Å. apart. Although the amount of repulsion of two such atoms is unknown, it must be considerable. The re-

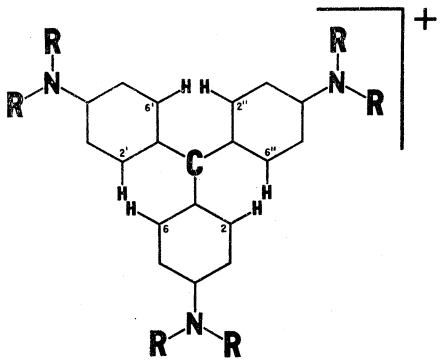


Fig. 6.—Representation of the crystal violet ion, the atomic distances being approximately to scale.

sulting strain can best be relieved by a small rotation of the benzene rings around their axes (the lines connecting the central carbon atom with an atom para to it). Such a rotation at the beginning meets no restoring forces, but these forces of restoration become large as the amount of rotation increases. The nature of these forces of restoration will best be understood if we ascribe to each bond from the central carbon atom one-third double bond character.

As a result of these rotations, we visualize the actual structure of the crystal violet ion as a non-planar one in which two adjacent ortho hydrogens have moved far enough from each other so that the force of repulsion is balanced by the force that opposes free rotation. If in the figure the atoms 2, 2′ and 2″ lie above the plane of the diagram and 6, 6′ and 6″ lie below, we have a model analogous to a windmill or propeller of three blades. It has complete screw or helical symmetry.[10] If in this model one pair of adjacent hydrogens such as 2 and 6″ are forced by each other, or if one of the rings rotates through nearly 180°, we obtain a form like a propeller of three blades in which one blade is turned in the opposite sense from the other two. This distorted helical structure would presumably have more energy than the symmetrical one. Also, since the kind of resonance that favors light absorption would presumably be more inhibited, we should expect for it a lower value of $\lambda_{max.}$. On both these grounds we believe that our isomer A is of the symmetrical helical type and isomer B is of the distorted helical type. The transition from one isomer to the other is apparently rapid in alcohol even at 114°K., so that presumably the heat of activation for isomerization is not more than 2 or 3 kcal. We cannot judge whether the actual process takes place chiefly through the rotation of one ring or the slipping by each other of two adjacent hydrogen atoms. The latter may occur only when the rings are momentarily separated by the vibrations of the molecule.

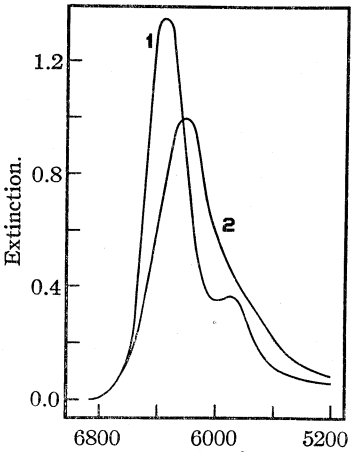


Fig. 7.—Extinction of the same sample of malachite green in 95% ethanol, corrected for temperature expansion. (1) 114°K. and (2) 294°K.

We have observed that the shoulder on the absorption band, indicating two isomers, is nearly always found in dyes of the triaminotriphenylmethyl group. On the other hand, we know of no case in which it has been reported in the diaminotriphenylmethyl dyes such as malachite green (phenyl - bis - (dimethyl - *p* - aminophenyl) - methyl chloride). In these dyes the unsubstituted phenyl group does not participate in the main resonance of the molecule. It should, therefore, be nearly free to occupy various positions of rotation about its axis. We should expect, however, two positions to be of somewhat lower energy than the rest, corresponding to the A and B forms of crystal violet. In fact, we have found that at low temperatures the absorption curve of malachite green is resolved into two narrower bands A and B as shown in Fig. 7. The great increase in $\alpha_{max.}$ of 35% (correction having been made for temperature contraction of the solvent) and the appearance of the two narrow bands indicate pretty clearly that the molecules with varying positions of rotation that exist at room temperature, and each of which has a different $\lambda_{max.}$, have at the low temperature been largely converted into the A and B forms. Our experiments at several low temperatures show that the difference in energy between these two forms is too small to measure.

Absorption Spectra in Solvents of Classes II and III.—In solvents of low dielectric constant it has been shown by the work of Kraus and his associates[11] that the number of free ions is extremely small. While we have reason to believe that the number of free ions is greater in our case than in theirs, most of the dissolved salt must be present as ion pairs and larger ion clusters. It is the absorption spectra of such aggregates that we obtain in Figs. 2 and 3 and it is surprising, therefore, that these curves show as little difference as

(10) The term symmetry is not used in the same sense as in discussing optical isomerism. Indeed, each of the two isomers here discussed must represent a pair of optical isomers, which may ultimately be resolved.

(11) For example, Fuoss and Kraus, THIS JOURNAL, **55**, 3614 (1933), and Batson and Kraus, *ibid.*, **56**, 2017 (1934).

they do from the absorption curve of the free ion. Even this difference can be made to disappear in part.

The absorption curve in chloroform at 5×10^{-7} M is given again as Curve 1 of Fig. 8. As the concentration of the crystal violet is increased, at first there is little change in the curve except a slight broadening, but by the time we reach 1×10^{-4} M (Fig. 8, Curve 3) a shoulder appears at the position of the B band. This phenomenon, which looks at first like an ordinary case of polymerization, proves to be a real enhancement of the B band through a salt effect. Identical results may be obtained by adding foreign salts to the very dilute solution. Thus, Fig. 8, Curve 2 shows the absorption of 5×10^{-7} crystal violet in the presence of 10^{-2} M tetra-*n*-butylammonium iodide, and in this solution the absorption curve is independent of the crystal violet concentration. While the addition of the tetra-*n*-butylammonium iodide produces the same result as an increase in the concentration of the crystal violet chloride, its effectiveness is far less. When the solution contains only 10^{-4} M tetra-*n*-butylammonium iodide the absorption curve hardly differs from Curve 1.[12]

The salt effect is much less noticeable in solvents of Class III than in those of Class II, but a careful examination of many absorption curves

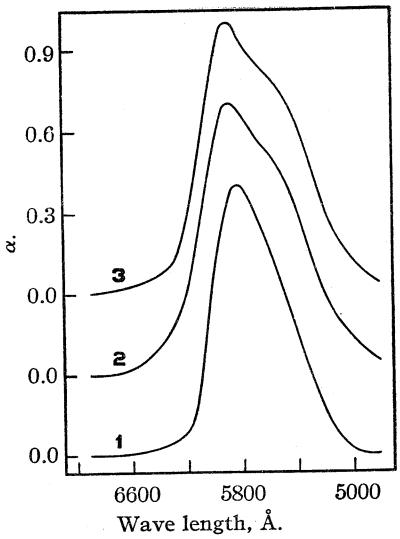


Fig. 8.—Relative extinction coefficient of crystal violet (chloride) in chloroform at 293°K.: (1) dye at 5×10^{-7} M; (2) dye at 5×10^{-7} M, but 10^{-2} M in tetra-*n*-butylammonium iodide; (3) dye at 1×10^{-4} M.

shows that the effect exists and, in this case also, increasing salt concentration brings the curve nearer to the curve in alcohol. In the solutions in toluene (plus β-naphthol) in going from 5×10^{-6} to $2 \times 10^{-4}M$, $\lambda_{max.}$ (A) remains unchanged but $\lambda_{max.}$ (B) becomes about 50 Å. greater and the B band appears to be a little broader. These changes in the B band may be reproduced and enhanced in the very dilute solutions in benzene or toluene by the addition of tetra-*n*-butylammonium iodide or silver perchlorate.[12]

For the difference between the absorption curves of Classes II and III we have no definite explanation. It appears not to be due to differences in dielectric constant and we may surmise that it depends upon the extent and the manner in which the solvent itself goes into the polyionic clusters, as it sometimes enters into crystals as "solvent of crystallization."

The Phosphorescent States of Crystal Violet.—In studying the absorption curve of crystal violet in glycerol, we encountered a phenomenon so strange that it was not understood until we had turned aside to make a thorough study of the phosphorescent state.[13] The phenomenon is illustrated in Fig. 9 where Curves 1 and 2 show the measured extinction of a given sample of crystal violet in glycerol at 228° and 178°K., respectively. As we cool the solution from room temperature, there is a gradual increase in the ab-

(12) We are thus led, merely by a careful inspection of absorption curves, to suspect the existence of a salt effect, in electrolytes such as crystal violet chloride, at concentrations far below those in which similar effects have been obtained with other electrolytes. Preliminary experiments fully justify this suspicion. While Vernon, Luder and Giella [THIS JOURNAL, **63**, 862 (1941)] found that the solubility of tetrabutylammonium iodide in benzene is about doubled in the presence of tetrabutylammonium picrate or nitrate at 10^{-3} M, we find similar and indeed greater effects with salts of crystal violet at concentrations as low as 10^{-6} M.

Vernon, Luder and Giella postponed a theoretical consideration but state that "it seems likely that association is the primary factor," and this is certainly correct. When a very dilute solution of a salt consists chiefly of the species X^+Y^-, $X_2^+Y_2^-$, $X_3^+Y_3^-$, . . ., and we add a second salt which consists chiefly of the species X^+Z^-, $X_2^+Z_2^-$, $X_3^+Z_3^-$, . . ., the species of one set will not sensibly affect the activities of the other species as such. However, new species are now possible, since we have what may formally be written as the two new species $X_2^+Y^-Z^-$ and $X_2^+Z^-Y^-$ for the quadruplet and $X_3^+Y_2^-Z^-$, $X_3^+Z^-Y_2^-$, $X_3^+Y^-Z_2^-$ and $X_3^+Z_2^-Y^-$ for the sextuplet. In the special case that Y^- and Z^- are sufficiently similar so that their interchange in the clusters produces little change in energy or entropy, but not similar enough so that the solid salts form solid solutions, the mutual solubility effect, when the equilibrium between species of each set is known, could be calculated from probability considerations alone.

In the crystal violet ion the positive charge may be considered to be shared equally by the three amino groups, and when a negative ion comes as close as possible to one of these groups, even allowing for induction, the resulting dipole moment must be at least 50% greater than in any of the ion pairs studied by Kraus. The ion pair should therefore be far less stable in our case, but on the other hand the higher multiplets, especially the sextuplet, should be extremely stable even at dilutions where other types of salts would show no appreciable association.

(13) Lewis, Lipkin and Magel, THIS JOURNAL, **63**, 3005 (1941).

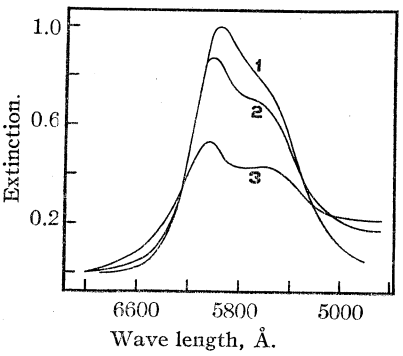


Fig. 9.—Extinction of a single sample of crystal violet (chloride) in glycerol: (1) at 233°K., with or without illumination by mercury arc; (2) at 178°K., no illumination except that used in measurements; and (3) at 178°K., illuminated also by mercury arc.

sorption corresponding to the contraction of the medium. However, at about 200°K. the apparent absorption begins to diminish rapidly and the absorption curve becomes broader. The whole phenomenon occurs in the same range of temperature where Gibson and Giauque[14] found the specific heat of glycerol to diminish about one-half. It is in this range that glycerol changes from a very viscous liquid to a rigid glass, and it is in this same region that the solution of crystal violet in glycerol begins to phosphoresce. A similar diminution in the apparent absorption coefficient of crystal violet in alcohol appears when the temperature is so low that the alcohol is rigid.

We have shown that when fluorescein in a rigid solvent is exposed to intense illumination, the greater part of the molecules go over into the isomer that is characteristic of the phosphorescent state. In that case the phosphorescent molecules had an absorption in a different part of the spectrum from that in which the normal molecules absorbed. Unfortunately in the case of crystal violet the molecules in the phosphorescent state have an absorption of smaller intensity and lying in the same region as the normal absorption. It has not been possible, therefore, to obtain the pure spectrum of the isomeric phosphorescent state, but it probably is not far different from that shown in Curve 3 of Fig. 9, which is obtained when the sample is exposed to illumination of high intensity from a high-pressure mercury arc. The difference between Curves 1 and 2 was found to be due to illumination by the light used in the measurements. At 228°K., where there is no phosphorescence, Curve 1 was obtained regardless of the intensity of the light to which the sample was exposed. At 178°K. the extinction at 5960 Å. fell off with increasing intensity of illumination in a way entirely parallel to that shown for fluorescein in Curve 2, Fig. 8, of our preceding paper.[13] The resemblance between Curves 2 and 3, the former being obtained with light containing almost no ultraviolet, indicates that the phenomenon is not connected with the green phosphorescence to be described later.

The Fluorescence and Phosphorescence Spectra.—We have already[13] mentioned and discussed the fact that crystal violet shows appreciable fluorescence only when the solvent is nearly in a rigid state; as in alcohol a little above the temperature of liquid air, in glycerol at about 215°K., and in supercooled glucose at room temperature. At these or slightly lower temperatures phosphorescence also appears.

When a solution of crystal violet, for example in glycerol, is illuminated at various temperatures with a mercury arc, and the phosphorescence observed, an apparently anomalous result is obtained. At 160°K. a bright red phosphorescence is seen, but at 90°K. the phosphorescence is green. It was found, however, that the green phosphorescence is due to an entirely distinct phosphorescent state which is excited only at wave lengths less than 4000 Å. When excited by visible light there is a strong red phosphorescence at the higher temperature (sufficiently intense to mask the green in the preceding experiment) which nearly disappears at the lower temperature. The visible red phosphorescence is nearly all due to an alpha band, the intensity of which diminishes as the temperature is lowered, but there is also a beta band that lies chiefly below the visible.

We have studied photographically the phosphorescence and fluorescence of crystal violet in glycerol at 178°K. From the spectrograms, together with suitable calibrations described later, we have obtained the Curves 1 and 2 of Fig. 10. The ordinates of each curve are proportional to the absolute emission at each wave length, but the ordinates of one curve are not comparable with those of the other. Curve 2 shows the spectrum of fluorescence accompanied by a small amount of phosphorescence. Curve 1 shows the pure phosphorescence spectrum as excited by visible light. For reference we give also Curve 3, the absorption spectrum, (Curve 1 of Fig. 9), as well as Curve 4, which is a rough determination of

(14) Gibson and Giauque, THIS JOURNAL, **45**, 93 (1923).

the spectrum of the green phosphorescence. In both curves the ordinates involve an arbitrary factor. It will be seen that as in other cases the alpha band is identical with the band of fluorescence. This band diminishes as the temperature is lowered and nearly disappears at the temperature of liquid air.

The lifetime of the phosphorescent state is much less than that of fluorescein, being of the order of 10^{-1} second for the green phosphorescence and 10^{-2} second for the red and infrared phosphorescence. We have not, therefore, measured the heat of activation corresponding to the alpha process, but we may obtain it by the principle of Jablonski.[15] From the positions of the emission maxima of Fig. 9 we find that the fluorescent state is 43.8 kcal. and the phosphorescent state 38.0 kcal. above the ground state. The difference, which represents the heat of activation from the phosphorescent to the fluorescent state, is 5.8 kcal. When we compare this with the 9 kcal. similarly obtained for fluorescein in boric acid we understand why the alpha band of fluorescein disappears at only a little below room temperature, while the alpha band of crystal violet is still prominent at 178°K.

We believe that all of the observed fluorescence and phosphorescence of crystal violet are due to the A isomer alone. If we correct Curve 2 for the small contribution of phosphorescence (say 10% of Curve 1 as drawn) the fluorescence spectrum looks very like a mirror image of one of our A bands of absorption. If there were any contribution of isomer B to the fluorescence we should have an emission band to the right of Curve 2, and such a band is certainly missing. The situation seems to be analogous to that of *cis*- and *trans*-stilbene where we have shown[16] that *trans*-stilbene fluoresces strongly while *cis*-stilbene, the isomer of greater steric strain, gives no observable fluorescence.

The green phosphorescence of crystal violet[17] which is stimulated by ultraviolet shows that the molecule is capable of existence in a second phosphorescent state. That this green phosphorescence is due to a beta process is certain, since we have observed it down to 20°K. From the frequency of the emission maximum we find that the energy of the corresponding phosphorescent state is 60 kcal. above the ground state, while the phosphorescent state corresponding to the infrared beta emission we have seen to be 38 kcal. above the normal state. It would be interesting to find whether any dye has a still greater number of phosphorescent states. Such observations might clarify our ideas as to the exact nature of the phosphorescent state itself.

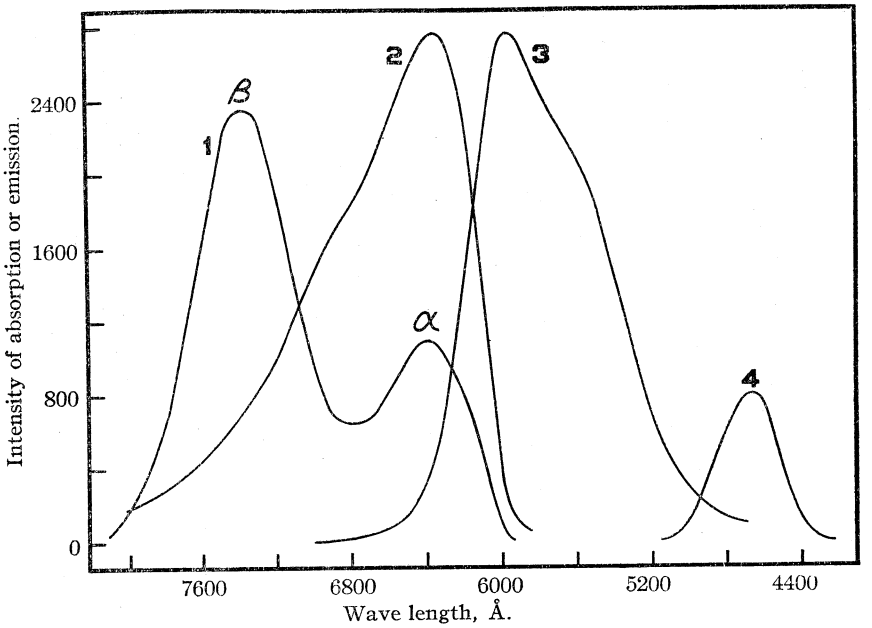


Fig. 10.—Curve 1: absolute intensity (except for an arbitrary constant) of the phosphorescent emission of crystal violet in glycerol at 178°K., showing the alpha and beta bands. Curve 2: similar absolute intensity of fluorescent emission (plus 5–10% phosphorescence), at 178°K. Curve 3: for reference, the absorption spectrum. Curve 4: intensity of green phosphorescence band (not corrected for plate characteristics).

Evidence for Another Isomeric State.—In addition to the two stereoisomers A and B, and the two fleeting isomers or electromers produced from the former when it goes into its phosphorescent states, we have found some evidence of still another isomeric condition of the crystal violet ion in rigid media. When a colorless compound of

(15) Jablonski, *Z. Physik*, **94**, 38 (1935).

(16) Lewis, Magel and Lipkin, THIS JOURNAL, **62**, 2973 (1940).

(17) Nearly half a century ago in a similar dye, methyl violet, a green phosphorescence was observed by Schmidt [*Ann. Physik*, **58**, 103 (1896)].

crystal violet ion with a strongly basic anion such as cyanide, borate or sulfide is ionized, the crystal violet ion would initially have a pyramidal structure and in a rigid solvent might have difficulty in going over to one of the nearly planar forms which are strongly colored. In fact, we sometimes find that, when one of these compounds, in a rigid solvent at liquid air temperature, is illuminated by ultraviolet light, the solution remains colorless or nearly so, but after the illumination has ceased and the solution is slowly warmed the characteristic absorption of crystal violet appears, although the color may disappear at a still higher temperature. This phenomenon is being further investigated.

Experimental

Many of our experiments were made with commercial crystal violet but for all crucial cases the dye was purified as follows. To a large volume of nearly saturated crystal violet chloride in water a small amount of sodium hydroxide was added. After the lapse of sufficient time for the formation of the carbinol, the latter was extracted by shaking several times with benzene and discarded. To the remaining aqueous solution a larger amount of sodium hydroxide was added to convert about one-half of the chloride into carbinol. This was shaken into benzene and kept. This last solution was shaken several times with water containing a little hydrochloric acid, and finally with water containing hydrochloric acid equivalent to one-half the remaining carbinol. From the aqueous solution thus obtained, after washing with benzene, the final product was obtained by crystallization. Other salts of crystal violet were obtained in a similar way.

The absorption and emission of light were measured by methods which we have already described.[13] In the present case the fluorescence and phosphorescence spectra shown in Fig. 10 were obtained as absolute values, except for a constant factor attending each curve, in the following way. On the same plates as the emission spectrograms, photographs were taken, through wire screens of varying transparency, of the light from a tungsten lamp operating at a color temperature of 2430°K. From the photometric tracings of all the plates, and from the known spectral distribution of the lamp, the absolute emission spectra were obtained by familiar methods.

Summary

The absorption of light by crystal violet has been studied under varying conditions and in numerous solvents. With respect to the appearance of the absorption curves solvents may be roughly placed in three classes, of which the first is typified by ethanol, the second by chloroform, and the third by toluene. All three types of curves show on analysis two absorption bands called A and B. The curve in ethanol is entirely independent of every isothermal change. With diminishing temperature the relative height of the B band in alcohol decreases and the two bands are thus shown to belong to two isomers of crystal violet ion, A and B, of which B has the higher energy by 580 cal. A theory as to the nature of these stereoisomers is given and is supported by experiments on the absorption curve of malachite green at low temperatures.

In solvents of Classes II and III (all of low dielectric constant) there is no appreciable number of free ions, but rather ion clusters of the sort described by Fuoss and Kraus. Small changes in the curves of Class III and a remarkable change in the chloroform curve, with increasing concentration of dye, are shown to be due to a salt effect and can be duplicated by adding other salts. That such salt effects exist, and in much higher degree than in any other known cases, is shown by other experiments.

The fluorescent and phosphorescent emission from crystal violet has been studied quantitatively. As in the previously described case of fluorescein, visible light of high intensity converts most of the dye into the phosphorescent state, so as to change greatly the absorption spectrum. The phosphorescent state gives rise to alpha and beta bands in the red and infrared, respectively. In this case the heat of activation from the phosphorescent to the fluorescent state is only 5.8 kcal. With ultraviolet light a new phosphorescent state is produced giving a green emission band. All the phosphorescence and fluorescence are attributed to isomer A.

There is evidence of still another isomeric condition of crystal violet ion, when produced from a leuco compound by illumination in a rigid solvent. This condition persists in the dark until the solvent is melted.

BERKELEY, CALIF. RECEIVED MARCH 23, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

The Formation of Cyclopropanes from Monohalides. III.[1] Action of Sodium Alkyls on Aliphatic Chlorides. Relation to the Wurtz Reaction

BY FRANK C. WHITMORE AND HARRY D. ZOOK[2]

The formation of benzene and ethylene in addition to ethylbenzene from the reaction of sodium phenyl and ethyl bromide has been explained by Schlubach and Goes[3] on the basis of a disproportionation between two free radicals. Since the postulation of sodium alkyls as intermediates in the Wurtz reaction,[4] Morton has studied the reaction of sodium amyl, prepared from amyl chloride and sodium, with various alkyl halides.[5] Low yields of the coupling products were obtained. Little attention has been given, however, to the "disproportionation products" from such reactions.

It appeared to us that, since sodium alkyls are strong hydrocarbo bases, the so-called disproportionation products may not arise by a free radical mechanism, but may be formed by the action of the hydrocarbo base on the halide.[6] Such a mechanism would give the saturated hydrocarbon corresponding to the sodium alkyl and the olefin corresponding to the halide in each case, rather than two saturated and two unsaturated hydrocarbons.

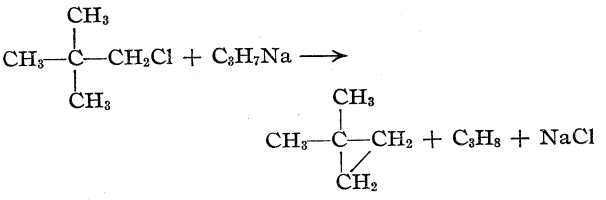
We have prepared sodium ethyl and sodium propyl from the corresponding mercury compounds and have treated these sodium alkyls with alkyl halides.

The reaction of sodium with excess mercury diethyl in *n*-pentane solution at 25° gave an 80% yield of sodium ethyl, the other product being a 5.8% sodium amalgam. This reaction mixture, when treated with *n*-hexyl chloride at −10° to 0°, gave a 40% yield of *n*-octane, a 46% yield of 1-hexene, and a 52% yield of ethane along with a small amount (2%) of ethylene.

$$C_2H_5Na + C_6H_{13}Cl \longrightarrow \begin{cases} C_4H_9CH{=}CH_2 + C_2H_6 + NaCl \\ n\text{-}C_8H_{18} + NaCl \end{cases}$$

To see what would happen when a halide having no alpha hydrogen atoms was treated with an alkylsodium compound, we have investigated the reaction of sodium *n*-propyl and neopentyl chloride. This sodium alkyl was prepared in 88% yield from sodium and excess mercury di-*n*-propyl in *n*-octane solution. No appreciable reaction took place between the sodium propyl and neopentyl chloride at temperatures below 50°, in contrast to the action of sodium ethyl and *n*-hexyl chloride. However, reaction proceeded smoothly at 50–60° to give a 75% yield of **1,1-dimethylcyclopropane** and a 4% yield of the coupled product, 2,2-dimethylhexane. The other products were **propane** (70%) and propene (5%), the latter compound probably coming from the decomposition of part of the propyl sodium at the temperature used. No neopentane was formed. It was found that neopentyl chloride would not react with a 6% sodium amalgam such as was present in this case from the preparation of the sodium propyl.

The hydrocarbo base has caused cyclization by the removal of a beta hydrogen atom as hydrogen halide.



Although 3-ring closure has been accomplished many times by the removal of hydrogen halide with an aquo or alcoholo base, the hydrogen removed has usually been activated by an adjacent carboxyl or other strongly negative group.[7] The first step in our reaction may be the removal of one of the nine beta hydrogens by the sodium propyl to give propane.[8] Some indication of the base strength of the sodium alkyl may be seen from the fact that neopentyl chloride is inert to alcoholic potassium hydroxide in a sealed tube for twenty hours at 100°.[9] The reaction of sodium alkyls as well as other bases on halides of this type is being investigated further.

Yields of sodium alkyls from the mercury compounds were obtained indirectly in three ways: from the mercury recovered from the hydrolysis

(1) Whitmore and Carney, THIS JOURNAL, **63**, 2633 (1941).
(2) Allied Chemical and Dye Corporation Fellow, 1941–1942.
(3) Schlubach and Goes, *Ber.*, **55B**, 2889 (1922).
(4) *Cf.* Wooster, *Chem. Rev.*, **11**, 1 (1932).
(5) Morton and Fallwell, THIS JOURNAL, **59**, 2387 (1937).
(6) *Cf.* Whitmore and Thurman, *ibid.*, **51**, 1491 (1929).
(7) See, for example, Fuson in Gilman "Organic Chemistry," John Wiley and Sons, New York, N. Y., 1938, p. 21.
(8) *Cf.* Hauser, THIS JOURNAL, **62**, 933 (1940).
(9) Whitmore and Fleming, *ibid.*, **55**, 4161 (1933).

of the amalgam, from the sodium hydroxide thus obtained, and from the sodium chloride formed in the main reaction. The yields of sodium ethyl calculated by these three methods were 80 ±1%. Quantitative sodium and chlorine material balances were obtained in each case. Solvents were recovered in better than 90% yields, showing that metalation of the normal paraffin hydrocarbons is not appreciable under the conditions used.

Mechanism of the Wurtz Reaction

Sodium alkyls[4] and free radicals[10] have been postulated by many workers as intermediates in the Wurtz reaction.

It has been shown that the Wurtz reaction may be carried out in such a manner that sodium alkyls play a major part in the mechanism.[11] Morton and Richardson found that by increasing the sodium surface per mole of amyl chloride the yields of acids formed by carbonation of the intermediate sodium compounds may go as high as 95% as the decane formed approaches zero.[11]

Part of the evidence for the free radical theory is based on the formation of disproportionation products such as ethane and ethylene in equimolar amounts from the reaction of ethyl iodide and sodium.[10b] Our work indicates that in cases where sodium alkyls play a major part in the reaction, the by-product saturated and unsaturated hydrocarbons obtained do not arise from the disproportionation of free radicals but from the action of the sodium alkyl as a hydrocarbo base with the alkyl halide.

Thus *n*-hexyl chloride and sodium ethyl give 40% *n*-octane by coupling and about 50% each of 1-hexene and ethane. The coupling product may be formed by a Walden inversion type of reaction. This is similar to the action of *n*-hexyl chloride with alcoholic bases to give mainly *n*-hexyl ethyl ether and a little 1-hexene.[12] The failure of neopentyl chloride and sodium propyl to give more than a few per cent. of coupling product is probably connected with the sluggishness of this halide in metathetical reactions of the Walden type.[13] In this case the by-product hydrocarbons become the main product and the "unsaturated" one appears as 1,1-dimethylcyclopropane. It would thus seem that the earlier work from this Laboratory on the action of sodium with neopentyl chloride[10a] and neohexyl chloride[1] may go through sodium alkyls formed from free radicals. These would react with the halides as does sodium propyl in the present study.

(10) (a) *Cf.* ref. 1, and Whitmore and co-workers, THIS JOURNAL, **63**, 124 (1941); (b) Richards, *Trans. Faraday Soc.*, **36**, 956 (1940); (c) Bachmann and Clarke, THIS JOURNAL, **49**, 2089 (1927).

(11) Morton and Richardson, *ibid.*, **62**, 123 (1940).

(12) Unpublished results by A. H. Popkin of this Laboratory.

(13) Ref. 9: also *cf.* Bartlett and Rosen, THIS JOURNAL, **64**, 543 (1942).

Experimental

The Reaction of Sodium Ethyl and *n*-Hexyl Chloride.—The apparatus consisted of a three-necked flask equipped with a reflux condenser, thermometer, dropping funnel, and mercury sealed stirrer. Gases were led from the reflux condenser through two dry-ice–acetone traps and collected over saturated sodium chloride solution. The air from the entire apparatus was swept out by a stream of nitrogen.

Exactly 23.1 g. of freshly cut sodium was weighed out in a glass-stoppered bottle under pentane. The sodium was then cut into very thin slices under pentane, the pentane decanted, and the sodium dried with a stream of nitrogen. The dry sodium was transferred in an atmosphere of nitrogen to the reaction flask and covered with 122.5 g. of olefin-free *n*-pentane; b. p. 36° (737 mm.), $n^{20}D$ 1.3580. The addition of 200 g. of mercury diethyl, b. p. 67.5° (30 mm.), required thirty minutes during which time the flask was held at 25° by adding small pieces of dry-ice to an acetone-bath in which it was immersed. Reaction was rapid giving a fine suspension of sodium ethyl and sodium amalgam. No gas was formed. The mixture was allowed to stir for an hour, after which the flask was cooled to −10°.

The addition of 121.5 g. of *n*-hexyl chloride, b. p. 134° (738 mm.) and $n^{20}D$ 1.4200, took place over a period of two and one-half hours. Gas was evolved at the rate of a liter an hour for twelve hours at temperatures between −10° and 0°. The reaction mixture was charged directly to a 13-plate column and 118 g. (96%) of the pentane solvent was removed; b. p. 35.5–37° (734 mm.); $n^{20}D$ 1.3580–1.3592.

The clear liquid portion of the residue was decanted. The solid amalgam and sodium chloride were washed with small portions of pentane and filtered. The amalgam was decomposed with 500 cc. of water and 250 cc. of 0.927 *N* sulfuric acid. Back-titration with 23.7 cc. of standard sodium hydroxide (1 cc. base = 1.08 cc. of acid) indicated the presence of 4.76 g. of sodium in the amalgam. The mercury, after washing well with water, acetone, and dry ether, weighed 78.5 g. Analysis of the neutralized aqueous solution showed the presence of 47.1 g. of sodium chloride.

The yields of sodium ethyl in the first step of the reaction calculated from the mercury formed, from the sodium present in the amalgam, and from the sodium chloride formed by the reaction are 40.8, 41.4 and 41.8 g., respectively.

The liquid organic products from the reaction were fractionated at 733 mm. through a 13-plate column. Fractions: 3–9, 10.9 g., b. p. 44–62°, $n^{20}D$ 1.3605–1.3872; 10–18, 23.7 g., 62–65°, 1.3880–1.3881; 19–21, 6.3 g., 75–123°, 1.3898–1.4000; 22–27, 29.9 g., 123°, 1.4020–1.4032; 28–31, 19.1 g., 124° (733 mm.) to 60° (40 mm.). The yields of 1-hexene and *n*-octane, taken from boiling point and refractive index curves, were 30.7 g. and 36.1 g., respectively.

The gas from the reaction was analyzed in a modified Orsat apparatus using a solution saturated with bromine and sodium chloride to remove the ethylene.[14] The gas evolved consisted of 0.50 g. of ethylene and 12.6 g. of ethane.

Identification of 1-Hexene.—Fractions 9–18 (24 g.) from the products of the reaction of sodium ethyl and *n*-hexyl chloride were diluted with 200 cc. of olefin-free pentane, and a stream of oxygen containing 3% ozone passed through at an average rate of 25 l. per hour for seven hours. The ozonide was decomposed according to the method of Whitmore and Church.[15] Formaldehyde was found in the water layer from the decomposition, and was identified by its dimethylcyclohexanedione derivative; m. p. 190.5–191.5°. Fractionation of the oil layer gave 8.2 g. of valeraldehyde; b. p. 95–99° (715 mm.); identified by its 2,4-dinitrophenylhydrazone, m. p. 107–108° and mixed m. p. with an authentic sample 107.5–108.5°.

Reaction of Sodium *n*-Propyl and Neopentyl Chloride.—The same apparatus and technique were used as for the reaction of sodium ethyl and *n*-hexyl chloride. The two cold traps were held at −40° in order to retain 1,1-dimethylcyclopropane but not propane. *n*-Octane, 232 g., b. p. 124.5° (729 mm.) and $n^{20}D$ 1.3982, was used as the dispersing medium. The propyl sodium was prepared from 23.0 g. of sodium and 202.5 g. of mercury di-*n*-propyl; b. p. 86.5° (25 mm.). No gas was evolved while stirring for an hour at room temperature. The reaction mixture was cooled to 0° for the addition of 89.5 g. of neopentyl chloride; b. p. 82–84° (740 mm.) and $n^{20}D$ 1.4048. After about a third of the chloride was added the mixture was slowly warmed to 50° at which temperature a slow evolution of gas began. The remainder of the chloride was added over a period of three hours. Gas was evolved at the rate of 500 cc. per hour for a period of about eight hours. At this point the stirrer was replaced by a 10-plate column to which was attached a series of traps held at −15, −80 and −80°, respectively. Ice water was circulated through the head and jacket of the column as the flask was gradually heated to 107° over a period of fifteen hours in order to complete the reaction and drive off all low boiling products. The residue was decomposed with water and standard acid as previously described. There was obtained 87.7 g. of mercury representing an 88% yield of sodium propyl. The amount of sodium in the amalgam (4.56 g.) and the sodium chloride from the reaction (46.1 g.) correspond to a 79% yield of sodium propyl. (Some sodium propyl decomposed, however, to give propylene.)

Material collected in the traps held at −80° was distilled through a low temperature micro column to give 22.0 g. boiling below −38° and a residue which, together with material collected in the traps held at −40°, was fractionated at 730 mm. through a 40-plate low temperature column. Obtained were fractions: 1–4, 2.3 g., b. p. −15 to 17°; 5–6, 7.7 g., 18–19.8°; 7–11, 31.0 g., 20.2–20.8°, $n^{20}D$ 1.3660–1.3675. The material from fractions 7–11 would not react with bromine in carbon tetrachloride. The residue from this distillation was combined with the other liquid organic products from the reaction and fractionated through a 40-plate column. From a complete distillation curve of both fractionations there was calculated to be 41.3 g. (75%) of 1,1-dimethylcyclopropane; 3.0 g. of recovered neopentyl chloride; 4.0 g. (4%) of impure 2,2-dimethylhexane, b. p. 104–111° (722 mm.), $n^{20}D$ 1.3998–1.4001; 214 g. (92.5%) of recovered octane solvent, b. p. 120° (722 mm.) to 70° (40 mm.), $n^{20}D$ 1.3982–1.3986; and 74 g. of recovered mercury dipropyl, b. p. 95–97° (40 mm.).

The material collected below −38° was vaporized, and the gas collected over saturated sodium chloride solution. Analysis of all the gaseous products indicated that there was present 1.85 g. (5%) of propene and 27.5 g. (71%) of propane. Again, a solution saturated with sodium chloride and bromine was used to absorb the olefin.

Attempted Reaction of Neopentyl Chloride with Sodium Amalgam.—Into a 500-cc. flask was placed 59 g. of neopentyl chloride, b. p. 82–84° (740 mm.), $n^{20}D$ 1.4048 and 209 g. of freshly prepared 6% sodium amalgam. The flask was attached to a 20-plate column and the neopentyl chloride refluxed for six hours. Fractionation then gave 6 fractions, 56.3 g., b. p. 83° (745 mm.), $n^{20}D$ 1.4048 along with 1.8 g.; $n^{20}D$ 1.4060 driven from the column when the jacket was heated to 160°. No low boiling products were collected in a dry-ice trap connected to the column. The recovery of neopentyl chloride was 98%.

Summary

1. Sodium ethyl and sodium propyl were prepared from sodium and the corresponding mercury compounds in yields of 80 and 88%, respectively. No appreciable reaction took place between the alkylsodium compounds and *n*-paraffin hydrocarbon solvents.

2. Sodium ethyl reacts with *n*-hexyl chloride to give octane (40%), ethane (52%), 1-hexene (46%), and a trace of ethylene.

3. The products of the reaction of sodium propyl and neopentyl chloride were 1,1-dimethylcyclopropane (75%), propane (70%), propene (5%), and the coupled product, 2,2-dimethylhexane (4%).

4. The major reaction is one of a hydrocarbo base splitting out hydrogen chloride from an alkyl chloride.

5. The possible relationship of these results to the mechanism of the Wurtz reaction is discussed.

STATE COLLEGE, PENNSYLVANIA

RECEIVED APRIL 27, 1942

(14) Lang, *Ind. Eng. Chem., Anal. Ed.*, **7**, 150 (1935).

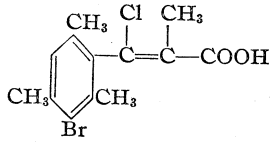
(15) Whitmore and Church, THIS JOURNAL, **54**, 3710 (1932).

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

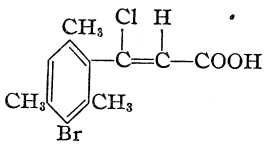
Restricted Rotation in Aryl Olefins. IV. Preparation and Resolution of β-Chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-α-methylacrylic and the Corresponding Acrylic Acid

BY ROGER ADAMS AND W. J. GROSS[1]

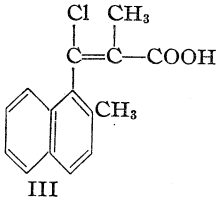
The molecules shown by formulas I, II, III and IV and a few of their derivatives have been resolved and the active forms shown to be very resistant to racemization. The half-life periods in boiling *n*-butanol are for I, no racemization; for II, two hundred minutes; for III, seventy hours; for IV, seventy minutes. These values show semi-



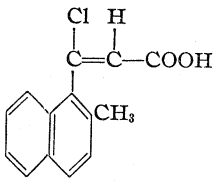
I



II



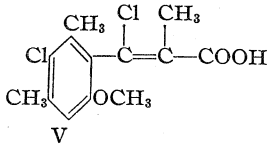
III



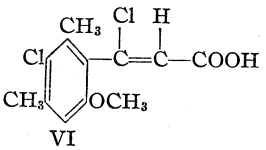
IV

quantitatively the relative interference effects of the hydrogen and methyl on the α-carbon to the carboxyl (compare I and II; also III and IV) and of the *ortho* methyl and —CH= group in the aromatic nucleus (compare I and III; also II and IV).

Analogous derivatives to compounds I and II have now been synthesized and resolved in which an *ortho* methyl group in the benzene ring has been substituted by the smaller methoxyl group (V and VI).



V



VI

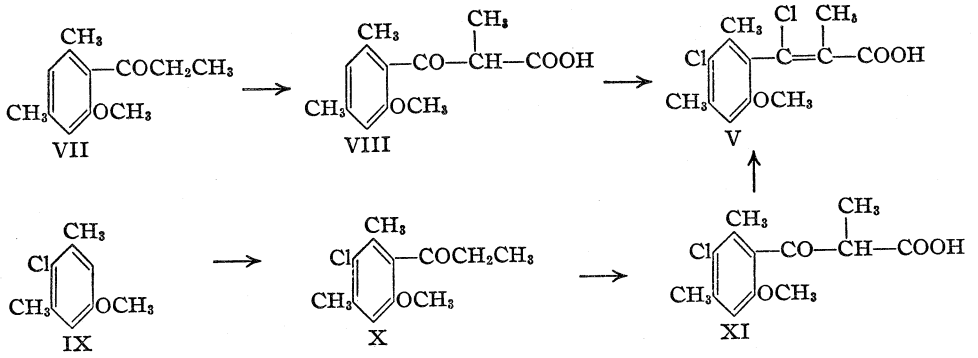
The active forms of these molecules racemized so rapidly in boiling *n*-butanol that quantitative racemization measurements were impossible under these conditions. The active form of compound V was consequently racemized in *n*-butanol at 44° and the half-life determined as one hundred and seventy-three minutes; the active form of compound VI had a half-life period of about nine minutes in *n*-butanol at 20°. Although the racemization values of compounds I, II, III and IV taken in boiling *n*-butanol cannot be compared quantitatively with those of compounds V and VI taken at other temperatures, the relative ease of racemization of the latter two is striking. It demonstrates forcibly the enormous difference in the interference effects of the methoxyl and methyl groups in the ring and again of the methyl and hydrogen on the α-carbon to the carboxyl. The alkaloidal salts of acids V and VI were obtained in only one form though mutarotation was not observed at room temperature.

No attempt has been made to determine whether compounds V and VI have the carboxyl *cis* or *trans* to the side-chain chlorine. From considerations presented in the previous papers,[1a,1b] the assumption is that the carboxyl is *trans*. A study of a model of compound VI indicates that only if the carboxyl is *trans* to the side-chain chlorine is interference possible.

The synthesis of compound V was effected in two ways. 1-Methoxy-3,5-dimethylbenzene was converted to 1-methoxy-3,5-dimethyl-2-propiophenone (VII) by means of propionic anhydride and aluminum chloride. Ethylmagnesium bromide followed by carbon dioxide gave α-methyl-(2-methoxy-4,6-dimethylbenzoyl)-acetic acid (VIII). The yield was only 40% and an unidentified by-product was obtained which probably originated from the action of the Grignard reagent on the keto form of the propiophenone. Since completely hindered ketones usually react entirely in the enol form with the Grignard reagent, the large by-product may be indicative of the decreased interference present as compared with that in the mesitylene analogs.

The usual procedure for obtaining the desired β-chloro-acrylic acid from the keto acid is by the use of phosphorus pentachloride in phosphorus oxychloride. In this instance, however, chlorination of the ring took place at the same time giving a mixture from which two compounds were isolated, one postulated as having structure V and

(1) For previous papers see (a) Adams and Miller, THIS JOURNAL, **62**, 53 (1940); (b) Adams, Anderson and Miller, *ibid.*, **63**, 1589 (1941); (c) Adams and Binder, *ibid.*, **63**, 2773 (1941).



the other with no chlorine in the ring. The position of the chlorine in the ring in V was determined by preparing 1-methoxy-3,5-dimethyl-4-chlorobenzene (IX) and converting it to the 1-methoxy-3,5-dimethyl-4-chloro-2-propiophenone (X). By following the same series of reactions through the keto acid (XI) as previously described, compound V was obtained. This latter method of preparation of V was distinctly superior to the former since the use of 1-methoxy-3,5-dimethyl-4-chlorobenzene as a raw material in place of 1-methoxy-3,5-dimethylbenzene served not only to prove the position of the chlorine in the ring but also permitted the formation of only one product in the final chlorination reaction.

The corresponding β-chloroacrylic acid (VI) was synthesized from 1-methoxy-3,5-dimethyl-4-chlorobenzene in a similar manner.

By starting with 1-ethoxy-3,5-dimethyl-4-chlorobenzene the 2-ethoxy derivatives corresponding to compounds V and VI were formed but no salts were found with suitable characteristics to make resolution studies possible.

Experimental

1-Methoxy-3,5-dimethyl-2-propiophenone.—To a mechanically stirred mixture of 300 g. of carbon disulfide, 136 g. of 1-methoxy-3,5-dimethylbenzene[2] and 130 g. of propionic anhydride, was added 267 g. of anhydrous aluminum chloride at such a rate that the solvent refluxed gently. Upon completion of the addition a plastic mass formed making further stirring impossible. After the reaction mixture had stood for twelve hours the solvent was decanted and the residue decomposed using iced hydrochloric acid. The oil which separated was extracted with ether, washed with aqueous sodium hydroxide and finally with dilute hydrochloric acid. Distillation gave a water-white liquid; b. p. 120–122° (2 mm.), $n^{24}D$ 1.5160; yield 144 g. (75%).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 75.00; H, 8.40. Found: C, 75.46; H, 8.44.

Demethylation, observed in every experiment, increased as the excess of aluminum chloride was increased. The yield reported is that obtained when minimum demethylation occurred.

1-Hydroxy-3,5-dimethyl-2-propiophenone.—Acidification of the sodium hydroxide washings obtained in the preparation of 1-methoxy-3,5-dimethyl-2-propiophenone gave 1-hydroxy-3,5-dimethyl-2-propiophenone. The crude product was recrystallized from a small amount of methanol, white crystals, m. p. 78° (cor.).

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.11; H, 7.92. Found: C, 73.93; H, 7.98.

This substance was remethylated readily by dissolving it in the appropriate amount of aqueous sodium hydroxide and adding dropwise, with stirring, an excess of dimethyl sulfate. After heating the reaction mixture at 100° for one hour, it was cooled and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and then distilled to give 1-methoxy-3,5-dimethyl-2-propiophenone.

α-Methyl-(2-methoxy-4,6-dimethylbenzoyl)-acetic Acid.—A solution of 20 g. of 1-methoxy-3,5-dimethyl-2-propiophenone in 25 cc. of dry ether was added to 100 cc. of an ether solution containing slightly more than one mole equivalent of ethylmagnesium bromide. The mixture was refluxed for thirty minutes, then transferred to a catalytic hydrogenation apparatus, cooled in an ice-bath, and carbon dioxide[3] passed in at a pressure of 2–3 atm. After forty-five minutes the temperature was allowed to rise to that of the room and the addition of carbon dioxide continued for six hours.

The reaction mixture was then chilled in an ice-bath, and poured slowly into iced hydrochloric acid. The ether layer was extracted with aqueous sodium hydroxide and the aqueous extract immediately acidified with iced hydrochloric acid. The product was purified by dissolving it in an excess of petroleum ether (b. p. 60–110°) and concentrating by means of an air stream; white crystalline powder, m. p. 88–89° (cor.); yield 8 g. (30%). When pure the material is stable for several weeks.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.07; H, 6.82. Found: C, 66.57; H, 7.18.

Evaporation of the ether solution after extraction with aqueous sodium carbonate did not give the expected unreacted ketone but rather a substance of lower boiling point. This liquid, postulated as being a mixture of the tertiary alcohol and the corresponding dehydration product arising

(2) Rowe, Bannister, Seth and Storey, *J. Chem. Ind.*, **46T**, 469 (1930).

(3) Kohler and Baltzly, THIS JOURNAL, **54**, 4015 (1932); Fuson, Fugate and Fisher, *ibid.*, **61**, 2362 (1939).

from the normal Grignard addition reaction, was treated with acetic anhydride to effect complete dehydration. The purified product did not give the proper analysis, however, and no further investigation was attempted.

β-Chloro-β-(2-methoxy-4,6-dimethylphenyl)-α-methylacrylic Acid.—To a solution of 10 g. of α-methyl-(2-methoxy-4,6-dimethylbenzoyl)-acetic acid in 50 cc. of ice cold phosphorus oxychloride, was added 25 g. of phosphorus pentachloride. After heating at 70° for one hour, the solution was poured onto 300 g. of ice. The product separated as an oil which solidified on standing. The crude material, after many careful fractional crystallizations from benzene, was shown to be a mixture of β-chloro-β-(2-methoxy-4,6-dimethylphenyl)-α-methylacrylic acid and β-chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-α-methylacrylic acid. Each was separated in a pure state but only in small amounts. β-Chloro-β-(2-methoxy-4,6-dimethylphenyl)-α-methylacrylic acid was obtained from benzene as white crystals, m. p. 163–164° (cor.).

Anal. Calcd. for $C_{13}H_{15}O_3Cl$: C, 61.29; H, 5.89. Found: C, 61.15; H, 6.03.

β-Chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-α-methylacrylic acid was obtained from benzene as white crystals, m. p. 178–179° (cor.).

Anal. Calcd. for $C_{13}H_{14}O_3Cl_2$: C, 54.00; H, 4.88; neut. equiv., 289. Found: C, 54.43; H, 5.05; neut. equiv., 287.

1-Methoxy-3,5-dimethyl-4-chlorobenzene (IX).—A solution of 313 g. of 1-hydroxy-3,5-dimethyl-4-chlorobenzene[4] in 85 g. of sodium hydroxide dissolved in a small amount of water was stirred and to it was added dropwise an excess of dimethyl sulfate. After refluxing for two hours, the resulting oil was removed and the water layer extracted with ether. The oil and ether extracts were combined and dried by means of anhydrous magnesium sulfate, the ether was then removed and the residue distilled; b. p. 94–96° (6 mm.), $n^{20}D$ 1.5365; yield 273 g. (80%).

Anal. Calcd. for $C_9H_{11}OCl$: C, 63.31; H, 5.91. Found: C, 64.09; H, 6.75.

1-Methoxy-3,5-dimethyl-4-chloro-2-propiophenone (X).—This product was prepared in a similar manner to 1-methoxy-3,5-dimethyl-2-propiophenone using 1-methoxy-3,5-dimethyl-4-chlorobenzene in place of 1-methoxy-3,5-dimethylbenzene. It was a white, crystalline solid, readily purified from petroleum ether (b. p. 60–110°), m. p. 66.5–67.5° (cor.); yield 125 g. (55%).

Anal. Calcd. for $C_{12}H_{15}O_2Cl$: C, 63.54; H, 6.66. Found: C, 64.01; H, 6.70.

Acidification of the sodium hydroxide washings gave 1-hydroxy-3,5-dimethyl-4-chloro-2-propiophenone, a white crystalline solid. This substance was not purified but was remethylated as described for the corresponding unchlorinated compound, 1-hydroxy-3,5-dimethyl-4-propiophenone.

Demethylation, observed in every experiment, increased as the excess of aluminum chloride was increased. The yield reported was that obtained when minimum demethylation occurred.

(4) Lesser and Gad, *Ber.*, **56B**, 974 (1923).

α-Methyl-(2-methoxy-4,6-dimethyl-5-chlorobenzoyl)-acetic Acid (XI).—A solution of 20 g. of 1-methoxy-3,5-dimethyl-4-chloro-2-propiophenone in 25 cc. of dry ether was added to 100 cc. of an ether solution containing slightly more than one mole equivalent of ethylmagnesium bromide. The mixture was refluxed for thirty minutes and carbonated as described for the corresponding unchlorinated propiophenone. The product was purified by crystallization from petroleum ether (b. p. 60–110°) and finally from benzene by dissolving it in an excess of the solvent and then concentrating; white crystalline powder, m. p. 118° (cor.); yield 12 g. (50%). When pure, the material was stable for several weeks. The crude product was satisfactory for conversion to β-chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-α-methylacrylic acid.

Anal. Calcd. for $C_{13}H_{15}O_4Cl$: C, 57.76; H, 5.58. Found: C, 57.65; H, 5.61.

Evaporation of the ether solution after extraction with sodium carbonate yielded a liquid which was probably a mixture of the tertiary alcohol and the corresponding dehydration product, arising from the normal Grignard addition reaction to the keto form of the propiophenone.

β-Chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-α-methylacrylic Acid (V).—A sample of 10 g. of α-methyl-(2-methoxy-4,6-dimethyl-5-chlorobenzoyl)-acetic acid was converted to the chloroacrylic acid derivatives by the procedure described for the corresponding unchlorinated phenyl derivative. It was purified by recrystallization first from petroleum ether (b. p. 60–110°) and then several times from benzene; white crystals, m. p. 178–179° (cor.); yield 5.5 g. (50%).

Anal. Calcd. for $C_{13}H_{14}O_3Cl_2$: C, 54.00; H, 4.88; neut. equiv., 289. Found: C, 54.00; H, 5.02; neut. equiv., 287.

Resolution of β-Chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-α-methylacrylic Acid (V).—A solution of 2.7 g. of β-chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-α-methylacrylic acid in 40 cc. of warm acetone was added to a solution of 2.9 g. of quinine in 40 cc. of warm acetone. After filtration the solution was allowed to stand for five days after which fraction A (2.5 g.) was removed. This was unchanged in rotation after recrystallization from acetone. The filtrate was then evaporated to 60 cc. and after standing two days fraction B (0.55 g.) was collected. Evaporation of the filtrate to 25 cc. yielded fraction C (1.2 g.) after standing four days. Evaporation to dryness gave fraction D. The rotations of fractions B and C were essentially identical with those of fraction A from which it was deduced that only one salt was obtained. No mutarotation was observed over a short period of time at room temperature.

Anal. Calcd. for $C_{33}H_{38}O_5Cl_2N_2$: C, 64.57; H, 6.24. Found: C, 64.68; H, 6.46. *Rotation.* (*l*BdA) 0.050 g. made up to 25 cc. with benzene at 20° gave αD −0.12°; *l*, 2; $[\alpha]^{20}D$ −30.0°.

***d*-β-Chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-α-methylacrylic Acid.**—To a suspension of 2 g. of salt (fraction A) in 30 cc. of water was added 5 cc. of concentrated hydrochloric acid. After stirring at 5° for thirty minutes the product was filtered, washed with 5% hydrochloric acid and finally with water. The above was re-

peated until the product was quinine free; m. p. 177° (cor.).

Rotation. (*d*-acid) 0.100 g. made up to 25 cc. with *n*-butanol at 20° gave α_D +0.18; *l*, 2; $[\alpha]^{20}D$ +22.5°.

Racemization of *d*-β-Chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-α-methylacrylic Acid (V).—A solution of 0.1 g. of the above *d*-acid in 25 cc. of *n*-butanol was placed in a polarimeter tube equipped with a water jacket through which was passed water at 44° from a constant temperature bath. The following α_D values were obtained: at the start +0.18; after thirty minutes +0.16; after one hour +0.15; after one and a half hours +0.13; after two hours +0.11; after two and a half hours +0.09; after three and a half hours +0.07; after four and a half hours +0.06; after seven and a half hours +0.02. Calculated for a reversible unimolecular reaction, the half-life period is 173 minutes.

1-Methoxy-3,5-dimethyl-4-chloro-2-acetophenone.—To 300 g. of carbon disulfide, 171.5 g. of 1-methoxy-3,5-dimethyl-4-chlorobenzene and 102 g. of acetic anhydride, was added 267 g. of anhydrous aluminum chloride using exactly the same procedure employed to produce 1-methoxy-3,5-dimethyl-4-chloro-2-propiophenone. Distillation gave a white crystalline solid; b. p. 134–136° (3 mm.). It was purified by crystallization from dry ether, m. p. 76–77° (cor.); yield 127 g. (50%).

Anal. Calcd. for $C_{11}H_{13}O_2Cl$: C, 62.09; H, 6.16. Found: C, 61.92; H, 6.23.

As in the preparation of 1-methoxy-3,5-dimethyl-4-chloro-2-propiophenone, demethylation occurred. The product could be remethylated and purified readily, however, in exactly the same manner as the 1-hydroxy-3,5-dimethyl-4-chloro-2-propiophenone previously described.

2-Methoxy-4,6-dimethyl-5-chlorobenzoyl Acetic Acid.—A solution of 20 g. of 1-methoxy-3,5-dimethyl-4-chloro-2-acetophenone in 25 cc. of dry ether was added to 100 cc. of an ether solution containing slightly more than one mole equivalent of ethylmagnesium bromide. The bromomagnesium enolate precipitated and was carbonated in the same manner as 1-methoxy-3,5-dimethyl-4-chloro-2-propiophenone. Recrystallization of the crude product gave a white crystalline powder, m. p. 113° (cor.); yield 11 g. (45%).

Anal. Calcd. for $C_{12}H_{13}O_4Cl$: C, 56.11; H, 5.11. Found: C, 55.73; H, 5.24.

As in the case of α-methyl-(2-methoxy-4,6-dimethyl-5-chlorobenzoyl)-acetic acid (XI), normal addition of the Grignard reagent apparently took place, for the main constituent of the residue was a liquid which was presumably the dehydrated tertiary alcohol.

β-Chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-acrylic Acid (VI).—To a solution of 10 g. of 2-methoxy-4,6-dimethyl-5-chlorobenzoyl acetic acid in 50 cc. of ice-cold phosphorus oxychloride was added 25 g. of phosphorus pentachloride. The mixture was heated in a water-bath at 70° for one hour, then poured onto 300 g. of ice. A solid separated and was purified by crystallization from petroleum ether (b. p. 60–110°) and finally from benzene; white crystals, m. p. 181–182° (cor.); yield 5.2 g. (48%).

Anal. Calcd. for $C_{12}H_{12}O_3Cl_2$: C, 52.34; H, 4.34. Found: C, 52.18; H, 4.49.

Resolution of β-Chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-acrylic Acid (VI).—A solution of 6.3 g. of β - chloro - β - (2 - methoxy - 4,6 - dimethyl - 5 - chlorophenyl)-acrylic acid in 50 cc. of ethyl acetate was added to a solution of 7.5 g. of quinine in 70 cc. of ethyl acetate. After filtration the solution was evaporated to 40 cc. and at two-day intervals the crystals were filtered and 5 cc. of solvent was removed. The rotations of the various fractions thus obtained were essentially the same and the same *d*-acid was obtained from all fractions, indicating the formation of only one salt. The various fractions were unchanged in rotation after recrystallization from ethyl acetate. No mutarotation was observed over a short period of time at room temperature.

Anal. Calcd. for $C_{32}H_{36}O_5N_2Cl_2$: C, 64.05; H, 6.05. Found: C, 64.15; H, 6.22. *Rotation.* (*l*B*d*A) 0.050 g. made up to 25 cc. with benzene at 20° gave α_D −0.10°; *l*, 2; $[\alpha]^{20}D$ −25.00°.

***d*-β-Chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-acrylic Acid.**—To a suspension of 2 g. of salt in 30 cc. of water was added 5 cc. of concentrated hydrochloric acid. After stirring at 5° for thirty minutes the product was filtered and washed with 5% hydrochloric acid and finally with water. The above was repeated until the product was quinine free; m. p. 180° (cor.).

Rotation. (*d*-acid) 0.100 g. made up to 25 cc. with *n*-butanol at 20° gave α_D 0.10°; *l*, 2; $[\alpha]^{20}D$ +12.5°.

Racemization of *d*-β-Chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-acrylic Acid (VI).—A solution of 0.100 g. of the *d*-acid made up to 25 cc. with *n*-butanol at 20° gave the following values: at the start +0.10; after five minutes +0.08; after eight minutes +0.06; after fifteen minutes +0.04; after twenty minutes +0.02; after twenty-five minutes 0.00. Calculated for a reversible unimolecular reaction, the half-life period is approximately nine minutes.

1-Ethoxy-3,5-dimethyl-4-chlorobenzene.—This compound was prepared from 1-hydroxy-3,5-dimethyl-4-chlorobenzene in exactly the same manner as 1-methoxy-3,5-dimethyl-4-chlorobenzene was obtained from 1-hydroxy-3,5-dimethyl-4-chlorobenzene except that diethyl sulfate was used in place of dimethyl sulfate. The yield was 85%.

Anal. Calcd. for $C_{10}H_{13}OCl$: C, 65.00; H, 7.09. Found: C, 65.31; H, 7.15.

1-Ethoxy-3,5-dimethyl-4-chloro-2-propiophenone.—To 300 g. of carbon disulfide, 185 g. of 1-ethoxy-3,5-dimethyl-4-chlorobenzene and 130 g. of propionic anhydride was added 267 g. of anhydrous aluminum chloride using exactly the same procedure employed to produce 1-methoxy-3,5-dimethyl-4-chloro-2-propiophenone. It had a b. p. of 155–156° (7 mm.) and solidified to a crystalline mass which was purified from petroleum ether (b. p. 60–110°); white crystals, m. p. 53–54° (cor.); yield 123 g. (62%).

Anal. Calcd. for $C_{13}H_{17}O_2Cl$: C, 64.83; H, 7.10. Found: C, 64.77; H, 7.21.

As in the preparation of 1-methoxy-3,5-dimethyl-4-chloro-2-propiophenone deëthylation occurred. However, the product could be reëthylated and purified readily. The yield reported was that obtained when minimum deethylation occurred.

α-Methyl-(2-ethoxy-4,6-dimethyl-5-chlorobenzoyl)-acetic Acid.—A solution of 20 g. of 1-ethoxy-3,5-dimethyl-4-chloro-2-propiophenone was added to 100 cc. of an ether solution containing slightly more than one mole equivalent of ethylmagnesium bromide. The bromomagnesium enolate was insoluble and was carbonated in the same manner as the previously described bromomagnesium enolate of 1-methoxy-3,5-dimethyl-4-chloro-2-propiophenone. The crude product was recrystallized from dry ether; white crystalline powder turning yellow upon standing for twenty-four hours, m. p. 115.5–116.5° (cor.); yield 10 g. (41%).

Anal. Calcd. for $C_{14}H_{17}O_4Cl$: C, 59.02; H, 6.01. Found: C, 58.75; H, 5.95.

As in the preparation of α-methyl-(2-methoxy-4,6-dimethyl-5-chlorobenzoyl)-acetic acid (XI), normal addition of the Grignard reagent to the keto form was observed. The main component of the residue was a liquid which boiled lower than the original ketone and was postulated as the corresponding dehydrated tertiary alcohol.

β-Chloro-β-(2-ethoxy-4,6-dimethyl-5-chlorophenyl)-α-methylacrylic Acid.—This compound was prepared in exactly the same manner as β-chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-α-methylacrylic acid using α-methyl-(2-ethoxy-4,6-dimethyl-5-chlorobenzoyl)-acetic acid as starting material. It formed faintly pink crystals from benzene, m. p. 141–142° (cor.); yield 6 g. (56%).

Anal. Calcd. for $C_{14}H_{16}O_3Cl_2$: C, 55.42; H, 5.31. Found: C, 55.41; H, 5.22.

1-Ethoxy-3,5-dimethyl-4-chloro-2-acetophenone.—To 300 g. of carbon disulfide, 185 g. of 1-ethoxy-3,5-dimethyl-4-chlorobenzene and 102 g. of acetic anhydride was added 267 g. of anhydrous aluminum chloride using the same procedure employed to produce 1-methoxy-3,5-dimethyl-4-chloro-2-propiophenone. It had a boiling point of 145–147° (7 mm.) and solidified on cooling to a crystalline mass which was purified by crystallization from petroleum ether (b. p. 60–110°); white crystals, m. p. 74° (cor.); yield 136 g. (60%).

Anal. Calcd. for $C_{12}H_{15}O_2Cl$: C, 63.54; H, 6.66. Found: C, 63.36; H, 6.73.

Deëthylation occurred to a certain extent. However, the product from the aqueous sodium hydroxide extract could be reëthylated.

The yield reported was that obtained when minimum deëthylation occurred.

2-Ethoxy-4,6-dimethyl-5-chlorobenzoylacetic Acid.—A solution of 20 g. of 1-ethoxy-3,5-dimethyl-4-chloro-2-acetophenone in 25 cc. of dry ether was added to 100 cc. of an ether solution containing slightly more than one mole equivalent of ethylmagnesium bromide. The bromomagnesium enolate precipitated and was carbonated in the same manner as 1-methoxy-3,5-dimethyl-4-chloro-2-propiophenone. Recrystallization of the crude product from dry ether gave a white crystalline powder, m. p. 103–104° (cor.); yield 13 g. (55%).

Anal. Calcd. for $C_{13}H_{15}O_4Cl$: C, 57.65; H, 5.88. Found: C, 57.65; H, 5.56.

The usual liquid by-product was observed, similar to that obtained in the carbonation experiments previously described.

β-Chloro-β-(2-ethoxy-4,6-dimethyl-5-chlorophenyl)-acrylic Acid.—This compound was prepared in exactly the same manner as β-chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-α-methylacrylic acid using 2-ethoxy-4,6-dimethyl-5-chlorobenzoylacetic acid as starting material. It formed faintly pink crystals from benzene, m. p. 176–177° (cor.); yield 5.5 g. (51%).

Anal. Calcd. for $C_{13}H_{14}O_3Cl_2$: C, 53.96; H, 5.40. Found: C, 54.05; H, 5.01.

Summary

1. β-Chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-acrylic acid, β-chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-α-methylacrylic acid, β-chloro-β-(2-ethoxy-4,6-dimethyl-5-chlorophenyl)-acrylic acid, and β-chloro-β-(2-ethoxy-4,6-dimethyl-5-chlorophenyl)-α-methylacrylic acid have been synthesized. The first two were resolved. The last two did not form salts suitable for resolution.

2. The active forms of the first two compounds had half-life periods, respectively, of nine minutes in *n*-butanol at 20° and one hundred and seventy-three minutes in *n*-butanol at 44°. This demonstrates the large increase in interference effected by substitution of the α-hydrogen by an α-methyl group. By comparison of these half-life periods with those of the previously described analogous mesitylene derivatives, the increased interference effect produced by an *ortho* methyl over an *ortho* methoxyl is exemplified once again.

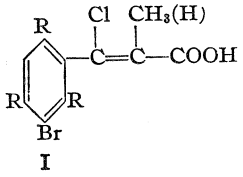
URBANA, ILLINOIS RECEIVED APRIL 21, 1942

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

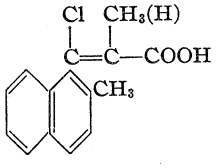
Restricted Rotation in Aryl Olefins. V. β-Bromo-β-(2-alkoxynaphthyl)-α-alkylacrylic Acids[1]

BY ROGER ADAMS, L. O. BINDER[2] AND F. C. MCGREW

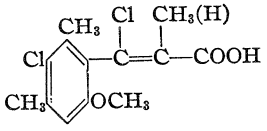
The half-life periods of the active forms of the molecules of the substituted β-arylacrylic acid type shown in I, II and III have been described in previous papers.[3]



I



II

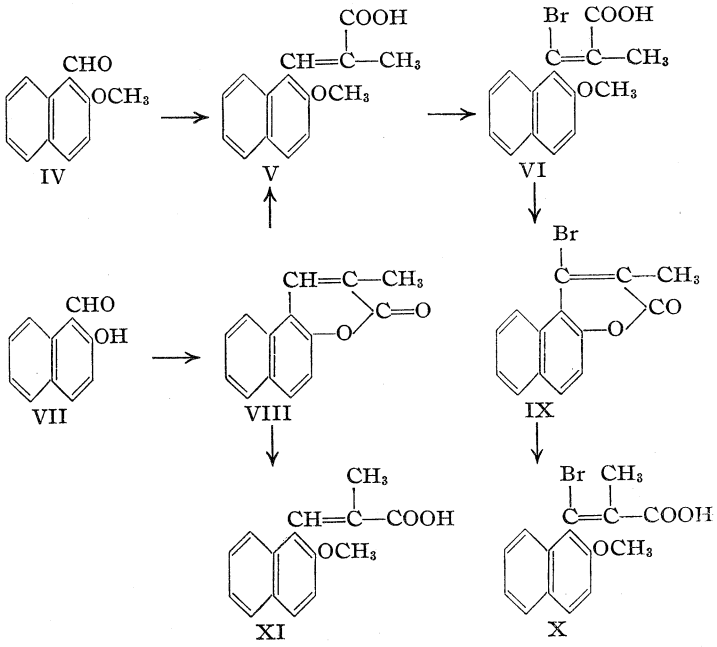


III

The remarkable stability of types I and II as contrasted to that of type III demonstrated the relatively greater steric effect of the methyl than the methoxyl when *ortho* to the acrylic acid side chain. The effect of the —CH= group of the aromatic nucleus in II is much smaller than that of an *ortho* methyl group in type I. An investigation of certain analogous derivatives from β-methoxynaphthalene was carried on simultaneously with the study of the xylenol derivatives (III). The synthesis of β-bromo-β-(2-methoxy-1-naphthyl)-α-methylacrylic acid was accomplished and both geometric forms were obtained (VI and X). The series of reactions employed is shown in formulas IV–X.

By a Perkin synthesis with propionic anhydride and sodium propionate, β-methoxynaphthaldehyde (IV) was converted to the β-(2-methoxy-1-naphthyl)-α-methylacrylic acid (V, α-form). A single geometric isomer was always obtained. Upon bromination of compound V two atoms of bromine added to the double bond and hydrogen bromide was eliminated to give β-bromo-β-(2-methoxy-1-naphthyl)-α-methylacrylic acid (VI, α-form). The position of the bromine in the side chain was established by oxidation of VI to β-methoxynaphthoic acid. By means of hydrobromic acid compound VI was demethylated after which rearrangement and ring closure took place with formation of 2-methyl-3-bromo-4,3-β-naphthopyrone (IX). This pyrone, on hydrolysis and methylation, gave the β-bromo-β-(2-methoxy-1-naphthyl)-α-methylacrylic acid (X, β-form) isomeric with compound VI. From the procedure used for synthesis it is reasonable to conclude that compound X has the carboxyl *cis* to the methoxyl while in its isomer VI the carboxyl group is *trans* to the methoxyl.

β-Hydroxynaphthaldehyde (VII) by a similar



Perkin synthesis led to the 2-methyl-4,3-β-naphthopyrone (VIII). Upon hydrolysis and methylation this pyrone was converted either to the acrylic acid (V) or to its geometric isomer (XI, β-form). The exact conditions for controlling the direction of this synthesis were not found. In two experiments the expected isomer (XI) resulted but in

(1) For previous paper, see Adams and Gross, THIS JOURNAL, **64**, 1786 (1942).

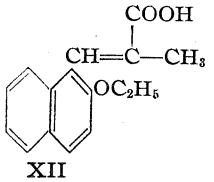
(2) An abstract of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

(3) Adams and Miller, *ibid.*, **62**, 53 (1940); Adams, Anderson and Miller, *ibid.*, **63**, 1589 (1941); Adams and Binder, *ibid.*, **63**, 2773 (1941).

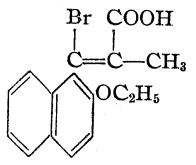
most trials rearrangement occurred and only compound V was isolated.

The assignment of the structure with the carboxyl *trans* to the methoxyl to isomer V, obtained directly from β-methoxynaphthaldehyde is based on the results (1) of similar reactions in the benzene series in which the methyl ether of salicylaldehyde gives *trans*-*o*-methoxycinnamic acid whereas the *cis* form is produced by hydrolysis of coumarin followed by methylation and (2) of the condensation of β-methoxynaphthaldehyde and β-hydroxynaphthaldehyde with *n*-butyric anhydride which is to be discussed later. If the formulas proposed for the brominated acids (VI and X) are correct, it must be concluded that no rearrangement occurs during bromination of compound V to form the bromo derivative (VI). The isomeric acid (XI) with the carboxyl *cis* to the methoxyl did not undergo smooth bromination. From the reaction was isolated a small amount of compound VI along with non-acidic material which was not identified. The pyrone (VIII) brominated only with difficulty and no pure substance was isolated from the product.

β-Ethoxynaphthaldehyde, in a similar Perkin synthesis, gave a single product, β-(2-ethoxy-1-naphthyl)-α-methylacrylic acid, assigned the configuration XII. It brominated to β-bromo-β-(2-ethoxy-1-naphthyl)-α-methylacrylic acid (XIII).

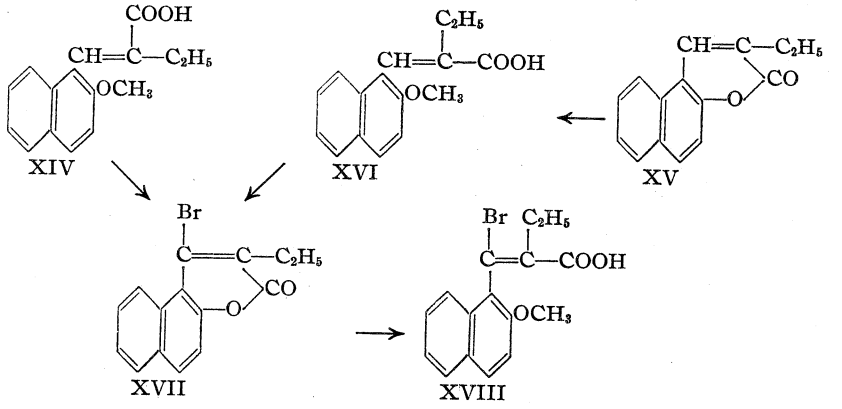


XII



XIII

β-Methoxynaphthaldehyde in a Perkin synthesis with *n*-butyric anhydride and sodium *n*-butyrate gave a single product, β-(2-methoxy-1-naphthyl)-α-ethylacrylic acid postulated as the *trans* isomer (XIV); β-hydroxynaphthaldehyde in a similar reaction yielded 2-ethyl-4,3-β-naphthopyrone (XV) which was hydrolyzed and methylated to XVI, the geometric isomer of XIV. Unlike the experience in the hydrolysis of the 2-methyl-4,3-β-naphthopyrone which yielded sometimes one and sometimes the other geometric isomer, always one product resulted which was isomeric with that from the direct condensation of the β-methoxynaphthaldehyde. Both acids (XIV and XVI) upon bromination yielded the same compound, 2-ethyl-3-bromo-4,3-β-naphthopyrone (XVII), even when the precaution was taken to have present an alkaline reagent to react with the hydrogen bromide liberated. The bromopyrone (XVII) was hydrolyzed and methylated to the β - bromo - β - (2 - methoxy - 1 - naphthyl) - α - ethylacrylic acid (XVIII).



XIV XVI XV XVII XVIII

From these experiments, it may be concluded, (1) that, in general, when no pyrone formation is possible the geometric isomer formed from the aldehyde has the carboxyl group *trans* to the alkoxyl, and (2) that the hydrolysis and methylation of a pyrone leads to an isomeric acid with the carboxyl *cis* to the alkoxyl.

Attempts to resolve acids VI, X, XIII and XVIII failed. The acids formed well-crystallized salts but only single salts which did not mutarotate were obtained and decomposition of each salt resulted in an inactive acid.

Although deductions from negative experiments on resolution are hazardous, the physical properties of these salts were so favorable that it is believed these acids cannot be resolved. If these conclusions are correct the relatively minor change in the molecule III (half-life, 173 minutes in *n*-butanol at 44°), consisting of replacement of the *ortho* methyl by a —CH= of a fused ring, serves to eliminate restricted rotation. Even the replacement of the β-methoxyl by β-ethoxyl or the α-methyl by an α-ethyl was not sufficient to render resolution possible. The bromine and chlorine atoms have been shown in the biphenyl series to have essentially the same effect, so that this modification should not alter the results.

Experimental

2-Methoxy-1-naphthaldehyde.—This was prepared either by the method of Adams and Montgomery[4] or according to the directions in "Organic Syntheses" for 2-ethoxy-1-naphthaldehyde,[5] using 2-methoxynaphthalene in place of 2-ethoxynaphthalene. Material prepared by the latter method was more easily purified.

β-(2-Methoxy-1-naphthyl)-α-methylacrylic Acid (V, α-Form).—A mixture of 9 g. of 2-methoxy-1-naphthaldehyde, 9 g. of fused sodium propionate, and 36 g. of propionic anhydride was refluxed for twenty-four hours at 170°. The mixture was poured into iced dilute aqueous sodium hydroxide, and the alkaline solution extracted with ether to remove colored impurities. Upon acidification of the aqueous solution, the product separated as a gummy mass which crystallized on rubbing. It was recrystallized from water–acetic acid mixture and then from ethanol; colorless needles, m. p. 155–156° (cor.); yield, 7.9 g. (62%).

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.35; H, 5.83. Found: C, 74.21; H, 5.87.

β-Bromo-β-(2-methoxy-1-naphthyl)-α-methylacrylic Acid. (VI, α-Form).—To 4.6 g. of β-(2-methoxy-1-naphthyl)-α-methylacrylic acid in 30 cc. of chloroform was added 3.1 g. of bromine in 15 cc. of chloroform. The solution was set aside in the dark for sixty hours. After evaporating the chloroform by means of an air stream, the solid residue was taken up in dilute aqueous potassium hydroxide, and the alkaline solution was extracted with ether to remove colored impurities. The solution was then treated with decolorizing charcoal at 90° and filtered. Upon acidification of the filtrate, the product appeared as an oil which solidified on rubbing. The material was recrystallized from water–acetic acid mixture and from ethanol giving nearly white needles, m. p. 208° (cor.); yield, 2.3 g. (38%).

Anal. Calcd. for $C_{15}H_{13}O_3Br$: C, 56.07; H, 4.08. Found: C, 55.62; H, 4.03.

The bromine was shown to be in the side chain by oxidation to 2-methoxy-1-naphthoic acid. A mixture of 0.1 g. of β-bromo-β-(2-methoxy-1-naphthyl)-α-methylacrylic acid and 0.5 g. of potassium permanganate in 25 cc. of water was refluxed for six hours. The manganese dioxide was removed by filtration and the filtrate acidified. The fine needles which formed were filtered and recrystallized from ethanol; colorless needles, m. p. 176°. The value found in the literature for 2-methoxy-1-naphthoic acid is 176°.[5a]

2-Methyl-4,3-β-naphthopyrone (VIII).—A mixture of 5 g. of 2-hydroxy-1-naphthaldehyde,[6] 5 g. of sodium propionate, and 20 g. of propionic anhydride was refluxed at 170° for twenty-four hours. The mixture was decomposed with aqueous sodium bicarbonate solution, and the material remaining undissolved was washed thoroughly on a filter and then recrystallized from ethanol; fine white needles, m. p. 156° (cor.); yield, 4.1 g. (60%).

Anal. Calcd. for $C_{14}H_{10}O_2$: C, 79.97; H, 4.80. Found: C, 80.22; H, 4.63.

β-(2-Methoxy-1-naphthyl)-α-methylacrylic Acid. (XI, β-Form).—By heating to 90° for one hour, 4 g. of 2-methyl-4,3-β-naphthopyrone was dissolved in a solution of 2.48 g. of potassium hydroxide in 120 cc. of water. After cooling, 5.6 g. of dimethyl sulfate was added slowly with vigorous stirring. The precipitate which formed was dissolved by making the solution strongly alkaline and warming. Acidification of the resulting clear solution caused the product to separate as an oil which solidified on cooling. Several crystallizations from a water–acetic acid mixture and then four or five times from benzene resulted in the formation of thick yellow rhombs, m. p. 167° (cor.); yield, 1 g. (23%).

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.35; H, 5.83. Found: C, 74.69; H, 5.95.

Various attempts to repeat this experiment resulted sometimes in obtaining the same product and sometimes in formation of the α-form. The critical conditions for each were not found.

β-(2-Ethoxy-1-naphthyl)-α-methylacrylic Acid (XII).—From 2-ethoxy-1-naphthaldehyde,[2] by the same method used for the preparation of β-(2-methoxy-1-naphthyl)-α-methylacrylic acid, β-(2-ethoxy-1-naphthyl)-α-methylacrylic acid was obtained; white needles from water–acetic acid mixture, then from ethanol, m. p. 130° (cor.); yield 8 g. (43%).

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.97; H, 6.30. Found: C, 74.51; H, 6.32.

β-Bromo-β-(2-ethoxy-1-naphthyl)-α-methylacrylic Acid (XIII).—By bromination of 8 g. of β-(2-ethoxy-1-naphthyl)-α-methylacrylic acid in the manner described for the formation of β-bromo-(2-methoxy-1-naphthyl)-α-methylacrylic acid the bromo ethoxy derivative was obtained; white needles, m. p. 172° (cor.); yield, 3 g. (29%).

Anal. Calcd. for $C_{16}H_{15}O_3Br$: C, 57.31; H, 4.51. Found: C, 57.03; H, 4.51.

2-Methyl-3-bromo-4,3-β-naphthopyrone (IX).—A mixture of 5 g. of β-bromo-β-(2-methoxy-1-naphthyl)-α-methylacrylic acid (VI), 15 cc. of 48% hydrobromic acid and 45 cc. of glacial acetic acid was refluxed for four hours and then poured into 400 cc. of water. The crude product which separated was filtered, taken up in chloroform and treated with decolorizing charcoal. The solvent was removed by evaporation and the residue recrystallized from ethanol; long, nearly white needles, m. p. 186° (cor.); yield, 2.5 g. (56%).

Anal. Calcd. for $C_{14}H_9O_2Br$: C, 58.13; H, 3.14. Found: C, 58.46; H, 3.42.

β-Bromo-β-(2-methoxy-1-naphthyl)-α-methylacrylic Acid (X, β-Form).—A solution of 2.5 g. of 2-methyl-3-bromo-4,3-β-naphthopyrone in 50 cc. of absolute ethanol containing 1 g. of potassium hydroxide was refluxed for ten minutes. The solvent was removed under diminished pressure on a steam cone and the residue taken up in 75 cc. of water. An additional 1 g. of potassium hydroxide was added to the solution, and then 2 g. of dimethyl sulfate, over a period of thirty minutes, with stirring. The mixture was stirred for three hours and then acidified with hydrochloric acid and extracted with ether. The ether solution was extracted with two 30-cc. portions of 5% aqueous sodium hydroxide. On acidification of the

(4) Adams and Montgomery, THIS JOURNAL, **46**, 1520 (1924).
(5) "Organic Syntheses," Vol. 20, 1940, p. 11.
(5a) Bretscher, Rule and Spence, *J. Chem. Soc.*, 1493 (1928).
(6) Adams and Levine, THIS JOURNAL, **45**, 2373 (1923).

alkaline extract the product separated as a solid which was recrystallized from ethanol: slightly yellow rhombs, m. p. 187° (cor.).

Anal. Calcd. for $C_{15}H_{13}O_3Br$: C, 56.07; H, 4.08. Found: C, 56.27; H, 4.23.

Evaporation of the ether solution resulted in the recovery of 1.5 g. of unchanged pyrone.

Bromination of β-(2-Methoxy-1-naphthyl)-α-methylacrylic Acid (XI, β-Form).—To 1 g. of β-(2-methoxy-1-naphthyl)-α-methylacrylic acid (XI) dissolved in 15 cc. of chloroform was added 0.75 g. of bromine, and the solution was set aside in the dark for twenty-four hours. The solvent was then removed by evaporation without removing the precipitate which had formed, and the residue was taken up in 150 cc. of chloroform. The chloroform solution was extracted with two 30-cc. portions of 5% aqueous sodium hydroxide. Acidification of the alkaline extract precipitated the product, which was recrystallized from glacial acetic acid. The material melted at 208° (cor.), and gave no depression of the melting point when mixed with β-bromo-β-(2-methoxy-1-naphthyl)-α-methylacrylic acid (VI, α-form).

Evaporation of the chloroform solution yielded an alkali-insoluble material which crystallized from glacial acetic acid in fine needles; m. p. 93° (cor.); this was not investigated.

β-(2-Methoxy-1-naphthyl)-α-ethylacrylic Acid (XIV, α-Form).—The product was obtained from 20 g. of 2-methoxy-1-naphthaldehyde, 20 g. of fused potassium butyrate and 80 g. of butyric anhydride; crystallized from water–acetic acid mixture, it formed nearly colorless needles, m. p. 110° (cor.); yield, 11 g. (40%).

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.97; H, 6.30. Found: C, 75.15; H, 6.73.

Bromination of β-(2-Methoxy-1-naphthyl)-α-ethylacrylic Acid (XIV. α-Form).—Treatment of 10 g. of β-(2-methoxy-1-naphthyl)-α-ethylacrylic acid (XIV) with bromine in the usual fashion yielded no alkali-soluble material. The dark solid was extracted thoroughly with petroleum ether (b. p. 60–110°). The extract was evaporated to dryness and the solid residue crystallized repeatedly from carbon tetrachloride and finally from water–acetic acid mixture. It proved to be 2-ethyl-3-bromo-4,3-β-naphthopyrone (XVII); light brown needles, m. p. 137° (cor.); yield, 3 g. (25%).

Anal. Calcd. for $C_{15}H_{11}O_2Br$: C, 59.41; H, 3.66. Found: C, 59.98; H, 3.81.

2-Ethyl-4,3-β-naphthopyrone (XV).—From 20 g. of 2-hydroxy-1-naphthaldehyde, 20 g. of fused potassium butyrate, and 80 g. of butyric anhydride by the method used for the preparation of 2-methyl-4,3-β-naphthopyrone, 2-ethyl-4,3-β-naphthopyrone was obtained; white needles, m. p. 111° (cor.); yield, 13 g. (51%).

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.32; H, 5.40. Found: C, 80.49; H, 5.36.

β-(2-Methoxy-1-naphthyl)-α-ethylacrylic Acid (XVI, β-Form).—A solution of 10 g. of 2-ethyl-4,3-β-naphthopyrone (XV) and 6 g. of solid potassium hydroxide in 100 cc. of absolute ethanol was refluxed for ten minutes. On cooling the potassium salt separated. This was filtered and dissolved in 150 cc. of water containing 6 g. of potassium hydroxide. To this solution was added 6 g. of dimethyl sulfate over a period of thirty minutes with stirring. and the mixture was then stirred for three hours. The solution was acidified and extracted with ether and the ether solution extracted with 5% aqueous sodium hydroxide. Acidification of the alkaline extract precipitated the product. It was recrystallized from ethanol to which was added water at the boiling point of the solution until incipient turbidity; white crystals, m. p. 120° (cor.); yield, 3.5 g. (30%).

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.97; H, 6.30. Found: C, 75.13; H, 6.36.

About 3.5 g. of unchanged pyrone was recovered.

β-Bromo-β-(2-methoxy-1-naphthyl)-α-ethylacrylic Acid (XVIII).—A solution of 2 g. of 2-ethyl-3-bromo-4,3-β-naphthopyrone (XVII) in 50 cc. of absolute ethanol containing 1 g. of potassium hydroxide was refluxed for ten minutes. The solvent was then removed under reduced pressure, and the residue dissolved in 75 cc. of water to which was added 1.5 g. of solid potassium hydroxide. With stirring, 2.5 g. of dimethyl sulfate was added over a period of thirty minutes and stirring continued for three hours. The solution was then acidified, extracted with chloroform, and the chloroform solution extracted with 5% aqueous sodium hydroxide. Upon acidification of the alkaline extract the product appeared as an oil which solidified on standing. The material was recrystallized from an ethanol–water mixture; fine white needles, m. p. 138° (cor.).

Anal. Calcd. for $C_{16}H_{15}O_3Br$: C, 57.31; H, 4.51. Found: C, 57.27; H, 4.52.

From the chloroform solution 1.5 g. of unchanged pyrone was recovered.

Bromination of β-(2-Methoxy-1-naphthyl)-α-ethylacrylic acid (XVI, β-Form).—To 2 g. of β-(2-methoxy-1-naphthyl)-α-ethylacrylic acid in 16 cc. of chloroform was added 1.5 g. of bromine, and the solution was set aside in the dark for twenty-four hours. The solvent was then removed, the residue taken up in chloroform and the chloroform solution extracted with 5% aqueous sodium hydroxide. Acidification of the alkaline extract gave no product. The chloroform was evaporated and the residue recrystallized from ethanol–water mixture; light yellow needles, m. p. 137° (cor.); yield 1.5 g. (57%). This material gave no depression when melted with 2-ethyl-3-bromo-4,3-β-naphthopyrone obtained by bromination of the α-form of the acid.

Summary

1. The synthesis of the two geometric forms of β-bromo-β-(2-methoxy-1-naphthyl)-α-methylacrylic acids, one geometric form of β-bromo-β-(2-ethoxy-1-naphthyl)-α-methylacrylic acid and one geometric form of β-bromo-β-(2-methoxy-1-naphthyl)-α-ethylacrylic acid has been effected.

2. None of these molecules could be resolved. This is probably due primarily to the decreased steric effect of the —CH= group of the benzene nucleus as compared to a methyl group.

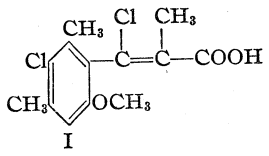
URBANA, ILLINOIS RECEIVED APRIL 21, 1942

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

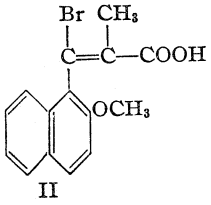
Restricted Rotation in Aryl Olefins. VI. Substituted β-(2,7-Dimethoxy-1-naphthyl)-α-methylacrylic Acids[1]

BY ROGER ADAMS, M. W. MILLER, F. C. MCGREW AND A. W. ANDERSON

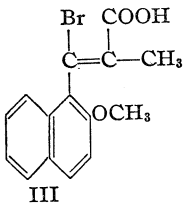
Failure to resolve the aryl olefins II, III, IV and V was reported in the preceding paper.[1] Compound I, on the other hand, was resolved[2] and an active form had a half-life period of 173 minutes in *n*-butanol at 44°. The difference between I and



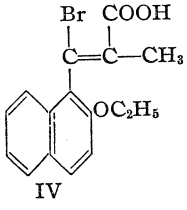
I



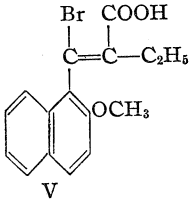
II



III

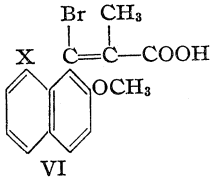


IV

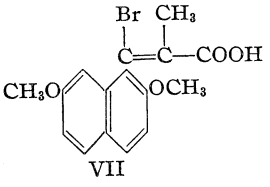


V

the other molecules lies primarily in the replacement of the methyl group in the 2-position of the benzene nucleus by the —CH= of an aromatic residue, thus allowing free rotation and resulting in non-resolvability of the molecules. The present investigation was undertaken to obtain molecules of the type shown in VI which resemble II, III, IV and V in all respects except for the additional group in the 8-position. Such a group should increase the interference and might result in a steric effect sufficient to allow resolution.

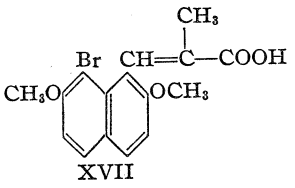


VI

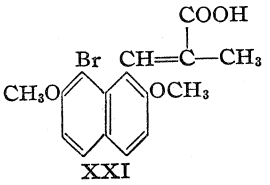


VII

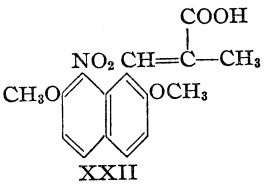
The synthetic problem of preparing such molecules was not simple. The approach selected was that involving the preparation of a compound (VII) by the general procedure used in the previous paper.[1] It contains a methoxyl group in the 7-position which should activate substitution in the 8-position and thus allow the formation of a molecule of the desired type (VI) after the substituent groups in the 1- and 2-positions have been introduced. Unfortunately, complications prevented the attainment of the proposed objective. The compounds actually obtained and studied are shown in formulas XVII, XXI and XXII. The syntheses of these compounds and the factors which interfered with the preparation of the substances particularly desired are described below.



XVII



XXI



XXII

2,7-Dihydroxynaphthaldehyde (VIII) was methylated to 7-methoxy-2-hydroxynaphthaldehyde (IX) which by means of the Perkin synthesis, using propionic anhydride and potassium propionate, was converted to 2-methyl-9-methoxy-4,3-β-naphthopyrone (X). This last product was formed also by another route; treatment of the 2,7-dihydroxynaphthaldehyde with propionic anhydride and potassium propionate led to the 2-methyl-9-propionoxy-4,3-β-naphthopyrone (XI) which was saponified readily to 2-methyl-9-hydroxy-4,3-β-naphthopyrone (XII), and then methylated to give compound X.

Upon nitration, the 2-methyl-9-methoxy-4,3-β-naphthopyrone (X) gave a mononitro product, 2-methyl-10-nitro-9-methoxy-4,3-β-naphthopyrone (XIII), and upon bromination, 2-methyl-10-bromo-9-methoxy-4,3-β-naphthopyrone (XIV). The position of the bromine atom was established as in the ring by direct bromination of 7-methoxy-2-hydroxynaphthaldehyde to 7-methoxy-8-bromo-2-hydroxynaphthaldehyde (XV) and conversion of this product by a Perkin synthesis to compound XIV.

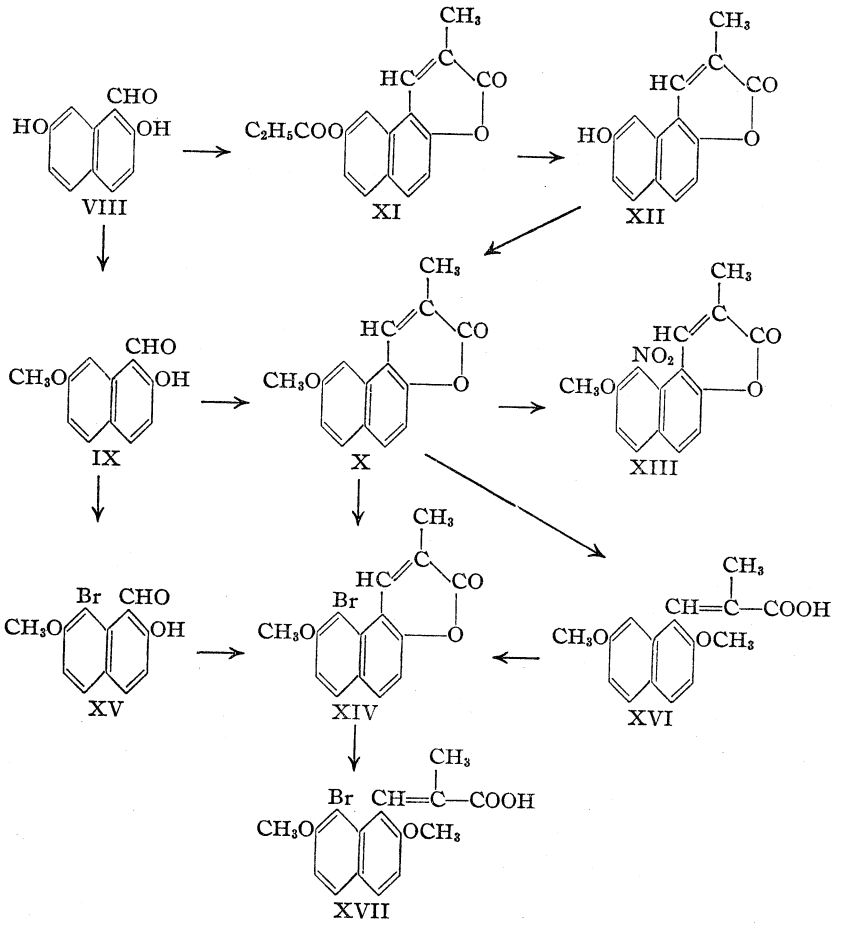
The 2-methyl-9-methoxy-4,3-β-naphthopyrone

(1) For previous paper, see Adams, Binder and McGrew, THIS JOURNAL, **64**, 1791 (1942).

(2) Adams and Binder, *ibid.*, **63**, 2773 (1941).

(X) was hydrolyzed and methylated to β-(2,7-dimethoxynaphthyl)-α-methylacrylic acid (XVI). Upon attempted bromination of compound XVI, however, compound XIV was produced, demethylation and pyrone formation taking place simultaneously. On the other hand, the bromination product, β-(2,7-dimethoxy-8-bromonaphthyl)-α-methylacrylic acid (XVII) resulted upon hydrolysis and methylation of the corresponding pyrone (XIV).

CHART I



2,7-Dihydroxynaphthalene was methylated to 2,7-dimethoxynaphthalene (XVIII) into which an aldehyde group was introduced to give 2,7-dimethoxynaphthaldehyde (XIX). A Perkin synthesis with potassium propionate and propionic anhydride converted this aldehyde to β-(2,7-dimethoxynaphthyl)-α-methylacrylic acid (XX). In contrast to compound XVI, this isomer (XX) brominates without demethylation and is converted to β-(2,7-dimethoxy-β-bromonaphthyl)-α-methylacrylic acid (XXI). Similarly, nitration gives the analogous nitro compound, β-(2,7-dimethoxy-8-nitronaphthyl)-α-methylacrylic acid (XXII).

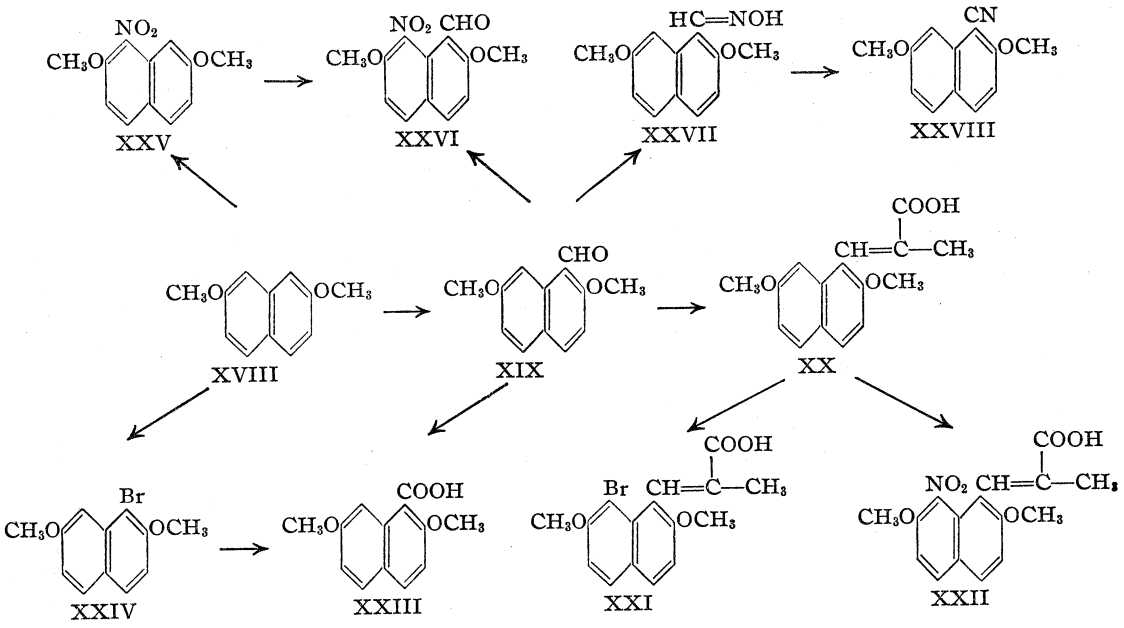
The position of the aldehyde group in 2,7-dimethoxynaphthaldehyde (XIX) was established by oxidation of the molecule to 2,7-dimethoxynaphthoic acid (XXIII). This same acid was obtained by bromination of 2,7-dimethoxynaphthalene (XVIII) to 2,7-dimethoxybromonaphthalene (XXIV) and replacement of the halogen by a carboxyl group through the corresponding lithium derivative and carbonation. Nitration of 2,7-dimethoxynaphthalene gave 2,7-dimethoxy-8-nitronaphthalene (XXV), into which an aldehyde group was introduced to form 2,7-dimethoxy-8-nitronaphthaldehyde (XXVI). This latter product was prepared also by direct nitration of 2,7-dimethoxynaphthaldehyde.

The 2,7-dimethoxynaphthaldehyde (XIX) formed an oxime (XXVII) which dehydrated to the nitrile (XXVIII). This nitrile proved very resistant to hydrolysis.

The configuration of compound XVI is assigned on the basis of its formation from the pyrone; the brominated product (XVII) probably has a similar structure. The carboxyl is *cis* to the 2-methoxyl group. The compounds XX and XXI are stereoisomeric with XVI and XVII prepared from 2,7-dimethoxynaphthaldehyde and consequently are written with the carboxyl group *trans* to the 2-methoxyl group. This conforms to the results previously reported on analogous compounds derived from β-methoxynaphthaldehyde.[1] Compounds XX and XXI are more soluble in organic solvents than their geometric isomers (XVI and XVII). By ultraviolet irradiation compound XVI is converted to its isomer (XX).

The position taken by the bromine atom in the bromination of compound X was shown to be in

CHART II



the naphthalene nucleus. Similarly, the bromine probably entered the 8-position in bromination of compound XX, although this was not proved. Compound XXI could not be brominated further which confirms the probability that the 8-position is substituted and indicates the steric influence of an 8-substituent upon the reactivity of the aliphatic double bond. Compound XVII, in which the position of the bromine atom is established, also could not be brominated. In an attempt to prove the nitro group to be in the 8-position in compound XXII, an effort was made to synthesize structure XXII by conversion of the nitroaldehyde (XXVI) to the acrylic acid; the Perkin condensation did not take place under the conditions usually used for effecting such a synthesis.

The acids XVII, XXI, and XXII were converted into alkaloidal salts and resolution attempted. Only a single salt was obtained in each instance and decomposition resulted in inactive acids. A study of Stuart models of these acids leads to the prediction that restricted rotation should exist in these molecules in spite of the presence of a hydrogen atom on the carbon atom attached to the ring, a condition which previously has been shown always to result in molecules with no restricted rotation.[3] The unreliability of accurate deductions from Stuart models is illustrated again.

(3) Maxwell and Adams, THIS JOURNAL, **52**, 2959 (1930).

Experimental

2,7-Dihydroxynaphthaldehyde (VIII).—A mixture of 20 g. of 2,7-dihydroxynaphthalene, 22 g. of anhydrous zinc cyanide and 200 cc. of dry ether was cooled with ice. Agitation was started and a brisk stream of dry hydrogen chloride was bubbled through until the yellow aldimine hydrochloride was precipitated completely. This usually took about an hour. The yellow precipitate was dissolved in 500 cc. of 30% ethanol and heated on a steam cone. During the hydrolysis, the excess ether distilled and the remaining solution was treated with Norite and filtered. On cooling the filtrate, it became semi-solid with greenish yellow crystals of the aldehyde; yield, 18 g. This product was pure enough for subsequent use. It can be recrystallized from 30% ethanol; yellow crystals; m. p. 159–160° (cor.). Morgan and Vining[4] report m. p. 159.5–160.5° when crystallized from benzene.

7-Methoxy-2-hydroxynaphthaldehyde (IX).—A solution of 10 g. of 2,7-dihydroxynaphthaldehyde in 100 cc. of water containing 6 g. of potassium hydroxide was stirred and 10 g. of dimethyl sulfate added over a period of two hours. The reaction mixture was filtered and the filtrate acidified with dilute sulfuric acid. The precipitate thus obtained was purified by crystallization from ethanol; white crystals, m. p. 128–129° (cor.); yield 6.2 g. (60%).

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.29; H, 4.95. Found: C, 71.30; H, 5.30.

2-Methyl-9-methoxy-4,3-β-naphthopyrone (X).—A mixture of 2 g. of 7-methoxy-2-hydroxynaphthaldehyde, 2 g. of fused potassium propionate and 10 cc. of propionic anhydride was refluxed for six hours at 175–180°. After cooling, the excess anhydride was decomposed with 10% aqueous potassium hydroxide, the solid filtered by suction and recrystallized from ethanol; long silky needles, m. p.

(4) Morgan and Vining, *J. Chem. Soc.*, **119**, 177 (1921).

186.5–187.5°. The substance showed a blue fluorescence in ethanol solution.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 75.00; H, 5.04. Found: C, 74.94; H, 4.93.

2-Methyl-9-propionoxy-4,3-β-naphthopyrone (XI).—A mixture of 10 g. of 2,7-dihydroxynaphthaldehyde, 10 g. of freshly fused potassium propionate and 20 g. of propionic anhydride was refluxed for twenty-four hours. After cooling, the excess of propionic anhydride was decomposed with 10% aqueous sodium hydroxide and the pink precipitate filtered, washed well with water and dried. It was purified by crystallization from ethanol; slightly pinkish crystals, m. p. 161–162° (cor.); yield, 8.5–9 g. (60%).

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.35; H, 5.02. Found: C, 72.32; H, 5.12.

2-Methyl-9-hydroxy-4,3-β-naphthopyrone (XII).—A mixture of 25 g. of 2-methyl-9-propionoxy-4,3-β-naphthopyrone and 200 cc. of 25% aqueous potassium hydroxide was refluxed for three hours. The solution was filtered while still hot and the filtrate upon cooling deposited a yellow precipitate of the potassium salt. The salt was not isolated but the mixture was acidified with 50% sulfuric acid and a purplish, gelatinous precipitate formed. It was purified by a crystallization from ethanol followed by solution in aqueous potassium hydroxide, refluxing the solution with Norite, precipitation with acid and finally crystallization again from ethanol; white needles, m. p. 263–266° (bloc Maquenne); yield, 18 g. (80%).

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.34; H, 4.47. Found: C, 74.22; H, 4.62.

2-Methyl-9-methoxy-4,3-β-naphthopyrone (X).—To a mixture of 20 g. of 2-methyl-9-hydroxy-4,3-β-naphthopyrone and 100 cc. of dioxane, which was mechanically stirred until complete solution had taken place, was added 24 g. of pure dimethyl sulfate. Over a period of five to six hours, 150 cc. of 1% aqueous potassium hydroxide was allowed to run in. Colorless platelets of the product separated as the reaction proceeded. The compound was purified by recrystallization from ethanol; long silky needles, identical with the product prepared directly from 7-methoxy-2-hydroxynaphthaldehyde.

A third procedure was by direct conversion of the propionoxy compound to the methyl ether by the general method of Nierenstein.[5]

A solution of 0.5 g. of 2-methyl-9-propionoxy-4,3-β-naphthopyrone and 1 cc. of piperidine in 20 cc. of dioxane was treated with an ether solution of diazomethane and the mixture allowed to stand at room temperature for about three weeks. Upon evaporation nearly to dryness and addition of water a solid precipitated. This was purified by crystallization from ethanol. Unchanged material was first recovered. The more soluble portion proved to be the 9-methoxy derivative; yield, 0.1 g. The balance of the pyrone was recovered.

2-Methyl-10-nitro-9-methoxy-4,3-β-naphthopyrone (XIII).—To a suspension of 0.5 g. of 2-methyl-9-methoxy-4,3-β-naphthopyrone in 8 cc. of glacial acetic acid was added 1 cc. of nitric acid (sp. gr. 1.42). After shaking thoroughly, the reaction mixture was allowed to stand for one hour. The colorless crystals of the pyrone dissolved and yellow crystals separated. They were purified from ethanol, m. p. 276–278° (cor.); yield, 0.3 g. (50%).

Anal. Calcd. for $C_{15}H_{11}O_5N$: N, 4.90. Found: N, 4.74.

2-Methyl-10-bromo-9-methoxy-4,3-β-naphthopyrone (XIV).—To a solution of 10 g. of 2-methyl-9-methoxy-4,3-β-naphthopyrone in 150 cc. of chloroform was added 6.66 g. of bromine in 50 cc. of chloroform. The mixture was then placed in an icebox overnight. The hydrogen bromide was removed by a stream of air bubbled through the solution, then the chloroform was distilled. The red solid residue was washed with ethanol, then with dilute aqueous potassium hydroxide, and finally with water. It was purified by recrystallization from ethanol; white needles m. p. 218–219° (cor.); yield, 12 g. (91%).

Anal. Calcd. for $C_{15}H_{11}O_3Br$: C, 56.50; H, 3.45. Found: C, 56.11; H, 3.49.

The same product was made from 8-bromo-7-methoxy-2-hydroxynaphthaldehyde (XV) described below. A mixture of 0.25 g. of the bromoaldehyde, 0.25 g. of potassium propionate and 2 g. of propionic anhydride was allowed to react according to the procedure used for similar compounds previously described. It proved to be identical with the compound prepared by bromination of the bromine-free pyrone.

A third method for synthesis of this compound was also found. To a solution of 0.25 g. of the less-soluble β-(2,7-dimethoxynaphthyl)-α-methylacrylic acid (XVI), described below, in 25 cc. of carbon tetrachloride was added 0.117 g. of bromine dissolved in 5 cc. of carbon tetrachloride. The residue after evaporation of the solvent was alkali-insoluble and crystallized as colorless needles from ethanol, m. p. 218–219° (cor.).

7-Methoxy-8-bromo-2-hydroxynaphthaldehyde (XV).—To a solution of 5 g. of 7-methoxy-2-hydroxynaphthaldehyde in 200 cc. of carbon tetrachloride was dropped in slowly with stirring 4.25 g. of bromine in 25 cc. of carbon tetrachloride. After stirring for one hour the solution was washed with aqueous sodium bisulfite. The carbon tetrachloride was distilled until the solution was clear and then evaporated completely with a stream of air. The product was recrystallized from methanol; flaky yellow crystals, m. p. 97–99° (cor.); yield 4 g. (57%).

Anal. Calcd. for $C_{12}H_9O_3Br$: C, 51.27; H, 3.23 Found: C, 50.63; H, 3.18.

Less-soluble β-(2,7-Dimethoxynaphthyl)-α-methylacrylic Acid (XVI).—A mixture of 5 g. of 2-methyl-9-methoxy-4,3-β-naphthopyrone (X) and 5 g. of potassium hydroxide dissolved in 75 cc. of absolute ethanol was heated for about twenty minutes until complete solution had taken place. On cooling, long yellow needles of the potassium salt crystallized and were filtered. The potassium salt thus obtained was dissolved in 200 cc. of 5% aqueous potassium hydroxide. Over a period of four days with constant stirring at room temperature, 25 g. of dimethyl sulfate was added. If the dimethyl sulfate was added too rapidly, the unmethylated lactone precipitated. After complete addition, the red solution containing a small amount of precipitate was made acid to congo red with dilute sulfuric acid, then basic with 20% aqueous potassium hydroxide.

(5) Nierenstein, THIS JOURNAL, **52**, 4012 (1930).

The precipitate (about 2.3 g.) of unchanged lactone and methyl ether methyl ester separated and was filtered. The filtrate was acidified with dilute sulfuric acid whereupon there formed a gummy precipitate of the compound with only the phenolic group methylated. The mixture of lactone and methyl ether methyl ester was refluxed for one hour with 50 cc. of 20% aqueous potassium hydroxide, acidified and finally again made alkaline. This procedure served to give a precipitate of pyrone, the filtrate containing the potassium salt of the ether acid. Upon acidification of the filtrate, the ether acid was obtained and combined with the same material obtained in the earlier part of the procedure. It was purified by crystallization from ethanol; white needles, m. p. 158–159° (cor.); yield, 2.5 g. (44%).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.59; H, 5.88; neut. equiv., 272. Found: C, 70.64; H, 6.08; neut. equiv., 272.

Less-soluble β-(2,7-Dimethoxy-8-bromonaphthyl)-α-methylacrylic Acid (XVII).—The same procedure as used in other hydrolyses and methylations was employed with 2-methyl - 10 - bromo - 9 - methoxy - 4,3 - β - naphthopyrone (XIV). From 14.5 g. of bromopyrone was obtained 12 g. of crude product which after several recrystallizations from ethanol followed by crystallization from a mixture of chloroform and petroleum ether (b. p. 60–110°) was pure; white crystals, m. p. 166° (cor.) with decomposition; yield, 7.5 g. (47.5%).

Anal. Calcd. for $C_{16}H_{15}O_4Br$: C, 54.69; H, 4.27. Found: C, 54.67; H, 4.49.

Attempted Resolution of Compound XVII.—From 7 g. of β - (2,7 - dimethoxy - 8 - bromonaphthyl) - α - methylacrylic acid and 6.5 g. of quinine in 200 cc. of ethyl acetate was deposited 7.3 g. of salt on cooling. This and subsequent fractions and also the recrystallized salts all had the same rotation. No mutarotation was observed in the salt solutions and decomposition of the salts resulted in an inactive acid; m. p. of salt, 98–99° (cor.).

Anal. Calcd. for $C_{16}H_{15}O_4Br \cdot C_{20}H_{24}O_2N_2$: C, 64.00; H, 5.81. Found: C, 63.78; H, 5.99. *Rotation.* 0.0501 g. made up to 25 cc. with ethyl acetate at 28° gave α_D −0.26°; *l*, 2; $[\alpha]^{28}D$ −64.8°.

2,7-Dimethoxynaphthaldehyde (XIX).—To a solution of 10 g. of 2,7-dihydroxynaphthaldehyde (VIII) in 100 cc. of 10% aqueous potassium hydroxide was added slowly, with stirring, 10 cc. of dimethyl sulfate. The greenish gummy precipitate that formed was redissolved by addition to the reaction mixture of 25 cc. of 30% aqueous potassium hydroxide. This was followed by a slow addition of dimethyl sulfate until the solution was acid. The solid was filtered and washed with dilute aqueous sodium hydroxide, then purified by crystallization from methanol; colorless needles, m. p. 99–100° (cor.); yield, 8 g. (69%). Acidification of the alkaline wash waters gave 1 g. of crude 7-methoxy-2-hydroxynaphthaldehyde.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.19; H, 5.60. Found: C, 71.84; H, 5.45.

The product was made also by dissolving the 2,7-dihydroxynaphthaldehyde in toluene, adding solid potassium carbonate and then dimethyl sulfate, or by the zinc cyanide–hydrogen chloride method for 2,7-dimethoxynaphthalene (XVIII).

The semicarbazone, prepared in ethanol, formed colorless needles from cellosolve; m. p. 247° (bloc Maquenne).

Anal. Calcd. for $C_{14}H_{15}O_3N_3$: C, 61.51; H, 5.54; N, 15.38. Found: C, 61.13; H, 5.39; N, 15.18.

More-soluble β-(2,7-Dimethoxynaphthyl)-α-methylacrylic Acid (XX).—A mixture of 20 g. of dry crude 2,7-dimethoxynaphthaldehyde, 20 g. of fused potassium propionate and 80 cc. of propionic anhydride was refluxed at 170° for ten hours. Then a solution of 62 g. of potassium hydroxide in 200 cc. of water was added and the mixture heated until all but a small amount of tar dissolved. It was treated with Norite then acidified to congo red. The product was purified by crystallization from ethanol; colorless needles, m. p. 153° (cor.); yield, 12 g. (48%).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.59; H, 5.88. Found: C, 70.65; H, 6.00.

A mixed melting point of this isomer with the less-soluble gave a depression. This more-soluble geometric isomer was also formed by irradiation of the less-soluble acid (IX) with ultraviolet light.

In a 50-cc. quartz flask was placed a solution of 0.4 g. of the acrylic acid (XVI) in 40 cc. of ethanol. This solution was irradiated with ultraviolet light for sixty hours, then evaporated to dryness. The solid obtained was dissolved in dilute alkali, filtered and recovered by acidification. The compound was purified by several crystallizations from dilute ethanol; white, feathery needles; m. p. 152–153° (cor.). A mixed melting point with the parent compound was depressed to 127–129° while a mixed melting point with the more-soluble acid prepared from 2,7-dimethoxynaphthaldehyde gave no depression.

More-soluble β-(2,7-Dimethoxy-8-bromonaphthyl)-α-methylacrylic Acid (XXI).—A mixture of 8.6 g. of β-(2,7-dimethoxynaphthyl)-α-methylacrylic acid (XX) in 150 cc. of chloroform and 20.6 cc. of solution of 25 g. of bromine in 100 cc. of chloroform was allowed to stand in the dark for sixty-five hours. The chloroform was evaporated with a stream of air and the residue purified from ethanol using Norite, then from acetic acid; colorless needles, m. p. 190° (cor.); yield, 5 g. (45%).

Anal. Calcd. for $C_{16}H_{15}O_4Br$: C, 54.69; H, 4.27; Br, 22.82. Found: C, 54.80; H, 4.34; Br, 23.28.

Attempted Resolution of Compound XXI.—From 5.4 g. of β-(2,7-dimethoxy-8-bromonaphthyl)-α-methylacrylic acid and 5.1 g. of quinine, dissolved in 200 cc. of ethanol, was obtained upon cooling 4.35 g. of salt. More salt was obtained by concentrating the solution, but the rotations on each fraction and also on the salts obtained by recrystallization of these fractions were essentially the same. No mutarotation was observed in the salt and decomposition of the salt resulted in an inactive acid; m. p. of salt 183–184° (cor.).

Anal. Calcd. for $C_{16}H_{15}O_4Br \cdot C_{20}H_{24}O_2N_2$: C, 64.00; H, 5.81. Found: C, 63.51; H, 5.96. *Rotation.* 0.0501 g. made up to 25 cc. with ethanol at 28° gave α_D −0.31°; *l*, 2; $[\alpha]^{28}D$ −77.4°.

From 62 g. of acid and 8.3 g. of brucine in 100 cc. of ethyl acetate was deposited 7.0 g. of salt on cooling. Subsequent fractions and all the salts obtained by recrystallization had identical rotations. No mutarotation was observed in the salt and decomposition of it resulted in an

inactive acid; m. p. of salt, 208–210° (cor.) with decomposition.

Anal. Calcd. for $C_{16}H_{15}O_4Br \cdot C_{23}H_{26}O_4N_2$: C, 62.81; H, 5.54. Found: C, 62.49; H, 5.42. *Rotation.* 0.0500 g. made up to 25 cc. with ethyl acetate at 28° gave α_D −0.21°; *l*, 2; $[\alpha]^{28}D$ −52.5°.

β-(2,7-Dimethoxy-8-nitronaphthyl)-α-methylacrylic Acid (XXII).—A suspension of 2 g. of more-soluble β-(2,7-dimethoxynaphthyl)-α-methylacrylic acid (XX) in 20 cc. of glacial acetic acid was stirred rapidly and 2 cc. of concentrated nitric acid (sp. gr. 1.42) was dropped in slowly. After twenty minutes the starting material had been replaced by orange crystals. The mixture was cooled to 15° and filtered. The product was washed with water, extracted with boiling ethanol to remove color and then crystallized from acetic acid; yellow microcrystals; m. p. 197–198°; yield, 1.2 g. (50%).

Anal. Calcd. for $C_{16}H_{15}O_6N$: N, 4.42. Found: N, 4.86.

Attempted Resolution of Compound XXII.—This compound was converted to its quinine salt by mixing equivalent amounts of acid and base in an equal mixture of dioxane and ethanol. Five fractions were isolated by evaporation of the solvent and filtration at intervals. All five fractions gave essentially the same melting point and rotation and upon decomposition at 0° with 2 *N* hydrochloric acid only an optically inactive product was isolated; white crystals; m. p. 156°.

Anal. Calcd. for $C_{36}H_{39}O_8N_3$: N, 6.55. Found: N, 6.26. *Rotation.* 0.1482 g. made up to 10 cc. with pyridine at 0° gave α_D −0.508°; *l*, 1; $[\alpha]^0D$ −34.3°.

2,7-Dimethoxynaphthoic Acid (XXIII).—A mixture of 5 g. of 2,7-dimethoxynaphthaldehyde and a solution of 2.5 g. of potassium permanganate and 0.5 g. of sodium carbonate in 100 cc. of water was stirred for one hour at room temperature until the permanganate decolorized. The manganese dioxide was filtered and the alkaline filtrate on acidification gave the product. It was purified by crystallization from dilute ethanol; colorless needles, m. p. 112–113° (cor.); yield, poor.

Anal. Calcd. for $C_{13}H_{12}O_9$: C, 67.30; H, 5.18; neut. equiv., 232. Found: C, 67.50; H, 5.39; neut. equiv., 230.

The same compound was prepared from 2,7-dimethoxybromonaphthalene described below. To 0.200 g. of lithium in 50 cc. of dry ether was added 2.8 g. of butyl chloride and the reaction was stirred for one hour. A solution of 5 g. of 2,7-dimethoxybromonaphthalene in 40 cc. of dry ether was then added and the stirring continued for thirty minutes. The ether solution was cooled to 0° and carbonated with dry-ice chips. After warming to room temperature the addition compound was decomposed with iced hydrochloric acid and extracted several times with ether. The ether layer was extracted with dilute sodium hydroxide, the alkaline layer then acidified and the product filtered. It was purified by recrystallization from dilute ethanol; white needles, m. p. 112–113° (cor.); yield, 2.9 g. (68%). A mixed melting point of this compound with that obtained by the oxidation gave no depression.

2,7-Dimethoxybromonaphthalene (XXIV).—A solution of 10 g. of 2,7-dimethoxynaphthalene in 50 cc. of chloroform was brominated by slowly dropping in a solution of 8.5 g. of bromine in 20 cc. of chloroform. The reaction mixture was washed with water and evaporated to dryness. The pinkish residue was recrystallized from methanol; colorless crystals, m. p. 88–89° (cor.); yield, 13 g. (91%).

Anal. Calcd. for $C_{12}H_{11}O_2Br$: C, 53.92; H, 4.12; Br, 29.97. Found: C, 53.82; H, 4.07; Br, 30.29.

2,7-Dimethoxy-8-nitronaphthaldehyde (XXVI).—Into a suspension of 1 g. of 2,7-dimethoxynaphthaldehyde in 10 cc. of glacial acetic acid was dropped slowly with vigorous stirring 0.5 cc. of nitric acid (sp. gr. 1.42). After two hours the solution was poured into water. The precipitate was purified from acetic acid; yellowish crystals, m. p. 190° (cor.); yield, 0.8 g. (65%).

Anal. Calcd. for $C_{13}H_{11}O_5N$: C, 59.75; H, 4.25; N, 5.36. Found: C, 59.55; H, 4.17; N, 5.49.

A second method[6] involved the introduction of an aldehyde group into the 2,7-dimethoxy-8-nitronaphthalene (XXV). Into a mixture of 16.8 g. of 2,7-dimethoxy-8-nitronaphthalene (XXV), 29.5 g. of zinc cyanide and 84 g. of benzene, dry hydrogen chloride was passed for one hour. Then 25 g. of powdered anhydrous aluminum chloride was added and hydrogen chloride passed in for six hours. The mixture was decomposed by refluxing with dilute hydrochloric acid, cooled and filtered. The product was dried and extracted with boiling toluene to remove the product from tar. From the toluene crystals formed. They were further purified from ethanol; tan needles, m. p. 190° (cor.); yield, 4.7 g. (25%).

This product could not be made to condense in the Perkin reaction with potassium propionate and propionic anhydride.

2,7-Dimethoxynaphthaldoxime (XXVII).—A mixture of 0.5 g. of hydroxylamine hydrochloride in 3 cc. of water, 1.5 g. of 2,7-dimethoxynaphthaldehyde in 15 cc. of dioxane and 5 cc. of water, and 0.6 g. of sodium acetate was heated for twenty minutes on a steam-bath. After cooling, a precipitate formed. It was purified from ethanol; colorless prisms, m. p. 181–182° (cor.); yield, 1.5 g. (93%). The product was insoluble in aqueous alkali.

Anal. Calcd. for $C_{13}H_{13}O_3N$: N, 6.06. Found: N, 6.21.

2,7-Dimethoxynaphthonitrile (XXVIII).—A mixture of 1 g. of 2,7-dimethoxynaphthaldoxime and 5 cc. of acetic anhydride was refluxed for one hour. After addition of about 30 cc. of water, crystals appeared. These were purified from ethanol; colorless needles, m. p. 129° (cor.); yield, 0.9 g. (98%).

Anal. Calcd. for $C_{13}H_{11}O_2N$: N, 6.57. Found: N, 6.51.

No method was found for hydrolysis of the nitrile to the corresponding acid.

Summary

1. The following α-naphthylacrylic acids have been prepared: β-(2,7-dimethoxy-8-bromonaphthyl)-α-methylacrylic acids (both geometric isomers), and β-(2,7-dimethoxy-8-nitronaphthyl)-α-methylacrylic acid. None of these three compounds could be resolved.

(6) Weber, *Ber.*, **14**, 2206 (1881).

2. 7-Methoxy-2-hydroxynaphthaldehyde is converted by a Perkin synthesis to 2-methyl-9-methoxy-4,3-β-naphthopyrone. This compound brominates or nitrates in the 10-position. The resulting bromopyrone is hydrolyzed and methylated to β-(2,7-dimethoxy-8-bromonaphthyl)-α-methylacrylic acid. The unbrominated pyrone is also hydrolyzed and methylated and yields β-(2,7-dimethoxynaphthyl)-α-methylacrylic acid. Upon bromination of this acid, the halogen enters the 10-position, simultaneous hydrolysis of the methoxyl group occurs and pyrone formation results. The mode of preparation of the acrylic acid and the bromoacrylic acid leads to the conclusion that the carboxyl is *cis* to the 2-methoxyl group of the naphthalene nucleus.

3. These acids are both less soluble than the corresponding geometric isomers made directly by the appropriate Perkin reaction on 2,7-dimethoxynaphthaldehyde and bromination. No tendency to pyrone formation appears in this last reaction. The less-soluble acrylic acid is converted to the more soluble by irradiation with ultraviolet light.

URBANA, ILLINOIS RECEIVED APRIL 21, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Higher Hydrocarbons.[1] II. Five 11-Substituted Heneicosanes

BY F. C. WHITMORE, J. N. COSBY, W. S. SLOATMAN AND D. G. CLARKE

In the first paper[2] of this series the methods of preparation and the properties for seven alkyl substituted docosanes were given. A brief survey was made of the literature relating to the preparation of hydrocarbons containing more than twenty carbon atoms.

Whereas the first paper covered only isoparaffins, this paper reports on a variety of mixed type compounds. In this group of compounds the paraffin chain remains constant, but different type substituents are located in the 11-position. Changes of this type have considerably greater influence on the properties than moving a side chain or varying the molecular weight.[2]

Lubricating oil fractions in a given molecular weight range show large variations in properties. From the extensive studies[3] of Research Project No. 6 of the American Petroleum Institute these differences in the properties of the various lubricant fractions can only be due to differences in the hydrocarbon type. Therefore, this and future papers will describe series of hydrocarbons in which there are variations in hydrocarbon type. Generalizations on the properties and comparison with those in the literature will be published later.

Special emphasis has been placed on obtaining pure compounds. The requirements of purity and the methods of obtaining and determining the purity have been discussed in the earlier paper.[2]

The synthesis of these compounds involved the addition of an excess of *n*-decylmagnesium bromide to the following esters: ethyl caproate, methyl 2-ethylbutyrate, ethyl cyclopentanecarboxylate, and methyl benzoate. The resulting tertiary carbinols were dehydrated over copper sulfate in an atmosphere of nitrogen. The purified olefins were hydrogenated in a high pressure bomb over various nickel catalysts.

Only one intermediate, ethyl cyclopentanecarboxylate, presented any serious problem. Methods for its preparation in the literature did not seem promising. The method used in this work was the little used reaction[4] involving the addition of cyclopentylmagnesium bromide to an excess of ethyl carbonate.

With 11-phenyl-11-heneicosanol only one olefin can be obtained on dehydration. Therefore this was isolated and purified as usual. However it is probably an inseparable mixture of the *cis*- and *trans*-isomers.

The selective hydrogenation of the olefinic double bond in the presence of the phenyl group as in the case of 11-phenylheneicosane required special study. It was found possible to carry out this hydrogenation if the olefin was first very carefully purified by distillation and passage through silica gel. The hydrogenation was then carried out at room temperature over very active Raney nickel at a pressure of 1500 to 1800 lb. per sq. in.

Table I is a summary of the important properties of these hydrocarbons. The methods used

(1) American Petroleum Institute Research Project No. 42.

(2) Whitmore, Sutherland and Cosby, THIS JOURNAL, **64**, 1360 (1942).

(3) Mair, Willingham and Streiff, *Ind. Eng. Chem.*, **30**, 1256 (1938).

(4) Loder and Whitmore, THIS JOURNAL, **57**, 2727 (1935).

TABLE I

THE PROPERTIES OF THE SUBSTITUTED HENEICOSANES AND OF 11-PHENYL-10-HENEICOSENE

$$(C_{10}H_{21})-\underset{\displaystyle R}{\overset{\displaystyle H}{\overset{|}{C}}}-(C_{10}H_{21}) \text{ and } (C_{10}H_{20})=\underset{\displaystyle C_6H_5}{\overset{}{\overset{|}{C}}}-(C_{10}H_{21})$$

R	Formula	M. p., °C.	B. p., °C. (1.0 mm.)	$n^{20}D$	d^{20}_4	Molecular refraction Found	Molecular refraction Calcd.	Viscosity 20°C. (centip.)	Moles[a] in run	Yield,[b] %	Purity,[c] mole %	Analyses,[d] % Calcd. C	Calcd. H	Found C	Found H
n-Amyl	$C_{26}H_{54}$	−9.1	192	1.4497	0.8038	122.3	122.3	14.89	1.07	60	95.5	85.1	14.9	84.5	14.7
(3-Pentyl)-	$C_{26}H_{54}$	forms glass	187	1.4517	.8092	121.9	122.3	15.58	2.25	36	95–7	85.1	14.9	85.5	14.9
Cyclopentyl-	$C_{26}H_{52}$	−12.7	186	1.4610	.8329	120.1	120.0	20.28	1.89	42	97.1	85.6	14.4	85.7	14.4
Phenyl-10-	$C_{27}H_{46}$	forms glass	203	1.4922	.8636	124.4	122.8	20.80	3.0	75	97–8	87.7	12.3	87.5	12.0
Phenyl-	$C_{27}H_{48}$	20.8	204	1.4788	.8531	123.6	123.3	26.41	1.5	95	97.6	87.0	13.0	86.7	12.5
Cyclohexyl-	$C_{27}H_{54}$	−7.2	209	1.4639	.8373	124.5	124.7	30.23	1.2	95	96.1	85.6	14.0	85.4	14.7

[a] In the first four cases based on the ester, in the last two on olefin used. [b] Based on pure hydrocarbon obtained. [c] The purity of the compounds was calculated from time–temperature melting curves. With compounds 2 and 4 glasses were formed on cooling which made the use of melting curves impossible. [d] Analyses of three of the compounds were carried out by the Esso Laboratories through the courtesy of Dr. L. A. Mikeska.

in the measurements and the designations are the same as those given for the earlier series of hydrocarbons.[2] None of these compounds has been reported before.

Experimental

Intermediates.—The greatest of care has been taken to obtain pure intermediates. Fractional distillation columns[5] with efficiencies of 25 to 35 theoretical plates have been used on all preparations. The thermometer readings on the boiling points of the intermediates are uncorrected. The constants given are those of the constant boiling point, constant index refraction fractions. Only this material was used as intermediates.

(a) **Decyl Bromide.**—Technical *n*-decanol was refluxed with the hydrobromic and sulfuric acids mixture resulting from the reduction of bromine with sulfur dioxide. This was described in detail in an earlier paper,[2,6] b. p. 124° (20 mm.); $n^{20}D$ 1.4558; yield 73%.

(b) **Cyclopentyl Bromide.**—This was prepared by passing hydrogen bromide into pure cyclopentanol at 100°. This was washed with one-half its volume of cold 95% sulfuric acid and then twice with an equal volume of water. After drying for twenty hours over anhydrous potassium carbonate, the product was distilled through an all-glass 25-plate column. The yield of pure bromide was 70%; b. p. 137° (737 mm.); $n^{20}D$ 1.4890.

(c) **Ethyl Caproate.**—Eastman Kodak Co. technical ethyl caproate was carefully fractionated: b. p. 165° (730 mm.); $n^{20}D$ 1.4078.

(d) **Methyl 2-Ethylbutyrate.**—Technical 2-ethylbutyric acid obtained from Carbide and Carbon Chemicals Corp. was dried over calcium chloride for several days. Of this, 812 g. (7.0 moles) was added to 2.0 l. of anhydrous methanol and 100 cc. of concentrated sulfuric acid. A heavy precipitate of calcium sulfate formed. This was filtered off, and the clear solution refluxed for four days. Part of the excess methanol was distilled off, and the reaction mixture then diluted with twice its volume of water. The ester layer was separated, and the water layer extracted with ether. This after drying over anhydrous sodium sulfate was fractionally distilled. The yield of pure ester was 75%, b. p. 134° (728 mm.); $n^{20}D$ 1.4018.

(e) **Ethyl Cyclopentanecarboxylate.**—Cyclopentylmagnesium bromide was prepared from 62 g. (2.5 moles) of magnesium, 363 g. (2.4 moles) of cyclopentyl bromide, and 500 cc. of anhydrous ether. After standing overnight the Grignard solution was removed from the reaction flask under an atmosphere of nitrogen, and filtered. The Grignard solution was added to 590 g. of distilled diethyl carbonate in 500 cc. of anhydrous ether over a period of five hours, with stirring, while the mixture was cooled in an ice-bath. After standing overnight the mixture was decomposed by pouring over crushed ice containing 35 cc. of concentrated sulfuric acid. Two such runs were made, and the combined products distilled through a 25-plate column; yield 275 g., 48.5%; b. p. 171.9° (737 mm.), 89.3° (45 mm.) (both Cottrell); d^{20}_4 0.9523; $n^{20}D$ 1.4360. Faworski and Boshowski[7] report a boiling point of 172–174° (752 mm.).

(f) **Methyl Benzoate.**—Methyl benzoate prepared by students in a preparation course was carefully fractionated; b. p. 95° (25 mm.); $n^{20}D$ 1.5170.

11-*n*-Amylheneicosane.—A Grignard solution was prepared from 660 g. (3.0 moles) of *n*-decyl bromide and 73 g. (3.0 moles) of magnesium in the usual manner. Titration of a sample of the Grignard solution indicated a yield of 95%. To this was added 154 g. (1.07 moles) of ethyl caproate. After stirring for several hours and allowing to stand overnight, the reaction products were poured on 1700 g. of ice and 150 cc. of concentrated sulfuric acid. After standing overnight the ether layer was separated and the water layer was extracted with ether. These ether solutions were combined and the ether removed by distillation through an indented column. In this preparation the tertiary alcohol was isolated. Distillation of the crude products indicated 80 g. of decane, 40 g. of 7-hexadecanone, and 345 g. of di-*n*-decylamylcarbinol; b. p. 225–229° (1 mm.); $n^{20}D$ 1.4580).

The tertiary alcohol was then dehydrated over anhy-

(5) Described in a separate publication to be submitted to the *Analytical Edition of Industrial and Engineering Chemistry*.

(6) Recently we have found that these higher alkyl bromides may be prepared in much better yields with less trouble by passing hydrogen bromide from the direct combustion of bromine and hydrogen into the alcohol at 110°.

(7) Faworski and Boshowski, *J. Russ. Phys.-Chem. Soc.*, **50**, 587 (1920).

drous copper sulfate in an atmosphere of nitrogen at 160–180°. The olefins were passed through a 50 × 1.5 cm. tube of silica gel. This step gave a water-white product, 310 g., which was then hydrogenated over 20 g. of U. O. P. nickel catalyst[8] at 120° and 1100 lb. per sq. in. pressure. At least 95% of the required hydrogen was absorbed in ten minutes. Hydrogenation conditions were continued for three hours to ensure completion. The nickel was removed by filtration and the product distilled slowly through the high vacuum column.[5] The fractions having constant refractive indices were combined and passed through a column of silica gel. The product, 11-*n*-amylheneicosane, was water-white and odorless. Table I gives the percentage yields and the analyses.

11-(3-Pentyl)-heneicosane and 11-Cyclopentylheneicosane.—These were prepared from the appropriate esters in the same manner as the 11-*n*-amylheneicosane. In each case approximately 2 moles of the ester was used. The tertiary alcohol was not isolated.

11-Phenyl-10-heneicosene.—In the usual manner a 7-mole Grignard solution was prepared from pure *n*-decyl bromide. To this was added 408 g. (3.0 moles) of methyl benzoate dissolved in an equal volume of ether. After stirring for a total of ten hours and allowing to stand overnight, the product was poured on ice and 200 cc. of concentrated sulfuric acid. The ether-product layer was separated and the water layer extracted once with 800 cc. of ether. These were combined, the ether removed, and most of the low boiling by-products (*n*-decane), etc., removed by distillation from a modified Claisen flask at 20 mm. pressure. The crude tertiary alcohol was then dehydrated over anhydrous copper sulfate at 160° in an atmosphere of nitrogen. This was then filtered through a column of silica gel to give an almost water-white product. Following this step the crude olefin was distilled through the vacuum column at a pressure of 0.95 mm. Ninety per cent. of the distillate had a constant index of refraction. These constant fractions were combined and passed through silica gel again to give a water-white, odorless finished product.

11-Phenylheneicosane.—The obtaining of this compound by the selective hydrogenation of the related olefin, 11-phenyl-10-heneicosene, required special study. The first two attempts failed. In the first, complete hydrogenation of the olefinic double bond was not obtained and in the second, hydrogenation of the phenyl group took place to the extent of about 5%. This was shown by the melting point curves, systematic solvent extraction[9] using acetone as a solvent, and chemical test.

It was found that if the olefin was purified (see the preparation of 11-phenyl-10-heneicosene) to the greatest possible extent, hydrogenation of 560 g., 1.5 moles, of the olefin proceeded smoothly and completely in a period of six hours over 30 g. of very active Raney nickel at room temperature and 1800 lb./sq. in. pressure of hydrogen. The product was then filtered through silica gel to remove the nickel and any remaining olefin. Distillation of the product through the vacuum column gave no evidence of other substances being present. All fractions had exactly the same index of refraction. This was not found in the other two attempts to prepare the compound. Some indication of separation was found if the compound was under or over hydrogenated.

11-Cyclohexylheneicosane.—The combined fractions, 445 g., 1.2 moles, from the distillations of the attempted preparations of 11-phenylheneicosane were combined and completely hydrogenated over 25 g. of U. O. P.[8] nickel at 150° and 1500 to 1800 lb./sq. in. pressure of hydrogen in a time of ten hours. The product was filtered through a tube of silica gel to remove the nickel and any remaining aromatic compounds. This product was then distilled through the vacuum column at 0.5 mm. Ninety-five per cent. of the distillate had a constant index of refraction. These constant fractions were combined and passed through a tube of silica gel a second time. This gave a water-white, odorless product.

Summary

The methods of preparation and six important properties of six new high molecular weight hydrocarbons are given.

STATE COLLEGE, PENNA. RECEIVED APRIL 16, 1942

(8) Supplied by the Universal Oil Products Co., Chicago, Ill.

(9) By Dr. K. A. Varteressian of this Laboratory.

[CONTRIBUTION FROM THE DEPARTMENT OF ANIMAL AND PLANT PATHOLOGY OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

The Concentration and Purification of Tobacco Mosaic Virus by Means of the Sharples Super-centrifuge

BY W. M. STANLEY

When the infectious juice pressed from frozen macerated mosaic-diseased Turkish tobacco plants is clarified and centrifuged at a sufficiently high speed, there may be recovered from the solid jelly-like sediment about 3 mg. of tobacco mosaic virus per cc. of juice.[1] Three or four successive sedimentations at high centrifugal force, each followed by clarification at low centrifugal force are required to yield a virus preparation sufficiently pure for most chemical work. The method is especially suitable for plant viruses, since in most cases practically all material of high molecular weight except the viruses is rendered insoluble by the freezing process.[2] The method should also be suitable for any virus that can be produced in a medium free of material possessing a sedimentation constant comparable to that of the virus. During the past five years, air-driven vacuum centrifuges of the type described by Bauer and Pickels[3] and by Biscoe, Pickels and Wyckoff[4] have been used to provide the high centrifugal force necessary to sediment medium and small sized viruses. In this laboratory duraluminum or magnesium–aluminum alloy heads from 6 to 8 inches in diameter and carrying from 6 to 14 Lusteroid tubes 0.75 × 3 inches in size have been spun at speeds from 24,000 to 36,000 r. p. m. to yield a centrifugal force of about 50,000 times gravity at the centers of the Lusteroid tubes. Since acceleration and deceleration each requires eight to ten minutes and the tobacco mosaic virus must be spun about an hour in order to secure complete sedimentation, about two working days with 2 centrifuges having a combined capacity of 350 cc. are required to prepare about 4 g. of purified tobacco mosaic virus. The equipment is admirably suited for the centrifugation of solutions up to a liter or so in volume and for work with unstable viruses, since the virus solution may be centrifuged near its freezing point.[5] However, for certain types of work amounts of tobacco mosaic virus of 100 g. or more are needed, and it is obvious that the centrifugation of the necessary 30 liters or so of infectious juice not only requires much time and effort, but also places a severe strain on the physical equipment. Consequently, during the past year other means for the centrifugation of large volumes of virus solutions have been sought.

In 1927 McKinney[6] attempted to use the commercially available Sharples Laboratory Super-centrifuge for the concentration of tobacco mosaic virus, but, because of the large volumes of liquid required, soon discarded it in favor of a small, specially constructed centrifuge with a closed bowl holding about 10 cc. of solution. However, by means of this centrifuge, which yielded a centrifugal force of about 50,000 times gravity, McKinney was able to demonstrate that tobacco mosaic virus could be concentrated by centrifugation. In 1933 Schlesinger[7] showed that a coli-bacteriophage could be concentrated and purified by means of a similar, specially constructed centrifuge having a closed hollow cylinder. The first real test with viruses of the Sharples Super-centrifuge equipped with a bowl for continuous flow, and hence useful for large volumes of fluid, appears to have been made by McIntosh and Selbie[8] in 1940. Using a considerably modified centrifuge, these workers demonstrated that the infectivity of large volumes of fluids containing bacteria, vaccine virus or either of two bacteriophages could be reduced at least 100 times by passage through the centrifuge. The infective particles that were removed from the effluent liquid were recovered in the sediment. In view of these results, it appeared desirable to make a thorough study of the usefulness of the Sharples Laboratory Super-centrifuge for the concentration and purification of tobacco mosaic virus.

Experimental

A regular model Sharples Laboratory Super-centrifuge with a compressed-air turbine drive and a monel metal

(1) W. M. Stanley, *J. Biol. Chem.*, **121**, 205 (1937).
(2) W. M. Stanley, *Ann. Rev. Biochem.*, **9**, 548 (1940).
(3) J. H. Bauer and E. G. Pickels, *J. Bact.*, **31**, 53 (1936); *J. Exp. Med.*, **64**, 503 (1936).
(4) J. Biscoe, E. G. Pickels and R. W. G. Wyckoff, *Rev. Scient. Instruments*, **7**, 246 (1936); *J. Exp. Med.*, **64**, 39 (1936).
(5) W. M. Stanley and R. W. G. Wyckoff, *Science*, **85**, 181 (1937).
(6) H. H. McKinney, *J. Agr. Res.*, **35**, 13 (1927).
(7) M. Schlesinger, *Biochem. Z.*, **264**, 6 (1933).
(8) J. McIntosh and F. R. Selbie, *Brit. J. Exp. Path.*, **21**, 153 (1940).

clarifier bowl was used. This model develops 62,000 times the force of gravity at the speed of 50,000 r. p. m. which was used in this work. A sheet of celluloid or of cellulose acetate, 14.5 × 19.8 cm. and about 0.4 mm. thick, was used as a liner for the bowl, and inside this was placed a second liner of filter paper. A cooling coil mounted between the rotating bowl and the outer shell of the centrifuge and composed of about 14 feet of 0.25-inch copper tubing, through which ice water was passed by means of a small electric centrifugal pump, was used to absorb heat generated by the rotating bowl. In preliminary experiments the smallest delivery jet supplied with the centrifuge was used with the infectious juice from mosaic-diseased Turkish tobacco plants or with purified preparations of tobacco mosaic virus in 0.1 *M* phosphate buffer to determine the effect of factors such as rate of flow, temperature, and *p*H of ingoing liquid on the yield of virus. Centrifugation at *p*H 5, 6, or 7 appeared to have no significant effect on the yield of virus. The temperature of the ingoing liquid also appeared to be of little importance for, regardless of this temperature, that of the bowl contents was usually 20–25° and that of the effluent liquid was usually about 17°. The temperature of the effluent liquid appeared to be governed by the evaporation caused by the rapid flow of air through the centrifuge. The evaporation was usually sufficient to reduce the volume of the effluent liquid by about 20%. The concentration of the effluent liquid caused by evaporation was neglected in the calculations of the yields of virus. The factor having the greatest influence on the yield of virus was found to be the rate of flow of the preparation. Flow rates of 30 cc. per minute or greater resulted in yields of 50% or less, whereas flow rates between 20 and 25 cc. per minute gave yields of 60 to 75%. In order to secure a uniform slow rate of flow, a short length of tubing from a No. 22 hypodermic needle was soldered into the original delivery jet. This gave a rate of flow of about 15 cc. per minute, which, as may be seen from the data presented in Table I, resulted in yields of 3 to 4 mg. of virus per cc. in the case of infectious juices and of 75 to 93% in the case of purified virus preparations.

TABLE I

REPRESENTATIVE DATA FOR SUPER-CENTRIFUGE RUNS IN WHICH A SATISFACTORY RECOVERY OF TOBACCO MOSAIC VIRUS WAS ACHIEVED

Volume, cc.	Starting material: Protein, mg./cc.	Rate of flow, cc./min.	Effluent protein, mg./cc.	Yield of virus, mg./cc. of juice
	Infectious juice			
5000	9.0	14	5.37	3.4
3560	9.0	13.4	4.37	3.9
5000	10.0	13.2	6.65	3.7
2400	10.0	13.0	6.55	4.1
5000	8.75	13.2	5.63	3.2
4000	8.75	12.0	..	3.0
5000	9.1	14.0	6.0	2.7
5000	9.1	13.0	5.0	3.4
	Purified virus 0.1 *M* PO_4 *p*H 7			%
995	3.1	15	0.34	89
5600	3.0	16.5	.75	75
4100	3.0	15.3	.69	77
1000	10.4	12.3	.69	93
1400	10.4	15	.94	91
1200	10.4	14	1.69	84
3000	9.3	15	0.69	93

In one experiment the virus in 200 cc. of infectious juice containing 9.0 mg. of protein per cc. was purified by 3 successive sedimentations in the vacuum centrifuge and the virus in 5 liters of the same juice was purified by means of the Sharples Super-centrifuge. The supernatant fluid from the first centrifugation in the vacuum centrifuge contained 2.4 mg. of protein per cc., and the yield of virus following 3 sedimentations was 733 mg., equivalent to 3.66 mg. per cc. of juice. The effluent from the Sharples Super-centrifuge, on the other hand, contained 5.37 mg. of protein per cc. In order to remove the last portions of the juice from the bowl, there was introduced, immediately following the juice and without stopping the centrifuge, 500 cc. of 0.4 *M* phosphate buffer at *p*H 7. This buffer had the same density as that of the juice. On stopping the centrifuge, the material on the liner was dissolved in the bowl contents consisting of about 250 cc. of the buffer. The celluloid and filter paper liners were well washed with sufficient water, which, when added to the bowl contents, gave a final solution containing 0.1 *M* phosphate buffer. This solution, which was found to contain 16.9 g. of protein, was diluted with 0.1 *M* phosphate buffer at *p*H 7, so that the final protein concentration was 3 mg. per cc. This solution was passed through the Sharples Super-centrifuge under the same conditions described above, and the effluent was found to contain 0.75 mg. of protein per cc. The liner and bowl contents which contained 12.4 g. of protein were diluted to a protein concentration of 3 mg. per cc. and again passed through the centrifuge. The effluent was found to contain 0.69 mg. of protein per cc. and the liner and bowl contained 9.6 g. of virus. Under the conditions of the experiment, the yield of virus was 52.5% of that obtainable by means of the vacuum centrifuge.

However, the two final sedimentations with the vacuum centrifuge were carried out at a protein concentration of about 10 mg. per cc., as is customary in our laboratory, whereas in the case of the Sharples Super-centrifuge the 2 final sedimentations were made at a protein concentration of only 3 mg. per cc. It seemed possible that this might account in part for the difference in yields; hence, a test run was made by passing a liter of a solution containing 10.4 mg. of virus per cc. in 0.1 *M* phosphate buffer at *p*H 7 through the Sharples Super-centrifuge. Although the same delivery jet was used, the rate of flow of this solution was reduced to 12.3 cc. per minute, presumably due to the increased viscosity. The effluent was found to contain but 0.69 mg. of protein per cc.; hence, 93% of the virus was removed. As may be seen from the data presented in the second part of Table I, yields of the same order of magnitude were obtained in several experiments in which purified virus at a concentration of about 10 mg. per cc. was used. The fact that the protein concentration of the ingoing liquid could be increased from 3 to 10 mg. per cc. without appreciably affecting the concentration of protein in the effluent demonstrates that a more efficient recovery of virus may be accomplished at the higher virus concentration. When protein concentrations of about 10 mg. per cc. were used for all runs after the original juice was sedimented, the over-all yield of virus was increased to about 65%.

Discussion

The need for easily available and relatively inexpensive equipment by means of which purified tobacco mosaic virus may be prepared readily in quantity is met by the Sharples Super-centrifuge equipped with a cooling coil. It is necessary only to solder a short piece of tubing from a No. 22 hypodermic needle into the original delivery jet and to use a double liner of celluloid and filter paper in the rotating clarifier bowl. It is possible during the course of ten hours to prepare 10 to 15 g. of tobacco mosaic virus, purified by 4 sedimentations by using a flow rate of about 15 cc. per minute for the infectious juice used as starting material, and a flow rate of 12–15 cc. per minute for the final 3 sedimentations of the virus at a concentration of about 10 mg. per cc. The fact that the over-all recovery of virus from the starting material is somewhat less than that obtainable with the vacuum type centrifuge is more than offset by the fact that during a given period of time the amount of purified virus obtainable with the Sharples Super-centrifuge is over ten times that obtainable with a vacuum type centrifuge.

The amount of virus directly isolable from the infectious juice may be increased somewhat if the effluent juice is immediately passed through the centrifuge a second time. Although this expedient is hardly worth while in the case of tobacco mosaic virus, due to the relatively high virus concentration and the ease with which large amounts of infectious juice may be obtained, Dr. Knight of this laboratory has found the second passage of effluent juice to be quite advantageous in the case of cucumber virus 4. The concentration of this virus in the infectious juice from cucumber plants is only a few tenths of a mg. per cc.,[9] and it is somewhat more difficult to obtain large quantities of the infectious juice. After an initial concentration of this virus to about 10 mg. per cc., the recovery on sedimentation should be equivalent to that obtainable with a similar concentration of tobacco mosaic virus, since the two viruses have approximately the same sedimentation constant. It seems likely that, in general, a second passage of infectious juice will be advantageous in those cases where the concentration of the virus is less than about 1 mg. per cc. and in those cases where the sedimentation constant of the virus is appreciably less than that of tobacco mosaic virus.

The experiments described were conducted with the assistance of Mr. Marshall Barbour.

Summary

The concentration and purification of tobacco mosaic virus have been accomplished efficiently by means of a Sharples Laboratory Super-centrifuge, equipped with a regular clarifier bowl operated at a speed of 50,000 r. p. m. by means of compressed air. It was found advantageous to use a cooling coil, a celluloid and a filter paper liner in the bowl, and a modified delivery jet constructed from a small hypodermic needle. Using the clarified juice from mosaic-diseased Turkish tobacco plants as starting material, it was possible to prepare 10 to 15 g. of tobacco mosaic virus, sufficiently pure for most purposes, during the course of ten hours by means of such equipment

PRINCETON, NEW JERSEY RECEIVED APRIL 15, 1942

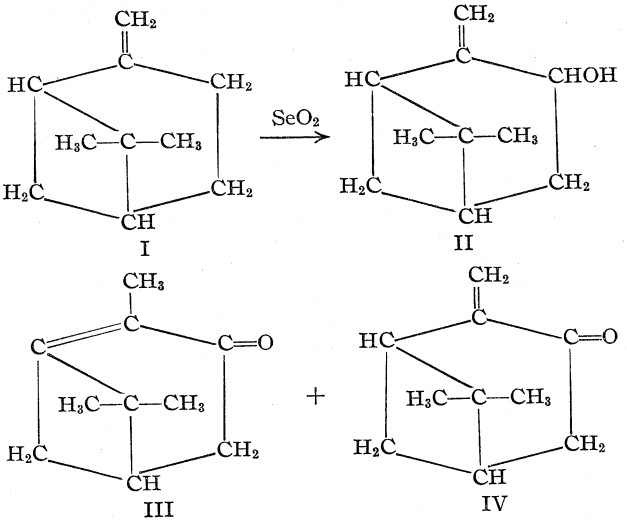
(9) C. A. Knight and W. M. Stanley, *J. Biol. Chem.*, **141**, 29 (1941).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF FLORIDA]

Reactions of β-Pinene. II. With Selenium Dioxide in Acetic Acid[1]

BY W. DAVID STALLCUP* AND J. ERSKINE HAWKINS

In the first paper of this series[2] it was pointed out that pinocarvone (IV) and carvopinone (III) are the steam-volatile products of the reaction of one mole of β-pinene (I) with one mole of selenium dioxide. Joshel and Palkin[3] have shown that pinocarveol (II) is the predominant steam volatile product if slightly less than one-half mole of selenium dioxide is used per mole of β-pinene.



In order to more completely study the formation of these compounds, the reaction has been carried out in acetic acid and acetic anhydride using both molar and half molar amounts of selenium dioxide per mole of β-pinene.

Experimental

β-Pinene was prepared by fractionating commercial material[4] through an efficient spiral screen column[5,6] and had a b. p. 59.2° (20 mm.), $n^{25}D$ 1.4768; $[\alpha]^{30}D$ −21.4°.

Selenium dioxide was prepared by nitric acid oxidation of selenium, washing, crystallizing and drying the product.

Oxidation of β-Pinene by Selenium Dioxide.—Selenium dioxide was added with stirring to β-pinene and 200 cc. of solvent in the amounts shown in Table I, the rate of addition being such that the temperature of the reaction mixture did not rise above 70°. When addition was complete the mixture was refluxed for four hours. It was then filtered to remove selenium and the filtrate was steam distilled. The distillate was treated with sodium bicarbonate and the ether extract distilled at 2–3 mm. pressure.

Separation of the Steam Volatile Oil

For Pinocarveol.—The oil was added to an equal volume of ethyl borate and heated for one hour at 125°. The non-alcoholic materials[7] were then removed by lowering the pressure and raising the temperature to 150°. The tarry residue was impure pinocarvyl borate. This was then hydrolyzed and simultaneously steam distilled from a sodium carbonate solution. The ether extract of the distillate was quite pure pinocarveol.

For Pinocarvyl Acetate.—The non-alcoholic oil from the borate treatment was extracted with twice its volume of sodium bisulfite as previously described.[2] When the ketonic materials were absorbed, the bisulfite was twice extracted with ether. Distillation of the ether extract at 2–3 mm. gave nearly pure pinocarvyl acetate.

For Carvopinone and Pinocarvone.—The bisulfite solution above was then selectively decomposed by the method previously developed.[2]

Essentially the same results as above were obtained when the oxidation mixture was first extracted with bisulfite and then treated with ethyl borate.

TABLE I

All oxidations listed were between 1 mole of β-pinene and 0.5 mole of selenium dioxide except the first reaction, which was between 1 mole of β-pinene and 1 mole of selenium dioxide and the second reaction which was between 0.5 mole of β-pinene and 0.5 mole of selenium dioxide.

Solvent	Se recov., g.	Steam volatile oil, g.	% Steam volatile oil recovered as Pinocarveol	Pinocarvyl acetate	Carvopinone	Pinocarvone
Ac_2O	49	68	0.6	65	1	3.7
AcOH	20	14.5		20		
Ac_2O	5	53	None	66	1	2
AcOH	None	41	3.7	22	20	2
AcOH–Ac_2O	6	27	13	44	2	8.5

Pinocarveol obtained by the above procedure was identical with that prepared from β-pinene and selenious acid in absolute ethanol by the method described by Joshel and Palkin.[3] It had the constants: b. p. 78–80° (3–4 mm.); $n^{25}D$ 1.4980; $[\alpha]^{25}D$ +65.5; d^{25}_4 0.976; MD calcd. 45.52,[8] found 45.72. This pinocarveol solidified at about 5°. Schmidt[9] reports a thaw point of 7° for pinocarveol purified through the phenylurethan. The phenylure-

* Present address, American Cyanamid Co., Stamford, Conn.

(1) This material has been abstracted from a thesis submitted to the Graduate Council of the University of Florida by W. David Stallcup in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Stallcup and Hawkins, THIS JOURNAL, **63**, 3339 (1941).

(3) Joshel and Palkin, through the courtesy of a private communication the contents of which now appear in THIS JOURNAL, **64**, 1008 (1942).

(4) Furnished through the courtesy of the Southern Pine Division of The Glidden Company, Jacksonville, Florida.

(5) Lecky and Ewell, *Ind. Eng. Chem., Anal. Ed.*, **12**, 544 (1940).

(6) Stallcup, Fuguitt and Hawkins, *ibid.*, **14**, 503 (1942).

(7) Separate experiments proved pinocarvyl acetate to be stable in the presence of ethyl borate under the conditions used.

(8) Based on values of Auwers and Eisenlohr, and 0.48 for cyclobutane ring. No value assigned for methylene group attached to ring.

(9) Schmidt, *Ber.*, **63**, 1129 (1930).

than was prepared as described by Schmidt.[9] If the pinocarveol is not carefully purified, the urethan will crystallize only with great difficulty, if at all. The m. p. was 82–84°. Joshel and Palkin[3] report 84–86°. Schmidt[9] reports 84–85° and 88–90° for recrystallized products.

Pinocarvyl Acetate.—When prepared from β-pinene as described above it had the constants: b. p. 88–90° (2–3 mm.), 225° (cor.) (760 mm.); $n^{25}D$ 1.4750; d^{25}_4 0.991, $[\alpha]^{25}D$ −38°; saponification number calcd. 194.26, found 195 (or 100.3%). Schmidt[9] reports b. p. 227–8°; d^{20} 0.997; αD +15.8° for the *d*-isomer.

When prepared by the esterification of pinocarveol with acetic anhydride in the presence of sodium acetate[9] the constants are: b. p. 88–90° (2–3 mm.); $n^{25}D$ 1.4760; d^{25}_4 0.993; $[\alpha]^{25}D$ −20°. Saponification number calcd. 194.26, found 194 (or 100%). No explanation is offered for the variations in the values of the rotations of the esters when prepared by different methods.

Pinocarveol, like most secondary and tertiary terpene alcohols, will not readily esterify with acetic anhydride unless sodium acetate is present. It will not react to any observable extent with acetic acid even when refluxed in the presence of sodium acetate for two hours.

Pinocarvone.—When prepared as described above it had almost the same constants as previously given[2]; b. p. 83–84° (3–4 mm.); $n^{20}D$ 1.5039; semicarbazone, m. p. 210–212° recrystallized.

Carvopinone.—The constants of this compound, obtained as described above, were also similar to those previously reported[2]; b. p. 84–85° (3–4 mm.); $n^{25}D$ 1.4924. Its semicarbazone did not melt below 300°.

The Action of Selenium Dioxide on Pinocarveol

Twenty-five grams of pinocarveol was dissolved in 75 cc. of ethanol in a flask equipped with a reflux condenser and mechanical stirrer. Ten grams of selenium dioxide was slowly added. Upon heating, the solution first turned yellow, then red and finally brown. After refluxing for five hours, three and one-half grams of selenium was obtained and the liquid portion was steam distilled. This gave 15 g. of an oil; b. p. 84–85° (3–4 mm.); $n^{25}D$ 1.4931; d^{25}_4 0.982; αD +60.5° (10-cm. tube). This was largely impure carvopinone which was purified through the bisulfite compound to give 6.1 g. of carvopinone; b. p. 84–85° (3–4 mm.); $n^{25}D$ 1.4935; d^{25}_4 0.981; $[\alpha]^{25}D$ +62.7°. About 0.3 g. of pinocarvone was isolated, this had $n^{25}D$ 1.5010. Approximately one-half gram of oil was not extracted by the bisulfite. Judging by its refractive index and its action to heat, it was impure carvopinone.

Reduction Experiments

***d-cis*-Pinocampheol** is formed in nearly theoretical yield by the catalytic hydrogenation of pinocarveol in cyclohexane using a 10% palladium on charcoal catalyst and heating the mixture to 100° under a hydrogen pressure of 1200 lb. for two hours in a bomb. The catalyst was removed by filtration and the pinocampheol purified by distillation at reduced pressure. The constants were: m. p. 55.5–56.0°; $n^{25}D$ 1.4830 (super-cooled); $[\alpha]^{25}D$ +39° (10.5% in ether). When recrystallized from pet. ether (boiling range 35–65°) the α-naphthylurethan had a m. p 87.5–88.0° (cor.) which is the same as that reported by Kuwata[10] and Schmidt and Schultz[11] for *d-cis*-pinocampheol.

***d-cis*-Pinocamphyl acetate** may be obtained quite pure by the catalytic reduction of pinocarvyl acetate under the conditions described above. The reduction product is purified from the solvent by distillation at reduced pressure. It had the constants: b. p. 80–82° (2–3 mm.), 227–8° (cor.) (760 mm.); $n^{21}D$ 1.4641; d^{25}_4 0.979; $[\alpha]^{25}D$ +23°. Saponification number, calcd. 196.28, found 197 (or 100.3%). Upon saponification this ester produced *d-cis*-pinocampheol whose constants were in close agreement with those above. Kuwata[10] reports for *l-cis*-pinocamphyl acetate: b. p. 82–84° (3 mm.); d^{20}_4 0.9781; $n^{20}D$ 1.4638.

***l-trans*-Pinocamphone** is obtained by the catalytic hydrogenation of carvopinone by the procedure described above. The product was purified by washing with neutral bisulfite and distilling the unextracted oil at 2–3 mm. (b. p. about 70°); b. p. 212° (cor.) (760 mm.); $n^{25}D$ 1.4735; d^{25}_4 0.964; $[\alpha]^{25}D$ −13.5°. Its semicarbazone recrystallized as very fine white needles from dilute methanol, m. p. 227.5–228.0° (cor). Schmidt and Schultz[11] report for the semicarbazone of *l-trans*-pinocamphone m. p. 227° and for the semicarbazone of *l-cis*-pinocamphone, 219°.

Another pinocamphone was obtained upon the reduction of pinocarvone under the same conditions. It had the constants: b. p. 75° (2–3 mm.); $n^{29}D$ 1.4772; αD −29° (10-cm. tube). It forms a semicarbazone melting at 185°. This is apparently the β-form of the semicarbazone described by Gildemeister and Kohler.[12] The α-form described by these authors has a m. p. of 218–219° which corresponds to the semicarbazone of *cis* pinocamphone of Schmidt and Schultz.[11]

Discussion

The effect of the selenium dioxide β-pinene ratio in these solvents was not nearly as pronounced as it was for ethanol.[2,3]

It may be seen from Table I that the major portion of the steam volatile oil is pinocarvyl acetate. This finding is in accord with the mechanism proposed by Guillemonat[13] for the oxidation of ethylenic hydrocarbons in which a selenium complex is formed with the hydrocarbons. This, in turn, is decomposed by the solvent. In this case it results in the formation of pinocarvyl acetate.

Water is a product of the reaction in which the selenium complex is formed. A reaction between the complex and the water thus formed would account for the formation of pinocarveol. As already pointed out, pinocarveol is not esterified by acetic acid and the alcohol therefore becomes subject to oxidation by selenium dioxide. This would account for the formation of the ketones.

(10) Kuwata, THIS JOURNAL, **59**, 2509 (1937).
(11) Schmidt and Schultz, *Ber. Schimmel*, 91 (1934).
(12) Gildemeister and Kohler, *Chem. Centr.*, **80**, II, 2158 (1909).
(13) Guillemonat, *Ann. chim.*, **11**, 143 (1939).

It is believed that this latter oxidation also takes place through the medium of a selenium complex. This is supported by the fact that the reaction mixture becomes yellow, then red and finally deposits selenium, and upon steam distillation leaves a non-volatile selenium compound.

Since carvopinone yields *trans*-pinocamphone upon reduction it may be seen, by setting up a model, that the carbonyl group of carvopinone is close to the *gem*-dimethyl group. This proximity would tend to hinder the rate of reaction of the carbonyl group with large molecules. The slowness of the reactivity of the carbonyl group was pointed out in the previous paper[2] in respect to the formation of the semicarbazone. This steric relation may also be the cause of the relative ease of the rupture of the cyclobutane ring to form carvone.

The pinocarveol formed by the action of selenium dioxide on β-pinene is probably the *trans* form with respect to the hydroxyl group and the *gem*-dimethyl group. It is believed that the method of formation and purification would tend to give rise to the more stable form, which is *trans*.

Summary

1. The oxidation of β-pinene with selenium dioxide in acetic acid and acetic anhydride gave pinocarvyl acetate, pinocarveol, pinocarvone and carvopinone as steam volatile products. The main product was the acetate.

2. The oxidation product of pinocarveol by selenium dioxide is largely carvopinone.

3. The catalytic reduction of carvopinone yields 1-*trans*-pinocamphone.

4. The method of formation and the structure of some of these compounds have been proposed.

GAINESVILLE, FLORIDA RECEIVED APRIL 10, 1942

[CONTRIBUTION FROM THE GEOCHEMICAL SECTION OF THE ILLINOIS STATE GEOLOGICAL SURVEY]

The Oxidizing Power of Illinois Coal. II. The Effects of Extended Time[1]

BY G. R. YOHE[2] AND MYRON H. WILT[2]

Previous work[3] has shown that Illinois coals take on the ability to act as oxidizing agents toward titanous chloride upon exposure to air or oxygen, even for very short periods of time. In the present work, a similar study has been applied to another group of coals with emphasis upon the changes in oxidizing power over longer times of exposure to air.

Preparation of Samples.—The coal samples were obtained in the form of large fresh blocks at the mines, brought to the laboratory as soon as possible, and ground to pass a 100-mesh sieve. No precautions were taken to prevent atmospheric oxidation during the preparation of the samples. After grinding, portions were taken for analyses, and the remaining stocks were placed in 2-quart mason jars and deliberately exposed to air by leaving the covers loose and by occasionally mixing the contents of each jar. The time of exposure to air was measured in days from the date of grinding.

Determination of Oxidizing Power.—The determinations of oxidizing power were made by the titanous chloride–ferric chloride method previously described.[3] Parallel determinations of soluble ferric iron extractable from the coals under similar conditions were made, and the oxidizing power data reported here are corrected for soluble ferric iron. As a rule, the soluble ferric iron values were low compared to total oxidizing power. The results obtained with five whole coal samples are shown in Fig. 1 expressed in milliequivalents per gram of coal dried in contact with laboratory air, but not calculated to a moisture- and ash-free basis. Analytical data for the coals are given in Table I.

Measurement of Specific Surface.—In order to determine whether the variations in magnitude of oxidizing power were due entirely to differences in surface exposed, specific surface measurements were made. The procedure used is an adaptation of the air-permeability method of Lea and Nurse[4] with apparatus constructed according to specifications obtained from Battelle Memorial Institute.[5] Table II gives the results obtained and a comparison of the maximum oxidizing power values per unit surface.

Discussion

The mechanism of the reaction of oxygen with coal is obscure and will doubtless remain so until the chemical nature of coal is more clearly revealed. A number of workers in this field have considered that the initial step is the formation of a "coal-oxygen complex" or an unstable surface

(1) Presented before the Division of Gas and Fuel Chemistry at the Memphis meeting of the American Chemical Society, April 22, 1942. Published with permission of the Chief, Illinois State Geological Survey.

(2) Associate Chemist and Research Assistant, respectively.

(3) Yohe and Harman, THIS JOURNAL, 63, 555 (1941).

(4) Lea and Nurse, *J. Soc. Chem. Ind.*, 58, 277–83 (1939).

(5) Private communication from R. A. Sherman to O. W. Rees.

TABLE I

ANALYTICAL DATA, ILLINOIS COALS

Laboratory number	County	Seam	"As received" basis Moisture	"As received" basis Ash	Ash- and moisture-free basis C	H	N	O	S	Calorific value, cal. per g.[a]	Bituminous coal rank (A. S. T. M.), high volatile
C-2413	LaSalle	6	10.2	9.2	78.38	5.62	1.22	9.25	5.53	7182	C
C-2414	Fulton	5	11.7	7.4	79.93	5.57	1.47	10.43	2.60	7003	C
C-2415	Sangamon	5	11.3	6.8	78.02	5.49	1.48	9.70	5.31	7040	C
C-2422	Vermilion	6	13.1	3.2	81.05	5.65	1.76	10.05	1.49	7035[b]	C
C-2423	Gallatin	5	2.6	10.4	81.36	5.78	1.80	7.78	3.28	7832[c]	A

[a] Moist mineral-matter-free basis. Multiply by 1.8 to obtain the B. t. u. per lb. values used in A. S. T. M. classification by rank. [b] Calculated from ultimate analysis. [c] Value obtained on another sample (C-2416) from the same source.

TABLE II

SPECIFIC SURFACE DATA

Coal number	Specific surface sq. cm./gram	Maximum O. P. × 10^5 / Specific surface
C-2413	3270	5.84
C-2414	5450	2.86
C-2415	3510	4.37
C-2422	3410	3.30
C-2423	3850	1.96

combination.[6-9] Although some assume this to be adsorbed oxygen,[7] others believe it to be chemically combined, since evacuation does not lead to oxygen recovery in the way such treatment of an adsorption complex should do.[10] This "complex" has been referred to as "peroxide,"[8,11,12] yet little is known of its nature or properties.[13] Nevertheless, this loosely bound oxygen is commonly mentioned as an intermediate stage in the atmospheric oxidation of coal.[6,7,8]

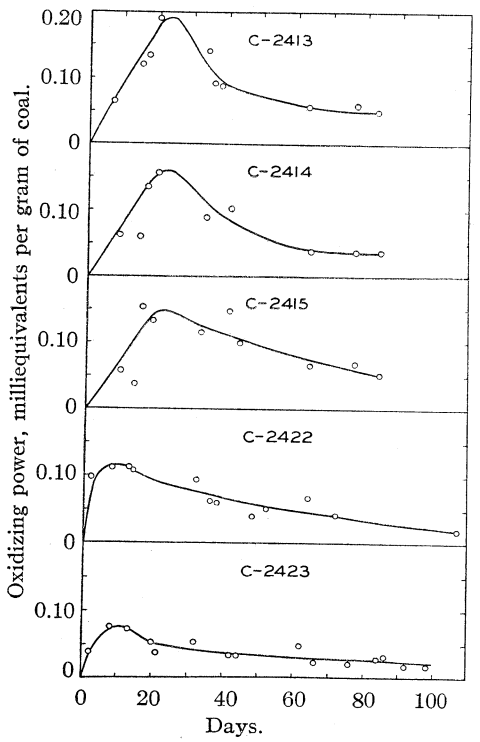


Fig. 1.—Change in oxidizing power with time of exposure to air.

In general form, the curves of Fig. 1 are suggestive of the existence of an intermediate such as B in consecutive reactions of the type

$$A \longrightarrow B \longrightarrow C^{14}$$

Although the atmospheric oxidation of coal is undoubtedly a complex process, the data presented herein may be considered as evidence supporting the hypothesis that loosely held oxygen (perhaps of a peroxide type) constitutes an intermediate stage in a part, at least, of the total change occurring in the oxidative degradation of these coals. It is of interest to note that data for the change in peroxide number of glyceryl trilinolen-

(6) Wheeler, *J. Chem. Soc.*, **113**, 945–55 (1918).
(7) Parr and Milner, *Ind. Eng. Chem.*, **17**, 117 (1925).
(8) Davis and Byrne, *ibid.*, **17**, 125 (1925).
(9) Porter and Ralston, *U. S. Bur. Mines Tech. Paper*, **65**, 21–6 (1914).
(10) Winmill, *Trans. Inst. Mining Engrs.* (London), **48**, 503–7 (1914–15).
(11) Bunte and Brückner, *Angew. Chem.*, **47**, 84–6 (1934).
(12) F. Fischer, *Ges. Abhandl. Kenntnis Kohle*, **4**, 454–5 (1920).
(13) Attempts to demonstrate the presence of peroxides in coal in this Laboratory have given inconclusive results. The common potassium iodide test is rendered valueless because of the avidity with which coal combines with iodine. The chemiluminescent oxidation of magnesium phthalocyanine [Cook, *J. Chem. Soc.*, 1845 (1938); Helberger and Hever, *Ber.*, **72B**, 11–15 (1939)] was tried with magnesium phthalocyanine kindly provided by Dr. R. P. Linstead of Harvard University. This reaction is apparently inhibited by coal; a chlorobenzene solution of tetralin which produced red luminescence ceased to do so when a small amount of powdered coal was added. The use of powdered coals as catalysts in the peroxide-catalyzed side chain chlorination of toluene and the addition of chlorine to the ethylenic double bond [Kharasch and Brown, THIS JOURNAL, **61**, 2142–60, 3432 (1939)] gave results which could be explained without assuming the presence of peroxides. A modification of the Yule–Wilson ferrous sulfate test [Yule and Wilson, *Ind. Eng. Chem.*, **23**, 1254–9 (1931)] gave positive results essentially like those obtained with the titanous chloride method. Although proof of the presence of peroxide structures is lacking, such groups must still be considered as possible causes of the oxidizing power observed.
(14) Getman and Daniels, "Outlines of Theoretical Chemistry," 6th Edition, John Wiley and Sons, New York, N. Y., 1937, pp. 329–31.

ate[15] and of a soybean oil[16] give curves similar to those shown in Fig. 1.

There is no apparent correlation between the magnitude of the oxidizing power and properties within the group of coals having high-volatile C bituminous rank. It will be seen, however, that the one coal of higher rank (C-2423) exhibits a definitely lower oxidizing power per unit surface. It seems obvious from Table II that the magnitude of oxidizing power attained is not simply a function of the extent of the surface, but that the nature of the surface (which undoubtedly varies with the rank and source of the coal) is of utmost importance in this respect. It is hoped that this investigation may be extended to cover a series of coals of widely differing ranks.

It is possible that the different petrographic or "banded" ingredients of the coal may differ in their ability to take on oxidizing power. Such differences, as well as errors in sampling, might contribute to the irregularities in the curves. The present study is being continued with samples of separated banded ingredients of an Illinois coal.

Acknowledgment.—The authors wish to extend their thanks to Drs. F. H. Reed and O. W. Rees for valuable suggestions; to Mr. C. C. Boley for assistance in collecting samples and to Mr. K. F. Bursack and Mr. W. F. Wagner who made the coal analyses and specific surface measurements under the direction of Dr. Rees.

Summary

The oxidizing power exhibited by five Illinois coals has been shown to reach a maximum value and then decrease, suggesting that this "reactive oxygen" may play the role of an intermediate in the oxidative degradation of these coals.

URBANA, ILLINOIS RECEIVED MAY 1, 1942

(15) Elm, *Ind. Eng. Chem.*, **23**, 882 (1931).
(16) Clark and Rugg, *Ind. Eng. Chem., Anal. Ed.*, **13**, 243 (1941).

[CONTRIBUTION FROM THE MORLEY CHEMICAL LABORATORY OF WESTERN RESERVE UNIVERSITY]

The Oxidation of *n*-Butylboron Oxide[1]

BY OLIVER GRUMMITT

The reported[2] auto-oxidation of *n*-butaneboronic acid (n-BuB(OH)$_2$) to the mono-*n*-butyl ester of boric acid (n-BuO-B(OH)$_2$) suggested a parallel study of the auto-oxidation of *n*-butylboron oxide, (n-BuBO)$_3$, which is the trimeric anhydride of the boronic acid. This oxidation, because of the six-electron configuration of the boron atom, offered the possibility of proceeding through the intermediate formation of an oxygen coördination compound (or peroxide) comparable to those postulated for many oxidation processes.[3]

Preliminary measurements[4] on several alkylboron oxides showed that oxidation occurred readily but at widely different rates depending upon the nature of the alkyl group (Table I).

TABLE I

R of R–BO	Time required for the consumption of 2.0 cc. oxygen, 25°, min.
Et	33
n-Pr	36
n-Bu	71
s-Bu	3
t-Bu	2
n-Hex	105

Apparently the ease of oxidation decreases with an increasing chain length of the alkyl group and increases sharply in the order primary, secondary, and tertiary. The relative stability of the corresponding boronic acids in air is also of this order.[2,5]

Experimental Procedure

Apparatus.—The reaction flask is shown in Fig. 1. The total volume of this two-bulb flask is approximately 125 cc. and since none of the dimensions is of critical importance, they are not shown. Connected to the side arm of the flask are two mercury-filled gas burets in series. The first of these burets was made of a 10-cc. delivery pipet calibrated in divisions of 0.05 cc. and a three-way stopcock and was used to measure the consumption of oxygen during the earlier stages of the reaction. The second buret was the orthodox 100-cc. type with 0.2-cc. divisions. Each gas buret was fitted with a leveling bulb and a jacket through which thermostated water could be circulated. The use of two burets permitted accurate readings at the start of the auto-oxidation when an induction

(1) Presented before the Division of Organic Chemistry at the Detroit meeting of the American Chemical Society, September 12, 1940.
(2) Snyder, Kuck and Johnson, THIS JOURNAL, **60**, 105 (1938).
(3) Bailey, "Retardation of Chemical Reactions," Longmans, Green and Co., New York, 1937.
(4) The author wishes to thank Professor J. R. Johnson for his permission to use these data which were obtained during a du Pont Post-Doctorate Fellowship at Cornell University, 1936–1938, and for his suggestions on this problem.
(5) Johnson, Van Campen and Grummitt, THIS JOURNAL, **60**, 111 (1938); and unpublished work of Johnson and Grummitt.

period might be present and also allowed total volumes of oxygen up to about 100 cc. to react and be measured with fair accuracy.

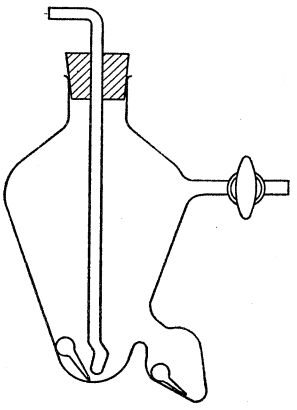


Fig. 1.—Reaction flask.

A small sample of the alkylboron oxide contained in a sealed ampoule made in the shape of a bulb with a fine capillary stem was placed stem-down in the bottom bulb of the reaction flask. A similar ampoule, tared and empty, was placed stem-down in the side bulb. The reaction flask and burets were very carefully dried and filled with dry oxygen so that the small buret contained about 7–8 cc. of gas, the large buret about 70 cc. of gas. The gas buret stopcocks were open to the flask and the leveling bulbs were adjusted so that atmospheric pressure existed in the whole system. The temperature of the system was maintained at 25° by circulating water from a thermostat through the buret jackets and through a container surrounding the flask. When the buret readings no longer changed over a ten-minute period showing that the enclosed gas had reached constant temperature, the stopcock on the large buret was shut off from the reaction flask. The bent rod in the reaction flask was twisted so as to smash the ampoule against the wall of the flask and the time was noted. Frequent adjustments of the leveling bulb on the small buret were made in order to maintain atmospheric pressure and readings were taken at the same time. When 2–5 cc. of oxygen had been consumed, the small buret was shut off and the large buret, by means of its stopcock, was opened to the reaction flask and occasional time–volume readings were made.

When the sample was completely oxidized as shown by a constant volume reading after a period of one-half hour, the stopcock at the connection between the flask and the first buret was closed and the rubber connection removed from the buret. The flask was connected to a vacuum pump through an arrangement of stopcocks which permitted the flask to be evacuated and then filled with dry, oxygen-free nitrogen without opening the flask to the atmosphere. The flask was thoroughly evacuated and rinsed with nitrogen four times while clamped in a vertical position. It was then tilted so that the product drained into the side-bulb, re-evacuated, and again filled with nitrogen. As the pressure approached atmospheric the liquid product filled the empty, tared ampoule. This was then removed, sealed by touching the tip in a flame, and, after weighing, was ready for analysis, molecular weight determination, etc.

The flask shown in Fig. 1 may be useful for other reactions where the reactants are gases and liquids which cannot be exposed to the atmosphere and where the product is also a liquid which cannot be exposed. A somewhat similar device described by Stock and Zeidler[6] does not permit the product to be removed in an ampoule.

(6) Stock and Zeidler, *Ber.*, **54**, 533 (1921).

Relative Oxidation Rates.—Samples of the various alkyl boron oxides listed in Table I were prepared by dehydration of the corresponding boronic acids with thionyl chloride.[2] A 0.2–0.3 g. (about 3.0 millimoles) sample was oxidized in the apparatus described above and the time noted for the consumption of 2.0 cc. of oxygen at 25°. Duplicate determinations were made. In each case there was practically no induction period so the data show in an approximate way the relative reactivity of the various compounds with respect to oxygen.

Oxidation of *n*-Butylboron Oxide.—A 0.2060-g. (2.46 millimoles) sample of *n*-butylboron oxide was quantitatively oxidized in the apparatus previously described. Volume readings were taken at two-minute intervals for the first eighteen minutes, at three-minute intervals for the next thirty-five minutes, and then at longer intervals until no more oxygen was consumed. These data are plotted in Fig. 2. As the curve shows there is no induction period. At the end of 800 minutes 31.5 cc. of oxygen had been consumed as compared to a theoretical consumption of 31.6 cc. (at 25° and 735 mm. pressure) based on the oxidation of *n*-butyl boron oxide to *n*-butyl metaborate (Eq. 1).

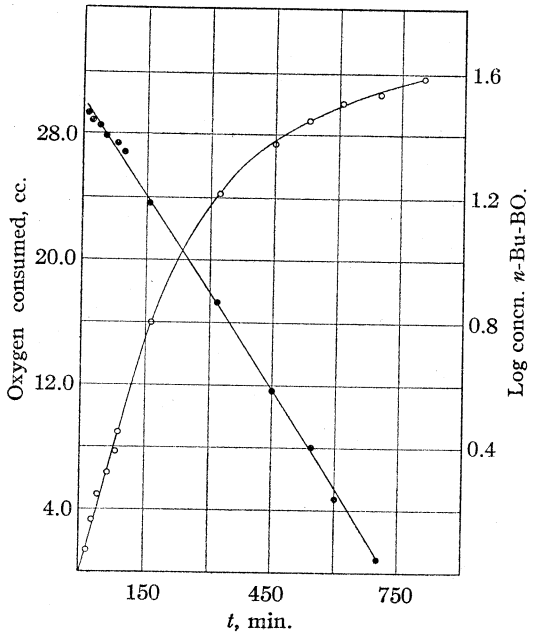


Fig. 2.—Oxidation of *n*-butylboron oxide.

The product from the oxidation of 0.6 g. of *n*-butylboron oxide was distributed into tared ampoules. The saponification equivalent of one of these samples was found to be 98.6; calculated for n-C_4H_9OBO, 99.9. A molecular weight determination by freezing point depression in benzene gave 97.6. This determination was very difficult because of the great ease of hydrolysis of the sample; not only must the apparatus and benzene be absolutely dry, but it must be so maintained by slowly passing dry nitrogen into one sidearm of the freezing point tube so as to prevent any air from entering while stirring.

One sample of the ester was hydrolyzed by the dropwise addition of water; some heat was generated and the odor

of *n*-butyl alcohol was apparent. A neutralization equivalent of the boric acid formed was determined by adding mannitol and titrating with standard sodium hydroxide in the presence of phenolphthalein; found 61.5, calculated 61.8. Another sample was hydrolyzed with a slight excess of water, distilled, and the *n*-butyl alcohol identified as the 3,5-dinitrobenzoate derivative, m. p. 63–64°, no depression in a mixed m. p. with an authentic sample.

Anal.[2] Calcd. for $C_4H_9BO_2$: B, 10.83. Found: B, 11.05.

Peroxide Tests.—Partially oxidized samples of *n*-butylboron oxide instantly liberated iodine from a slightly acidified solution of 5% potassium iodide in absolute ethanol. Further evidence that peroxides or peroxide-like compounds may be present was obtained by heating three 10-cc. portions of vinyl acetate on the water-bath at 70°; the first sample contained no catalyst, the second contained about 0.1 g. of partially oxidized *n*-butylboron oxide, and the third contained 0.1 g. of benzoyl peroxide. At the end of one-half hour the increase in viscosity, interpreted roughly as a measure of polymerization, was small for the blank, appreciable for the second, and very considerable for the third. It is possible of course that the partially oxidized butylboron oxide furnished other catalytic agents besides peroxides.

Catalytic Oxidation of *n*-Butylboron Oxide.—Samples containing approximately 0.1% of the catalyst were made by distilling *n*-butylboron oxide at reduced pressure into receivers containing inverted tared ampoules and a weighed portion of the catalyst. Before letting nitrogen into the system the receivers were gently warmed to dissolve the catalyst. Both hydroquinone and phenyl-β-naphthylamine dissolved readily, but cobalt linoleate and ammonium vanadate were only partially soluble. Nitrogen was admitted and the ampoules sealed and weighed in the usual way. These samples were then oxidized according to the procedure described before. The samples containing hydroquinone, cobalt linoleate, and ammonium vanadate gave time–oxygen consumed curves which substantially duplicated that shown in Fig. 2, but phenyl-β-naphthylamine inhibited the oxidation; for example, in 200 minutes only 1.2 cc. of oxygen had been consumed compared to 15.0 cc. in the absence of the catalyst and at the end of 13.5 hours where the oxidation normally would be completed only 10% of the theoretical amount of oxygen had been consumed.

Results and Discussion

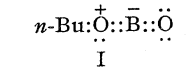
Oxidation of *n*-butylboron oxide was found to proceed quantitatively according to the equation

$$(n\text{-BuBO})_3 + 1^1/_2O_2 \longrightarrow 3\text{BuO-BO} \qquad (1)$$

the product being the *n*-butyl ester of metaboric acid. This substance is an oily liquid with a faint ester odor. Like esters of boric acid it hydrolyzes immediately on contact with the atmosphere forming *n*-butyl alcohol and a mixture of metaboric and boric acids.[7]

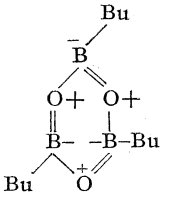
(7) Schiff, *Ann., Supp.*, **5**, 185 (1867), reported similar properties for methyl and ethyl metaborates which were prepared by the action of boric acid on the alkyl borate or alcohol.

Since *n*-butyl metaborate is monomeric,[8] the oxidation process has been accompanied by a depolymerization reaction. The failure of *n*-butyl metaborate to retain the trimeric structure of *n*-butylboron oxide is probably due in part to the contribution of resonating forms such as I[9] in which the boron atom can no longer function as an acceptor center.

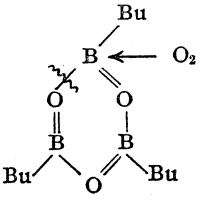


I

This function is necessary in order that the boron atom coördinate with oxygen to form the trimeric butylboron oxide[2,10,11]



The course of the oxidation of *n*-butylboron oxide is shown in Fig. 2, in which the volume of oxygen consumed is plotted against time. The shape of this curve differs from typical S-shaped auto-oxidation curves for benzaldehyde, linseed oil, etc.,[3] in that the induction period[12] is absent. This probably means that the concentration of peroxidic intermediate necessary for an appreciable rate of oxidation is established very rapidly. This intermediate could arise through the attack of a boron atom by oxygen with subsequent cleavage of the ring (2); the peroxide could then



$$\longrightarrow \text{Bu-BO(O}_2\text{)} + 2\text{Bu-BO}^{13} \qquad (2)$$

(8) Metaboric acid itself has been reported to be monomeric; Mellor, "Comprehensive Treatise of Inorganic Chemistry," Longmans, Green, and Co., New York, N. Y., 1924, Vol. 5, p. 48.

(9) Other resonating forms include *n*-Bu:Ö:B::Ö, *n*-Bu:Ö::B:Ö:$^-$, and *n*-Bu:Ö:B:::Ö$^+$. In the absence of bond length data the principal form cannot be selected, although ordinary valence considerations favor the first of these.

(10) Kinney and Pontz, THIS JOURNAL, **58**, 197 (1936), found that certain arylboric oxides are trimeric.

(11) Burg, *ibid.*, **62**, 2228 (1940), found that methylboric oxide is trimeric.

(12) The initial period of time in which the rate of oxygen absorption is zero or very low.

(13) An alternative initial step could involve peroxide formation from the action of oxygen directly on monomeric butylboron oxide if one assumes an equilibrium: $(\text{Bu-BO})_3 \rightleftarrows 3\text{Bu-BO}$. There is no evidence, however, for this dissociation.

oxidize monomeric butylboron oxide to form the metaborate in a reaction analogous to the interaction of benzoyl hydrogen peroxide with benzaldehyde to give two molecules of benzoic acid (3).

$$Bu\text{-}BO(O_2) + Bu\text{-}BO \longrightarrow 2BuO\text{-}BO \quad (3)$$

Some evidence in support of the intermediate peroxide is gained from experiments with partially oxidized butylboron oxide which show that it liberates iodine from alcoholic potassium iodide and catalyzes the polymerization of vinyl acetate as do other peroxides.

Efforts to establish a reaction mechanism on the basis of kinetic measurements were unsuccessful. When a sample of *n*-butylboron oxide was exposed to oxygen without agitation, the rate of oxygen absorption followed the unimolecular law as shown by the straight line in Fig. 2 obtained by plotting the logarithm of the concentration of *n*-butylboron oxide against time. The concentration of *n*-butylboron oxide was determined on the basis of the oxygen consumed in accordance with equation (1). This agreement with the unimolecular law is superficial, however, because mechanical agitation of the reaction mixture in other experiments not only increased the rate of oxidation but gave data which could not be interpreted kinetically. Apparently the rate of diffusion of unoxidized material to the surface of the reaction mixture is the rate-determining step in the absence of agitation.

The effect of catalysts on the rate of oxidation was observed in experiments with cobalt linoleate and ammonium vanadate as positive catalysts, and hydroquinone and phenyl-β-naphthylamine as typical anti-oxidants. The only one of these catalysts which had an appreciable effect on the rate of oxidation was phenyl-β-naphthylamine, which inhibited the reaction almost completely. It is interesting to note that aromatic amines are more effective anti-oxidants than phenols for aliphatic aldehydes.[14] This is a further point of resemblance between the alkylboron oxides (or boronic acids) and aliphatic aldehydes, Johnson, *et al.*,[2] having already pointed out that both types of compounds combine with oxygen, reduce ammoniacal silver oxide, and form cyclic trimers.

Summary

n-Butylboron oxide undergoes quantitative oxidation and depolymerization in the presence of dry oxygen to form monomeric *n*-butyl metaborate. There is evidence for the intermediate formation of a peroxidic substance. A possible reaction mechanism has been suggested, but could not be confirmed by rate measurements because the kinetics were complex. Phenyl-β-naphthylamine retards the oxidation but hydroquinone does not.

(14) Bailey, *Proc. Royal Irish Acad.*, **45B**, 373 (1939).

CLEVELAND, OHIO RECEIVED MARCH 23, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF SOILS, UNIVERSITY OF MISSOURI]

The Electrochemical Properties of Mineral Membranes. V. Beidellite Membranes and the Determination of Sodium[1]

BY C. E. MARSHALL[2] AND C. A. KRINBILL[2]

Introduction

Previous papers in this series[3] have dealt with the use of preheated montmorillonite membranes in the potentiometric determination of potassium and ammonium and with the application of this method to the electrochemical study of colloidal systems as typified by the clays. The hydrogen montmorillonite membranes used were preheated to 490°. This treatment conferred remarkable properties of stability and selectivity. The membranes were of high resistance (1–10 megohms), yet showed excellent reproducibility toward potassium and ammonium ions. Acids attacked them chemically and highly reproducible values could only be obtained at *p*H values above 4. Sodium salts alone gave poor reproducibility and asymmetry potentials were troublesome. However, mixtures of sodium and potassium salts measured against potassium chloride as standard gave values which suggested that the

(1) Contribution from the Department of Soils, Missouri Agricultural Experiment Station, Journal Series No. 820. Read before the Colloid Chemistry Division at the 103rd meeting of the American Chemical Society in Memphis on April 23, 1942.

(2) Associate Professor and Research Assistant in Soils, respectively.

(3) Marshall and Bergman, THIS JOURNAL, **63**, 1911 (1941); *J. Phys. Chem.*, **46**, 52 (1942); **46**, 325 (1942).

membrane was definitely sensitive to sodium ions and that both the mobility and the activity of the sodium were concerned in the establishment of the potential difference. These membranes possessed also the remarkable property of being insensitive to divalent and trivalent cations.

In an attempt to improve the conditions for the potentiometric estimation of sodium, W. E. Bergman in this Laboratory prepared hydrogen montmorillonite membranes (Wyoming bentonite, electrodialyzed fraction $< 0.2\ \mu$) preheated to 350°. These were found to lose their asymmetry potentials readily on soaking in N sodium chloride solution and then in 0.1 N solution. They gave potentials, for concentrations below 0.1 N, which agreed well with those calculated from the Nernst equation.

It was later found that these 350° membranes have quite different properties of ionic selectivity than those heated to 490°. They have a much lower resistance when wet, 5–20,000 ohms as against 1–10 megohms for the latter. They are sensitive to divalent cations as well as to monovalent. Hence their ionic behavior is qualitatively similar to that of chabazite and apophyllite membranes.[4] They have the advantages over the latter of easier preparation, of greater reproducibility and of lower resistance. However, a distinctly selective character is still present. Unlike the beidellite membranes described below, they are not sensitive to trivalent cations such as cerium.

In an attempt to secure even greater reproducibility toward sodium, membranes were prepared from another clay mineral, colloidal beidellite.[5] These membranes, whose preparation and properties are herein described, act as general cationic membranes. By their use we can look forward to the estimation of monovalent, divalent and possibly trivalent cations in pure solution. The present contribution is concerned chiefly with sodium. The application to calcium and other polyvalent cations will be considered in a later communication.

Experimental

Preparation of Membranes.—The beidellite membranes were prepared using essentially the same procedure as has been described for those of montmorillonite. The starting point was the heavy subsoil or B horizon of the Putnam silt loam soil taken from an experimental field at Moberly, Missouri. This is a calcium–hydrogen soil containing little organic matter. After treatment with hydrogen peroxide to remove the organic matter, the soil suspension in water was dispersed by adding sodium hydroxide to a pH of 7. The clay fraction was decanted after standing for twenty-four hours or more, and was then passed through a Sharples supercentrifuge running at 30,000 r. p. m., at such a rate of flow that all particles larger than 0.2 μ in equivalent spherical diameter were retained. The suspension of $< 0.2\ \mu$ clay which passed on was then concentrated by electrodialysis, the process being continued until all sodium and calcium were removed. The electrodialyzed clay was then diluted to 1–2% concentration. It was dispersed by being mechanically stirred for fifteen minutes at high speed and was then boiled to remove dissolved air. The hot suspension was poured into a shallow copper tray which had previously been rubbed over with a cloth saturated with neutral mineral oil. Evaporation was effected at about 80° by heating from above with an electric radiator. In this way a layer of suspension 1–2 cm. in depth evaporates to dryness and leaves a clay film 0.2–0.3 mm. in thickness which readily can be removed. This film consists of the mineral beidellite,[6] a clay of the montmorillonite group, but having a somewhat lower base exchange capacity than montmorillonite itself.

The beidellite film is less flexible than that of montmorillonite and, instead of using a cork borer, the membrane disks are prepared by breaking off corners from irregular fragments. They show some tendency to split or cleave parallel to the surface. They were mounted on the ground ends of 8-mm. Pyrex tubing with hard de Khotinsky cement or pliocene. Once mounted they showed remarkable stability and on soaking for only a few hours in salt solutions the asymmetry potentials disappeared. Over 90% of the membranes thus prepared gave reproducible potentials close to the anticipated values. Deviations of 1 millivolt were rarely found. Differences between individual membranes were most marked in the more concentrated and in the very dilute solutions.

The potentials were determined using saturated calomel electrodes with agar bridges on each side of the membrane. A known solution was placed inside the tube as standard. In some cases a silver chloride electrode was used with a standard chloride solution inside the membrane tube and a saturated calomel cell in the outer solution.

Special care was taken to make the liquid junction potentials as small and reproducible as possible. It was found, for instance, that a liquid junction potential of several millivolts could arise when a saturated calomel electrode with upturned agar tip was transferred from one solution of a sodium salt to another of different concentration. The reason for this was that in the first solution some potassium chloride was lost by diffusion and replaced by a more dilute mixture of potassium and sodium salts. This gave a junction potential against a second sodium salt solution; it diminished with time as more potassium chloride diffused toward the tip.

In making the final measurements, therefore, a calomel

(4) Marshall, *J. Phys. Chem.*, **43**, 1155 (1939).

(5) The preparation and properties of clay films were first described by Hauser and le Beau [*ibid.*, **42**, 961 (1938)], who used bentonite clay.

(6) Marshall, *Zeitschr. Kryst.*, **A90**, 8 (1935); **A91**, 433 (1935); Marshall, *J. Phys. Chem.*, **41**, 935 (1937).

cell was always used whose tip had been for some time in contact with saturated potassium chloride solution. A Leeds and Northrup thermionic amplifier was used in conjunction with a calibrated "student" type potentiometer and individual measurements were made to 0.1 millivolt. The amplifier could be dispensed with where the total resistance was less than 20,000 ohms. The resistances were determined approximately by applying a known voltage and measuring the current.

Comparison of Membranes.—The qualitative characteristics of membranes prepared in different ways are given in Table I.

It is evident that the effect of heat on the membrane characteristics is quite different for the two minerals. Further work will be needed to establish the exact causes of these differences in sensitivity to different cations.

In making quantitative comparisons of different membranes it is necessary to use a single salt such as potassium chloride. For details of the graphical method employed see ref. 3.

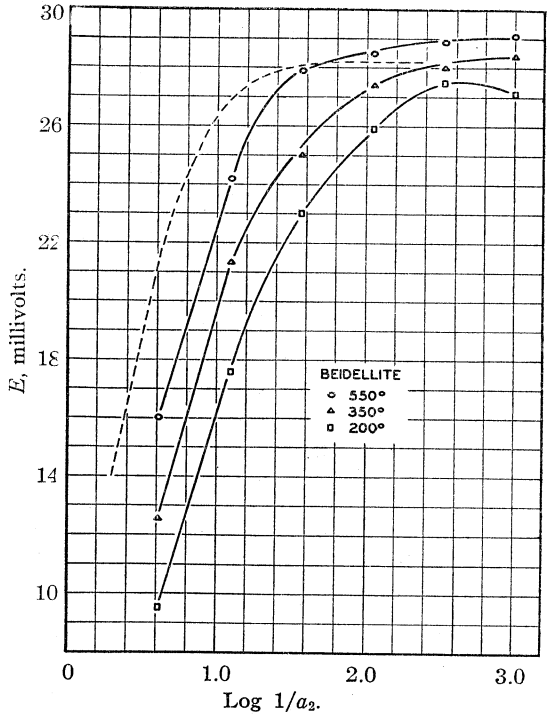


Fig. 1.—Experimental curves obtained with electrodialyzed beidellite membranes dried to various temperatures using potassium chloride solutions with an activity ratio $a_1/a_2 = 3$. The broken line is the theoretical curve for $Uc/U_A = 1$ and $A = 1$, A being the effective charge per unit volume of the membrane.

It will be seen from Fig. 1 that the beidellite membranes give curves lying farther to the right than those previously obtained with 490° montmorillonite.[3] This indicates a smaller ionic charge per unit volume, approximately 0.5 for the 550° beidellite whereas the 490° montmorillonite was 1.0. This is probably to be accounted for by the lower exchange capacity of the beidellite. In consequence, agreement within 1 millivolt with the Nernst equation can only be expected for solutions less concentrated than $N/30$. Even with this limitation the beidellite membranes are to be preferred over the 350 or 490° montmorillonite membranes where both can be used for the same ion. The beidellite membranes come to equilibrium with fresh solutions much more rapidly (within a few minutes, instead of after several hours), the initial asymmetry potentials disappear more rapidly on soaking, and the individual differences between membranes are smaller. This last point can perhaps best be seen by a comparison of typical numerical results for montmorillonite and beidellite membranes (Table II).

TABLE I

CHARACTERISTICS OF CLAY MEMBRANES PREPARED IN VARIOUS WAYS

Exchangeable cation	Temp. of pretreatment, °C.	Approximate resistance (megohms) Wet	Dry[a]	Cations to which sensitive
		Montmorillonite		
H	350	0.005–011	200	Mono-, divalent
H	490	1–10	400	Monovalent
H	550	Very low	...	None
		Beidellite		
H	110	0.005	3	Mono-, di-, trivalent
H	600	0.012	15–45	
H	750	0.015		
H	900	>1000	>1000	

[a] Dry indicates an atmosphere of 50% relative humidity.

TABLE II

COMPARISON OF INDIVIDUAL POTENTIALS FOR 350° MONTMORILLONITE AND 550° BEIDELLITE MEMBRANES IN SODIUM CHLORIDE SOLUTIONS AT 25°. THEORETICAL NERNST POTENTIAL IS 28.2 MILLIVOLTS

Activity ratio a_1/a_2	350° Montmorillonite 1	2	3	4	5
0.7101/0.2367	16.2	15.3	18.1	17.1	16.4
.2367/ .0789	23.0	20.5	24.2	22.9	22.0
.0789/ .0263	27.1	26.5	27.0	27.7	27.0
.0263/ .0088	29.0	28.1	28.4	29.2	28.9
.0088/ .0029	26.5	26.5	27.3	27.1	26.7
.0029/ .0010	27.6	27.2	27.1	27.6	27.3
	550° Beidellite				
0.7107/0.2367	16.3	16.0	15.8	16.7	16.6
.2367/ .0789	23.4	23.9	24.8	25.5	25.6
.0789/ .0263	27.5	27.2	27.6	27.6	27.5
.0263/ .0088	28.3	28.2	28.8	28.6	28.5
.0088/ .0029	28.4	28.3	28.4	28.3	28.3
.0029/ .0010	27.9	27.7	28.5	28.0	28.4

In Fig. 2 the results for sodium chloride solutions are presented, using the same 1:3 ratio of cationic activities as for potassium chloride in Fig. 1. It can be seen that the 550° beidellite membranes are superior both to the 750° beidellite and the 350° montmorillonite membranes.

Comparison of Different Sodium Salts.—Table III gives the mean potentials obtained for beidellite membranes with sodium salts. At least six membranes were used in each case. The standard solution used throughout was 0.1 N sodium chloride which gives an activity a_1 of 0.0789.

TABLE III

MEAN POTENTIALS OBTAINED WITH BEIDELLITE MEMBRANES IN SODIUM SALT SOLUTIONS (a_1 = 0.0789 Na^+)

Temp. of pretreatment, °C.	Salt	Activity of Na^+ in a_2	Observed potential, mv.	Calcd. potential, mv.
550	NaCl	0.0266	27.5	27.9
	NaCl	.00864	56.8	56.8
	NaCl	.00292	83.7	84.7
	NaCl	.00091	111.4	113.0
630	NaCl	.0263	27.5	28.2
	NaCl	.00877	56.1	56.4
	NaCl	.00292	83.7	84.7
	NaCl	.00097	111.2	112.9
550	Na_2SO_4	.0386	18.8	18.4
	Na_2SO_4	.00915	55.5	55.4
	Na_2SO_4	.00458	72.9	73.2
630	Na_2SO_4	.0386	18.5	18.4
	Na_2SO_4	.00915	55.2	55.4
	Na_2SO_4	.00458	72.9	73.2
550	Na citrate	.0395	21.2	17.8
	Na citrate	.00875	58.3	56.5
	Na citrate	.00452	75.4	73.5
630	Na citrate	.0395	21.0	17.8
	Na citrate	.00875	57.6	56.5
	Na citrate	.00452	74.6	73.5
610	$Na_4Fe(CN)_6$	.0410	16.8	16.8
	$Na_4Fe(CN)_6$	.00916	55.1	55.9
	$Na_4Fe(CN)_6$	.00475	71.2	72.1

Excellent agreement is found except in the case of the more concentrated solutions of sodium citrate where the experimental values are consistently high. It does not appear that this can be due to the high valence of the anion, since ferrocyanide gives almost perfect values. However, it has been shown[7] that sodium citrate solutions give low osmotic pressures at concentrations above 25 millimoles per liter. It seems logical, therefore, to assume that the activity of part of the sodium is reduced by some kind of complex formation.

(7) Adie, *J. Chem. Soc.*, **59**, 344 (1891).

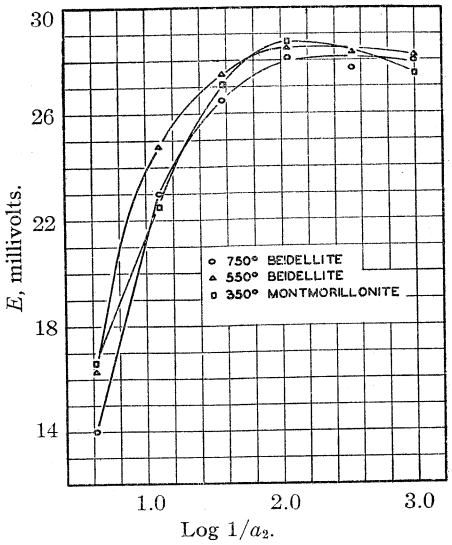


Fig. 2.—Experimental curves obtained with different membranes using sodium chloride solutions with an activity ratio $a_1/a_2 = 3$.

The Behavior of Cationic Mixtures.—In Part I[3] it was pointed out that the potentials established when a potassium salt is present on one side of the membrane and a sodium salt on the other may depend on the relative mobilities of the cations as well as on their activities. The exact relationship may be derived in two ways.

(1) In the range over which the membrane gives Nernst potentials for single salts, we can start out from the general Henderson equation for a liquid junction potential and incorporate the simplifying assumption that the mobility of the anions is negligible compared with that of the cations. For instance, with potassium chloride on one side of the membrane and a mixture of potassium and sodium chlorides on the other, the potential is given by the equation

$$E = \frac{RT}{F} \ln \frac{U_K a'_K}{U_K a''_K + U_{Na} a''_{Na}} \qquad (1)$$

If sodium chloride alone is present on one side of the membrane this reduces to the form

$$E = \frac{RT}{F} \ln \frac{U_K a'_K}{U_{Na} a''_{Na}} \qquad (2)$$

Here the mobilities, represented by U_K and U_{Na} are those of the respective cations within the membrane. These values are not necessarily those of the cations in pure water.

Using the Henderson equation as the starting point, more general cases can be dealt with. If the cation x accompanying potassium on the one side of the membrane has a valence n, then the equation becomes

$$E = \frac{RT}{F}\frac{U_K a''_K + U_x a''_x - U_K a'_K}{U_K a''_K + nU_x a''_x - U_K a'_K} \ln \frac{U_K a'_K}{U_K a''_K + nU_x a''_x} \quad (3)$$

and when there is only the polyvalent cation x on one side and potassium on the other, this reduces to

$$E = \frac{RT}{F}\frac{U_x a''_x - U_K a'_K}{nU_x a''_x - U_K a'_K} \ln \frac{U_K a'_K}{nU_x a''_x} \quad (4)$$

(2) An expression covering also the higher concentrations for which Nernst potential is not attained has been derived for binary salts by Meyer and Sievers.[8] In this equation the effective charge A of the membrane and the solubilities of the two salts in the membrane are additional variables. For those cases in which A is large compared with the cationic activities and in absence of solubility changes this equation reduces to the same form as (2) above.

These equations lend themselves readily to experimental verification and by their use the ratios of the mobilities of the cations within the membrane may be determined. For monovalent ions the most accurate procedure is to determine the mobility ratio under the conditions of Eq. 2 with one electrolyte on each side of the membrane. The validity of Eq. 1 may then be tested with mixtures using the determined value of the mobility ratio. It will be seen from Eq. 4 that for polyvalent cations the conditions are less favorable. However, if the activity of the monovalent ion is small compared with that of the polyvalent ion a satisfactory value of the mobility ratio should be obtained.

In Table IV, several determinations with monovalent cations are assembled. From the potentials the mobility ratios were calculated and these display reasonable constancy. Some variation of the mobility ratio with concentration might be expected. However, in Table IV the range covered runs only from about $N/30$ downward and the figures show no definite trend. In pure aqueous solutions also the variation in transport number is small for concentrations below $N/20$.

Values of the mobility ratios obtained are used in Table V in order to compare the experimental with the theoretical potentials.

The use of the mean mobility ratios U_{Na}/U_K and U_{Na}/U_H lead to excellent agreement between the observed and calculated potentials when measurements are made with a pure salt solution on one side of the membrane and a mixture on the other.

TABLE IV

DETERMINATION OF CATIONIC MOBILITY RATIOS WITHIN THE MEMBRANES

Membrane temp., °C.	Cations and activities Inside a_1		Outside a_2		Potential, mv.	Mobility ratio U_2/U_1
			Beidellite			
600	K^+	0.0270	Na^+	0.0263	26.0	0.373
550	K^+	.0270	Na^+	.0263	26.1	.371
630	K^+	.0270	Na^+	.0263	24.5	.396
600	K^+	.0270	Na^+	.00877	53.7	.372
600	K^+	.0270	Na^+	.00292	78.2	.430
600	K^+	.0090	Na^+	.00877	25.4	.395
600	K^+	.0090	Na^+	.00292	51.5	.409
			Mean value U_{Na}/U_K =			.392
610	Na^+	.00877	H^+	.000068	72.4	.130
610	Na^+	.00877	H^+	.000135	55.4	.134
610	Na^+	.00877	H^+	.000851	5.0	.119
			Mean value U_{Na}/U_H =			.128

(8) Meyer and Sievers, *Helv. Chim. Acta*, **19**, 649 (1936).

TABLE V

POTENTIALS OBTAINED WITH MIXTURES OF CHLORIDES OF MONOVALENT CATIONS, BEIDELLITE MEMBRANES

Membrane temp., °C.	Cations and activities Inside		Outside				Potential, mv. Observed	Calcd.
600	K^+	0.0270	K^+	0.00095	Na^+	0.00095	76.9	77.3
550	K^+	.0270	K^+	.00095	Na^+	.00095	77.0	77.3
630	K^+	.0270	K^+	.00095	Na^+	.00095	76.6	77.3
630	K^+	.0270	K^+	.00884	Na^+	.00443	23.4	24.0
630	K^+	.0270	K^+	.00442	Na^+	.00877	31.5	31.5
610	Na^+	.00877	Na^+	.00097	H^+	.000068	46.9	45.3
610	Na^+	.0877	Na^+	.00097	H^+	.000891	3.5	2.8

It is evident from the foregoing that the simple type of Nernst formula used in calculating the clay titration curves in Parts II and IV is inadequate. However, the difference in actual result between it and the correct expression involving the mobility ratio is negligible, except for those first additions of potassium or ammonium hydroxide which bring the clay to a pH below 4.5.

Acknowledgment.—The authors are indebted to the Research Council of the University of Missouri for a grant-in-aid which has made this work possible.

Summary

1. Clay membranes have been prepared which are sensitive only to monovalent cations (H-montmorillonite 490°); to monovalent and divalent cations (H-montmorillonite 350°); and to mono, di and trivalent cations (H-beidellite 600°).

2. For sodium estimations, beidellite membranes gave excellent reproducibility. The potentials obtained with solutions less concentrated than 0.03 N were within 1 millivolt of those calculated using the Nernst equation.

3. Sodium chloride, sulfate and ferrocyanide gave practically the theoretical potentials whereas low values were obtained with sodium citrate. This is ascribed to complex formation.

4. The behavior of mixtures of cations can be predicted and the mobility ratios of the cations within the clay membranes have been determined experimentally in certain cases. Using these values, the experimental and theoretical potentials for mixtures of cations are found to be in good agreement.

COLUMBIA, MISSOURI RECEIVED MAY 4, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE INSTITUTE OF TECHNOLOGY OF THE UNIVERSITY OF MINNESOTA]

Crystal-Chemical Studies of the Alums. IV. Coefficients of Linear Thermal Expansion[1]

BY HAROLD P. KLUG AND LEROY ALEXANDER

In the systematic study of the crystal chemistry of the alums now in progress in this Laboratory, as many as possible of the physical and chemical properties of their crystals are being investigated. The only thermal expansion data on the commoner alums seem to be the somewhat uncertain results of Spring,[2-4] who determined the change in density with temperature for several alums, and calculated the volume changes therefrom. Spring concluded that his earlier values[2,3] were vitiated by partial dehydration of the alums and repeated the measurements.[4] He was unwilling, however, to claim that his final results solely expressed the volume change brought about by thermal expansion because of the possibility of some dissociation of the hydrates with increasing temperature.

In view of the uncertainty of these results, and of the ease with which such measurements can be made by means of X-ray diffraction, it seemed desirable to determine the coefficients of expansion of a few alums by the X-ray technique. Since the characteristic powder diffraction pattern of the alums is particularly sensitive to the effects of dehydration,[1] the X-ray method presents an important advantage over the pyknometric and dilatometric methods. This communication presents the results of such measurements, for the approximate temperature range 20 to 50°, on the following alums: $KAl(SO_4)_2 \cdot 12H_2O$, $NH_4Al(SO_4)_2 \cdot 12H_2O$, $TlAl(SO_4)_2 \cdot 12H_2O$ and $NH_4Cr(SO_4)_2 \cdot 12H_2O$.

Experimental

The potassium and ammonium alums used were from lots prepared for a previous study.[5] The thallium alum was a sample prepared by Dr. N. O. Smith,[6] and presented by Professor J. E. Ricci for an earlier study.[1] The ammonium chrome alum was the reagent grade salt used without further purification.

The experimental technique followed was that of Straumanis and co-workers,[7] which involves precision determination of the lattice constants at two different temperatures by thermostating the camera. Details of the thermostat and X-ray technique have been described previously.[5,7] FeK radiation was used throughout the study except in the case of the chrome alum where CrK radiation was used.

Results

The mean coefficient of linear thermal expansion α, the average increase per unit length per degree centigrade, can be obtained from the expression

$$\alpha = \frac{a_{t_2} - a_{t_1}}{a_{t_1}(t_2 - t_1)}$$

where a_t is the lattice constant at the corresponding temperature t.

The results of the study are tabulated in Table I. For each alum the temperatures and corresponding lattice constants of the separate determinations are listed together with the mean value of $\alpha \cdot 10^6$ obtained by using all possible combinations of lattice constants separated by at least a 25° interval. The error is expressed as the probable error of the mean.

Spring gives no data which can be compared directly with the values of α in Table I. When his best data[4] are recalculated, they lead to the follow-

(1) Paper III, THIS JOURNAL, **62**, 2993 (1940).
(2) Spring, *Bull. classe sci. acad. roy. belg.*, [3] **3**, 331 (1882).
(3) Spring, *Ber.*, **15**, 1254 (1882).
(4) Spring, *ibid.*, **17**, 408 (1884).
(5) Klug and Alexander, THIS JOURNAL, **62**, 1492 (1940).
(6) Hill, Smith and Ricci, *ibid.*, **62**, 858 (1940).
(7) Straumanis, Ievins and Karlsons, *Z. anorg. allgem. Chem.*, **238**, 175 (1938).

TABLE I

LATTICE CONSTANTS AND COEFFICIENTS OF EXPANSION OF THE ALUMS BETWEEN 20–50°

$KAl(SO_4)_2 \cdot 12H_2O$ Temp., °C.	a, Å.	$NH_4Al(SO_4)_2 \cdot 12H_2O$ Temp., °C.	a, Å.	$TlAl(SO_4)_2 \cdot 12H_2O$ Temp., °C.	a, Å.	$NH_4Cr(SO_4)_2 \cdot 12H_2O$ Temp., °C.	a, Å.
19.3	12.1333	19.2	12.2141	18.8	12.2047	22.1	12.2501
19.9	12.1335	19.4	12.2142	19.0	12.2045	25.0	12.2510
25.0	12.1336	19.5	12.2148	19.1	12.2040	50.5	12.2539
50.5	12.1372	50.4	12.2180	25.0	12.2050	51.1	12.2543
51.1	12.1378	50.8	12.2181	50.6	12.2095		
52.2	12.1373	51.4	12.2179	51.1	12.2093		
$\alpha \cdot 10^6 = 11.0 \pm 0.3$		$\alpha \cdot 10^6 = 9.5 \pm 0.2$		$\alpha \cdot 10^6 = 13.1 \pm 0.3$		$\alpha \cdot 10^6 = 10.6 \pm 0.4$	

ing values of $\alpha \cdot 10^6$ for the first three alums listed above: 3.3, 6.8 and 18.3, respectively. These values are of the right order of magnitude but, otherwise, are in poor agreement with the X-ray values. No data are available for comparison with the result for ammonium chrome alum.

Potassium chrome alum was also studied at this same time but the inability, after numerous attempts, to get photographs in the vicinity of 50° without dehydration led to its abandonment.

The authors wish to express their thanks and appreciation to Dr. N. O. Smith and Professor J. E. Ricci for the sample of thallium alum. They also wish to acknowledge with gratitude a grant from the Graduate School of the University of Minnesota under which this study was carried out.

Summary

The linear thermal expansion coefficients α for several alums have been measured for the approximate range, 20–50°, by means of X-ray diffraction. The values of $\alpha \cdot 10^6$ observed are as follows: potassium alum, 11.0 ± 0.3; ammonium alum, 9.5 ± 0.2; thallium alum, 13.1 ± 0.3; and ammonium chrome alum, 10.6 ± 0.4.

MINNEAPOLIS, MINNESOTA RECEIVED APRIL 27, 1942

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF CALIFORNIA]

The Vapor Phase Photo Decomposition of Methyl Formate

BY DAVID H. VOLMAN[1]

Recently, experiments on the photolysis of methyl formate have been reported by Royal and Rollefson.[2] Experiments on this same problem had been in progress in this Laboratory. The results for the photolysis products in this investigation are in substantial agreement with those given by Royal and Rollefson. In addition, data on the determination of methanol in the reaction products, and an approximate evaluation of the quantum yield for the reaction were obtained.

In a subsequent paper on the photolysis of methyl acetate, Roth and Rollefson[3] have given data on the determination of methanol as a photolysis product by oxidizing the alcohol to formaldehyde and treating with Schiff reagent. However, they were unable to analyze for the small amounts of methanol usually obtained in the decomposition runs, and were forced to obtain comparatively large amounts of decomposition products by carrying out the reaction in a three-liter bulb. The method given below using a Grignard reagent suffices for the small amounts usually obtained and enables analyses to be made for all of the decomposition experiments conducted.

Experimental Method

The apparatus employed was essentially the same as already reported.[4] The source of radiation was an Hanovia Alpine mercury lamp. Quantum yields were determined approximately by using monochloroacetic acid as an actinometer in a manner previously described[4,5] using the reliable value for the hydrolysis quantum yield given by Smith, Leighton and Leighton.[6]

Methyl formate was synthesized by allowing formic acid and methanol to react in the presence

(1) On leave of absence. Present address: The Technological Institute, Northwestern University, Evanston, Illinois.

(2) Royal and Rollefson, THIS JOURNAL, **63**, 1521 (1941).

(3) Roth and Rollefson, *ibid.*, **64**, 490 (1942).

(4) Volman, *ibid.*, **63**, 2000 (1941).

(5) Weizmann, Bergmann and Hirshberg, *ibid.*, **58**, 1675 (1936).

(6) Smith, Leighton and Leighton, *ibid.*, **61**, 2299 (1939).

of hydrochloric acid. The methyl formate was removed by distillation and washed with concentrated potassium hydroxide. After a second distillation, the ester was dried over phosphorus pentoxide and fractionated. The fraction used distilled at 31.8–32.0°.

After irradiation for definite periods, the gases non-condensable in a liquid-air trap were collected by means of a Toepler pump and analyzed by the use of a Blacet–Leighton apparatus for micro gas analysis.

The following method was used in analyzing for methanol. A methyl Grignard reagent in ethyl ether solution was placed in a trap connected to the photolysis apparatus by means of a stopcock. Prior to an experiment the Grignard reagent was thoroughly outgassed and frozen by use of liquid air. When it was desired to analyze for methanol, the condensable reaction products plus undecomposed ester were distilled into the trap containing the Grignard reagent. Then the mixture was allowed to warm to room temperature and successively frozen and warmed several times. Finally, the non-condensable gas, methane, was collected and determined, both by volumetric measurement and by combustion.

An attempt was made to produce hydrogen from methanol by passing the photo-decomposition products over a sodium mirror. However, the results were not reproducible and were consistently lower than expected or found by the Grignard reagent method.

Complete analytical results and values of decomposition quantum yield, Φ_d, are given in the accompanying table. The pressure of methyl formate was 75.0 mm. in each experiment. Irradiation was for twenty minutes at 25°, and approximately 600 cu. mm. of gas was collected each time. Φ_d is based on the sum of carbon dioxide and carbon monoxide.

TABLE I

METHYL FORMATE PHOTOLYSIS PRODUCTS AND QUANTUM YIELDS

CO, %	H_2, %	CH_4, %	CO_2, %	C_2H_6, %	CH_3OH, %	Φ_d
41.3	10.3	5.1	15.0	1.3	27.2	0.7
40.5	9.3	5.6	14.9	0.7	29.1	.7
39.1	9.0	6.0	14.9	1.6	29.5	.8
38.2	9.3	7.3	14.4	0.9	29.9	.8

Discussion

The demonstration that methanol is produced in the photolysis of methyl formate is evidence that

$$HCOOCH_3 \longrightarrow CO + CH_3OH$$

one of the net reactions postulated by Royal and Rollefson,[2] does occur.

The reaction products were found to be the same as previously reported.[2] The small variation in the mole percentages of the non-condensable products from the values given by Royal and Rollefson may be attributed to the difference in experimental details, especially pressure of methyl formate and time of illumination.

The variety of products indicates that the overall photolysis is complex. However, since Φ_d is less than unity, no appreciable chains are involved.

Summary

1. The presence of methanol in the photolysis products of methyl formate has been shown.

2. The decomposition quantum yield for the photolysis was found to be approximately 0.75 for an ester pressure of 75.0 mm. at 25°.

3. The reaction products were found to have the following average values: H_2, 9.5%; CO, 40.0%; CH_4, 6.0%; CO_2, 14.8%; C_2H_6, 1.1%; CH_3OH, 29.0%.

DAVIS, CALIFORNIA RECEIVED MAY 18, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

The Compressibility of Liquid *n*-Octane

BY W. A. FELSING AND GEORGE M. WATSON[1]

Introduction.—This investigation forms a part of the general program of this Laboratory of determining the pressure–volume–temperature relations for pure hydrocarbons and of their known mixtures, both in the liquid and gaseous state. Reports have been made on some of the isomeric hexanes.[2] In addition to the normal octane here reported, work is in progress on 2,2,4-trimethylpentane and on tetramethylbutane. The results on these octanes and on the remaining hexanes will be reported soon.

This investigation deals with the compressibility of pure *n*-octane at eight temperatures: at 25° intervals beginning with 100° and including 275°. No data over this range were found in the literature; vapor pressure and density data up to critical temperature (t_c = 296.2°) and pressure (p_c = 24.61 atm.) were recorded by Young.[3]

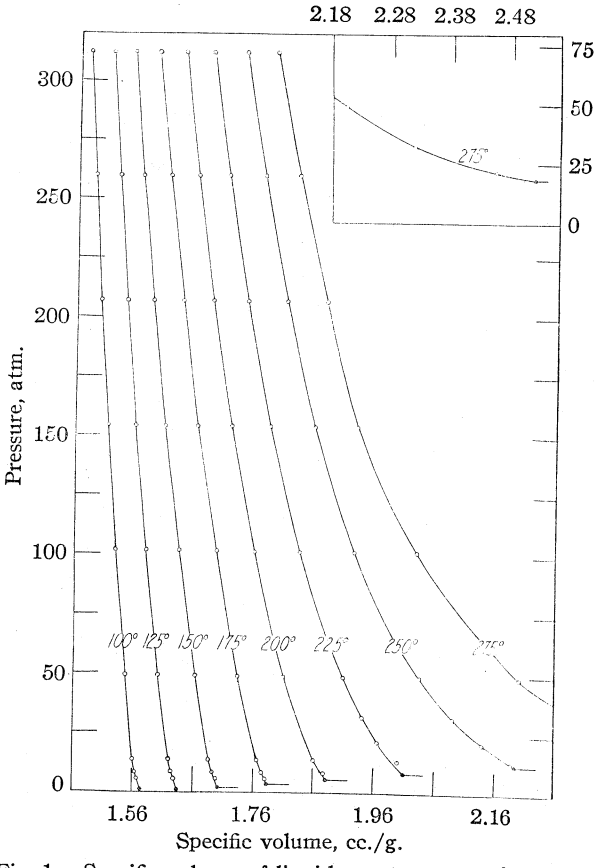


Fig. 1.—Specific volume of liquid *n*-octane as a function of the pressure (solid points from the data of Young[3]).

Method and Apparatus.—The dead-weight piston gage method and apparatus has been described elsewhere.[2,4] Minor improvements in accessory apparatus have been

TABLE I

COMPRESSIBILITY OF LIQUID *n*-OCTANE

Molecular weight, 114.224; pressures are in normal atmospheres and temperatures are on the International Temperature Scale.[a]

Press., atm.	Cc./g.	Moles/liter	Cc./g.	Moles/liter	Cc./g.	Moles/liter
	100.00°		125.00°		150.00°	
5.0	1.569	5.580	1.629	5.374	1.697	5.159
10.0	1.564	5.598	1.624	5.391	1.690	5.180
15.0	1.561	5.609	1.620	5.404	1.685	5.196
20.0	1.559	5.615	1.617	5.414	1.681	5.208
25.0	1.557	5.623	1.615	5.421	1.678	5.217
30.0	1.555	5.630	1.612	5.431	1.675	5.226
50.0	1.547	5.659	1.602	5.465	1.662	5.268
100.0	1.530	5.722	1.580	5.541	1.634	5.358
150.0	1.514	5.782	1.560	5.612	1.610	5.438
200.0	1.501	5.833	1.544	5.670	1.589	5.510
250.0	1.489	5.880	1.529	1.726	1.571	5.573
300.0	1.477	5.923	1.516	5.775	1.554	5.634
	175.00°		200.00°		225.00°	
5.0	1.780	4.918				
10.0	1.771	4.943	1.870	4.681	2.004	4.369
15.0	1.764	4.963	1.859	4.709	1.987	4.406
20.0	1.759	4.977	1.849	4.735	1.971	4.441
25.0	1.754	4.991	1.841	4.755	1.957	4.473
30.0	1.749	5.005	1.833	4.776	1.946	4.499
50.0	1.732	5.055	1.808	4.842	1.906	4.593
100.0	1.697	5.159	1.760	4.974	1.836	4.768
150.0	1.664	5.261	1.721	5.087	1.786	4.902
200.0	1.638	5.345	1.689	5.183	1.747	5.011
250.0	1.616	5.417	1.663	5.264	1.714	5.108
300.0	1.596	5.485	1.640	5.338	1.686	5.192
	250.00°		275.00°			
5.0						
10.0						
15.0	2.180	4.016				
20.0	2.149	4.074	2.484	3.524		
25.0	2.122	4.125	2.388	3.666		
30.0	2.099	4.171	2.336	3.748		
50.0	2.032	4.308	2.199	3.981		
100.0	1.928	4.541	2.033	4.306		
150.0	1.863	4.699	1.944	4.503		
200.0	1.814	4.826	1.883	4.649		
250.0	1.775	4.932	1.834	4.773		
300.0	1.743	5.023	1.795	4.877		

[a] Burgess, *Bur. Standards J. Research*, **1**, 635 (1928).

(1) Research Assistant, Project No. 1, University of Texas Research Institute.

(2) Kelso with Felsing, THIS JOURNAL, **62**, 3132 (1940); *J. Ind. Eng. Chem.*, **34**, 161 (1942).

(3) Young, *J. Chem. Soc.*, **77**, 1145 (1900).

(4) Beattie, *Proc. Am. Acad. Arts Sci.*, **69**, 389 (1934).

made; the most important change was the development of a more convenient contact indicator.

Material Used.—The *n*-octane sample used in this work was prepared under the direction of Professor C. E. Boord of the Department of Chemistry of the Ohio State University as part of the American Petroleum Institute Hydrocarbon Research Project in the Industrial Research Foundation of the University. The material was stated to have the following constants: d (g./cc.) at 20° = 0.7019 (0.7019); f. p. = −56.90°; b. p. (normal) = 125.6°; and $n^{20}D$ 1.3976 (1.3975_8); the values in parentheses were obtained by the authors of this paper.

The Data.—The experimental results are presented graphically in the accompanying figure, specific volumes (cc./g.) as functions of the pressure at different temperatures. From such large-scale graphs, the specific volumes at each temperature were read off at rounded pressures; these values, together with the calculated molar densities, are presented in Table I. Specific volumes of the liquid in contact with the saturated vapor at the different temperatures and corresponding vapor pressures are presented in Table II.

TABLE II

SPECIFIC VOLUMES OF LIQUID *n*-OCTANE IN CONTACT WITH ITS SATURATED VAPOR

Temp., °C.	Vapor press., atm.	Cc./g.
100.00	1.00	1.574[a]
125.00	1.00	1.634[a]
150.00	1.88	1.702[b]
175.00	3.30	1.783[b]
200.00	5.40	1.882[b]
225.00	8.44	2.009[b]
250.00	12.63	2.196[b]
275.00	18.34	2.518[b]

[a] Calculated from the equation listed in "I. C. T.," Vol. III, p. 29. [b] "I. C. T.," Vol. III, p. 245, or ref. 3.

Discussion of Results.—The density data are believed to be accurate to 0.10% at the lower pressures and temperatures and to 0.1 to 0.2% at the higher pressures and temperatures. The uncertainty in the measurement of pressures is less than 0.03%, in the determination of mass less than 0.01%, and the measurement of volume from 0.05 to 0.1%. Temperature measurements are correct at least to 0.01°. At 250° and 275°, there was evidence of decomposition; after keeping the octane at these temperatures for twenty-four hours, the densities at the same pressures showed a slight decrease. The density–pressure values listed in the table for these temperatures were determined as rapidly as possible and with the precision indicated. Hence the density data for these temperatures are believed to be accurate to 0.2%. An inspection of the figure reveals that an extrapolation of the data at the different temperatures yields results in splendid agreement with the boiling-point densities recorded by Young.[3]

Acknowledgments.—The authors wish to express their appreciation to Dr. George Calingaert of the Ethyl Gasoline Corporation and to Professor Cecil E. Boord of The Ohio State University for the donation of the sample of the pure octane. They also wish to acknowledge with thanks the grants received from the University of Texas Research Institute for equipment and research assistance.

Summary

1. The compressibility of liquid *n*-octane has been determined at 25° intervals from 100 to 275° at pressures ranging from the vapor pressures to approximately 300 atmospheres.

2. The data are presented tabularly and graphically, the specific volume being related to the pressure at different temperatures.

AUSTIN, TEXAS RECEIVED MAY 8, 1942

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

The Dissociation of Hexaarylethanes. XII.[1] The Effect of Naphthyl and Biphenyl Groups

BY C. S. MARVEL, JOHN W. SHACKLETON, CHESTER M. HIMEL AND JOHN WHITSON

Work by Bachmann and Kloetzel[2] has indicated that the very high dissociations reported in the older literature for triarylmethyls containing *p*-biphenyl, α-naphthyl and β-naphthyl groups are in error. This communication confirms their results and extends them to a larger number of derivatives. The dissociations were measured by the magnetic susceptibility method previously described.[3]

To be comparable degrees of dissociation should be measured at the same concentration. This is not always possible because of solubility difficulties. It is possible, however, to calculate all the dissociations at 0.1 molar concentration by applying the mass law. That this calculation is justified for toluene solution has been shown recently by Preckel and Selwood.[4] We have extended this to benzene solutions and determined the degree of dissociation of di-α-naphthyltetraphenylethane at 25° at different concentrations. The results of these experiments are given in Table I.

TABLE I

DISSOCIATION OF DI-α-NAPHTHYLTETRAPHENYLETHANE AT 25° IN BENZENE SOLUTION

% Ethane	Molarity	−χ Sol. × 10^6	α, %	α at 0.1 *M* calcd. from mass law, %
7.0	0.107	0.6315	25 ± 2	26 ± 2
6.63	.1	.6296	27 ± 2	27 ± 2
3.34	.05	.6550	36 ± 2	27 ± 2
1.67	.025	.6755	45 ± 4	26 ± 3
0.839	.0125	.6852	66 ± 7	29 ± 5

The aryl substituted ethanes which have been studied are reported in Table II.

TABLE II

Ethane	*M*	Concn. ethane, %	−χ Sol. × 10^6	α Measured, %	α calcd. at 0.1 *M*, %
Tetra-*p*-biphenyldiphenyl-	0.1	8.9	0.6539	18 ± 2	18 ± 2
Hexa-*p*-biphenyl-	.0125	1.34	.6874	56 ± 10	26 ± 5
Di-β-naphthyltetraphenyl-	.1	6.16	.6887	6 ± 2	6 ± 2
Tetra-β-naphthyldiphenyl-	.1	7.85	.6668	13 ± 2	13 ± 2
Hexa-β-naphthyl-	.0062	0.56	.6928	80 ± 15	21 ± 10
	.0125	1.113	.6869	53 ± 10	24 ± 5
Di-α-naphthyldi-*p*-biphenyldiphenyl-	.1	8.3	.5512	54 ± 2	54 ± 2

Discussion of Results

All except one of the ethanes have been studied previously, and our methods of preparation and the properties of the intermediates in general checked those reported. The new ethane, diphenyltetra-β-naphthylethane, was prepared by standard procedures and characterized as the peroxide. Bachmann and Kloetzel measured the molecular weight in freezing benzene and calculated the dissociation of di-*p*-biphenyltetraphenylethane as 16% at 0.032 *M*, of hexa-*p*-biphenylethane as 76% at 0.0086 *M*, of di-α-naphthyltetraphenylethane as 28–31% at 0.04 *M*, and of di-β-naphthyltetraphenylethane as 6–9% at 0.04 *M*. If these values are calculated to 0.1 *M* by means of the mass law they become 9, 36, 20 and 5%, respectively. These values are in fair agreement with the values determined by the magnetic susceptibility method.

It should be noted that Müller, Müller-Rodloff and Bunge,[5] have shown that tri-*p*-biphenylmethyl is 100% free radical in the solid state. Apparently the free radical is less soluble than the ethane and in the solid state only the one phase exists, whereas in solution the radical and ethane are in equilibrium.

The dissociations of the series of β-naphthyl derivatives show that there is a steady increase in dissociation as the number of β-naphthyl groups increases, but the degree of dissociation of the hexa-substituted compound is less than that reported by Tschitschibabin and Korjagin.[6] The marked difference in the dissociation of the di-β-naphthyl derivatives (6 ± 2%) and of the di-α-naphthyl derivative (26 ± 2%) indicates again

(1) For the eleventh communication in this series see THIS JOURNAL, **63**, 1892 (1941).

(2) Bachmann and Kloetzel, *J. Org. Chem.*, **2**, 362 (1937).

(3) Müller, *et al.*, *Ann.*, **520**, 235 (1935); **521**, 89 (1935); Roy and Marvel, THIS JOURNAL, **59**, 2622 (1937).

(4) Preckel and Selwood, *ibid.*, **63**, 3397 (1941).

(5) Müller, Müller-Rodloff and Bunge, *Ann.*, **520**, 251 (1935).

(6) Tschitschibabin and Korjagin, *J. prakt. Chem.*, **88**, 505 (1913).

the importance of the steric factor. This was also pointed out by Preckel and Selwood.[4]

Another point which should be emphasized is that there is a difference in the di- and tetra-substituted β-naphthyl derivatives (6 and 13%), whereas in the alkyl substituted compounds in this general series these differences between di- and tetra-substituted compounds were not found.[1] However, the hexa-substituted derivatives in the alkyl and aryl series all seem to fall in about the same range (25–35%). From the data of Gomberg and Schoepfle[7] it seems likely that our 0.1 *M* solutions of di-α-naphthyltetraphenylethane were supersaturated.

All of the aryl-substituted ethanes except tetra-*p*-biphenyldiphenylethane were relatively stable as indicated by the constant value for their magnetic susceptibilities over twenty-four hour periods. Tetra-*p*-biphenyldiphenylethane solutions deposited heavy white crystalline precipitates in twenty-four hours. Hexa-β-naphthylethane showed a decrease in color and a change in magnetic susceptibility on exposure to diffused daylight over a period of one week.

(7) Gomberg and Schoepfle, THIS JOURNAL, **39**, 1652 (1917).

The following new compounds were characterized:

Phenyldi-β-naphthylmethylperoxide, m. p. 168–169°.

Anal. Calcd. for $C_{54}H_{38}O_2$: C, 90.25; H, 5.30. Found: C, 90.12; H, 5.84.

Phenyldi-*p*-biphenylmethylperoxide, m. p. 151–152°.

Anal. Calcd. for $C_{12}H_{46}O_2$: C, 90.51; H, 5.59. Found: C, 90.54; H, 5.94.

Phenyldi-β-naphthylmethylchloride, m. p. 159–160°.

Anal. Calcd. for $C_{27}H_{17}Cl$: Cl, 9.42. Found: Cl, 8.92.

Summary

The degrees of dissociation of several hexaphenylethanes combining α-naphthyl, β-naphthyl and *p*-biphenyl radicals have been examined by the magnetic susceptibility method. The dissociations observed are lower than reported in the older literature. The difference in the effect of an α- and a β-naphthyl group on the degree of dissociation is very marked.

URBANA, ILLINOIS RECEIVED MAY 18, 1942

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

The Preparation of Orthoesters

BY S. M. MCELVAIN AND J. WALTER NELSON

The work in this Laboratory to date indicates that the only general method that is available for the preparation of ketene acetals of the type $RCH{=}C(OEt)_2$ involves the elimination of the elements of ethyl hypohalite from an α-halogenated orthoester by the action of metallic sodium.[1] Consequently, the preparation and study of these higher ketene acetals are dependent upon the availability of the corresponding orthoesters as starting materials. The present paper is a summary of a large number of experiments which had as their objective practical and reliable procedures for the preparation of the esters of ortho acetic acid, certain of its derivatives and higher homologs.

Two methods of preparation of orthoesters that would seem to be of general applicability have been reported in the literature. One of these is the Tschitschibabin procedure[2] which involves the reaction of a Grignard reagent with ethyl orthocarbonate

$$RMgX + C(OEt)_4 \longrightarrow RC(OEt)_3 + EtOMgBr$$

This procedure is analogous to the widely used Tschitschibabin method for the preparation of acetals by the reaction of a Grignard reagent with ethyl orthoformate, $HC(OEt)_3$. While the latter reaction is a very useful preparational method, all of the experience in this Laboratory points to the conclusion that the reaction between a Grignard reagent and orthocarbonic ester is not a satisfactory method of preparation of orthoesters. Instead of the desired orthoester the reaction products are practically wholly a mixture of the ketal $R_2C(OEt)_2$ and the ether R_3COEt and all attempts to alter this result have been consistently unsuccessful.[3]

(1) Walters and McElvain, THIS JOURNAL, **62**, 1482 (1940).

(2) Tschitschibabin, *Ber.*, **38**, 563 (1905).

(3) McBane, M.S. Thesis, University of Wisconsin, 1941.

The other general method that appears in the literature was originated by Pinner[4] and involves the alcoholysis of an iminoester hydrochloride which is obtained from a nitrile. These reactions are

$$RCN + EtOH + HCl \longrightarrow RC(OEt)=NH\cdot HCl \xrightarrow{EtOH} RC(OEt)_3 + NH_4Cl$$

Reiter and Hess[5] used Pinner's method and reported 40–64% yields of ethyl orthoacetate from the alcoholysis of the iminoester hydrochloride over a period of eight to fourteen days. Sah[6] used this procedure for the preparation of a number of alkyl esters of orthoacetic acid. He allowed the alcoholysis of the iminoester salt to proceed at room temperature for a period of two weeks. Brooker and White[7] have reported the preparation, by the same procedure, of the methyl esters of orthopropionic, -*n*-butyric, -*n*-valeric, -*n*-caproic and -isocaproic acids. With the exception of the propionate (69% yield) the yields of the orthoesters from the iminoester salts were quite low (9–40%) and the time required for the alcoholysis varied from five to thirty-five days.

In the work which is now reported it has been found possible to shorten considerably the time required for the alcoholysis of the iminoester hydrochlorides and to increase materially the yields of the esters of orthoacetic acid and certain of its higher homologs. This has been accomplished by carrying out the alcoholysis of these salts in a refluxing ether solution. Under these conditions the alcoholysis is complete in six to twenty-eight hours and the reaction temperature is kept below the point (60–80°) at which the competing decomposition of iminoester hydrochloride into the amide and ethyl chloride, $RC(OEt)=NH\cdot HCl \rightarrow RCONH_2 + EtCl$, occurs. In marked contrast to these results is the strange fact that the iminoester hydrochloride derived from the negatively substituted acetonitrile, chloroacetonitrile, gives a better yield of the orthoester if the alcoholysis is carried out simply with the alcoholic solution of the hydrochloride stirred at a temperature of approximately 40°. In this case the use of ether is detrimental to the yield of the orthoester.[8]

Table I is a summary of (a) the reaction time required for the alcoholysis of the iminoester hydrochlorides when a ratio of 15 moles of alcohol to 1 mole of the salt is used (this ratio of alcohol to salt is necessary to completely dissolve the salt), (b) the optimum ratio *by volume* of alcohol to ether, (c) the reaction temperature (which is the refluxing temperature when ether is used) and (d) the yields of ammonium chloride and the orthoesters. Each entry in this table covers at least eight runs. When the amount of ether in the alcoholysis mixture was less than the optimum ratio shown in Table I, the yields of the first six unsubstituted orthoesters dropped markedly. When no ether was used the yields were generally 30–50% of those shown in Table I. The yields of ethyl orthochloroacetate varied from 40% with an alcohol–ether ratio of 1:2 through 50% for a 1:1 ratio and up to the yields indicated in Table I when no ether was used.

Table I

Alcoholysis of Iminoester Hydrochlorides, $RC(OEt)=NH\cdot HCl$

R is	Reaction time, hr.	Alcohol ether ratio	Reaction temp., °C.	Yield, % NH_4Cl	Yield, % $RC(OEt)$
CH_3	6	1:1	46	100	75–78
C_2H_5	9	1:2	42	95	75–78
n-C_3H_7	18	1:3	41	96	60–63
i-C_3H_7	24	1:5	39	54	27–30
n-C_4H_9	12	1:3	42	88	59–61
i-C_4H_9[a]	28	1:5	39	56	21–23
$ClCH_2$	6	1:0	40	89	70–73

[a] This ester was prepared by Robert L. Clarke. In addition to the orthoester a 14% yield of isovaleramide and a 21% yield of ethyl isovalerate were isolated.

It is seen from the data in Table I that under these optimum reaction conditions the alcoholysis of those iminoester hydrochlorides in which R is a primary and normal alkyl group is quite complete. The yield of ammonium chloride is obviously the most accurate measure of this reaction since it is obtained by simply filtering off the salt from the alcoholysis reaction mixture. The nitrogen that is not in the form of ammonium chloride appears as the amide, $RCONH_2$, and in those cases (R is a branched chain) in which the yield of the ammonium salt is low, the amide is a troublesome factor in the purification of the orthoester. While the yield of the orthoester theoretically should be the same as that of the ammonium chloride, it is generally considerably lower due, quite probably, to some hydrolysis to the normal ester, RCOOEt, during the necessary washing of the ethereal reaction mixture to remove

(4) Pinner, *Ber.*, **16**, 356, 1644 (1883).
(5) Reiter and Hess, *ibid.*, **40**, 3020 (1907).
(6) Sah, This Journal, **50**, 516 (1928).
(7) Brooker and White, *ibid.*, **57**, 2485 (1935).
(8) Messrs. H. I. Anthes and P. M. Walters in this Laboratory have had similar experiences in the preparation of two other negatively substituted orthoacetates, ethyl orthophenylacetate and ethyl orthoethoxyacetate.

any unchanged salt and amide as well as to the incomplete separation of the orthoester by fractionation.

Experimental

Iminoester Hydrochlorides.—The following general procedure was followed for the preparation of these salts. To an ice-cooled solution of 1 mole of the appropriate nitrile (distilled from phosphorus pentoxide) in 1.1 moles of absolute alcohol, dry hydrogen chloride was added until 1.1 moles had been absorbed. The resulting solution then was allowed to stand at 0° in the refrigerator for the time indicated in the second column of Table II, after which time absolute ether was added in the quantity shown in the third column of Table II. In the cases of acetonitrile and chloroacetonitrile the precipitation of the hydrochloride was so rapid that it was found advisable to mix the ether with the alcohol solution of the nitrile *prior* to the addition of the hydrogen chloride in order to prevent the solidification of the reaction mixture before the addition of the hydrogen chloride was completed; upon cooling to −30° the first crop of crystals of these hydrochlorides could be filtered off immediately. In the cases of the other iminoester hydrochlorides the resulting ethereal solution[9] was allowed to stand in the refrigerator overnight after which it was cooled to −30° in dry-ice and the precipitated salt rapidly filtered by suction. The salt was dried in a vacuum desiccator over dishes of solid potassium hydroxide and phosphorus pentoxide after which it was triturated under sufficient cold (−40°) anhydrous ether to cover it and again filtered and dried in the desiccator. On standing for a few more days in the refrigerator the mother liquor generally yielded additional crops of crystals. After the ether washing the salt does not give an acid reaction to moistened congo red paper and is in the proper condition for alcoholysis. If placed in tightly stoppered bottles or in a vacuum desiccator it may be kept for several weeks without deterioration.

TABLE II

IMINOESTER HYDROCHLORIDES, RC(OEt)=NH·HCl

R is	Reaction time at 0°	Alcohol–nitrile ether ratio[a]	Yield, %, hydrochloride
CH_3	2 hr.	1:0.5[b]	85–95
C_2H_5	6 hr.	1:4	85–95
n-C_3H_7	4 days	1:4	65–70
i-C_3H_7	4 days	1:4	70–90
n-C_4H_9	5 days	1:4	70–80
i-C_4H_9	6 days	1:6	35–40
$ClCH_2$	..	1:8[b]	80–90

[a] This is the ratio *by volume* of the alcohol–nitrile mixture to ether. [b] In these runs the ether was added to the alcohol solution of the nitrile before the addition of the hydrogen chloride.

The conditions for the preparation and the yields of the various iminoester hydrochlorides are shown in Table II.

Preparation of Orthoesters.—A mixture of 0.2 mole of the iminoester hydrochloride and 3 moles of absolute alcohol in a flask of suitable size fitted with a reflux condenser, an efficient stirrer and a thermometer dipping into the reaction mixture was carefully protected against moisture and stirred until the salt went into solution. Then the quantity of anhydrous ether indicated in Table I was added through the neck holding the thermometer. The ethereal solution was refluxed (in the cases when ether was not used the alcohol solution was kept at 40°) by an electrically heated oil-bath for the time indicated in Table I. After this time the reaction mixture was cooled to 0° and the precipitated ammonium chloride filtered off by suction. The filtrate (50 ml. of ether was added before filtration in those cases in which ether was not used in the alcoholysis) was washed with an equal volume of 10% sodium carbonate solution and then with 50 ml. of a saturated solution of sodium carbonate and after drying over anhydrous potassium carbonate it was fractionated under about 10–30 mm. pressure. In the case of ethyl orthoacetate it was found necessary to carry out the fractionation at atmospheric pressure and with an efficient Widmer column to obtain the yields that are reported in Table I. The boiling points of the various orthoesters together with other properties and analyses of those not previously described in the literature are listed in Table III.

TABLE III

PROPERTIES AND ANALYSES OF ORTHOESTERS $RC(OC_2H_5)_3$

R is	Formula	B. p., °C.	mm.	d^{25}_4	$n^{25}D$	Analyses, % Calcd. C	Calcd. H	Calcd. EtO	Found C	Found H	Found EtO[a]
CH_3[b]	...	144–146	740	..	..	..	..	..	..	..	..
C_2H_5[c]	...	70– 72	32	...	....	..	..	..	..	..	..
n-C_3H_7	$C_{10}H_{22}O_3$	58– 59	7	0.875	1.4028	63.1	11.7	71.0	63.1	11.6	69.0
i-C_3H_7	$C_{10}H_{22}O_3$	50– 51	7	.871	1.4002	63.1	11.7	71.0	63.4	11.5	68.5
n-C_4H_9	$C_{11}H_{24}O_3$	49– 50	3	.873	1.4086	64.7	11.8	66.2	64.4	11.8	64.9
i-C_4H_9[d]	$C_{11}H_{24}O_3$	57– 59	7	.869	1.4056	64.7	11.8	66.2	64.7	11.8	..
$ClCH_2$[e]	...	68– 70	10	...	....	..	..	..	..	..	..

[a] Found ethoxy values of these orthoesters generally are lower than the theoretical just as they are with the ketene acetals. [b] Ref. 6. [c] Ref. 1. [d] Prepared and analyzed by Robert L. Clarke. [e] Beyerstedt and McElvain, THIS JOURNAL, **59**, 1273 (1937).

(9) The use of ether at this point is for the purpose of preventing the formation of a hard cake and to cause the salt to precipitate as small and more pure crystals.

Summary

The conversion of acetonitrile, certain of its higher homologs and chloroacetonitrile into iminoester hydrochlorides, and the alcoholysis of these salts to the corresponding orthoesters in good and reproducible yields are described.

MADISON, WISCONSIN RECEIVED MARCH 25, 1942

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

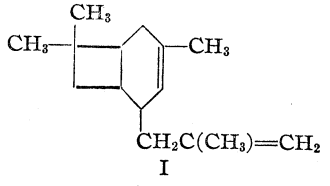
The Constituents of the Volatile Oil of Catnip. II. The Neutral Components. Nepetalic Anhydride

By S. M. McElvain, Philip M. Walters[1] and Robert D. Bright[2]

In the first paper[3] of this series the structures of the compounds, nepetalic acid (III) and nepetalactone (VI), that are extractable from the volatile oil of catnip by dilute alkali were discussed. These alkali-soluble components comprise 85–90% of the oil, depending upon the method of extraction; when the oil is shaken vigorously with a 10% solution of sodium hydroxide at 60° for fifteen minutes only about 10% of the oil remains undissolved. It is with this alkali-insoluble portion that the present paper deals.

Hixon[4] has reported an investigation of this alkali-insoluble portion of the oil. He subjected it to steam distillation and found that only about half of it was readily volatile and that a considerable portion of it did not distill with the steam. Fractionation of the steam-distilled material yielded a main fraction that boiled at 245–255° (11 mm.) and which from its odor and physical properties was thought to be a dicyclic sesquiterpene.

In the present work careful fractioning of this neutral portion of the oil divided it into a number of fractions that appeared to have constant boiling points and that attained maxima or minima in their refractive indices. The lowest boiling of these fractions was found to be a colorless azeotropic mixture that was composed of about 70% of a $C_{15}H_{24}$ hydrocarbon and 30% of nepetalactone (VI). The lactone was readily removed from the hydrocarbon when the mixture was refluxed with 10% aqueous sodium hydroxide. The properties of this hydrocarbon and of its dihydrochloride correspond to those of the sesquiterpene, β-caryophyllene (I), that has been isolated from oil of cloves by Ruzicka.[5]



I

The next fraction that distilled from the neutral portions of the oil was nepetalactone (VI) which was readily identified as the semicarbazone of nepetalic acid. After the nepetalactone two very small fractions (see Table I) were obtained. The first of these was colorless and from analyses and physical properties appeared to have the molecular formula, $C_{14}H_{24}O$. The oxygen of this compound seemed to be in the form of an ether since it shows no hydroxyl or carbonyl function. The other of these fractions is deep yellow in color and has a tea-like odor. Analyses show it to have an empirical formula of $C_9H_{14}O_2$; saponification in standard alkali indicates that it is an ester with a saponification equivalent of 176. On account of the scarcity of both of these materials, no further work was done on them.

The last fraction was relatively large and was obtained as a yellow, viscous oil that boiled at 200–210° (0.1 mm.). On standing this oil slowly crystallized. The crystalline material, after recrystallization from petroleum ether, melted at 139–140° and was optically active, $[\alpha]^{25}D$, 136° in chloroform. Analyses and molecular weight determinations showed it to have the molecular formula, $C_{20}H_{30}O_5$. It contained no readily oxidizable or titratable groups, but hydrolysis with dilute hydrochloric acid converted it into nepetalic acid. These facts lead to the conclusion that the compound is the anhydride (V) of nepetalic acid formed by the loss of a molecule of water between two molecules of the hydroxylactone form (II) of the acid. It is obvious that an anhydride formed from either of the other two tautomeric forms of nepetalic acid (III and IV) would contain highly reactive functional groups.

Nepetalic anhydride (V) is formed in considerable amounts together with the acetate of II when nepetalic acid is treated with acetyl chloride. In this connection it is interesting to note that acetic anhydride converts nepetalic acid quantitatively into the acetate.[3] The anhydride, V, slowly forms at ordinary temperatures in non-crystalline samples of nepetalic acid on standing; such samples, which originally were completely alkali soluble, after a year or more of standing may con-

(1) Wisconsin Alumni Research Foundation Research Assistant, 1941–1942.

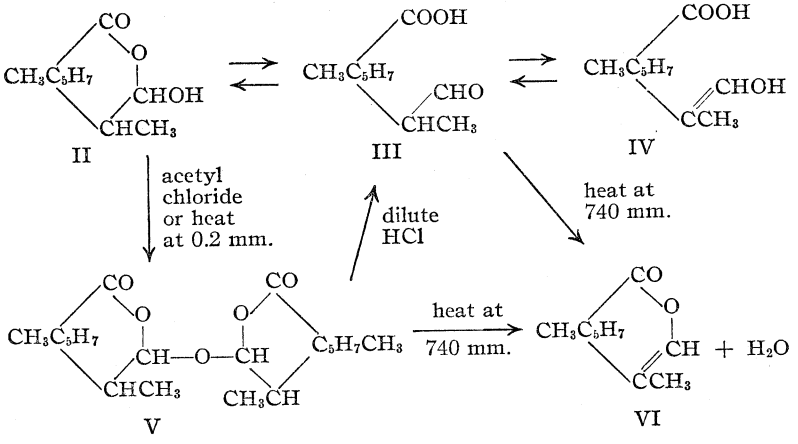
(2) Du Pont Post-doctorate Research Assistant, 1940–1941.

(3) McElvain, Bright and Johnson, This Journal, **63**, 1558 (1941).

(4) Hixon, *J. Am. Pharm. Assoc.*, **11**, 96 (1922).

(5) Ruzicka, *Chem. and Ind.*, **54**, 509–510 (1935); Ruzicka, Bardhan and Wind, *Helv. Chim. Acta*, **14**, 427 (1931).

tain as much as 4% of this anhydride. Nepetalic anhydride may also be prepared by heating nepetalic acid under 0.2 mm. pressure; at this pressure as high as 30% intermolecular dehydration occurs with the formation of V.[6] At atmospheric pressure the dehydration of nepetalic acid is intramolecular with the formation of nepetalactone[3] (VI). Similarly, when nepetalic anhydride either as pure crystalline material or as the viscous oil, obtained from the mother liquor after the crystallization of V, is heated at atmospheric pressure it readily decomposes into 2 molecules of VI and one molecule of water. The following formulas illustrate these transformations, in which $CH_3C_5H_7$ is a methylcyclopentane nucleus



In Table I are listed the various components that have been isolated from the portion of the volatile oil of catnip that is insoluble in aqueous alkali at 60°, the percentage of this neutral portion which each component comprises and certain of the physical properties of the pure compound. The percentage values in the second column of this table include both the pure material, having the properties shown, and that estimated to be present in the intermediate fractions from the chemical and physical properties of these fractions.

(6) A compound with a structure analogous to V has been reported by Carrière [*Ann. chim.*, **17**, 84 (1922)]. It was formed to the extent of about 25% when the trimer of the half-aldehyde of succinic acid was subjected to distillation and depolymerized into the monomer

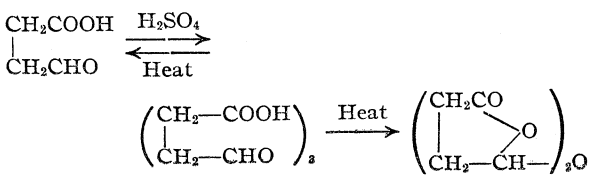


TABLE I

COMPONENTS OF THE NEUTRAL FRACTION OF THE VOLATILE OIL OF CATNIP

Component	% of neutral oil[a]	B. p., °C.	mm.	$n^{25}D$	d^{25}_4
β-Caryophyllene[b]	14	59–60	0.03	1.4962	0.9027
Nepetalactone	42	70–71	.03	1.4870	...
$C_{14}H_{24}O$	3	85–87	.03	1.4942	.9592
$C_9H_{14}O_2$[c]	2	115–117	.1	1.4790	...
Nepetalic anhydride[d]	36	200–210	.1	....	...

[a] This neutral oil comprises 10% of the original oil of catnip. [b] $[\alpha]^{25}D$, −11°; the dihydrochloride of this hydrocarbon melts at 68–69°. [c] Since this compound appears to be an ester it is likely that its molecular formula is double this empirical formula to account for the relatively high boiling point of the compound. [d] The melting point of the crystalline material from this fraction is 139–140°.

It is seen from the above table that β-caryophyllene, nepetalactone and nepetalic anhydride comprise over 90% of the alkali-insoluble portion of the oil of catnip. Since this portion represents only about 10% of the original oil it follows that over 99% of the volatile oil of catnip is accounted for as nepetalic acid (III) and its derivatives, nepetalactone (VI) and nepetalic anhydride (V), which comprise about 98% of the oil, and β-caryophyllene (I) which is present to the extent of about 1.4%. The ether, $C_{14}H_{24}O$, and ester, $C_9H_{14}O_2$, together represent only about 0.5% of the oil.

Since both nepetalic acid and its anhydride are odorless, it seemed probable that nepetalactone (VI) and possibly the caryophyllene are the constituents of the oil that are responsible for the odor of the catnip plant that is so attractive to many species of the cat family. Through the courtesy and coöperation of Mr. Fred Winkelmann, superintendent of the Vilas Zoo at Madison, it was possible to test this supposition. Small pledgets of cotton soaked in a dilute alcoholic solution of each of these constituents were placed, after the evaporation of the alcohol, in the different cages of the African lions at the Zoo. The nepetalactone that was used was prepared from the odorless nepetalic acid. There were ten of these animals available for the test. They represented both sexes and varied in age from cubs a few months old to a lioness so old (25–30 years) that she was partially blind. With the exception of the three cubs that were present, all of the

lions responded immediately to nepetalactone in the same manner that they do to the oil of catnip and to the fresh plant, the latter of which is given to them regularly during the summer. They showed no interest in the caryophyllene. The reaction of the lions to either nepetalactone or the catnip plant is quite similar to that of an ordinary house cat. They can be aroused immediately from a state of lethargy to one of intense excitement by the odor of the lactone, and will follow the odor to its source. When they acquire the material with the odor they become ludicrously playful and their main interest seems to be to get the odoriferous material transferred to their fur. They show no desire to eat the material, nor is there any evidence of sexual stimulation.

Experimental

Fractionation of the Neutral Portion of the Oil of Catnip.—A 100-g. sample of the neutral fraction of oil of catnip (which represented the undissolved material from 1 kg. of the oil of catnip that had been shaken with 10% aqueous sodium hydroxide at 60° for fifteen minutes) was distilled through an 8-cm. still-head at 0.1 mm. This crude fractionation separated the lower boiling fractions, 63 g., from the higher boiling material, principally nepetalic anhydride, 36 g., which remained as the residue. Careful fractionation of the distillate from the above distillation gave four fractions, (a) 23 g., b. p. 55–60° (0.03 mm.); $n^{25}D$ 1.4900–1.4921; (b) 31 g., b. p. 61–71° (0.03 mm.); $n^{25}D$ 1.4870–1.4900; (c) 5 g., b. p. 72–110° (0.03 mm.); $n^{25}D$ 1.4900–1.4920; (d) 3 g., b. p. 110–122° (0.03 mm.); $n^{25}D$ 1.4833–1.4880. Refractionation of each of the above fractions gave the quantities of material with a constant refractive index that are shown in Table II.

Table II

Fractions of the Lower Boiling Neutral Components of Oil of Catnip

Fraction	Weight, g.	B. p. °C.	Mm.	$n^{22}D$
a	20	59–61	0.03	1.4931
b	29	68–71	.03	1.4878
c	4	83–88	.03	1.4930
d	2	115–117	.1	1.4790

Isolation and Identification of β-Caryophyllene (Fraction a).—Carbon–hydrogen analyses and molecular weight determinations indicated fraction *a* to be a constant boiling mixture of about 70% of a C_{15} hydrocarbon and 30% of an oxygen-containing component. On the assumption that the oxygen compound was nepetalactone which had not been completely removed by the alkaline extraction of the oil, fraction *a* (20 g.) was refluxed with 10% sodium hydroxide for one hour, and then extracted thoroughly with ether. The ether extracts were combined and distilled. There was obtained 12 g. of a hydrocarbon that proved to be β-caryophyllene,[5] b. p. 112–113° (10 mm.); $n^{25}D$ 1.4962; d^{25}_4 0.9027; $[\alpha]^{25}D$ −11.42 (in chloroform); mol. wt. (Beckmann), 192 (calcd. 204); M_D, 66.13 (calcd. 66.16).

Anal. Calcd. for $C_{15}H_{24}$: C, 88.2; H, 11.8. Found: C, 88.0; H, 11.8.

β-Caryophyllene was further identified by conversion to its dihydrochloride; m. p. 68–69°. This was done by saturating a solution of 1 g. of the hydrocarbon in 10 ml. of anhydrous ether with dry hydrogen chloride. This solution was allowed to stand in the refrigerator for four days, after which time the ether was removed by evaporation under diminished pressure. The residual oil was dissolved in 2 ml. of absolute alcohol and crystallization induced by the introduction of a crystal of dry-ice into the alcoholic solution. The white crystalline dihydrochloride was filtered off and recrystallized from absolute alcohol. The yield of β-caryophyllene dihydrochloride so obtained amounted to 0.2 g. It melted at 68–69° and contained 25.9% chlorine (calcd. 25.6%).

Ruzicka[5] has reported the following properties for β-caryophyllene that was isolated from the oil of cloves, b. p. 119–121 (12 mm.); d^{16}_4 0.9074; $n^{16}D$ 1.5009 ($n^{25}D$ 1.4973); $[\alpha]D$ −8.9°; M_D 66.28 (calcd., 66.14); m. p. of dihydrochloride, 69°.

The alkaline extract of fraction *a* was acidified to congo red with 10% sulfuric acid, and thoroughly extracted with ether. The ether extracts were combined and on distillation yielded 5 g. of nepetalic acid, identified by its semicarbazone,[3] m. p. 158–159°, which showed no depression of melting point when mixed with an authentic sample of nepetalic acid semicarbazone.

Nepetalactone (Fraction *b*).—Analysis and physical constants of fraction *b* indicated it probably was composed of approximately 85% nepetalactone and 15% of β-caryophyllene. Accordingly a 12-g. sample of fraction *b* was shaken with 35 g. of 10% aqueous sodium hydroxide at 80° for thirty minutes, and then extracted thoroughly with ether. The ether extracts were combined and distilled to yield 1.8 g. of a material boiling from 112 to 135° (12 mm.) and which had the characteristic odor of β-caryophyllene. The alkaline extract was acidified with 10% sulfuric acid to congo red and thoroughly extracted with ether. The ether extracts were combined and on distillation yielded 9.6 g. of nepetalic acid.

Fractions *c* and *d*.—A 4-g. sample of fraction *c* on alkaline extraction with hot aqueous alkali solution yielded 2 g. of a neutral oil which showed no reaction with semicarbazide or with acetic anhydride in refluxing dioxane after two hours. This compound, which appears to be an ether, $C_{14}H_{24}O$, boils at 136–138° (9 mm.); $n^{25}D$ 1.4942; d^{25}_4 0.9592.

Anal. Calcd. for $C_{14}H_{24}O$: C, 80.7; H, 11.6. Found: C, 80.9; H, 11.2.

The alkaline extract of this fraction yielded 2 g. of nepetalic acid.

Fraction *d* was rich yellow in color and had a faint tea-like odor. It failed to give an oxime or semicarbazone when treated with hydroxylamine or semicarbazide. Its yellow color suggested a 1,2-diketone structure, but it failed to show any reduction of Fehling solution, a fact which would seem to eliminate that type of structure. Saponification with alcoholic alkali indicated that it is an ester with a saponification equivalent of 176. This compound boiled at 115–117° (0.1 mm.); $n^{25}D$ 1.4790. Analyses indicated it to have an empirical formula of $C_9H_{14}O_2$.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.1; H, 9.2. Found: C, 69.6; H, 9.3.

No further work was done with either the ether of fraction *c* or the yellow fraction *d*.

Nepetalic Anhydride.—A 15-g. sample of the residue remaining from the initial crude fractionation of the neutral portion of the oil was distilled from glass wool in a 25-ml. flask without a fractionating column and 13 g. of a yellow viscous oil, b. p. 200–210° (0.1 mm.), obtained. This viscous oil on standing slowly crystallized. Over a two-month period 2 g. of white crystalline nepetalic anhydride, m. p. 139–140°, was isolated from the semi-crystalline mass by recrystallization from petroleum ether (40–60°).

Nepetalic anhydride also was isolated from a sample of non-crystalline nepetalic acid that had been standing for several years. From a 40-g. sample of this acid 1.8 g. of the anhydride remained as alkali-insoluble material. Upon recrystallization from alcohol it melted at 139–140°; $[\alpha]^{25}D$ +136 (in chloroform); mol. wt. (Rast), 347 (calcd. 350).

Anal. Calcd. for $C_{20}H_{30}O_5$: C, 68.5; H, 8.7. Found: C, 68.7; H, 8.8.

Nepetalic anhydride was obtained from an acetylation of nepetalic acid with acetyl chloride. Fractionation of a solution of 3.9 g. of acetyl chloride and 5.0 g. of nepetalic acid in 5 ml. of carbon tetrachloride that had stood overnight at room temperature yielded 2.4 g. of nepetalic acid acetate,[3] b. p. 120–126° (0.1 mm.) and 2.7 g. of the anhydride, b. p. 203–206° (0.1 mm.). The latter fraction partially crystallized on cooling and after recrystallization from petroleum ether yielded the solid anhydride; m. p. 138–139°.

Hydrolysis of 0.65 g. of the anhydride in a refluxing solution of 2 ml. of concentrated hydrochloric acid in 10 ml. of water over a period of fourteen hours yielded 0.62 g. of nepetalic acid which was identified as the semicarbazone.

Nepetalactone from Nepetalic Anhydride.—In a distilling flask of about 2 ml. capacity 0.5 g. of nepetalic anhydride was carefully heated at its boiling point with a microburner for thirty minutes during which time a small amount of water distilled out. Then the residue was distilled under diminished pressure and 0.4 g. of nepetalactone, b. p. 67–70° (0.1 mm.); $n^{28}D$ 1.4843, was obtained as distillate.

A 10-g. sample of the viscous, non-crystalline material remaining from the petroleum ether crystallization of the anhydride distillate was heated in a metal bath at 280° for two hours. During this time 0.2 g. (38%) of water distilled out. The residue on distillation under diminished pressure yielded 3.9 g. (41%) of nepetalactone which was identified as the semicarbazone of nepetalic acid.

Summary

An investigation of the alkali-insoluble portion (10%) of the volatile oil of catnip shows that it consists of β-caryophyllene (14%), nepetalactone (42%) and nepetalic anhydride (36%). This latter compound is the anhydride of the hydroxylactone form of nepetalic acid.

In addition to these compounds two other substances which comprise not more than 0.5% of the oil have been isolated but not identified.

It is shown that nepetalactone is the component of the oil, the odor of which makes the catnip plant so attractive to certain species of the cat family.

MADISON, WISCONSIN RECEIVED MAY 4, 1942

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

α-Alkoxyvinyl- and α-Alkoxyethylbarbituric Acids

BY S. M. MCELVAIN AND HOWARD BURKETT[1]

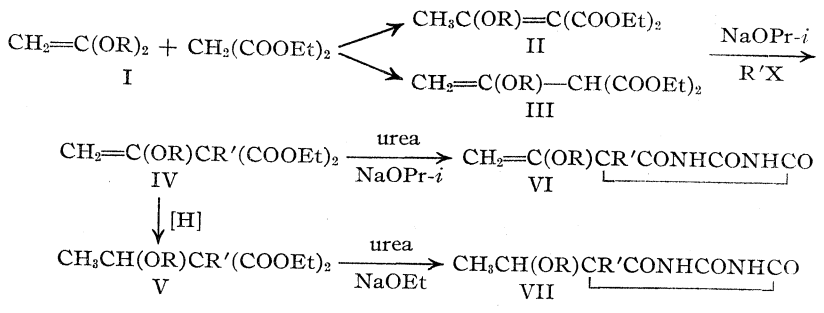
The formation of (α-ethoxyethylidene)-malonic ester (II, R is ethyl) from the reaction of ketene diethyl acetal and malonic ester[2] suggested a study of this reaction with other ketene dialkylacetals[3] (I) and the conversion of the resulting α-alkoxyethylidenemalonic esters into the corresponding 5-(α-alkoxyvinyl)-5-alkyl-barbituric acids (VI) by the sequence of reactions shown below. It seemed possible also that the vinyl group could be hydrogenated at the malonic ester stage (IV) and a series of 5-substituted (α-alkoxyethyl)-barbituric acids (VII) prepared from the saturated malonic esters (V).

In the original study of the reaction between ketene diethyl acetal and malonic ester the (α-ethoxyethylidene)-malonic ester (II), m. p. 26–27°, was obtained in 55% yield. It has been found possible in the present work to increase the yield of this product to 66% and to obtain in addition the isomeric (α-ethoxyvinyl)-malonic ester (III, R is ethyl) in 11% yield. The structure of the latter ester, which is a liquid, is shown by its ozonolysis into formaldehyde, and by the fact that the two isomers yield the same malonic ester and barbituric acid in the reactions shown below. By long heating (125° for twenty hours) with a trace of sodium ethoxide the liquid ester (III) may be converted into its solid isomer (II).

(1) Eli Lilly and Company Fellow, 1940–1942.

(2) Barnes, Kundiger and McElvain, THIS JOURNAL, **62**, 1281 (1940).

(3) McElvain and Walters, *ibid.*, **64**, 1059 (1942).



Only in the case of the compounds (II and III, R is ethyl) derived from ketene diethylacetal was an attempt made to separate the isomers. In each of the other cases the mixture of the isomers was directly alkylated. When this alkylation was carried out in ethyl alcohol the yields of the disubstituted malonic esters (IV) were quite low (20–25%) but with isopropyl or *t*-butyl alcohols as solvents the yields of these malonic esters generally were between 55–85% of the theoretical.

The hydrogenation of the vinyl substituted ester (IV) to the saturated ester (V) was carried out only with the compound in which R = R′ = ethyl. While the hydrogenation went quite satisfactorily, this method did not seem as practicable as the direct introduction of the alkoxyethyl group through the interaction of the appropriate chloroethyl ether prepared from acetaldehyde, the alcohol and hydrogen chloride[4] and the sodio derivative of the mono-substituted malonic ester as illustrated by the reactions

$$CH_3CHO + ROH + HCl \longrightarrow CH_3CHClOR \xrightarrow{NaCR'(COOEt)_2} V$$

It was found necessary to carry out this reaction in the sequence shown, since all attempts to further alkylate a malonic ester containing an α-alkoxyethyl substituent yielded only polymeric products.

As may be seen from Table V in the experimental part, the yields in the conversion of the vinyl substituted malonic esters (IV) into the corresponding barbituric acids were quite low due, in considerable part, no doubt, to the cleavage of the malonic ester into the corresponding acetic ester and derivatives thereof.[5] In fact, in two cases (IV, R is ethyl, R′ is *n*-propyl and R is *n*-butyl, R′ is ethyl) it was not possible to isolate any of the barbituric acid VI even when the condensation was carried out in isopropyl alcohol.

(4) Henze and Murchison, This Journal, **53**, 4077 (1931).
(5) *Cf.* Cope and McElvain, *ibid.*, **54**, 4319 (1932).

In contrast to this behavior, the saturated esters V condensed with urea in ethyl alcohol solution to give good yields of the barbituric acids (VII). In the case of the barbituric acid in which R is *n*-propyl and R′ is methyl-*n*-propylcarbinyl a pair of racemates that had sufficiently different physical properties to allow them to be separated were formed (see Table VI). The corresponding compound in which R is ethyl failed to yield a similar pair of racemates.

Pharmacological Data

The barbituric acids that have been prepared in this work are being studied pharmacologically by Mr. E. E. Swanson of The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, who has kindly furnished a preliminary report that is summarized in Table I. Corresponding data for amytal (Sodium Isoamyl Ethyl Barbiturate, Lilly) are included for comparison. The pharmacological values were determined intraperitoneally in white rats, and are expressed as minimum anesthetic dose (M.A.D.) and minimum lethal dose (M.L.D.) in mg. of barbiturate per kg. of animal weight. The "therapeutic index" is the ratio of these values. The pair of racemates in which R′ is the methyl-*n*-propylcarbinyl group are listed in Table I in the same order that they appear in Table VI.

Discussion of the Pharmacological Data

It may be seen from the M.A.D. column of Table I that the 5-(α-alkoxy-ethyl)-5-alkylbarbituric acids (no. 5–16) as a group are more effective anesthetics than the corresponding alkoxyvinyl compounds (no. 2–4). As a matter of fact quite a number of these alkoxyethyl substituted compounds appear to be more effective in producing anesthesia in white rats than is amytal (no. 1), although some of them cause very noticeable preanesthetic tremors or convulsions. Nos. 6 and 13 are particularly striking since each of them has a low anesthetic dose coupled with a sufficiently low toxicity (M.L.D.) to give them decidedly higher therapeutic indices than that shown by amytal. It should be noted also that the duration of the anesthesia produced in the white rat by both 6 and 13 are considerably less than that of amytal.

TABLE I

SUMMARY OF THE PHARMACOLOGICAL DATA

No.	R is	R′ is	M.A.D., mg./kg.	Duration of anesthesia, min.	M.L.D., mg./kg.	Therapeutic index, M.L.D./M.A.D
	5-(α-Alkoxyvinyl)-5-alkylbarbituric Acids $CH_2{=}C(OR)CR'CONHCONHCO$					
1	Amytal		90	200	200	2.22
2	Ethyl	Ethyl	200	600	400	2.00
3	Ethyl	Allyl	100	300	210	2.10
4	Isoamyl	Ethyl	120	63	240	2.00
	5-(α-Alkoxyethyl)-5-alkylbarbituric Acids $CH_3CH(OR)CR'CONHCONHCO$					
5	Ethyl	Ethyl	150[a]	460	400	2.67
6	Ethyl	*n*-Propyl	80	162	300	3.75
7	Ethyl	*n*-Butyl	150	120	300	2.00
8	Ethyl	Isoamyl	125	102	275	2.02
9	*n*-Propyl	Ethyl	80[b]	150	120	1.50
10	*n*-Butyl	Ethyl	60[b]	150	70	1.16
11	Isoamyl	Ethyl	80[b]	75	120	1.50
12	Ethyl	Allyl	100	300	160	1.60
13	Ethyl	Methyl-*n*-propylcarbinyl	60	108	160	2.67
14	*n*-Propyl	Allyl	50[a]	204	100	2.00
15	*n*-Propyl	Methyl-*n*-propylcarbinyl	300[a]	300	450	1.50
16	*n*-Propyl	Methyl-*n*-propylcarbinyl	120[a]	150	200	1.67

[a] Caused pre-anesthetic tremors. [b] Caused pre-anesthetic convulsions.

There is an interesting difference in the pharmacological behavior of the diastereoisomeric pair of racemates 15 and 16. Although they both have practically the same therapeutic indices, the lower melting (see Table VI) compound (no. 16) is over twice as effective as an anesthetic and twice as toxic as its higher melting isomer.

Experimental

Diethyl α-Ethoxyethylidenemalonate and Diethyl α-Ethoxyvinylmalonate.—One hundred and fifty grams (1.3 moles) of ketene acetal, 105 g. (0.65 mole) of diethyl malonate and 2.2 g. (0.03 mole) of sodium ethoxide were thoroughly mixed and heated by an oil-bath at 125–130° for twelve hours. The reaction mixture was then distilled rapidly. First, 95 g. (0.58 mole) of almost pure ethyl orthoacetate was collected. Following 5 g. of an intermediate fraction, 130 g. of material, b. p. 96–106° (0.4 mm.), $n^{25}D$ 1.4573, was collected. Upon cooling in an ice–salt mixture, this material became a thick slush, which then was poured onto a suction funnel surrounded by a freezing mixture. In this manner 83 g. of diethyl α-ethoxyethylidenemalonate, m. p. 25–27°, was obtained.

The filtrate (47 g.) from this cold filtration was carefully fractionated. After a small forerun, 16.4 g. (11%) of diethyl α-ethoxyvinylmalonate, b. p. 69–70° (0.03 mm.); $n^{25}D$ 1.4380; d^{25}_{25} 1.048; $M^{20}D$, calcd., 57.53; found, 57.62, was collected. This product contained 58.2% ethoxyl (calcd. 58.7%). Following an intermediate fraction, 16.7 g. of diethyl α-ethoxyethylidenemalonate, b. p. 84° (0.03 mm.); m. p. 26–27°; $n^{25}D$ 1.4634; d^{25}_{25} 1.068; $m^{20}D$ calcd., 57.53; found, 59.36, was collected. This exaltation of the molecular refraction would be expected in this structure. The total yield of diethyl α-ethoxyethylidenemalonate was 99.7 g., 66% of theoretical.

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.4; H, 7.9; OC_2H_5, 58.7. Found: C, 57.6; H, 7.9; OC_2H_5, 58.6.

The diethyl α-ethoxyvinylmalonate was ethylated and the resulting diethyl ethyl-(α-ethoxyvinyl)-malonate condensed with urea according to the procedures given below. The resulting barbituric acid melted at 188–189° and was identical with the one produced in like manner from diethyl α-ethoxyethylidenemalonate.

The liquid ethoxyvinylmalonic ester could be converted into its solid isomer by the following procedure: 9 g. of diethyl α-ethoxyvinylmalonate was heated with 0.25 g. of sodium ethoxide at 125° for twenty hours. Fractionation of the reaction mixture gave none of the starting material in the pure state but did yield 5.34 g. (59%) of diethyl α-ethoxyethylidenemalonate, b. p. 79–83° (0.03 mm.); m. p. 25–26°; $n^{25}D$ 1.4621.

Ozonolysis of Diethyl α-Ethoxyvinylmalonate.—A solution of 4.7 g. of diethyl α-ethoxyvinylmalonate in 14 ml. of glacial acetic acid and 1 ml. of acetic anhydride was treated with ozonized oxygen until no more was taken up. The solution was then poured into a three-necked flask containing 15 ml. of water, 4 g. of zinc dust, and a few crystals each of hydroquinone and silver nitrate. The flask was equipped with a stirrer and a reflux condenser, the upper end of which was connected to a tube leading to the bottom of a test-tube containing 10 ml. of water. Nitrogen was passed into the flask while it was heated on the steam-bath so that any formaldehyde liberated would be carried over into the test-tube of water. After four hours, the water containing the formaldehyde was poured into a solution of dimethyl dihydroresorcinol in aqueous potassium carbonate and the resulting solution just acidified with acetic acid. The precipitate which was obtained weighed 8 mg., melted at 184–185° and gave no depression when mixed with an authentic specimen prepared from formaldehyde and dimethyldihydroresorcinol.

Similar treatment of the diethyl α-ethoxyethylidenemalonate gave no detectable amount of formaldehyde.

Diethyl α-Alkoxyvinyl-alkylmalonate and Diethyl α-Alkoxyvinyl-malonate Mixtures.—A series of diethyl α-alkoxyethylidenemalonates were prepared by mixing the appropriate dialkyl ketene acetal,[3] diethyl malonate, and sodium ethoxide in the same molecular ratio as given in the previous section and heating the mixture in an oil-bath at the temperature and for the length of time given in Table II. No attempt was made to separate the isomers in these cases, but the material collected over the boiling range indicated in Table II was ethylated without further purification.

TABLE II

MIXTURES OF THE ISOMERIC DIETHYL α-ALKOXYETHYLIDENEMALONATES, $CH_3C(OR)=C(COOC_2H_5)_2$ AND DIETHYL α-ALKOXYVINYL-MALONATES, $CH_2=C(OR)CH(COOC_2H_5)_2$[a]

R is	Reaction temp., °C.	Reaction time, hr.	B. p., °C.	Mm.	Yield, %
Propyl	185	24	110–112	3	65
n-Butyl	165	3	135–140	2.5	42
n-Butyl	140	24	135–140	2.5	54
i-Amyl	130	24	120–130	0.05	81

[a] These esters were prepared by Mr. Bruce Stevenson, to whom the authors wish to acknowledge their indebtedness.

The α-alkoxyvinyl-alkylmalonic esters were prepared by the following general procedure. To a solution of 2.3 g. (0.1 atom) of sodium in about 15 times its weight of the solvent alcohol shown in Table III, 0.1 mole of the appropriate diethyl α-alkoxyethylidenemalonate was added. The alkyl bromide or iodide was then added to this alkaline solution and the mixture refluxed until it was neutral. After cooling, sufficient water was added to dissolve all of the salt, the oily layer separated and the aqueous layer extracted with ether. The combined ether extract and oily layer was washed with water, dried over anhydrous sodium carbonate and distilled. Since it was practically impossible to obtain analytically pure compounds when an alcohol other than ethyl was used as a solvent, fractions with the ranges of boiling points and refractive indices shown in Table III were used for the preparation of barbituric acids.

Diethyl α-Alkoxyethyl-alkylmalonates.—Diethyl α-ethoxyethyl-ethylmalonate was prepared by catalytic hydrogenation of the corresponding α-ethoxyvinylethylmalonic ester by the following procedure. A solution of 8 g. of the vinyl ester in 70 ml. of absolute ethyl alcohol together with 1 g. of Raney nickel was placed in a steel bomb and shaken with hydrogen at a pressure of 1850 pounds. The hydrogenation proceeded readily at 120°. Fractionation of the product gave 4.62 g. (53%) of diethyl α-ethoxyethyl-ethylmalonate, b. p. 73° (0.04 mm.); $n^{25}D$ 1.4279; d^{25}_{25} 1.000.

Anal. Calcd. for $C_{13}H_{24}O_5$: C_2H_5O, 51.9. Found: C_2H_5O, 51.9.

Diethyl α-ethoxyethyl-malonate was prepared from sodium malonic ester and α-chloro-ethyl ether in 28% yield as in the general procedure described below. It possessed the same properties as the product obtained from the catalytic hydrogenation of α-ethoxyethylidene-malonic ester.[2]

Attempts to ethylate diethyl α-ethoxyethyl-malonate produced only polymeric material. This may be due to a partial elimination of the ethoxyl group as ethyl alcohol and the polymerization of the resulting unsaturated ester. Support for this supposition comes from the fact that the highest ethoxyl analysis for diethyl α-ethoxyethylmalonate prepared by either of the above methods was 57.4% (calcd. 58.2%).

Diethyl α-ethoxyethyl-ethylmalonate was also prepared as follows. In a dry 1-liter 3-necked flask, equipped with an inlet tube, stirrer, and reflux condenser connected to a soda–lime drying tower, which in turn was connected to a gas trap, was placed 0.3 g. of hydrated ferric nitrate. The flask was cooled in a dry-ice–acetone bath and 300 ml. of liquid ammonia added. The stirrer was started, the cooling bath removed, and a small piece of sodium added. As soon as the initial blue color had disappeared, 12.7 g. (0.55 mole) of sodium in small pieces was added rapidly. As soon as all of the sodium had reacted as noted by the disappearance of the blue color, the cooling bath was replaced and 94 g. (0.5 mole) of diethyl ethylmalonate was added from a separatory funnel in a small stream. The reaction mixture was stirred for fifteen minutes with the cooling bath and for fifteen minutes without it. Then 50 ml. of dry ether and 300 ml. of dry benzene were added in a small stream. After the reaction mixture had reached

TABLE III

DIETHYL α-ALKOXYVINYL-ALKYLMALONATES, $CH_2=C(OR)CR'(COOC_2H_5)_2$

R is	R′ is	Solvent alcohol	Yield, %	B. p. °C.	Mm.	$n^{25}D$
Ethyl	Ethyl	Ethyl	20	130–133	9	1.4382–1.4400
Ethyl	Ethyl	*t*-Butyl	60	87– 91	0.1	1.4390–1.4402
Ethyl	Allyl	*i*-Propyl	59	92– 96	0.1	1.4469–1.4480
Ethyl	*n*-Propyl	*i*-Propyl	72	97– 98	1.0	1.4370–1.4400
Ethyl	*n*-Propyl	Ethyl	25	81– 84	0.03	1.4322–1.4420
Ethyl	*n*-Butyl	*i*-Propyl	85	88– 91	0.04	1.4400–1.4437
Ethyl	*i*-Amyl	*i*-Propyl	79	84– 90	0.01	1.4412–1.4429
n-Propyl[a]	Ethyl	*i*-Propyl	39	121–130	2.3	1.4400–1.4478
n-Butyl[a]	Ethyl	*i*-Propyl	24	110–120	0.5	1.4380–1.4462
Isoamyl	Ethyl	*i*-Propyl	55	104–110	0.04	1.4400–1.4429

[a] The authors are indebted to Mr. Bruce Stevenson for the preparation of these esters.

TABLE IV

DIETHYL α-ALKOXYETHYL-ALKYLMALONATES, $CH_3CH(OR)CR'(COOC_2H_5)_2$

R is	R' is	Formula	Yield, %	B. p., °C.	Mm.	$n^{25}D$	d^{25}_{25}	$M^{25}D$ Calcd.	$M^{25}D$ Found	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Ethyl	Ethyl	$C_{13}H_{24}O_5$	60	71–72	0.03	1.4282	1.0023	67.3	66.8	59.4	9.3	59.6	9.3
Ethyl	*n*-Propyl	$C_{14}H_{26}O_5$	66	81–82	.03	1.4291	0.9900	71.9	71.5	61.3	9.6	61.1	9.5
Ethyl	*n*-Butyl	$C_{15}H_{28}O_5$	68	85–86	.04	1.4317	.9779	76.5	76.2	62.5	9.8	62.4	9.8
Ethyl	*i*-Amyl	$C_{16}H_{30}O_5$	63	88–89	.03	1.4320	.9673	81.1	80.8	63.5	10.0	63.5	9.9
n-Propyl	Ethyl	$C_{14}H_{26}O_5$	62	77–78	.03	1.4290	.9905	71.8	71.5	61.3	9.6	61.2	9.5
n-Butyl	Ethyl	$C_{15}H_{28}O_5$	76	83–84	.03	1.4306	.9780	76.4	76.4	62.5	9.8	62.3	9.6
i-Amyl	Ethyl	$C_{16}H_{30}O_5$	71	89–90	.03	1.4320	.9699	81.1	81.9	63.5	10.0	63.7	9.9
Ethyl	Allyl	$C_{14}H_{24}O_5$	83	78–79	.04	1.4370	1.0030	71.4	71.1	61.6	8.9	61.7	8.6
Ethyl	Methyl-*n*-propyl carbinyl	$C_{16}H_{30}O_5$	84	83–84	.03	1.4369	0.9814	81.1	80.6	63.5	10.0	63.3	10.1
n-Propyl	Allyl	$C_{15}H_{26}O_5$	82	97–98	.18	1.4388	.9907	76.0	75.8	62.9	9.2	62.8	9.1
n-Propyl	Methyl-*n*-propyl carbinyl	$C_{17}H_{32}O_5$	69	101–102	.06	1.4380	.9726	85.0	85.2	64.5	10.2	64.6	10.2

room temperature, it was refluxed on the steam-bath until all of the ammonia was removed. This was facilitated by passing a slow stream of dry nitrogen into the flask. When all of the ammonia had been removed, the flask was cooled with cold water and 76 g. (0.7 mole) of α-chloroethyl ether added dropwise. After the addition of the chloroether, stirring was continued for about one hour at room temperature and for about ten minutes at the refluxing temperature of the benzene. The reaction mixture was then cooled and 300 ml. of water added. The benzene layer was separated and washed with two 100-ml. portions of water. The combined aqueous portions was extracted with ether. The benzene layer combined with the ether extract was washed with 50 ml. of 10% sodium carbonate, dried over anhydrous sodium carbonate, and finally distilled.

Other members of the series described in Table IV were prepared by the same procedure using the appropriate malonic ester and α-chloroethyl alkyl ether. All of the α-chloro-ethers were prepared by the procedure of Henze and Murchison.[4]

5-α-Alkoxyvinyl-5-alkylbarbituric Acids.—5-α-Ethoxyvinyl-5-ethylbarbituric acid was prepared as follows. To an alcoholic solution of sodium ethoxide, prepared from 4.6 g. (0.20 mole) of sodium and 75 ml. of absolute ethyl alcohol, was added 7.5 g. (0.125 mole) of urea and 17 g. (0.065 mole) of diethyl α-ethoxyvinylethylmalonate. After the mixture had refluxed for twelve hours, the alcohol was removed by distillation, and the residue dissolved in 80 ml. of ice-water. The aqueous solution then was extracted with ether. Evaporation of the ether left 6 g. of oil, the distillation of which gave 2 g. of material that was lower-boiling than the starting material and was probably the corresponding acetic ester $CH_3C(OC_2H_5)=C(C_2H_5)COOC_2H_5$; also, 4 g. of material with the boiling range of the starting ester was obtained. From this latter fraction was isolated 0.2 g. of a solid, m. p. 55–59°, which analyses indicated to be the amide $CH_3C(OC_2H_5)=C(C_2H_5)CONH_2$, corresponding to the above acetic ester.

Anal. Calcd. for $C_8H_{15}O_2N$: N, 8.98. Found: N, 8.92.

Crystallization from 50% ethyl alcohol of the precipitate produced by acidification of the aqueous alkaline solution yielded 3.8 g. (25% of theory) of 5-α-ethoxyvinyl-5-ethyl-barbituric acid. Properties of this compound and the others of this series that were prepared are listed in Table V. Other members of the series were prepared in a similar manner with certain variations. It was not possible to obtain any of either of the barbituric acids in which R and R' are, respectively, ethyl and *n*-propyl or *n*-butyl and ethyl. The time of reflux generally was between ten and twenty hours. Comparison of the yields, using ethyl, *i*-propyl, or *t*-butyl alcohol as the solvent, is shown in columns 3 and 4 of Table V. The ether extractable material from others of the series varied in amount but in no other case was an attempt made to fractionate this material or isolate a pure compound.

5-α-Alkoxyethyl-5-alkylbarbituric Acid.—5-α-Ethoxyethyl-5-ethylbarbituric acid was prepared as follows. To a solution of 3.5 g. (0.15 atom) of sodium in 50 ml. of absolute alcohol was added 6 g. (0.10 mole) of urea and 13 g.

TABLE V

5-(α-ALKOXYVINYL)-5-ALKYLBARBITURIC ACIDS $CH_2=C(OR)\overset{\displaystyle R'}{\overset{|}{C}}(CONHCONHCO)$

R is	R' is	Formula	Solvent alcohol	Yield, %	M. p., °C.	Analyses, % Calcd. N	Calcd. C_2H_5O	Found N	Found C_2H_5O
Ethyl	Ethyl	$C_{10}H_{14}O_4N_2$	Ethyl	25	189 –190				
Ethyl	Ethyl	$C_{10}H_{14}O_4N_2$	*i*-Propyl	37	189 –190				
Ethyl	Ethyl	$C_{10}H_{14}O_4N_2$	*t*-Butyl	42	189.5–190	12.4	19.9	12.4	19.8
Ethyl	Allyl	$C_{11}H_{14}O_4N_2$	*i*-Propyl	40	158 –160	11.7	18.9	11.2	18.8
Ethyl	*n*-Butyl	$C_{12}H_{18}O_4N_2$	*i*-Propyl	7	169 –170	11.0	17.7	11.2	17.5
Ethyl	*i*-Amyl	$C_{13}H_{20}O_4N_2$	*i*-Propyl	8	165.5–166	10.5		10.4	
n-Propyl	Ethyl	$C_{11}H_{16}O_4N_2$	*i*-Propyl	4.5	177 –179	11.7		11.6	
i-Amyl	Ethyl	$C_{13}H_{20}O_4N_2$	*i*-Propyl	5.4	153 –154	10.5		10.5	

Table VI

5-(α-Alkoxyethyl)-5-alkylbarbituric Acids $CH_3CH(OR)C(R')CONHCONHCO$

R is	R′ is	Formula	Yield, %	M. p., °C.	Analyses, % Calcd. N	Calcd. C_2H_5O	Found N	Found C_2H_5O
Ethyl	Ethyl	$C_{10}H_{16}O_4N_2$	32.5	181 –181.5	12.3	19.8	12.2	19.8
Ethyl	*n*-Propyl	$C_{11}H_{18}O_4N_2$	42	168.5–169	11.5	18.6	11.4	18.4
Ethyl	*n*-Butyl	$C_{12}H_{20}O_4N_2$	43	138 –139	10.9	17.6	10.9	17.5
Ethyl	*i*-Amyl	$C_{13}H_{22}O_4N_2$	44	136 –137	10.4	16.7	10.2	16.6
n-Propyl	Ethyl	$C_{11}H_{18}O_4N_2$	57	177.5–178	11.6		11.5	
n-Butyl	Ethyl	$C_{12}H_{20}O_4N_2$	58	132.5–133	10.9		10.8	
i-Amyl	Ethyl	$C_{13}H_{22}O_4N_2$	70	129.2–130	10.4		10.4	
Ethyl	Allyl	$C_{11}H_{16}O_4N_2$	57	127 –128	11.7	18.7	11.7	18.8
Ethyl	Methyl-*n*-propylcarbinyl	$C_{13}H_{22}O_4N_2$	64	159 –163[a]	10.4	16.7	10.3	16.6
n-Propyl	Allyl	$C_{12}H_{18}O_4N_2$	66	160 –160.5	11.0		11.0	
n-Propyl	Methyl-*n*-propylcarbinyl	$C_{14}H_{24}O_4N_2$	75	210.5–212	9.8		9.5	
n-Propyl	Methyl-*n*-propylcarbinyl	$C_{14}H_{24}O_4N_2$		153.5–154.5	9.8		9.6	

[a] After 3 recrystallizations from 50% alcohol the melting point of this product was 169–169.5°.

(0.05 mole) of diethyl α-ethoxyethylethylmalonate. After the mixture had refluxed eighteen hours, the alcohol was removed by distillation. About 100 ml. of ice-water was added to the residue. The resulting solution was extracted with 75 ml. of ether in three portions. Evaporation of the ether left 0.3 g. of oil, which slowly crystallized upon standing. This material was not characterized. The crude barbituric acid was precipitated by acidification of the aqueous alkaline solution with an excess of concentrated hydrochloric acid. Recrystallization from 35% ethyl alcohol gave 3.7 g. (32.5%) of 5-α-ethoxyethyl-5-ethyl barbituric acid.

Others of the series were prepared by the same procedure. In no case was the amount of material from the ether extract more than 0.5 g. In all cases except the two containing the methyl-*n*-propyl-carbinyl substituent one crystallization of the barbituric acid from 30–50% ethyl alcohol was sufficient to give each of the 5-α-alkoxyethyl-5-alkyl barbituric acids shown in Table VI in a pure state. The mixture of the pair of racemates that contained the methyl-*n*-propyl-carbinyl substituent was obtained in 75% yield, but after their separation into the products that melted as shown in Table VI the yield of each of these products amounted only to about 15%.

Summary

A number of ketene dialkylacetals have been condensed with malonic ester and the resulting mixture of (α-alkoxyethylidene)- and (α-alkoxyvinyl)-malonic esters have been alkylated to the (α-alkoxyvinyl)-alkylmalonic esters. These esters have been condensed with urea to produce the corresponding barbituric acids.

A number of related (α-alkoxyethyl)-alkylmalonic esters also have been prepared by the condensation of the appropriate chloroethers with alkylmalonic esters. The (α-ethoxyethyl)-ethylmalonic ester was also prepared from the (α-ethoxyvinyl)-alkylmalonic ester by catalytic hydrogenation. These malonic esters have been converted into barbituric acids.

A brief summary and a discussion of the pharmacological properties of these barbituric acids are given.

The reaction product from the condensation of ketene diethylacetal with malonic ester has been separated into the isomeric (α-ethoxyethylidene)-malonic ester and (α-ethoxyvinyl)-malonic ester, the structures of which have been proved by ozonolysis.

Madison, Wisconsin Received May 4, 1942

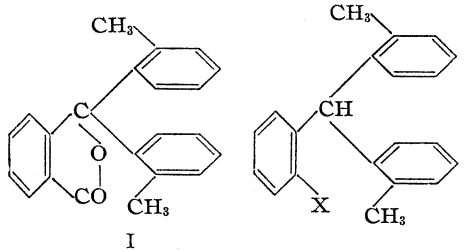
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Tri-*o*-tolylmethane

BY PAUL D. BARTLETT AND J. ELMORE JONES[1]

The results of Marvel and his co-workers[2] suggest that the unknown hexa-*o*-tolylethane would, if prepared, be largely if not completely dissociated into free radicals. Because the ortho-substituted triarylmethyls are incapable of assuming the coplanar arrangement demanded by the usual resonance structures,[3] their further study seems to offer an approach to the puzzling question of the role of resonance in promoting free radical dissociation. In connection with another research we had some 2,2′-dimethyl-2″-carboxytriphenylmethane (II); from this we have prepared the hydrocarbon tri-*o*-tolylmethane and studied its exchange reaction with phenylisopropylpotassium. This was done in the hope that from the potassium derivative so formed the free radical might be made by means of tetramethylethylene dibromide.

Our starting material was produced from di-*o*-tolylphthalide (I)[4] by high-pressure hydrogenation over copper chromite.

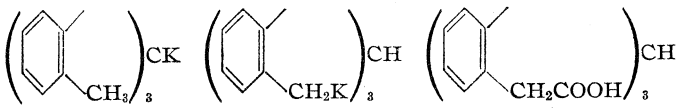


I

II X = COOH
III X = $CONHC_6H_5$
IV X = $CH{=}NC_6H_5$
V X = CHO
VI X = CH_3

This was reduced by way of the anilide (III) to the anil (IV) of the related aldehyde (V), which was characterized through its oxime. Wolff–Kishner reduction converted this aldehyde into tri-*o*-tolylmethane (VI), m. p. 130.5–131.5°. This hydrocarbon showed a behavior on melting like that of camphor, in that it sintered 4–5° below its melting point and showed large depressions of the melting point when impure.

When tri-*o*-tolylmethane was treated in ethereal solution with phenylisopropylpotassium a smooth exchange reaction took place with the precipitation of an orange–red potassium derivative. However, this was not the hoped-for potassium tri-*o*-tolylmethide (VII), but instead the tripotassium derivative VIII. Its structure was shown by carbonation yielding a tribasic acid which could be recovered unchanged after solution in concentrated sulfuric acid at 100°, and which was accordingly neither a triarylacetic acid nor a malonic acid. Since only the aliphatic hydrogen atoms would be expected to be acidic enough to yield potassium exchange, this constitutes evidence that the triacid has the structure IX. The triester could be formed by Fischer's method, showing that the carboxyl groups were not highly hindered.



VII VIII IX

In view of the fact[5] that triphenylmethane is much more strongly acidic than less arylated methanes, the metalation of tri-*o*-tolylmethane in the methyl groups, rather than on the central carbon atom, indicates an abnormally low activity of the hydrogen in the latter position. In seeking to explain this we investigated the potassium exchange by *o*-tolyldiphenylmethane, phenyldi-*o*-tolylmethane and tri-*p*-tolylmethane for comparison. All these hydrocarbons yielded monopotassium derivatives, which were carbonated to carboxylic acids that readily lost carbon monoxide on gentle warming in concentrated sulfuric acid. Even 3,3′,3″,5,5′,5″-hexamethyltriphenylmethane does likewise.[6] Tri-*o*-tolylmethane is, therefore, unique in its series in yielding only a side-chain rather than a central metalation product.

Phenyldi-*o*-tolylmethane represents a curious intermediate case. In 0.059 *N* solution of phenylisopropylpotassium it yields an exchange product which is carbonated to a mixture containing at

(1) Du Pont Post-Doctorate Fellow in Chemistry, 1941–1942.

(2) Marvel, Kaplan and Himel, THIS JOURNAL, **63**, 1892 (1941); Marvel, paper presented at the Ninth National Organic Symposium, Ann Arbor, Michigan, December 30, 1941.

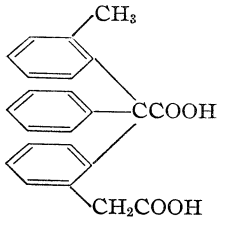
(3) Pauling and Wheland, *J. Chem. Phys.*, **1**, 362 (1933).

(4) Weiss and Korczyn, *Monatsh.*, **45**, 207 (1924).

(5) Conant and Wheland, THIS JOURNAL, **54**, 1212 (1932).

(6) Kleene and Wheland, *ibid.*, **63**, 3321 (1941).

least 86% phenyldi-*o*-tolylacetic acid and at least 8.6% of a dibasic acid. The latter, in contrast to the tribasic acid IX, is sensitive to concentrated sulfuric acid, no crystalline material being recoverable from the solution, although carbon monoxide is not evolved. In the absence of a satisfactory proof of structure it seems most likely that this is the acid X, with one carboxyl group on the central carbon atom and one on a methyl group. Increasing the concentration of the reactants to saturation (0.083 *N*) for phenylisopropylpotassium and 0.107 *N* for the hydrocarbon increases the fraction of the dibasic acid to 39%.



X

There are at least two admissible explanations of the behavior of tri-*o*-tolylmethane on metalation. In the first place, the acidity of the central hydrogen atom must bear some relation to the resonance energy of the carbanion which remains when the proton is transferred to another base. The resonance of the tri-*o*-tolyl carbanion involves the same type of secondary structures (with double bond character between the central carbon and the benzene rings) as is required for the resonance of the free radical, and this resonance must be damped in a carbanion which cannot occupy the coplanar position which this double-bond character demands. This explanation leaves something to be desired since, according to it, the central hydrogen atom should still be as acidic as the hydrogens in the *o*-methyl groups themselves, which are easily replaced by potassium. The second possible explanation is that the transfer of the central proton to the base, phenyldimethylcarbanion, naturally requires these two molecules to come into direct juxtaposition in the act of effecting the transfer. The hindrance in tri-*o*-tolylmethane is probably sufficient to make an effective collision of this kind very improbable. If this is the correct explanation, it is a rare example of prohibitive steric hindrance to a reaction which is essentially an acid–base interchange.

Another explanation has been considered, based upon the fact that only the acid and not the potassium derivative has been isolated and analyzed. The precipitated potassium derivative might in fact be a tetra-potassium compound, but the *carbonation* of the central potassium might be prohibitively hindered, in which case this link would merely be hydrolyzed eventually with the formation of the tribasic acid. Against this is the high yield of triacid on the basis of phenylisopropylpotassium used: 0.024 mole of the latter metalated 0.0073 mole of tri-*o*-tolylmethane with the final isolation of 0.0071 mole of pure triacid. The hypothesis of hindered carbonation would demand the waste of one potassium atom in four, which did not occur.

The fact that the *o*-methyl groups are metalated in the tri-*o*-tolylmethane, less in the di-*o*-tolylphenylmethane and not at all in *o*-tolyldiphenylmethane is probably not a sign of any enhanced activity of the side-chain hydrogens in the first compound, but merely a case of a reaction proceeding in the direction of the first insoluble product. We have observed a similar example in the interaction of excess phenylisopropylpotassium with toluene in dry ether solution to yield benzylpotassium. The difference in acidity of the α-hydrogen in the two benzene derivatives is probably small, but the equilibrium is shifted toward benzylpotassium by reason of its insolubility.

In contrast to the observations of Conant and Wheland[5] in the case of the exchange between triphenylmethane and phenylisopropylpotassium, in which the reaction was judged to go to completion almost instantaneously, the corresponding exchanges involving the various tolylmethanes appeared to proceed slowly, over a period of hours, to an equilibrium between the hydrocarbons and potassium derivatives involved. This may be regarded as somewhat favoring the idea that there is hindrance to the actual metal-exchange reaction and not merely to the carbonation, in the case of the tri-*o*-tolylmethane.

Experimental

Preparation of the Hydrocarbons

Di-*o*-tolylphthalide (I).[4]—To 75 g. of magnesium in a three-necked flask equipped with a mercury-sealed stirrer was added 370 cc. of *o*-bromotoluene in 1 liter of absolute ether over the course of seven hours. It was often necessary to add a crystal of iodine in order to start the reaction. After all the bromo compound had been added and the ether solution had ceased boiling, a hot suspension of 215 g. of phthalic anhydride in 2250 cc. of anhydrous benzene was added at a rate such that the solution boiled gently (two hours), after which the solution was allowed to stand overnight at room temperature. Decomposition by dilute

hydrochloric acid and steam distillation of the solvents produced a yellow solid from which the last traces of solvent were removed with difficulty. The residue was boiled with five 2-liter portions of 8% aqueous sodium hydroxide, filtered, washed thoroughly with water and sucked dry. Crystallization from glacial acetic acid produced 280 g. (61.5%) of the phthalide in two crops, m. p. 173–176°, suitable for use in the next step.

Di-*o*-tolylphenylmethane-*o*-carboxylic Acid (II).—A mixture of 31.4 g. of the phthalide and 3.0 g. of copper chromite 37KAF was shaken under hydrogen at 2325 lb. initial pressure and at 235°. In ten minutes the temperature had risen to 250° and the theoretical amount of hydrogen had been absorbed. The product was dissolved in 500 cc. of hot 1% aqueous sodium hydroxide and filtered to remove the catalyst. Acidification of the filtrate produced a white solid which was separated and crystallized from glacial acetic acid. There was obtained 26.2 g. (83%) of colorless needles in two crops, m. p. 241–242°. The acid was suitable for use in the next steps without further purification. Larger runs on one mole of slightly less pure phthalide afforded yields of 70–75%.

In one preliminary run a mixture of 6.28 g. of the phthalide, 0.6 g. of copper chromite, and 10 cc. of dioxane was shaken with hydrogen at 2000 lb. and 250°. In eight hours the theoretical amount of hydrogen had been absorbed. The contents of the bomb were added to 25 cc. of a hot 10% sodium hydroxide solution and the catalyst filtered. A small amount of an oily substance insoluble in alkali was noted at this point. Acidification produced a white precipitate which was crystallized from ethanol after being decolorized by Norit. Five fractional crystallizations afforded 3.24 g. (51%) of the monoacid and 0.18 g. (2.8%) of neutral colorless rhombic plates, m. p. 145.5–146.0°.[7] Mixed melting points with phthalide and with the monoacid were lower.

Anal.[8] Calcd. for $C_{22}H_{20}O_2$: C, 83.50; H, 6.38. Found: C, 83.78, 84.37, 84.31; H, 6.00, 6.13, 5.95.

Because of the small amount of material obtained and the fact that in no other reductions was it isolated, it was not investigated further. The analysis did not correspond to that calculated for any logical reduction product.

Di-*o*-tolylphenylmethane-*o*-carboxylic Acid Anilide (III).—To a suspension of 95.0 g. of the monoacid in 200 cc. of anhydrous benzene was added 65 g. of phosphorus pentachloride. After the initial vigorous reaction at room temperature had subsided, the solution was refluxed with gentle heating for one hour. The solvent and phosphorus oxychloride were removed by vacuum distillation at 120° (10 mm.), and 100 cc. of aniline was added. The solution became very hot and slowly solidified on cooling. The solid was dissolved in benzene–ether, and the solution was extracted with dilute hydrochloric acid, washed with a solution of 10% sodium carbonate, and finally with water. After drying over sodium sulfate, the solution was boiled down to a volume of about 100 cc. and 300 cc. of ligroin (70–90°) was added. Cooling to 0° produced a dark crystalline solid which was filtered and sucked dry. Crystallization from ethanol at 0° after clarification by Norit afforded 83.4 g. (71%) of the anilide in three crops, m. p. 163–165°. The third crop (5.2 g.) was somewhat dark in color, but it could be used in the next step without further purification.

Repeated crystallization from ethanol did not produce a product having a sharp melting point and seemed to cause some decomposition. The anilide crystallized from benzene–hexane in clusters of colorless prisms, m. p. 164.0–164.7°.

Anal. Calcd. for $C_{28}H_{25}ON$: C, 85.90; H, 6.44; N, 3.58. Found: C, 85.62, 86.33; H, 6.61, 6.69; N, 3.63.

Di-*o*-tolylphenylmethane-*o*-aldehyde (V).—To a solution of 66.0 g. of the anilide in 80 cc. of dry toluene was added 50.0 g. of phosphorus pentachloride. After the initial reaction at room temperature had subsided, the solution was heated on the steam-bath for one and one-half hours. The viscous oily residue remaining after removal of the toluene and phosphorus oxychloride by vacuum distillation at 100° was poured into a solution of 125 g. of anhydrous stannous chloride in 500 cc. of absolute ether saturated with dry hydrogen chloride at 0°. The mixture slowly turned deep red, two phases formed, and an orange-red solid crystallized from the solution. After two days the complex was filtered and boiled for four hours with 300 cc. of 3 *N* hydrochloric acid. The yellow solid was filtered, washed with water and sucked dry. There was obtained 22.4 g. (44%) of the aldehyde melting at 124–132° with previous sintering at 120°. This product was suitable for the next step without purification.

The aldehyde was purified best by sublimation at 140–150° (3 mm.). It formed colorless prisms, m. p. 134.5–135.5°, with previous sintering at 131°. The later sublimates were yellow but had essentially the same melting point.

Anal. Calcd. for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 88.18; H, 6.83.

The **oxime** crystallized from ligroin (70–90)–(90–120) in pale yellow micro-crystalline prisms, m. p. 174.8–175.2°.

Anal. Calcd. for $C_{22}H_{21}ON$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.64; H, 6.70; N, 4.92, 4.62.

In an attempt to make the semicarbazone colorless blades were obtained which melted at 208.5–209.5°, after crystallization three times from ethanol–water. Recrystallization and drying at 150° *in vacuo* did not alter the analysis.

Anal. Calcd. for $C_{23}H_{22}ON_3$: C, 77.50; H, 6.22; N, 11.08. Calcd. for: $C_{23}H_{24}O_2N_3$: C, 73.78; H, 6.46; N, 11.22. Found: C, 75.29, 75.33, 75.51; H, 6.49, 6.40, 6.51; N, 10.46.

All attempts to make a pure hydrazone failed. It is very likely that the aldehyde group is too hindered to allow the formation of a stable hydrazone.

Tri-*o*-tolylmethane (VI).—A mixture of 29.0 g. of the aldehyde, 4.0 g. of sodium dissolved in 50 cc. of absolute ethanol, and 30 cc. of 85% aqueous hydrazine hydrate was heated in the autoclave at 200–210° for twenty-four hours. The contents of the bomb were neutralized with dilute acetic acid and the hydrocarbon was extracted with benzene–ether. The residue obtained after boiling the extract to dryness was dissolved in ethanol and 10 g. of semicarbazide hydrochloride and 20 g. of sodium acetate were added

(7) All melting points below 230° are corrected. Those above 230° were made on a copper block and are correct to ±2°.

(8) All microanalyses are by Miss E. Werble.

to the boiling solution. Water was added until the solution became milky, and the hydrocarbon crystallized on cooling. Recrystallization from ethanol after decolorizing with Norit produced 15.8 g. (83%) of colorless blades, m. p. 130.5–131.5°, in three crops. The melting point of the product was similar to that of camphor in that noticeable sintering was observed about 4–5° below the true melting point. Slight amounts of impurities caused large depressions in the melting point.

Anal. Calcd. for $C_{22}H_{22}$: C, 92.26; H, 7.74. Found: C, 91.07, 92.03; H, 7.90, 7.75.

Diphenyl-*o*-tolylmethane.[9]—To 7.0 g. of magnesium was added a small amount of a solution of 50 g. of *o*-bromotoluene in 100 cc. of absolute ether. After the reaction had been started by the addition of a few drops of an ethylmagnesium bromide solution, the rest of the *o*-bromotoluene solution was added with stirring over the course of three and one-half hours, and the reaction mixture was refluxed for one and one-half hours longer. A solution of 18.0 g. of benzophenone in 100 cc. of dry benzene was added and the resulting solution was refluxed overnight. On decomposing the reaction mixture with dilute sulfuric acid and distilling volatile by-products with steam, there was obtained a viscous reddish-orange oil, which was taken up in ether. After removal of the ether, the residual oil was refluxed with 100 cc. of 85% formic acid[10] until the evolution of carbon dioxide ceased. The mixture was poured into water and extracted with ether. The ether extract was washed with 10% sodium hydroxide solution and by water and was dried over potassium carbonate. Vacuum distillation produced a colorless oil, b. p. 180–210° (9 mm.), which solidified on standing. Crystallization from methanol after cooling in ice afforded 13.5 g. (53%) of colorless prisms, m. p. 81–83°, in two crops. Recrystallization for use in the exchange experiments did not alter the melting point of the hydrocarbon.

Phenyldi-*o*-tolylmethane.[12]—The phenyldi-*o*-tolylcarbinol was prepared by the above procedure using 9.7 g. of magnesium, 62.8 g. of *o*-bromotoluene and 23.0 g. of ethyl benzoate. Treatment of the crude carbinol with 85% formic acid and vacuum distillation of the ethereal extract produced a colorless oil, b. p. 190–220° (11 mm.), which solidified on scratching. Crystallization from methanol afforded 18.7 g. (45%) of colorless prisms of the hydrocarbon, m. p. 100–104°. Recrystallization for use in the exchange reaction raised the melting point to 102–104°.

Tri-*p*-tolylmethane.—Tri-*p*-tolylchloromethane (14.0 g.), m. p. 163–168°, prepared by the method of Tousley and Gomberg,[11] was boiled under reflux with 100 cc. of 85% formic acid. Isolation by the usual procedure produced 10 g. (80%) of a colorless oil, b. p. 232° (11 mm.). Since a crystalline product could not be obtained, the oil was used in the exchange reaction.

Exchange Reactions with Phenylisopropyl Potassium

Tri-*o*-tolylmethane.—To 5.0 g. of tri-*o*-tolylmethane under an atmosphere of nitrogen was added 400 cc. of a 0.059 *N* ethereal solution of phenylisopropylpotassium. The resulting solution was allowed to stand at room temperature in the dark for twenty-four hours, during which time the deep red color slowly faded and an orange-red solid crystallized. Dry carbon dioxide was passed through the mixture slowly until all of the solid had been decolorized. By extraction of the ether suspension of the potassium salt with water and acidification of the extract with hydrochloric acid, there was obtained a white flocculent precipitate. Filtration and crystallization of the residue from glacial acetic acid afforded 2.95 g. (98.3% on the basis of the hydrocarbon used in the reaction) of microcrystalline prisms of the triacid (IX) in two crops. When heated on the copper block, the compound decomposed over the range 265–295°, but when it was dusted on the block at 310° and above, the product melted with subsequent decomposition. The triacid dissolves in concentrated sulfuric acid and can be recovered unchanged by dilution of the solution with water. Heating the sulfuric acid solution to 100° does not change the acid.

Anal. Calcd. for $C_{25}H_{22}O_6$: C, 71.76; H, 5.30; neut. equiv., 139.5. Found: C, 71.94; H, 5.50; neut. equiv., 139, 141.

After removal of the ether from the ether layer in the above extraction, there was obtained an oil from which 2.4 g. (86%) of isopropylbenzene, b. p. 150–160°, was distilled. The residue consisted of slightly impure tri-*o*-tolylmethane (2.9 g.) from which there was obtained 2.6 g. of pure hydrocarbon on crystallization from ethanol after decolorizing with Norit.

The **triethyl ester** was prepared by saturating a suspension of the acid in absolute ethanol with dry hydrogen chloride and refluxing it for twenty-four hours. At the end of this time the mixture was cooled and filtered. Recrystallization of the residue from ethanol afforded colorless blades, m. p. 196.5–197.5°.

Anal. Calcd. for $C_{31}H_{34}O_6$: C, 74.08; H, 6.82. Found: C, 74.08; H, 6.91.

Diphenyl-*o*-tolylmethane.—The solution from the addition of 200 cc. of a 0.059 *N* ethereal solution of phenylisopropylpotassium to 3.0 g. of diphenyl-*o*-tolylmethane was allowed to stand in the dark at room temperature for twenty-four hours. During this time the color of the solution did not change appreciably, and a small amount of a reddish-orange solid precipitated. Dry carbon dioxide was bubbled through the solution until it had been decolorized completely, and the white suspension was extracted with water. Acidification of the aqueous extract and crystallization of the residue from glacial acetic acid afforded 1.73 g. (98.7% based on the hydrocarbon used) of **diphenyl-*o*-tolylacetic acid** as colorless prisms, m. p. 228–229°. On a copper block the acid melts with decomposition at 190–200°.

A solution of 0.8 g. of the acid in 20 cc. concentrated sulfuric acid started evolving carbon monoxide at an appreciable rate at 50° and slowly changed in color from yellow to bright reddish-orange. On pouring the solution into water there was obtained a white suspension which was extracted with ether. A red color and all fluorescence from the ether solution were removed by washing it with 10% sodium hydroxide solution. Drying over potassium carbonate and removal of the ether produced 0.6 g. (82.5%) of diphenyl-*o*-tolylcarbinol, m. p. 95–98°. Recrystallization

(9) Acree, *Ber.*, **37**, 993 (1904).

(10) Kaufmann and Pannwitz, *ibid.*, **45**, 766 (1912); Kovache, *Ann. chim.*, [9] **10**, 184 (1918).

(11) Tousley and Gomberg, THIS JOURNAL, **26**, 1516 (1904).

from ligroin (70–90°) raised the melting point to 98–99° (lit., 98°).[9]

Anal. Calcd. for $C_{21}H_{18}O_2$: C, 83.35; H, 6.00; CO, 9.26; neut. equiv., 302.4. Found: C, 82.66, 83.72; H, 5.92, 6.00; CO, 8.94; neut. equiv., 298.

From the ether solution after removal of the acid was isolated 1.0 g. of isopropylbenzene and 1.5 g. of impure diphenyl-*o*-tolylmethane.

In another run in which 4.0 g. of the hydrocarbon was used and the reaction time was extended to forty-eight hours, there was obtained 2.25 g. of the acid.

Phenyldi-*o*-tolylmethane.—Upon standing for forty-eight hours in the dark at room temperature, a solution of 8.8 g. of phenyldi-*o*-tolylmethane in 400 cc. of a 0.059 *N* ethereal solution of phenylisopropylpotassium deposited a red-black film on the sides and bottom of the flask. Carbon dioxide was bubbled through the deep red solution until it and the sediment had been decolorized. The pale orange suspension was extracted with water, and the cold extract was acidified. Extraction with ether and evaporation of the ethereal solution produced a yellow oil which was taken up in dilute sodium hydroxide, filtered, and reprecipitated with acid. There was obtained 3.5 g. of a colorless product (neut. equiv., 318), m. p. 100–140°, which was a mixture of **phenyldi-*o*-tolylacetic acid** and a dibasic acid.

The high neutral equivalent shows that some inert material, possibly hydrocarbon retained in the aqueous layer in the extraction process, must be present in the crude mixture. From the ether solution after removal of the salts were obtained 2.0 g. of isopropylbenzene and 5.6 g. of the methane.

The crude product was boiled with two 300-cc. portions of ligroin (70–90°), and the filtered solution was allowed to crystallize at 0°. Three further crystallizations afforded 3.0 g. (80.7% based on the hydrocarbon used) of clusters of colorless prisms, m. p. 184.0–185°.

As the powdered acid dissolved at room temperature in concentrated sulfuric acid it started evolving carbon monoxide immediately at a high rate, and the color of the solution changed rapidly from orange to deep red. After the initial reaction had subsided, the removal of the carbon monoxide was completed by heating the solution to 100°.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37; CO, 8.83; neut. equiv., 316.4. Found: C, 83.65; H, 6.80; CO, 8.94; neut. equiv., 315.

Working up the product from the above carbon monoxide fission by the procedure outlined previously produced only a viscous red oil. By repeating the reaction but allowing the solution to stand at room temperature without heating until the reaction was complete, a colorless substance, m. p. 68–73°, could be isolated from the reaction mixture. Crystallization from ligroin (70–90°) gave colorless prisms with the same melting point. The product dissolved in concentrated sulfuric acid with an orange color.

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.34; H, 6.62.

Since presence of ketonic cleavage products was suspected, the substance was dissolved in ethanol with hydroxylamine hydrochloride and a few cc. of 10% sodium hydroxide solution was added. On evaporation the solution became cloudy, and cooling caused the separation of a colorless oil. Crystallization of the oil from ligroin (70–90°) produced a small amount of colorless prisms, m. p. 82–95°, possibly impure phenyldi-*o*-tolylcarbinol (m. p. 107–108°).[12] There was too little material for further crystallization.

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 86.98; H, 6.93.

From the ethanol solution there crystallized after further evaporation a small amount of colorless prisms, m. p. 75–81°, possibly impure di-*o*-tolylketoxime (m. p. 105°).[13]

Anal. Calcd. for $C_{15}H_{15}ON$: C, 79.97; H, 6.71. Found: C, 80.43; H, 7.03.

The residue from the ligroin extraction of crude phenyldi-*o*-tolylacetic acid was crystallized from glacial acetic acid, and there was obtained 0.30 g. (7.1%) of a dibasic acid in microscopic prisms, m. p. 265–267°, dec. A mixed melting point with the acetic acid was forty degrees lower. Its bright orange solution in concentrated sulfuric acid did not evolve carbon monoxide even at 125°, but all attempts to isolate any cleavage products or the unchanged acid were unsuccessful.

Anal. Calcd. for $C_{23}H_{20}O_4$: C, 76.65; H, 5.59; neut. equiv., 180.2. Found: C, 76.85; H, 5.89; neut. equiv., 182.

The **dimethyl ester**, prepared by refluxing a methanol solution of the acid saturated with dry hydrogen chloride for two hours, crystallized from methanol in colorless needles, m. p. 105.0–106°.

Anal. Calcd. for $C_{25}H_{24}O_4$: C, 77.31; H, 6.23. Found: C, 77.56; H, 6.24.

In a reaction in which a solution of 11.7 g. of the hydrocarbon and 10 g. of the methyl ether of phenyldimethylcarbinol in 400 cc. of absolute ether was shaken with sodium–potassium alloy (80% potassium) for three days, there was obtained 3.2 g. of the dibasic acid from 7.6 g. of hydrocarbon used up in the reaction. This doubling of concentration shifted the product composition in favor of the more insoluble product, a dipotassium derivative of the hydrocarbon.

Tri-*p*-tolylmethane.—A solution of 6.0 g. of tri-*p*-tolylmethane in 450 cc. of a 0.059 *N* ethereal solution of phenylisopropylpotassium was carbonated after standing for twenty-six hours. Acidification of the aqueous extract and crystallization from glacial acetic acid afforded 3.3 g. (73.5% based on the hydrocarbon used) of tri-*p*-tolylacetic acid as colorless prisms, m. p. 224–226° (lit.,[14] 226–228°).

Anal. Calcd. for $C_{23}H_{22}O_2$: CO, 7.84; neut. equiv., 320.4. Found: CO, 8.68; neut. equiv., 332.

The solution of the acid in sulfuric acid started evolving carbon monoxide slowly at 50–60° and the reaction was completed at 100°. Working up the product in the usual way afforded the tri-*p*-tolylcarbinol, m. p. 85–88°. Crystallization twice from ligroin (70–90°) raised the melting point to 92–94° (lit.,[11,15] 94°, 96.4°).

(12) Bredereck, Lehmann, Schönfeld and Fritzsche, *Ber.*, **72**, 1414 (1939).

(13) Grignard, Bellet and Cortot, *Ann. chim.*, [9] **12**, 381 (1919).

(14) Schmidlin and Hodgson, *Ber.*, **41**, 438 (1908).

(15) Kovache, *Ann. chim.*, [9] **10**, 199 (1918); Motwurf, *Ber.*, **37**, 3153 (1904).

From the ether solution there were isolated 2.55 g. of isopropylbenzene and 2.0 g. of tri-*p*-tolylmethane, b. p. 230–240° (13 mm.). The recovered methane contained an impurity, probably an anthracene derivative, which exhibited an intense blue–violet fluorescence. Not all the unused hydrocarbon was recovered as some of it could not be distilled from the tar remaining in the distilling flask, and some was carried into the aqueous layer by the salt in the extraction process.

Summary

Tri-*o*-tolylmethane undergoes slow exchange with phenylisopropylpotassium to yield a tripotassium derivative which is converted by carbonation into the potassium salt of triphenylmethane-2,2′,2″-triacetic acid. The related compounds, phenyldi-*o*-tolylmethane, diphenyl-*o*-tolylmethane and tri-*p*-tolylmethane, under the same conditions, all form monopotassium derivatives which by carbonation yield triarylacetic acids. Explanations based upon damped resonance and steric hindrance are considered for the relative inertness of the central carbon atom of tri-*o*-tolylmethane.

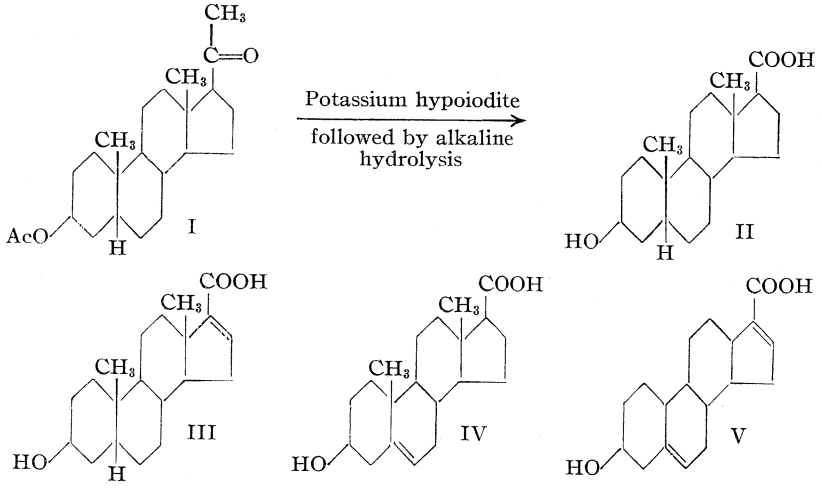
CAMBRIDGE, MASSACHUSETTS RECEIVED MAY 19, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. CXLIX. The Hypoiodite Oxidation of Pregnanolones and Pregnenolones

BY RUSSELL E. MARKER AND R. B. WAGNER

St. Goldschmidt, Middelbeek and Boasson[1] have recently shown that the claims of various patents[2] to the oxidation of 5-pregnen-3(β)-ol-20-one acetate with hypoiodite to obtain 3(β)-hydroxy-etio-5-cholenic acid are erroneous. We have investigated this type of reaction, treating not only 5-pregnen-3(β)-acetoxy-20-one but also 16-pregnen-3(β)-acetoxy-20-one, pregnan-3(β)-acetoxy-20-one (I) and 5,16-pregnadien-3(β)-acetoxy-20-one with excess hypoiodite. The reactions used by us gave in every case the corresponding etio-cholanic (II) and etio-cholenic acids (III), (IV), (V).



We wish to thank Parke, Davis and Company for their assistance.

(1) St. Goldschmidt, Middelbeek and Boasson, *Rec. trav. chim.*, **60**, 209 (1941).

(2) British Patent 493,055; French Patent 819,974; Swiss Patent 197,580; U. S. Patent 2,171,959.

Experimental

3(β)-Hydroxy-etio-cholanic Acid.—To a solution of 2 g. of pregnan-3(β)-ol-20-one acetate in 300 cc. of dioxane was added simultaneously in 5-cc. portions, 80 cc. of an aqueous solution of 20 g. of potassium iodide and 10 g. of iodine, and 80 cc. of an aqueous 10% potassium hydroxide solution. The mixture was stirred at room temperature for one hour and then warmed to 80°. The reaction mixture was cooled and acidified. After the excess iodine was destroyed with sodium bisulfite, the mixture was concentrated *in vacuo* and extracted with ether. The etheral solution was washed with 10% potassium hydroxide and the combined alkaline washings were warmed for thirty minutes on a steam-bath. After acidification the solid was extracted with ether. The product crystallized from methanol as white needles; m. p. and mixed m. p. with 3(β)-hydroxy-etio-cholanic acid, 224–226°; yield 0.6 g.

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 74.9; H, 10.1. Found: C, 74.6; H, 10.0.

The methyl ester was prepared by treating an ethereal solution of 50 mg. of the above acid with an ethereal solution of diazomethane. The solvent was evaporated and the residue crystallized from methanol to give white needles; m. p. 128°. This material gave no depression in the melting point of the methyl ester of an authentic sample of 3(β)-hydroxy-etio-cholanic acid methyl ester.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.4; H, 10.3. Found: C, 75.6; H, 10.2.

3(β)-Hydroxy-etio-16-cholenic Acid.—A solution of 2 g. of 16-pregnen-3(β)-ol-20-one acetate in 300 cc. of dioxane was treated as described above with hypoiodite. After hydrolysis the product crystallized from methanol; m. p.

254–256°; yield 0.3 g. This substance gave a 10° elevation when mixed with 3(β)-hydroxy-17,20-pregnenoic acid-21; m. p. 254–256°.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.6; H, 9.5.

The methyl ester was prepared as described above. It crystallized from methanol as white plates; m. p. 150–152°. It depressed the melting point of the methyl ester of 3(β)-hydroxy-17,20-pregnenoic acid-21 (m. p. 153–155°) twenty-five degrees.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.9; H, 9.8. Found: C, 75.8; H, 9.8.

Catalytic Reduction of 3(β)-Hydroxy-etio-16-cholenic Acid.—A solution of 100 mg. of the above 3(β)-hydroxy-etio-16-cholenic acid in 100 cc. of acetic acid was shaken with hydrogen and Adams catalyst for two hours at 3 atm. pressure and room temperature. The reaction mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was crystallized from methanol as white needles; m. p. and mixed m. p. with 3(β)-hydroxy-etio-cholanic acid, 224–227°. A mixed melting point with 3(β)-hydroxy-pregnanoic acid (m. p. 219–221°) was at 195°.

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 74.9; H, 10.1. Found: C, 75.0; H, 10.0.

3(β)-Hydroxy-etio-5-cholenic Acid.—From the reaction of 2 g. of 5-pregnen-3(β)-ol-20-one acetate with potassium hypoiodite as described above was isolated a product which crystallized from dioxane; m. p. and mixed m. p. with an authentic sample of 3(β)-hydroxy-etio-5-cholenic acid, 273–274°; yield 0.2 g. pure product.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.2; H, 9.3.

3(β)-Hydroxy-etio-5,16-choladienic Acid.—From the reaction of 2 g. of 5,16-pregnadien-3(β)-ol-20-one acetate as described above was isolated a product which crystallized from methanol as white plates; m. p. 255–257°; yield 250 mg.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.9; H, 8.9. Found: C, 76.0; H, 8.8.

Summary

Conditions are described for the hypoiodite oxidation of 20-keto-pregnane derivatives to the corresponding 20-carboxylic acids. 3(β)-Hydroxy-etio-cholanic (II), 3(β)-hydroxy-etio-16-cholenic (III), 3(β)-hydroxy-etio-5-cholenic (IV), and 3(β)-hydroxy-etio-5,16-choladienic (V) acids have been produced by this method.

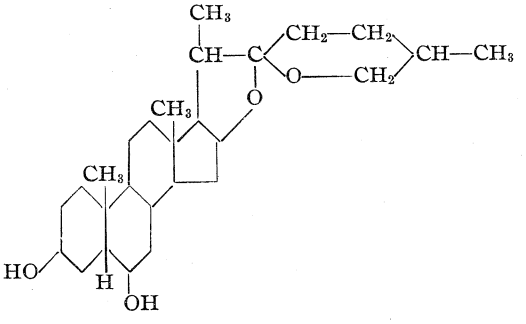
STATE COLLEGE, PENNA. RECEIVED APRIL 15, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. CL. Sapogenins. LXIII. The Position of the Hydroxyl Groups in Digitogenin*

BY RUSSELL E. MARKER, D. L. TURNER AND PAUL R. ULSHAFER

The position of the hydroxyl groups in chlorogenin has been established with certainty by a large number of interconversions reported from this Laboratory[1,2,3] and chlorogenin is undoubtedly 6-hydroxy-tigogenin (I). However, Noller[4]



is unable to reconcile this structure of chlorogenin with the fact that the oxidation of chlorogenin gives a keto-dibasic acid which is neither identical to digitoic acid nor to digitogenic acid. A revision of Noller's interpretation of the non-identity of the two acids is now necessary since the structure of chlorogenin is certain.

We find that oxidation of 6-keto-tigogenone[2,3] (tigogen-3,6-dione) prepared from diosgenin gives a keto-dibasic acid identical to that from natural chlorogenin and this acid differs from digitoic and digitogenic acid. The keto-dibasic acid melts with decomposition and gas evolution. Cholestane-3,6-dione was oxidized by Windaus[5] to a ketodibasic acid which melts with decomposition and gas evolution. This acid can be converted by Wolff–Kishner reduction[6] to cholestane–2,3–diacid the structure of which is certain.[6,7] We have also effected this reduction by the Clemmensen method. It, therefore, seems reasonable to suppose that the oxidation of 6-keto-tigogenone

* Original manuscript received July 2, 1941.

(1) Marker, *et al.*, THIS JOURNAL, **61**, 946 (1939); **61**, 1516 (1939); **62**, 2525 (1940); **63**, 767 (1941); **64**, 221 (1942).

(2) Marker, Jones and Turner, *ibid.*, **62**, 2537 (1940).

(3) Marker, Jones, Turner and Rohrmann, *ibid.*, **62**, 3006 (1940).

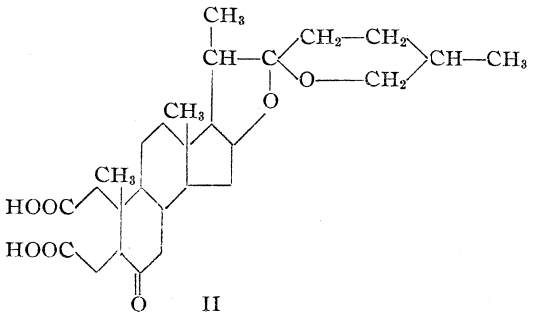
(4) Noller, *ibid.*, **59**, 1092 (1937).

(5) Windaus, *Ber.*, **36**, 3752 (1903).

(6) Windaus, Staden and Seng, *Z. physiol. Chem.*, **117**, 146 (1921).

(7) Windaus, *ibid.*, **213**, 147 (1932).

takes a similar course and gives an acid of structure II. Noller[8] found that the acid from chloro-

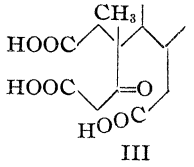


II

genin which he has named chlorogenonic acid can be reduced by the Wolff–Kishner method to gitogenic acid. Consequently, structure II is secure for chlorogenonic acid.

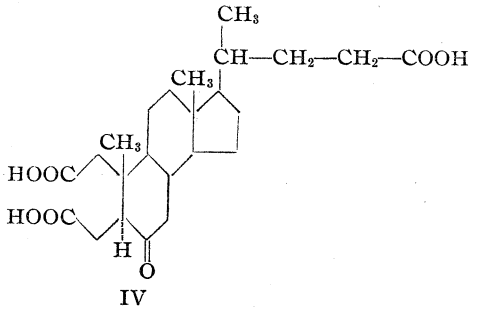
Neither digitogenic acid nor digitoic acid can have the same structure as chlorogenonic acid. Tschesche[9] has shown that digitogenic acid can be reduced to gitogenic acid and this indicates that two of the hydroxyl groups of digitogenin are at C–2 and C–3. If the third hydroxyl group of digitogenin is at C–6 as assumed by Tschesche, digitogenic acid and digitogenin would probably be of the coprostane configuration and digitoic acid of the cholestane configuration since the last acid is the stable form.[10,11,12] The side-chains of chlorogenin and digitogenic acid are the same because they have both been related to tigogenin. All three sapogenins are unaffected by treatment with hydrochloric acid in ethanol at the boiling point. This indicates that they all have the iso-configuration of the side-chain.[13]

The fact that chlorogenonic acid is not identical with digitoic acid therefore indicates that the assumption of Tschesche concerning the 6-position of the third hydroxyl group in digitogenin is incorrect.[14] Moreover the reactions of digitogenic acid and digitoic acid are completely different from those which would be expected from the known behavior of 6-keto-cholestane-2,3-diacid and similar substances of established structure. Thus 6-cholestanone was oxidized by Windaus[15] to cholestane-6,7-diacid using chromic acid or nitric acid.[16] The oxidation of digitogenic acid and digitoic acid, whether with permanganate or chromic acid, gives acids supposed by Tschesche to have structure III. These acids include oxydigitogenic acid, digitic acid[17] and acid "A" of Windaus and Willerding.[18] It would be peculiar that digitogenic and digitoic acids should not be oxidized to a 6,7-diacid if there was really a carbonyl group at C–6.



III

Much more significant is the result of catalytic reduction of digitoic and digitogenic acids. We have now found that hydrogenation in ethanol or acetic acid gives a hydroxydicarboxylic acid, the same acid being obtained from both digitoic acid and digitogenic acid. The fact that this product is not a lactone is incompatible with the supposed carbonyl group at C–6. Hyodesoxy-iso-bilianic acid (IV) was catalytically reduced by Windaus[11]



IV

and the resulting 6-hydroxy-"Staden acid" was not capable of existence as a hydroxy-acid, but immediately gave a lactone. The formation of lactones following the reduction of 6-keto-2,3-diacids of the type of IV is a general phenomenon.[19] Thus we have observed lactone formation in the reduction of 6-keto-cholestane-2,3-diacid. Only one carboxyl group of the product can be titrated in the cold.

It is interesting that the 6-keto-2,3-diacids melt with decomposition and gas evolution, *e. g.*, 6-keto-cholestane-2,3-diacid,[5] and chlorogenonic acid. This is not reported for digitogenic acid nor digitoic acid. The ester of digitoic acid can be distilled unchanged[18] *in vacuo*, and the ester of digitogenic acid is converted to that of digitoic acid. Distillation of the trimethyl ester of 6-

(8) Private communication from Professor Noller to one of us.
(9) Tschesche and Hagedorn, *Ber.*, **68**, 1090 (1935).
(10) Tschesche and Hagedorn, *ibid.*, **69**, 797 (1936).
(11) Windaus, *Ann.*, **447**, 233 (1926).
(12) Stange, *Z. physiol. Chem.*, **220**, 34 (1933).
(13) Marker and Rohrmann, THIS JOURNAL, **62**, 647 (1940).
(14) Fieser, "Chemistry of Natural Products related to Phenanthrene," 2nd. edition, New York, N. Y., 1937.
(15) Windaus and Dalmer, *Ber.*, **52**, 162 (1919).
(16) *Cf.* Windaus and Staden, *ibid.*, **54**, 1059 (1921).
(17) Windaus and Weil, *Z. physiol. Chem.*, **121**, 62 (1922).
(18) Windaus and Willerding, *ibid.*, **143**, 33 (1925).
(19) *Cf.* Windaus and Hoszfeld, *ibid.*, **145**, 177 (1925).

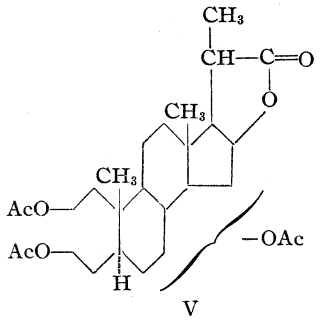
keto-Staden acid gives an unsaturated lactone with the loss of methyl alcohol.[20]

Another observation inconsistent with the C–6 position for the hydroxyl group in digitogenin is the fact that digitogenin was recovered unchanged after distillation with potassium bisulfate a method which readily dehydrates chlorogenin to 3,5-dehydrodesoxytigogenin.[21] In the case of hyodesoxycholic acid a similar dehydration occurs even more readily. Windaus[11,22] records that this acid gives hyocholadienic acid by simple distillation *in vacuo*.

Since it is impossible that digitogenin should have a hydroxyl group at C–6 it is necessary to revise all of the formulas proposed by Tschesche for the oxidation products of digitogenic acid. This is a difficult task at present because the assumption of Tschesche that oxydigitogenic acid, digitic acid, anhydrodigitic acid and their derivatives had an intact sapogenin side-chain is by no means a necessary one. Indeed, there are some indications that this may be true only of digitogenic and digitoic acids. Oxydigitogenic acid and digitic acids were prepared by treating digitogenic acid with alkaline permanganate. We have found that sarsasapogenin is oxidized to some extent by alkaline permanganate at room temperature, and this involves alteration of the side-chain.

Windaus and Weil[17] also treated oxydigitogenic acid with hydrochloric acid in acetic acid to decarboxylate it. Similar treatment of digitic acid gave anhydrodigitic acid. Heating a solution of sarsasapogenin or of gitogenin in acetic acid containing hydrochloric acid has been shown by Jacobs and Simpson[23] to remove the entire side-chain.[24] Windaus[17] records that similar treatment of oxydigitogenic acid merely caused the loss of 1 mole of carbon dioxide. The chemistry of the various acids obtained from digitogenic and digitoic acids is quite confused. It should be pointed out that the reasons given by Tschesche for considering oxydigitogenic acid a β-keto acid rather than an α-keto acid, as preferred by Windaus and Willerding,[18] depended on the 6-position of the hydroxyl group in digitogenin. The work of Bistrzycki and Siemiradzki[25] cited by Tschesche[10] is not relevant since oxydigitogenic acid loses carbon monoxide by simple heating without treatment with sulfuric acid.

In the case of acid "A" of Windaus and Willerding there is not only a difference of opinion between Windaus and Tschesche about the structure of the acid but even about the experimental facts. Indeed, it appears that only the following facts are known with any certainty about digitogenin. Two of the nuclear hydroxyl groups are at C–2 and C–3, the side-chain is identical to that of tigogenin and chlorogenin and the third hydroxyl group is adjacent to an asymmetric carbon atom and it is not at C–6. In addition the configuration at C–5 is *allo* since digitogenic acid has been converted to gitogenic acid and the side-chain is of the iso-configuration. The fact that digitogenin triacetate has been oxidized to the triacetate of a C_{22} lactone (V) by Marker and Rohrmann[26] indicates that the third hydroxyl



V

group is not in the side-chain. Consequently, only the positions 6, 7, 11 and 15 seem probable. We have eliminated the 6 position in this paper. Position 11 seems improbable because digitogenic and digitoic acids readily form semicarbazones[27] and digitogenin forms a triacetate without difficulty. The oxidation of a carbonyl group at C–7 leads to the formation of dicarboxylic acids. Thus cholestane-7-one was oxidized to cholestane-6,7-diacid[28] and 7-keto-cholanic acid to thilobilianic acid[29] (cholane-6,7,24-triacid). A hydroxyl group at C–7 is also improbable in digitogenin because it is not dehydrated by distillation over potassium bisulfate. Simple distillation of 3,7-dihydroxycholanic acid converts it to the diene acid.[30]

It would be premature to locate definitely the hydroxyl group at C–15, but there are indications that this may be the case. Digitoic acid and digi-

(20) Windaus and Bohne, *Ann.*, **442**, 7 (1925).
(21) Marker and Turner, THIS JOURNAL, **63**, 767 (1941).
(22) Windaus and Bohne, *Ann.*, **433**, 278 (1923).
(23) Jacobs and Simpson, *J. Biol. Chem.*, **105**, 501 (1934).
(24) Fieser and Jacobsen, THIS JOURNAL, **60**, 28 (1938).
(25) Bistrzycki and Siemiradzki, *Ber.*, **41**, 1665 (1908).
(26) Marker and Rohrmann, THIS JOURNAL, **61**, 2724 (1939).
(27) Steiger and Reichstein, *Helv. Chim. Acta*, **20**, 817 (1937).
(28) Stange, *Z. physiol. Chem.*, **218**, 74 (1933).
(29) Wieland and Dane, *ibid.*, **210**, 268 (1932).
(30) Wieland and Reverey, *ibid.*, **140**, 186 (1924).

togenic acid would be isomeric at C–14 or at C–16. The Wolff–Kishner reduction to gitogenic acid does not exclude this. The Wolff–Kishner reduction of 6-keto-Staden acid gives both acids isomeric at C–5 although the original acid is of the stable *allo*-configuration.[7,11] Dimroth[31] has recently shown the possibility of inversion of configuration with a carbonyl group adjacent to C–14.

There are some indications that digitogenin differs from the other sapogenins in the reactions of its side-chain. This could be conditioned by a hydroxyl group at C–15. Thus we have found that dihydro-digitogenin and bromodigitogenin are formed only with difficulty. Tetrahydrodigitogenin could not be made since digitogenin was recovered unchanged when submitted to the Clemmensen reduction for twenty-four hours. This is in contrast to the behavior of the other sapogenins which give tetrahydrosapogenins readily.[21,32] Digitogenin was also largely recovered unchanged when heated with acetic anhydride in a bomb-tube under conditions which give pseudosapogenins readily.[33]

Another fact which might indicate that the hydroxyl group may be in the neighborhood of the side-chain is that Windaus[18] oxidized pure digitogenic acid to α-methylglutaric acid without detecting a trace of methylsuccinic acid. Using a similar vigorous oxidation method with digitogenin triacetate in which the hydroxyl groups are protected, we have obtained methylsuccinic acid as the major product of the oxidation. Methylsuccinic acid was obtained by Kiliani[34,18] by the vigorous oxidation of impure digitogenic acid, and, as Windaus has pointed out,[18] this probably arises from the gitogenic acid which was present as the impurity. If the hydroxyl group is at C–15 these facts can be explained readily.

Fieser,[35] in his defense of the Tschesche–Hagedorn formulation of the side-chain, has attempted to trace the formation of α-methylglutaric acid in the Windaus oxidation to an extensive degradation of the nucleus. This seems most improbable and his citation of the case of Wieland's 3,12-diketo-nor-cholane-3,24-diacid[36] does not apply because the splitting of this acid is probably due to the carbonyl group at C–12.

We thank Parke, Davis and Company for their help.

Experimental Part

6-Keto-cholestane-2,3-diacid.—To a solution of 50 g. of 3,6-dihydroxycholestane in 1500 cc. of acetic acid was added a solution of 50 g. of chromic anhydride in 500 cc. of 90% acetic acid during a period of ninety minutes. It was stirred for an additional hour at 70° on a steam-bath. Water was added and the product was extracted with ether. The ethereal solution was washed free of acetic acid and extracted with alkali. The alkaline extract was acidified with hydrochloric acid and the acid which precipitated was filtered and washed. It was crystallized from glacial acetic acid, m. p. 228–230° with bubbling.

Anal. Calcd. for $C_{27}H_{44}O_5$: C, 72.5; H, 9.9. Found: C, 72.3; H, 9.8.

Clemmensen Reduction of 6-Keto-cholestane-2,3-diacid.—To a refluxing solution of 2 g. of 6-keto-cholestane-2,3-diacid in 100 cc. of ethyl alcohol mixed with 50 g. of amalgamated zinc (20 mesh) was added 5 cc. of concentrated hydrochloric acid every fifteen minutes for four hours. Water was added and the product was extracted with ether. The ether was washed with water and the solvent was removed. The residue was hydrolyzed by refluxing with alcoholic potassium hydroxide, acidified with hydrochloric acid, and extracted with ether. The solvent was removed and the residue was recrystallized from glacial acetic acid, m. p. 194–195°, and gave no depression in mixed melting point with an authentic sample of cholestane-2,3-diacid.

Anal. Calcd. for $C_{27}H_{46}O_4$: C, 74.9; H, 10.7. Found: C, 74.8; H, 10.7.

Catalytic Reduction of 6-Keto-cholestane-2,3-diacid.—A mixture of 2 g. of 6-keto-cholestane-2,3-diacid, 500 mg. of platinum oxide catalyst and 100 cc. of acetic acid was shaken for two hours with hydrogen at 40 pounds pressure and room temperature. The catalyst was filtered and the solvent was removed *in vacuo*. The residue was crystallized from 70% acetic acid and then from methyl alcohol, in which it is quite insoluble, m. p. 188–190°.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.7; H, 10.2; neut. equiv. (for one carboxyl), 432.4. Found: C, 74.9; H, 10.4; neut. equiv. cold, 435.8.

Distillation of Chlorogenin over Potassium Bisulfate.—A mixture of 1 g. of naturally occurring chlorogenin and 5.5 g. of powdered potassium bisulfate was heated in a high vacuum at 200–210° until no more product sublimed. The sublimate was crystallized from acetone as white needles, m. p. 166–168°. When mixed with 3,5-dehydrodesoxytigogenin, prepared from diosgenin, there was no depression in melting point.

Anal. Calcd. for $C_{27}H_{40}O_2$: C, 81.7; H, 10.2. Found: C, 81.6; H, 10.4.

Catalytic Reduction of Digitogenic and Digitoic Acids.—The digitogenic acid was prepared by the oxidation of 8 g. of digitogenin at room temperature with chromic anhydride in acetic acid. The digitogenin used in these experiments

(31) Dimroth and Jonsson, *Ber.*, **74**, 520 (1941).
(32) Marker and Rohrmann, THIS JOURNAL, **61**, 746 (1939).
(33) Marker and Rohrmann, *ibid.*, **62**, 518 (1940); **62**, 898 (1940).
(34) Kiliani, *Ber.*, **49**, 702 (1916).
(35) Fieser, "Chemistry of Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 2nd. ed., p. 326.
(36) Wieland and Vocke, *Z. physiol. Chem.*, **177**, 68 (1928).

was purified by crystallization of the triacetate. The digitogenic acid can be best purified by crystallization from ether, giving a product melting at 170–172°. The digitoic acid was prepared by isomerization of digitogenic acid with alkali and was crystallized from dilute acetic acid. It is very soluble in comparison with digitogenic acid.

A mixture of 500 mg. of digitogenic acid, 500 mg. of platinum oxide catalyst and 100 cc. of methyl alcohol was shaken with hydrogen at 40 pounds pressure and room temperature for one hour. The solution was filtered and the solvent was distilled *in vacuo*. The residue was very soluble in methanol, acetic acid and ethyl acetate. It was quite insoluble in ether and pentane. It was crystallized by dissolving in a few drops of methanol and adding ether, m. p. 285–290° dec. Reduction in acetic acid gave the same product. Reduction of digitoic acid also gave the same product.

Anal. Calcd. for $C_{27}H_{42}O_7$: C, 67.8; H, 8.8; neut. equiv. (2 acid groups), 239. Found: C, 67.9; H, 8.9; neut. equiv. cold, 243.

Oxidation of 6-Keto-tigogenone.—The 6-keto-tigogenone was prepared by the oxidation of diosgenin with chromic acid, followed by boiling the oxidation product with zinc dust and water. It melted at 239–241° when crystallized from ether and gave no depression when mixed with chlorogenone obtained by the oxidation of naturally occurring chlorogenin.

To a solution of 9 g. of 6-keto-tigogenone in 400 cc. of acetic acid at room temperature was added a solution of 5.0 g. of chromic anhydride in 5 cc. of water and 25 cc. of acetic acid, keeping the temperature below 30°. It was allowed to stand at room temperature for twenty-two hours, diluted with water and extracted with ether. The ether was washed with water, followed with alkali. The alkaline extract was acidified and extracted with ether. The solvent was removed and the residue was crystallized from aqueous acetic acid, followed by crystallization from glacial acetic acid, m. p. 230° with bubbling. When mixed with chlorogenonic acid prepared by the oxidation of natural chlorogenin there was no depression in melting point.

The acid was prepared in better yield by the oxidation of 6-keto-tigogenone with Kiliani's chromic anhydride–sulfuric acid–acetic acid mixture. This product melted at 231–234° with bubbling and gave no depression in melting point when mixed with a sample of the acid prepared from naturally occurring chlorogenin.

When crystallized from ether it gave a product melting at 232–234°, whereas when digitogenic acid is crystallized from ether it melts at 170–172°. It is stable to alkali as would be expected from the cholestane configuration at C–5. When mixed with digitoic acid (crystallized from dilute acetic acid) it shrunk at 172° and ran at 210°. The acid crystallized with one mole of acetic acid of crystallization.

Anal. Calcd. for $C_{27}H_{46}O_7 \cdot C_2H_4O_2$: C, 64.9; H, 8.3. Found: C, 64.7; H, 8.5.

When treated with diazomethane it gave a dimethyl ester which melted at 156–159° when crystallized from ligroin and gave no depression in melting point when mixed with a sample of the ester prepared from natural chlorogenin.

Anal. Calcd. for $C_{29}H_{44}O_7$: C, 69.0; H, 8.8. Found: C, 69.3; H, 8.9.

Oxidation of Digitogenin Triacetate.—To a solution of 10 g. of digitogenin triacetate in 300 cc. of glacial acetic acid was added a solution of 15 g. of chromic anhydride in 100 cc. of 80% acetic acid. The product was heated on a steam-bath for ninety minutes, cooled and a small amount of water was added. The product was well extracted with ether and the total solvent was removed by vacuum distillation on a steam-bath. The residue was dissolved in ether and the acid fraction was removed by shaking with a small amount of 10% alkali. The neutral fraction upon evaporation of the ether crystallized. It was very insoluble in ether and was crystallized from acetone and from ether, m. p. 282–284° and gave no depression with an authentic sample of digitogenin lactone triacetate.

The alkaline layer was acidified and extracted ten times with a liberal amount of ether. The solvent was removed and the residue was sublimed in a high vacuum at 100°. The sublimate was crystallized from ether–pentane and from chloroform, m. p. 105–109°. Mixed with α-methylglutaric acid it melted at 55–62°.

Anal. Calcd. for $C_5H_8O_4$: C, 45.4; H, 6.1; neut. equiv., 66. Found: C, 45.9; H, 6.3; neut. equiv., 68.

Other Reactions of Digitogenin.—Digitogenin is recovered unchanged after four days of boiling with strong alcoholic hydrogen chloride mixture, indicating that it has the iso-configuration.

The greater portion of digitogenin is recovered unchanged when treated with amalgamated zinc and alcoholic hydrochloric acid even for twenty-four hours of continuous addition. The other sapogenins are converted in high yields into the tetrahydrosapogenins with three to six hours of similar treatment.

The greater part of digitogenin is unchanged upon treatment with acetic anhydride in a bomb tube at 200° for ten hours. The other sapogenins are converted almost quantitatively by this treatment into the pseudosapogenins.

Sublimation of digitogenin with potassium bisulfate at 210–220° gave only recovered digitogenin and no apparent dehydration.

Summary

Evidence has been presented indicating that there is no hydroxyl group at C–6 in digitogenin.

STATE COLLEGE, PENNA. RECEIVED JUNE 3, 1942

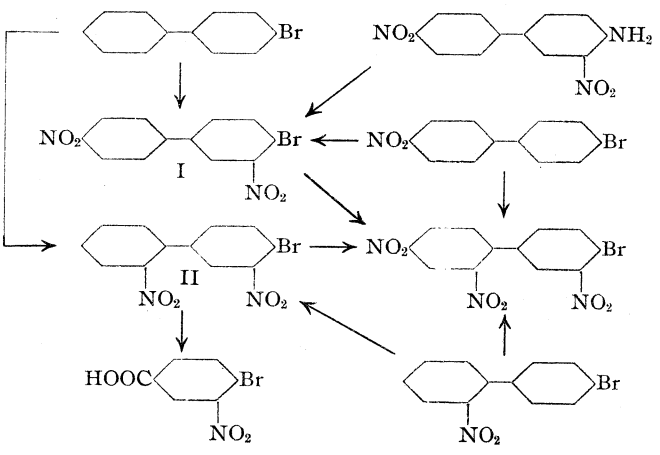
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

The Nitration of Certain Halobiphenyls. I. Nitro Derivatives of 4-Bromobiphenyl

BY FRANCIS H. CASE

In 1933 Mascarelli[1] obtained by the nitration of 4-bromobiphenyl two isomeric dinitrobromobiphenyls I (m. p. 205–206°) and II (m. p. 147–148°) whose structure was undetermined since they resisted oxidation. With a view to clearing up the structure of these compounds, we have repeated the nitration, again obtaining the two isomers with the revised melting points 210–211° and 154–155°, respectively. Isomer I, also obtained by the nitration of 4-nitro-4′-bromobiphenyl, has been shown by us to be identical with the product obtained from 3,4′-dinitro-4-aminobiphenyl by replacement of amino by bromine, and is therefore 3,4′-dinitro-4-bromobiphenyl. A substance[2] (m. p. 135°), obtained by the nitration of 4-nitro-4′-bromobiphenyl, was previously assigned this structure

FIG. 1.



without experimental proof. Isomer II has been shown by us to be identical with the dinitrobromobiphenyl obtained by Finzi and Bellavita[3] by the nitration of 4-bromo-2′-nitrobiphenyl. They assigned to it the structure 2′,3-dinitro-4-bromobiphenyl on the basis that it reacts with piperidine. We have confirmed this structure by oxidizing this substance to 3-nitro-4-bromobenzoic acid, thus avoiding the piperidine reaction,[3] which is sometimes misleading. LeFèvre and Turner[4] obtained by the nitration of either 4-bromo-2′-nitrobiphenyl or 4-bromo-4′-nitrobiphenyl the same trinitrobromobiphenyl. Since it reacts with piperidine they assigned to it the structure 2,3′,4-trinitro-4′-bromobiphenyl. This is confirmed without the use of piperidine by the fact that 3,4′-dinitro-4-bromobiphenyl also yields the same substance on nitration.

The nitration of 4-bromo-3′-nitrobiphenyl is of interest because in this compound the nitro group is in a position it would not normally assume on the nitration of 4-bromobiphenyl. It was found that if the nitration were carried out according to Mascarelli's general directions, *i. e.*, in a mixture of nitric and sulfuric acids initially kept below 40° but completed at 100° and the product extracted with ether, the ether-insoluble part yielded a constant-melting product III, the analysis of which indicates a trinitrobromobiphenyl mixed with a small amount of a dinitrobromobiphenyl. On oxidation the mixture yields 3-nitro-4-bromobenzoic acid. From the ether soluble portion could be isolated by fractional crystallization a dinitrobromobiphenyl IV (m. p. 143–144°), from alcohol–acetone.

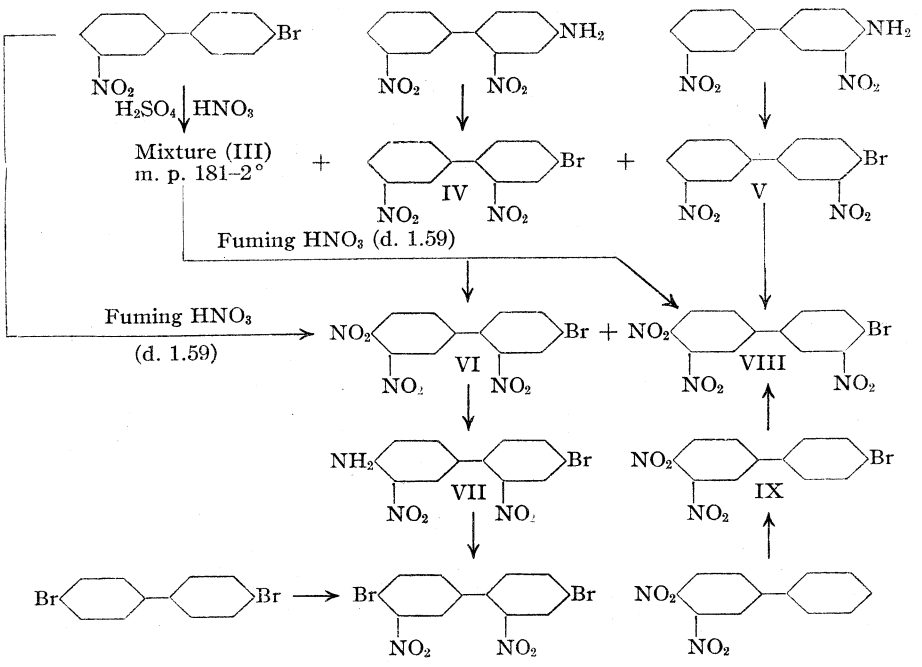
If the nitration were effected under milder conditions, *e. g.*, nitric and sulfuric acids below 40°, nitric acid (sp. gr. 1.5) below 15°, or ethyl nitrate, the reaction product, now soluble in ether, when repeatedly crystallized from alcohol–acetone yielded a constant-melting mixture which analyzed correctly for a dinitrobromobiphenyl. On repeated crystallization from benzene, it yielded a pure isomeric dinitrobromobiphenyl V, m. p. 187–188°. On oxidation the mixture was partially converted into 3-nitro-4-bromobenzoic acid, leaving a residue of the pure isomer IV.

On more drastic nitration with nitric acid (sp. gr. 1.59), at 100°, 4-bromo-3′-nitrobiphenyl is converted into the isomeric trinitrobromobiphenyls VI (predominantly) and VIII.

The structure of isomer IV, suggested by the fact that it does not react with piperidine and on total reduction followed by oxidation yields no acid, was established by the following method: 4-amino-3′-nitrobiphenyl was nitrated to 2,3′-dinitro-4-aminobiphenyl (structure proven by de-

(1) Mascarelli, *Gazz. chim. ital.*, **63**, 654 (1933).
(2) LeFèvre, Moir and Turner, *J. Chem. Soc.*, 2330 (1927).
(3) Finzi and Bellavita, *Gazz. chim. ital.*, **68**, 77 (1938).
(4) LeFèvre and Turner, *J. Chem. Soc.*, 2044 (1926).

FIG. 2.



amination to 2,3′-dinitrobiphenyl), and the compound resulting from this by replacement of amino by bromine proved identical with IV.

Isomer V was synthesized by nitration of 4-acetamino-3′-nitrobiphenyl to 3,3′-dinitro-4-acetaminobiphenyl (structure proven by hydrolysis and deamination to 3,3′-dinitrobiphenyl) followed by hydrolysis and replacement of amino by bromine.

Isomers IV and V were now separately nitrated further (nitric acid (sp. gr. 1.59) at 100°). The trinitrobromo compound yielded by IV was now found to be identical with VI, obtained by the direct nitration of 4-bromo-3′-nitrobiphenyl under the same conditions. It was found that one nitro group of VI is replaced completely by amino in alcoholic ammonia at 150°. On deamination of the resulting compound (VII), however, IV is regenerated, indicating that the new nitro group is the one attacked by the ammonia. If, however, VII is subjected to the Sandmeyer reaction, the resulting dibromodinitro compound is shown to be identical with 2,3′-dinitro-4,4′-dibromobiphenyl, obtained by the nitration of 4,4′-dibromobiphenyl.[4,5]

Since the positions of both bromine atoms are known in one compound, and of both nitro groups in the other, the identity of these compounds constitutes a proof of the structure of VI and an independent proof of the structure of the dinitration product of 4,4′-dibromobiphenyl.

The replacement of a *p*- instead of a *m*-nitro group by amino in 2,3′,4′-trinitro-4-bromobiphenyl seemed somewhat surprising in view of the fact that such compounds as 3,4-dinitromethyl-, iodo-, chloro-, and bromo-benzene all yield *m*-amino derivatives under similar conditions. A study of the reaction of 3,4-dinitrobiphenyl with alcoholic ammonia showed that here, also, the nitro group para to the phenyl nucleus is substituted by amino.

The trinitrobromo compound VIII obtained by the further nitration of V was synthesized as follows: 3,4-dinitrobiphenyl, prepared by the action of copper on phenyl iodide and 3,4-dinitroiodobenzene at 270°, was brominated, and the resulting product (IX) on nitration yielded VIII. Since in IX the position of the two nitro groups is known and in VIII the positions of the bromine atom and of the other nitro group are known, the structures of both VIII and IX are simultaneously proved.

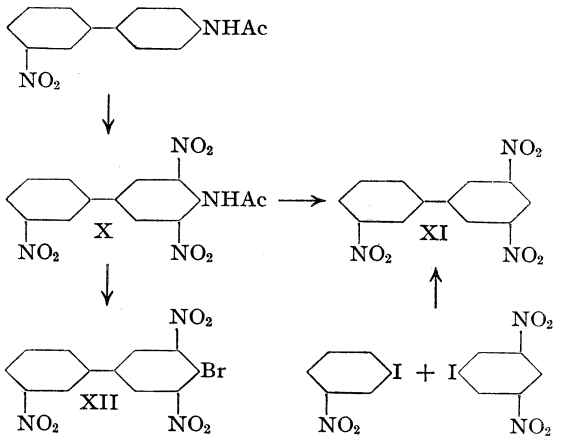
Since on nitration with nitric acid (sp. gr. 1.59) at 100° the previously described mixture (III) yields VIII and in view of the analytical data, it is concluded that it consists largely of VIII mixed with a small amount of a dinitrobromobiphenyl.

The synthesis of 3,3′,5-trinitro-4-bromobiphenyl (XII), another theoretically possible result

(5) Dennett and Turner, *J. Chem. Soc.*, 476 (1926).

of the further nitration of 3,3′-dinitro-4-bromobiphenyl, was accomplished by the dinitration of 4-acetamino-3′-nitrobiphenyl followed by hydrolysis and application of the Sandmeyer reaction. The structure of the intermediate trinitro base (X) was proven by deaminizing it to a trinitrobiphenyl (XI), which proved identical with that obtained by the Ullmann reaction on a mixture of 3,5-dinitroiodobenzene and *m*-nitroiodobenzene. From two moles of 3,5-dinitroiodobenzene, the hitherto undescribed 3,3′,5,5′-tetranitrobiphenyl was obtained. It was hoped to reduce one nitro group of this substance and convert it into the trinitro compound mentioned above, but the reduction proved to be unsuccessful.

FIG. 3.



Experimental

Nitration of 4-Bromobiphenyl.—The procedure was the same as that of Mascarelli.[1] Isomer I (ether-insoluble), crystallized from acetone, melted at 210–211°.

Anal. Calcd. for $C_{12}H_7N_2O_6Br$: Br, 24.74. Found: Br, 24.78.

Isomer II (ether-soluble), crystallized from alcohol, melted at 154–155°.

Anal. Calcd. for $C_{12}H_7N_2O_6Br$: Br, 24.74. Found: Br, 24.86.

Synthesis of 3,4′-Dinitro-4-bromobiphenyl (Method of Schoutissen[6]).—To a solution at 0° of 5.2 g. of 3.4′-dinitro-4-aminobiphenyl in 20 cc. of concd. sulfuric acid was added a solution of 2 g. of sodium nitrite in 20 cc. of concd. sulfuric acid. Phosphoric acid (70 cc.) was then added with stirring, keeping the temperature below 2°. After standing one-half hour the resulting solution was poured into a solution of 15 g. of bromine and 15 g. of sodium bromide in 100 cc. of ice-water. After one hour, copper powder was added and the mixture allowed to stand overnight. It was then heated for one hour and the precipitate filtered off and recrystallized from acetone; m. p. 207–208°. This was not depressed by admixture with isomer I, above.

(6) Schoutissen, THIS JOURNAL, **55**, 4538 (1933).

Nitration of 4-Nitro-4′-bromobiphenyl.—The procedure was again the same as that of Mascarelli.[1] From 17.7 g. of starting material, the ether-insoluble portion yielded 2.5 g. of pure isomer I.

Nitration of 4-Bromo-2′-nitrobiphenyl.—Six grams of 4-bromo-2′-nitrobiphenyl was added gradually to a mixture of 20 cc. of concd. sulfuric acid and 26 cc. of concd. nitric acid, keeping the temperature below 30°. After one hour of stirring at room temperature the mixture was poured into water and the precipitated solid crystallized from alcohol–acetone; yield 3 g., melting at 154–155°, and unchanged when mixed with isomer II. On oxidation with chromic acid, this substance yields 3-nitro-4-bromobenzoic acid.

Preparation of 2,3′,4-Trinitro-4′-bromobiphenyl.—This substance (m. p. 180–181°) was obtained by the action of fuming nitric acid (sp. gr. 1.59) at 100° on each of the following: 3,4′-dinitro-4-bromobiphenyl, 2,3′-dinitro-4-bromobiphenyl, 4-nitro-4′-bromobiphenyl, 2-nitro-4′-bromobiphenyl.

Nitration of 4-Bromo-3′-nitrobiphenyl

Method A.—4-Bromo-3′-nitrobiphenyl (17.7 g.) was added slowly to a mixture of 30 g. of concd. sulfuric acid and 20 g. of concd. nitric acid, keeping the temperature below 40°. The reaction was completed by heating on the steam-bath for one hour. The mixture was then poured into ice-water, filtered, washed and dried. After five extractions with ether, an insoluble residue was obtained which on crystallization from acetone–alcohol yielded 2 g. of a product melting constantly at 181–182°. The analysis indicated it to be an impure trinitrobromo derivative.

Anal. Calcd. for $C_{12}H_6N_3O_6Br$: Br, 21.72; N, 11.42 Found: Br, 22.42; N, 11.08.

On oxidation with chromic acid it yielded 3-nitro-4-bromobenzoic acid.

The ether soluble material was evaporated to dryness, and on repeated crystallization from alcohol–acetone yielded 2.5 g. of a product (IV) melting at 143–144°.

Method B.—Fifteen grams of 4-bromo-3′-nitrobiphenyl was added gradually to a stirred mixture of 30 g. of sulfuric acid and 20 g. of nitric acid, keeping the temperature below 40°. The reaction mixture, which proved to be soluble in ether, was poured into water, washed and dried. After eight crystallizations from benzene 0.4 g. of a product (V) melting at 189–190° was obtained. If the nitration mixture were crystallized from alcohol–acetone, 8.7 g. of a mixture melting at 129–130° was obtained.

Anal. Calcd. for $C_{12}H_7N_2O_6Br$: Br, 24.74. Found: Br, 24.91.

On oxidation with chromic acid the mixture yielded 3-nitro-4-bromobenzoic acid and pure isomer IV.

Method C.—Twenty grams of 4-bromo-3′-nitrobiphenyl was dissolved in 170 cc. of fuming nitric acid (sp. gr. 1.59) and the mixture heated for one hour on the steam-bath. It was then poured into water, and the resulting solid (VI) crystallized four times from alcohol–acetone; yield, 5 g.; m. p. 170–171°.

Anal. Calcd. for $C_{12}H_6N_3O_6Br$: Br, 21.72. Found: Br, 22.01.

From the filtrate of the first crystallization a solid separated on standing which after repeated crystallization from alcohol–acetone yielded 0.7 g. of a solid melting at 191–192° and unchanged when mixed with VIII.

Nitration of the Mixture (III).—Nitration according to the above procedure yielded a trinitrobromobiphenyl (VIII), m. p. 192–193°.

2,3′-Dinitro-4-aminobiphenyl.—Fifteen grams of 3-nitro-4′-aminobiphenyl was dissolved in a mixture of 13 cc. of 15% oleum and 50 cc. of concd. sulfuric acid. Potassium nitrate (7.5 g.) was added slowly, keeping the temperature below 6°. The reaction mixture was then allowed to warm to room temperature, poured into ice water and neutralized with potassium hydroxide. On crystallization from benzene, 11 g. of crude base, m. p. 154°, was obtained. The acetyl derivative was crystallized from alcohol, m. p. 215–216°.

Anal. Calcd. for $C_{14}H_{11}N_3O_5$: N, 13.96. Found: N, 13.84.

The pure base was obtained by hydrolysis of the acetyl derivative in dilute sulfuric acid. It was crystallized from benzene, m. p. 157–158°.

Anal. Calcd. for $C_{12}H_9N_3O_4$: N, 16.22. Found: N, 16.44.

On deamination the above base yielded a product melting unchanged when mixed with 2,3′-dinitrobiphenyl.

2,3′-Dinitro-4-bromobiphenyl.—This was prepared by Schoutissen's[6] method from 2,3′-dinitro-4-aminobiphenyl. After crystallization from alcohol–acetone it melted at 143–144°. The melting point was unchanged by admixture with isomer IV.

Anal. Calcd. for $C_{12}H_7N_2O_4Br$: Br, 24.74. Found: Br, 24.99.

3,3′-Dinitro-4-aminobiphenyl.—To a solution of 6 g. of 4-acetamino-3′-nitrobiphenyl in 30 cc. of glacial acetic acid and 10 cc. of acetic anhydride at 70° was added a solution of 1.5 cc. of nitric acid (sp. gr. 1.5) in 5 cc. of acetic acid. After one hour of stirring at this temperature, the mixture was poured into ice water, and the precipitated solid recrystallized from glacial acetic acid, yielding 4.5 g., m. p. 241–242°.

Anal. Calcd. for $C_{14}H_{11}N_3O_5$: N, 13.96. Found: N, 13.74.

The free base was liberated by hydrolysis with dilute sulfuric acid at 120°. On crystallization from benzene, it melted at 206–207°.

Anal. Calcd. for $C_{12}H_9N_3O_4$: N, 16.22. Found: N, 16.51.

On deamination the base was converted into 3,3′-dinitrobiphenyl.

3,3′-Dinitro-4-bromobiphenyl.—This was prepared from the above base in the same way as 2,3′-dinitro-4-bromobiphenyl. On crystallization from acetone–alcohol it melts at 187–188°.

Anal. Calcd. for $C_{12}H_7N_2O_4Br$: Br, 24.74. Found: Br, 24.95.

The melting point was unchanged by admixture with isomer V.

2,3′,4′-Trinitro-4-bromobiphenyl (VI).—This was prepared from 2,3′-dinitro-4-bromobiphenyl by the same method used to prepare it from 4-bromo-3′-nitrobiphenyl.

2,3′-Dinitro-4′-amino-4-bromobiphenyl.—2,3′,4-Trinitro-4-bromobiphenyl (4.5 g.), suspended in a solution of alcoholic ammonia, was heated in a sealed tube for ten hours at 150°. After evaporation of the alcohol, the residue was taken up in benzene and treated with dry hydrogen chloride. From the precipitated hydrochloride the free base was liberated with ammonium hydroxide and crystallized from alcohol–acetone; m. p. 223–224°.

Anal. Calcd. for $C_{12}H_8N_3O_4Br$: Br, 23.65. Found: Br, 23.85.

Deamination.—One gram of the above base suspended in 90 cc. of alcohol was treated with 20 cc. of 1–1 sulfuric acid and 3 g. of solid sodium nitrite. After one hour of heating on the steam-bath, the deaminized product was precipitated in ice-water and recrystallized from alcohol. It melted unchanged when mixed with 2,3′-dinitro-4-bromobiphenyl.

2,3′-Dinitro-4,4′-dibromobiphenyl.—This was obtained from the 2,3′-dinitro-4′-amino-4-bromobiphenyl by the method of Schoutissen as in the case of 2,3′-dinitro-4-bromobiphenyl. It melted at 152–153°, and was shown by mixed melting point to be identical with the product obtained by Dennett and Turner[5] from the nitration of 4,4′-dibromobiphenyl.

3,4-Dinitrobiphenyl.—The following method of synthesis was adopted after attempts to oxidize 3-nitro-4-aminobiphenyl with Caro's acid, and to apply Sandmeyer's reaction to it had failed. A mixture of 19 g. of 3,4-dinitroiodobenzene, 20 g. of iodobenzene and 22 g. of copper powder was heated for three hours in a sealed tube at 280°. The copper compounds were then removed by extraction with acetone, the acetone evaporated off, and the residue distilled in vacuum. The fraction boiling at 180–210° (3 mm.) was found to be unchanged 3,4-dinitroiodobenzene. The fraction boiling at 210–245° (3 mm.) was recrystallized from methanol, yielding 3.4 g. of 3,4-dinitrobiphenyl, m. p. 86–87°. The pure product melts at 87–88°.

Anal. Calcd. for $C_{12}H_8N_2O_4$: N, 11.48. Found: N, 11.70.

Ammonolysis of 3,4-Dinitrobiphenyl.—3,4-Dinitrobiphenyl (2.5 g.), dissolved in a large excess of alcoholic ammonia, was heated in a sealed tube at 150° for ten hours. After evaporation of the solvent the residue on crystallization from alcohol yielded 1 g. of product melting at 162–163°, or 0.6 g., m. p. 168°. This melted unchanged when mixed with 3-nitro-4-aminobiphenyl. From the filtrate no other pure compound could be isolated.

3,4-Dinitro-4′-bromobiphenyl (IX).—A solution containing 7.1 g. of 3,4-dinitrobiphenyl, 3.5 cc. of bromine, and 0.1 g. of ferric chloride in 30 cc. of glacial acetic acid was heated at 90° for forty hours until the bromine color had disappeared. The mixture was then poured into water, and the resulting solid crystallized eight times from alcohol, yielding 0.5 g. of a product melting at 167–168°. Since very incomplete bromination was indicated, the filtrates were all evaporated down and rebrominated, yielding an additional 1.2 g.

Anal. Calcd. for $C_{12}H_7N_2O_4Br$: Br, 24.74. Found: Br, 24.80.

3,3′,4-Trinitro-4′-bromobiphenyl (VIII).—This was obtained by the nitration of 3,3′-dinitro-4-bromobiphenyl

with nitric acid (sp. gr. 1.59) at 100°. When crystallized from benzene it melts at 192–193°.

Anal. Calcd. for $C_{12}H_6N_3O_6Br$: Br, 21.72. Found: Br, 22.08.

The same product was also obtained by the nitration of IX or of the mixture III.

3,3′,5-Trinitro-4-aminobiphenyl (X).—Ten grams of 3,3′-dinitro-4-acetaminobiphenyl was added gradually to 60 cc. of nitric acid (sp. gr. 1.5) keeping the temperature below 8°. On pouring the solution into water and recrystallizing from acetone–alcohol, the acetylated base was obtained yielding 4.5 g., m. p. 241–242°. The pure product melts at 242–243°.

Anal. Calcd. for $C_{14}H_{10}N_4O_7$: N, 16.19. Found: N, 15.83.

This product could also be obtained in a lower state of purity by direct nitration of 4-acetamino-3′-nitrobiphenyl.

The free base was obtained by hydrolysis of the acetamino compound with dilute sulfuric acid at 120°. On crystallization from glacial acetic acid it melted at 233°.

Anal. Calcd. for $C_{12}H_8N_3O_6$: N, 18.43. Found: N, 18.19.

Deamination of 3,3′,5-Trinitro-4-aminobiphenyl.—The deamination of 3,3′,5-trinitro-4-aminobiphenyl by the simple method used to prepare 2,3′-dinitro-4-bromobiphenyl proved ineffective in this case, as the base was recovered unchanged. The following procedure was therefore adopted: 3.5 g. of the trinitro base, dissolved in 30 cc. of concd. sulfuric acid, was treated at 0° with a solution of 1.5 g. of sodium nitrite in 20 cc. of concd. sulfuric acid. The mixture was treated at 2° with a solution of 70 cc. of phosphoric acid, and then with 40 cc. of 20% oleum, at 15–20°. The resulting solution was poured into 250 cc. of boiling ethanol, and refluxed for one hour. After pouring into ice-water, the resulting solid was filtered and crystallized from methanol–acetone, yielding 1 g. of a product melting at 167–168°. This was further purified by treatment with chromic acid which appeared to remove traces of unchanged base. The melting point of the pure product was 177–178°.

Anal. Calcd. for $C_{12}H_7N_3O_6$: N, 14.54. Found: N, 14.48.

3,3′,5-Trinitrobiphenyl (XI).—A mixture of 12 g. of 3,5-dinitroiodobenzene, 7.5 g. of *m*-nitroiodobenzene and 8 g. of copper powder was heated for an hour at 270°. From the ether extract it was possible to obtain by repeated crystallization from alcohol–acetone a small amount of a solid melting at 173–174° and unchanged when mixed with the deamination product of 3,3′,5-trinitro-4-aminobiphenyl.

3,3′,5-Trinitro-4-bromobiphenyl (XII).—This was prepared from the corresponding base by Schoutissen's method. From 3.5 g. of base was obtained 3 g. of pure product, melting at 222–223° (from alcohol–acetone).

Anal. Calcd. for $C_{12}H_6N_3O_6Br$: Br, 21.72. Found: Br, 22.04.

3,3′,5,5′-Tetranitrobiphenyl.—A mixture of 13 g. of 3,5-dinitroiodobenzene and 8.5 g. of copper powder was heated with stirring at 270° for one and one-half hours. The acetone extract, after evaporation, was crystallized from toluene, yielding 0.7 g. of a solid melting at 228–229°.

Anal. Calcd. for $C_{12}H_6N_4O_8$: N, 16.77. Found: N, 16.52.

The nitrogen analyses were carried out by Messrs. Richard Schock and Chester White.

Summary

1. The nitration of 4-bromobiphenyl according to Mascarelli is shown to yield 3,4′-dinitro-4-bromobiphenyl and 2′,3-dinitro-4-bromobiphenyl.

2. Depending on conditions, the following substances have been obtained from the nitration of 4-bromo-3′-nitrobiphenyl: 2,3′-dinitro-4-bromobiphenyl, 3,3′-dinitro-4-bromobiphenyl, 2,3′,4′-trinitro-4-bromobiphenyl and 3,3′,4′-trinitro-4-bromobiphenyl.

3. Proof of the structures of the above substances is given.

PHILADELPHIA, PENNSYLVANIA RECEIVED MAY 11, 1942

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Syntheses of Epi-lactose and Lactose

BY W. T. HASKINS, RAYMOND M. HANN AND C. S. HUDSON

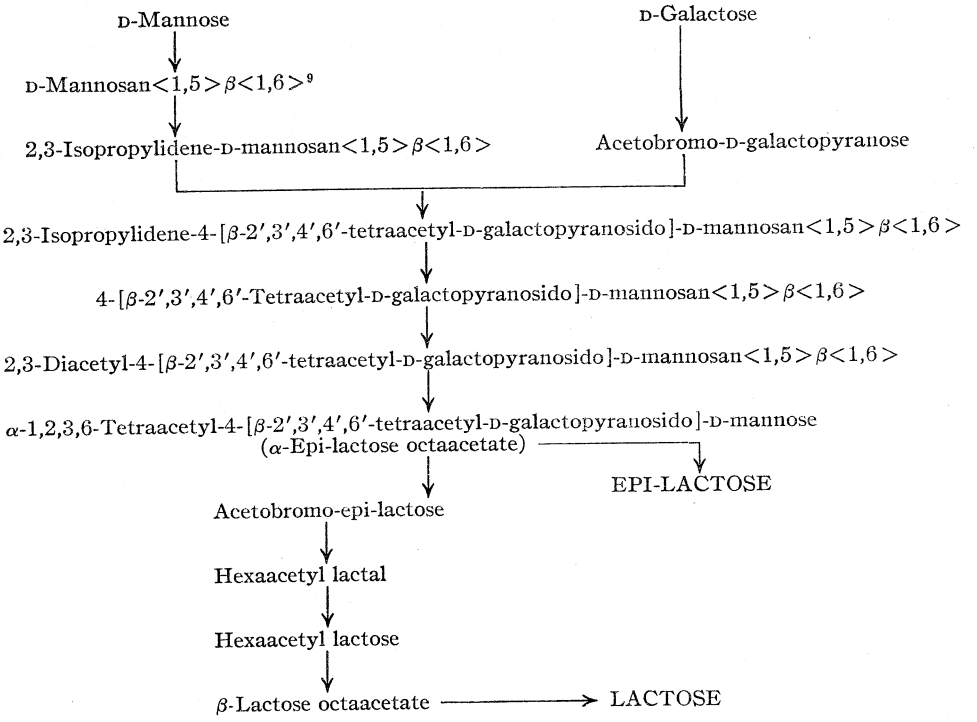
In continuation of our use of acetone-D-mannosan $<1,5>\beta<1,6>$[1] for the synthesis of disaccharides[2] having their linkage at carbon atom 4, we have now combined this substance with acetobromo-D-galactose and thereby produced, first, the epimer of lactose (4-[β-D-galactopyranosido]-D-mannose), which we shall designate epi-lactose for brevity, and, second, lactose (4-[β-D-galactopyranosido]-D-glucose) itself. Bergmann, Schotte and Rennert[3] discovered epi-lactose by the epimerization of lactose through the reactions *lactose → acetobromolactose → hexaacetyl lactal → lactal → epi-lactose.* The reverse transformation of epi-lactose to lactose, which has now assumed importance, has been accomplished readily by the reactions *epi-lactose → acetobromo-epi-lactose → hexaacetyl lactal → lactose hexaacetate → lactose octa-*

(1) Knauf, Hann and Hudson, THIS JOURNAL, **63**, 1447 (1941).

(2) Haskins, Hann and Hudson, *ibid.*, **63**, 1724 (1941); **64**, 1490 (1942).

(3) Bergmann, Schotte and Rennert, *Ann.*, **434**, 94 (1923).

acetate → lactose, following the general method of Levene and Tipson[4] in the oxidation of the glycal hexaacetate, as used by us[2] recently in the transformation of epi-cellobiose to cellobiose. Several of the essential designations in the structure of lactose were established by Haworth and Long[5] when they identified the products of the acid hydrolysis of fully methylated lactobionic acid as 2,3,4,6-tetramethyl-D-galactopyranose and 2,3,5,6-tetramethyl-D-gluconic acid. The β-configuration of the galactose moiety has been inferred in the past from the fact that the enzyme lactase, which hydrolyzes lactose, likewise hydrolyzes β-methyl-D-galactopyranoside, but is without action on the α-modification; and also from a comparison of the rotatory powers of the methyl esters of the octamethyl derivatives of lactobionic, cellobionic and maltobionic acids, before and after acid hydrolysis.[6] The β-configuration of the galactose moiety is now conclusively established from the fact that acetobromo-D-galactose, which yields β-methyl-D-galactopyranoside when treated with methyl alcohol and silver carbonate by the Koenigs–Knorr reaction,[7] was employed in the present syntheses. The syntheses also represent total syntheses since such have been accomplished previously for D-mannose and D-galactose.[8] *Lactose, the unique disaccharide of mammalian life, is producible in the chemical laboratory, by structurally definitive reactions of organic chemistry, from the elements carbon, hydrogen and oxygen.* A flow diagram of the synthetic steps, beginning with D-mannose and D-galactose, is shown.



The synthesis of the enantiomorph of lactose, namely, 4-[β-L-galactopyranosido]-L-glucose, unquestionably could be made by parallel reactions provided sufficient supplies of the rare L-mannose and L-galactose should become available.

Historical Note.—A formation of lactose by the direct combination under catalytic conditions of supposedly pure glucose and galactose was reported in 1879 by Demole.[10] Pictet and Vogel[11] also reported such a formation. The reality of these reported formations of lactose remains in grave doubt; in any event, they have not contributed any new knowledge concerning the structure of lactose. In 1902 Emil Fischer and

(4) Levene and Tipson, *J. Biol. Chem.*, **93**, 631 (1931).
(5) Haworth and Long, *J. Chem. Soc.*, 544 (1927).
(6) Haworth, "The Constitution of Sugars," Edward Arnold & Co., London, 1929 edition, pp. 59, 65.
(7) Levene and Sobotka, *J. Biol. Chem.*, **67**, 771 (1926); Dale and Hudson, THIS JOURNAL, **52**, 2537 (1930).
(8) Fischer, *Ber.*, **23**, 2114 (1890); Fischer and Ruff, *ibid.*, **33**, 2142 (1900).
(9) Montgomery, Richtmyer and Hudson, THIS JOURNAL, **64**, 1483 (1942).
(10) Demole, *Ber.*, **12**, 1935 (1879); *cf.* Berthelot, *Bull. soc. chim.*, [2] **34**, 82 (1880).
(11) Pictet and Vogel, *Helv. Chim. Acta*, **11**, 209 (1928).

E. F. Armstrong[12] reported a synthesis of a galactosido-glucose from acetochloro-D-galactose and sodium glucosate ("glucose-natrium"); a crystalline osazone, which was thought by them to be possibly melibiose osazone, was described; a later re-investigation of the subject by Schlubach and Rauchenberger[13] suggested that the osazone may be that of lactose. Biochemical syntheses of lactose from its constituent hexoses through the enzymotic activity of mammary gland tissue have been reported.[14]

Experimental

Acetobromo-D-galactose.—The general method of Levene and Raymond[15] was followed. A solution of 25 g. of β-D-galactopyranose pentaacetate (m. p. 140–142°; $[\alpha]^{20}D$ +24.0° in chloroform)[16] in 50 cc. of glacial acetic acid was cooled to 0° and saturated with gaseous hydrobromic acid; after standing two hours at 5°, the solution was diluted with 100 cc. of toluene and concentrated *in vacuo* at 45° to a thin sirup; three successive 100-cc. portions of toluene were added and removed in the same manner; the residual sirup was dissolved in 25 cc. of warm ether and as the solution cooled the acetobromogalactose crystallized. The yield was 23.6 g. (90%). The substance was recrystallized by solution in two parts of ether and the addition of one part of isopentane; it formed fine needles which melted at 84–85° (cor.). and showed a rotation of +217° (*c*, 1.2)[17] in chloroform and +242° (*c*, 1.2) in benzene. Fischer and Armstrong[18] report a melting point of 82–83° and a specific rotation $[\alpha]^{20}D$ of +236.4° in benzene for acetobromogalactose; Ohle, Marecek and Bourjau[19] record a melting point of 85° for the compound, but did not measure its rotation. Apparently the rotation in chloroform has not been recorded previously; its value is now found to be near that which was predicted some years ago.[20]

Anal. Calcd. for $C_{14}H_{19}O_9Br$: Br, 19.4. Found, Br, 19.7.

2,3-Diacetyl-4-[β-2′,3′,4′,6′-tetraacetyl-D-galactopyranosido]-D-mannosan<1,5>β<1,6>.—A solution of 10.1 g. (0.05 mole) of 2,3-isopropylidene-D-mannosan <1,5>β<1,6> in 100 cc. of dry alcohol-free chloroform, 50 g. of "Drierite," 25 g. of silver oxide and 35 g. of glass beads (4 mm. diameter) was placed in a 500-cc. brown glass stoppered bottle and agitated on a machine for one hour to ensure drying of the reagents; 2.5 g. of solid iodine and a solution of 20.6 g. (0.05 mole) of acetobromo-D-galactose in 50 cc. of pure chloroform were then added and shaking was resumed for seven days at room temperature (24°). The solid reaction products and excess of reagents were removed by filtration, and the filtrate (which gave no test for ionizable halogen) containing the 2,3-isopropylidene - 4 - [β - 2′,3′,4′,6′ - tetraacetyl - D - galactopyranosido]-D-mannosan<1,5>β<1,6>, was concentrated *in vacuo* to a sirup. A solution of the sirup in 200 cc. of 80% acetic acid was heated on the steam-bath until the rotation became constant (two hours), to remove the isopropylidene residue; the solvent was removed by concentration *in vacuo*, and the residual sirup, containing the partly acetylated 4-[β-D-galactopyranosido]-D-mannosan<1,5>β-<1,6>, was heated for one hour on the steam-bath with 2.5 g. of fused sodium acetate and 25 cc. of acetic anhydride. The reaction mixture was poured over crushed ice and the gum which precipitated was washed with water and dissolved in 10 cc. of warm alcohol; the new crystalline material (2,3-diacetyl-4-[β-2′,3′,4′,6′-tetraacetyl-D-galactopyranosido]-D-mannosan < 1,5 > β < 1,6 >) which deposited as the solution cooled was recrystallized from 15 parts of absolute alcohol and obtained in the form of elongated prisms which melted at 193–194° (cor.) and showed a rotation of −62.7° (*c*, 0.8) in chloroform. The yield was 8.8 g. (30%).

Anal. Calcd. for $C_{24}H_{32}O_{16}$: C, 50.00; H, 5.60; CH_3CO, 44.8. Found: C, 50.11; H, 5.62; CH_3CO, 44.7.

α-1,2,3,6 Tetraacetyl-4-[β-2′,3′,4′,6′-tetraacetyl-D-galactopyranosido]-D-mannose (α-Epi-lactose Octaacetate).—A solution of 12.5 g. of 2,3-diacetyl-4-[β-2′,3′,4′,6′-tetraacetyl-D-galactopyranosido]-D-mannosan<1,5>β<1,6> in 100 cc. of an acid acetylating solution (prepared by adding 2 cc. of concentrated sulfuric acid dropwise to an ice-cold mixture of 70 cc. of acetic anhydride and 30 cc. of glacial acetic acid) changed in rotation from +50.8°, after fifteen minutes, to a constant value of +55.1° in two hours at 20°. The reaction mixture was poured over crushed ice and the crystalline precipitate which formed was recrystallized from 3 parts of absolute alcohol. The yield was 14.5 g. (99%). The new substance (α-epi-lactose octaacetate) crystallized as elongated prisms which melted at 96–97° (cor.) and rotated +41.2° (*c*, 0.8) in chloroform.

Anal. Calcd. for $C_{28}H_{38}O_{19}$: C, 49.56; H, 5.64; CH_3CO, 50.8. Found: C, 49.44; H, 5.66; CH_3CO, 50.5.

4-[β-D-Galactopyranosido]-D-mannose (Epi-lactose).—To an ice-cold solution of 5.0 g. of epi-lactose octaacetate in 50 cc. of absolute methyl alcohol, 5 cc. of 0.5 *N* barium methylate solution was added and the mixture was allowed to stand at 5° for sixteen hours; the barium was precipitated by the addition of an equivalent amount of 0.1 *N* sulfuric acid and, following the removal of the barium sulfate, the solution was concentrated to a sirup, which was dissolved in 10 cc. of warm methyl alcohol. The β-form of the disaccharide deposited from the solution as it cooled; it was recrystallized by solution in 1 part of warm water and the addition of 5 parts of methyl alcohol and was obtained

(12) Fischer and Armstrong, *Ber.*, **35**, 3146 (1902).

(13) Schlubach and Rauchenberger, *ibid.*, **58**, 1184 (1925); **59**, 2102 (1926).

(14) Grant, *Biochem. J.*, **30**, 2027 (1936); Peterson and Shaw, *Science*, **86**, 398 (1937).

(15) Levene and Raymond, *J. Biol. Chem.*, **90**, 247 (1931).

(16) Hudson and Parker, THIS JOURNAL, **37**, 1589 (1915); Hudson and Johnson, *ibid.*, **38**, 1224 (1916).

(17) All of the crystalline compounds described in the experimental part were recrystallized to constant melting point and specific rotation $[\alpha]^{20}D$; *c* is the concentration in grams in 100 cc. of solution; the tube length was 4 dm. The microchemical analyses reported were performed by Dr. A. T. Ness to whom we express our appreciation.

(18) Fischer and Armstrong, *Ber.*, **35**, 837 (1902).

(19) Ohle, Marecek and Bourjau, *ibid.*, **62**, 833 (1929).

(20) Hudson, THIS JOURNAL, **46**, 462 (1924). The difference between the molecular rotations in the pyranose pair, acetobromo-D-glucose and β-D-glucose pentaacetate, is +81,400 − 1,500 = 79,900, and in the similar pair, acetobromo-D-galactose and β-D-galactose pentaacetate, it is now found to be 89,200 − 9,000 = 80,200. According to the isorotation rules an equality of these differences, which are $(A_{Br} + A_{ac})$ in each case, is to be expected.

in the form of fine needles which melted at 195–196° (cor.); an aqueous solution (*c*, 1.2) of the substance exhibited a rotation of +18.0° three minutes after preparation and its equilibrium rotation was +27.2°. The unimolecular coefficient of the mutarotation at 20° was 0.0151, using minutes and decimal logarithms; the initial rotation of this β-form of the sugar is thus approximately +17°, in good agreement with the value (+16°) which Haworth, Hirst, Plant and Reynolds[21] obtained indirectly, through solubility measurements of the α-form. Bergmann, Schotte and Rennert[3] report a melting point of 196–197° and an equilibrium rotation of +30.0° for β-epi-lactose, and Haworth and co-workers[21] record an equilibrium value of +27° for anhydrous epi-lactose (calculated from that of α-epi-lactose monohydrate). It may be summarized for reference purposes that the initial rotations of the α- and β-forms of epi-lactose are +38°[21] and +17°, respectively, by direct measurements, and that the equilibrium rotation is +27°.

Anal. Calcd. for $C_{12}H_{22}O_{11}$: C, 42.10; H, 6.48. Found: C, 42.00; H, 6.53.

Lactal Hexaacetate from Epi-lactose Octaacetate.—To a solution of 10.0 g. of synthetic epi-lactose octaacetate in a mixture of 10 cc. of glacial acetic acid and 5 cc. of acetic anhydride, 40 g. of a 30% solution of hydrobromic acid in glacial acetic acid was added. The reaction mixture was allowed to stand at 5° overnight and after dilution with 50 cc. of chloroform, it was poured into 250 cc. of ice-cold water. The aqueous solution was extracted with chloroform in the usual manner, and the washed and dried chloroform extract was concentrated *in vacuo* to a sirup. A solution of the sirup, coutaining the acetobromo-epi-lactose, in 100 cc. of 50% acetic acid was cooled to 0° and 20 g. of zinc dust and 2 drops of a 0.5% solution of chloroplatinic acid in 50% acetic acid were added and the reaction mixture was stirred vigorously for two hours; the zinc was removed by filtration and the filtrate was poured into 200 cc. of ice-cold water; the crystalline lactal hexaacetate (4.1 g.; 50%) which precipitated was separated by filtration and recrystallized by solution in 3 parts of warm alcohol and the addition of 7 parts of water, being deposited in the form of needles which melted at 114° (cor.) and rotated −18.0° (*c*, 0.8) in chloroform. A mixed melting point with authentic lactal hexaacetate (from acetobromolactose) showed no depression. Haworth, Hirst, Plant and Reynolds[21] record a melting point of 114° and a specific rotation of −18° for lactal hexaacetate.

Anal. Calcd. for $C_{24}H_{32}O_{15}$: C, 51.43; H, 5.75; CH_3CO, 46.1. Found: C, 51.62; H, 5.69; CH_3CO, 46.2.

Lactose Octaacetate from Lactal Hexaacetate.—A solution of 5.0 g. of lactal hexaacetate in a mixture of 30 cc. of ethyl acetate, 5 cc. of water and 30 cc. of a 0.3335 *M* ether solution of perbenzoic acid (1.12 molecular equivalents) was agitated for twenty hours at 25°; at the expiration of this period titration of a one cubic centimeter aliquot indicated that 0.9 of a molecular equivalent of perbenzoic acid had been consumed in the oxidation. The reaction mixture was agitated with 10 cc. of water and 4.0 g. of sodium bicarbonate until the ether–ethyl acetate layer was neutral, and the aqueous layer was separated and extracted with chloroform; the combined ether and chloroform extracts were dried and concentrated *in vacuo* to a thick sirup. The sirup, which presumably contained lactose hexaacetate, was acetylated with acetic anhydride and fused sodium acetate and yielded 3.8 g. (58%) of β-lactose octaacetate. The product was recrystallized from 1.5 parts of alcohol and obtained as prisms which melted at 88–90° (cor.) and showed a rotation of −4.5° (*c*, 0.8) in chloroform solution, in good agreement with the reported values[22] of 90° and −4.7°, respectively, for β-lactose octaacetate. A mixed melting point with authentic β-lactose octaacetate showed no depression.

Anal. Calcd. for $C_{28}H_{38}O_{19}$: C, 49.56; H, 5.64; CH_3CO, 50.8. Found: C, 49.60; H, 5.58; CH_3CO, 50.9.

Lactose Monohydrate from β-Lactose Octaacetate.—A solution of 4.0 g. of β-lactose octaacetate in 100 cc. of methyl alcohol was deacetylated by barium methylate in the usual manner. The disaccharide monohydrate (2.0 g., 94%) was obtained in the form of prisms which melted with decomposition at 202° (cor.); a mixed melting point determination with authentic lactose monohydrate showed no depression; an aqueous solution of the substance exhibited initial and final rotations of +81° and +52.7° (*c*, 2.0), respectively, with a mutarotation rate of 0.0042 at 20°. Isbell and Pigman[23] report an initial rotation of +85.0° (*c*, 7.6), a final rotation of +52.6° and a mutarotation rate of 0.0047 for α-lactose monohydrate. The over-all yield of lactose monohydrate from epi-lactose octaacetate was 27% and from acetobromo-D-galactose it was 8%.

Anal. Calcd. for $C_{12}H_{22}O_{11}\cdot H_2O$: C, 40.00; H, 6.71; H_2O, 5.00. Found: C, 39.99; H, 6.80; H_2O, 5.04.

Summary

The condensation of 2,3-isopropylidene-D-mannosan<1,5>β<1,6>with acetobromo-D-galactopyranose yields a product from which, after removal of its acetone residue followed by acetylation of the two hydroxyl groups thus liberated, there was obtained crystalline 2,3-diacetyl-4-[β-2′,3′,4′,6′-tetraacetyl-D-galactopyranosido]-D-mannosan<1,5>β<1,6> in 30% yield. The action of an acid acetylating mixture upon this substance opened its 1,6-anhydro ring and produced the α-octaacetate of epi-lactose, from which epi-lactose was obtained by deacetylation. Epi-lactose octaacetate was converted by customary procedures to the known lactal hexaacetate, which, upon oxidation at the double bond with perbenzoic acid, generated the new hydroxyl group mainly in a position *trans* to the acetylated hydroxyl group on carbon three, since it was found that the product, upon complete acetylation, gave a 58% yield of the crystalline β-octaacetate of lactose, from which lactose was obtained by de-

(21) Haworth, Hirst, Plant and Reynolds, *J. Chem. Soc.*, 2644 (1930); see also Hudson and Watters, THIS JOURNAL, **52**, 3472 (1930).

(22) Hudson and Johnson, *ibid.*, **37**, 1270 (1915).

(23) Isbell and Pigman, *J. Res. Natl. Bur. Standards*, **18**, 158 (1937).

acetylation. The over-all yield of lactose, based upon the acetobromo-D-galactose used in its synthesis, was 8%. The results constitute the structurally definitive syntheses of epi-lactose and lactose from D-mannose and D-galactose. They are total syntheses, since such syntheses of these hexoses were accomplished by Emil Fischer. The new crystalline substances that are described are 2,3-diacetyl-4-[β-2′,3′,4′,6′-tetraacetyl-D-galactopyranosido]-D-mannosan<1,5>β<1,6> and α-octaacetyl-epi-lactose; some other new substances, intermediates in the syntheses, were not isolated in crystalline form.

BETHESDA, MARYLAND RECEIVED MAY 22, 1942

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 879]

Isomerization of β-Carotene. Isolation of a Stereoisomer with Increased Adsorption Affinity

BY A. POLGÁR AND L. ZECHMEISTER

In spite of the fact that the phenomenon of carotenoid isomerization was first detected for β-carotene,[1] our knowledge in this special case is still very incomplete. These authors crystallized an isomer which they termed pseudo-α-carotene. and which appears immediately below β-carotene on the Tswett column. Gillam first assumed that the chromatographic process itself was responsible for the partial conversion, but it was shown later that the phenomenon occurs spontaneously and independently of a chromatographic experiment.[2] This conclusion was confirmed by Carter and Gillam.[3]

Early experiments in our laboratory showed that the reversible isomerization, for the explanation of which *trans–cis* shifts were suggested, can either increase or decrease the adsorptive power as compared with that of the respective all-*trans* carotenoid.[4] It was stated[5] as a rule that carotenoids with at least two free hydroxyl groups yield isomers which are adsorbed at higher sections of the column than the starting pigment. This result is in accordance with observations on the hydroxy-ketones capsanthine and capsorubine[6] as well as with investigations of Strain[7] concerning leaf xanthophylls. In the case of the monohydroxy-compound cryptoxanthin and especially of the hydrocarbons $C_{40}H_{56}$ the opposite behavior was observed; to this rule, however, the present paper provides an exception.

(1) A. E. Gillam and M. S. El Ridi, *Biochem. J.*, **30**, 1935 (1936).
(2) L. Zechmeister and P. Tuzson, *ibid.*, **32**, 1305 (1938).
(3) G. P. Carter and A. E. Gillam, *ibid.*, **33**, 1325 (1939).
(4) L. Zechmeister and P. Tuzson, *Ber.*, **72**, 1340 (1939).
(5) L. Zechmeister, L. Cholnoky and A. Polgár, *ibid.*, **72**, 1678, 2039 (1939).
(6) L. Zechmeister and L. Cholnoky, *Ann.*, **543**, 248 (1940).
(7) H. H. Strain, "Leaf Xanthophylls," Carnegie Inst. Washington, No. 490, Washington (1938); *cf.* also F. W. Quackenbush, H. Steenbock and W. H. Peterson, THIS JOURNAL, **60**, 2937 (1938).

In systematic experiments now being carried out in our laboratory with a series of carotenoids mainly four methods of isomerization are applied, *viz.*, refluxing the pigment solution, iodine catalysis, hydrochloric acid catalysis (both at room temperature), and melting the crystals.[8] The first two procedures have already been described.[2,4,5] As a convenient method for the acid catalysis, a mechanical shaking of the petroleum ether solution with concentrated hydrochloric acid is used. The catalysis is here mainly effective at the continuously shifting intersurface of the two liquids.

It was assumed and confirmed by experiment that stereoisomers of a carotenoid which are formed and are present in the melt can be separated by rapid cooling and chromatography. Such a treatment, which is much milder than the so-called "thermal decomposition" of carotenoids,[9] is best carried out in a sealed tube, in the absence of oxygen. Under suitable conditions no carbonization occurs. The melting of β-carotene gave us four main types of products, *viz.*, unchanged starting material, reversibly formed stereoisomers of β-carotene, pigments with a much shorter chromophore than that of carotene, and finally colorless, strongly fluorescent substances with very low adsorption affinity. The ratio of these types depends on the conditions, especially on the temperature. A solution of a crude melt was found to show about one-half the initial color intensity, whereas "thermal decomposition" as practiced earlier leads to complete bleaching.

(8) It is intended to report on photochemical isomerization later.
(9) (a) J. F. B. van Hasselt, *Rec. trav. chim.*, **30**, 1 (1911); **33**, 192 (1914). (b) R. Kuhn and A. Winterstein, *Helv. chim. acta*, **11**, 427 (1928). *Ber.*, **65**, 1873 (1932); **66**, 429, 1733 (1933). L. Zechmeister and L. Cholnoky, *Ann.*, **478**, 95 (1930).

In the end-product of the heat, iodine, and melt isomerization the stereoisomers may be accompanied by minor pigments formed in an irreversible way. It is therefore important to test each zone of the chromatogram from this point of view. Only such pigments are qualified as stereoisomers of the starting material of which the solutions on addition of some iodine in the spectroscopic cell show a typical shift of the bands. The spectrum of an equilibrium mixture appears almost instantaneously in which the maxima are only a few millimicrons lower in wave length than those of the all-*trans* compound which was formed and predominates in the mixture. The result of the test may be confirmed by subsequent chromatography and the main zone of the chromatogram can be identified by means of a mixed chromatogram with a sample of the original carotenoid. The spectra of the chromatographic zones containing β-carotene stereoisomers are listed in Table I. All four isomerization methods yielded the pigments 1, 3, 5 and 8, while appreciable amounts of 2, 4 and 6 have been observed so far, mainly after melting or hydrochloric acid catalysis of β-carotene; 7 was obtained in a melt chromatogram of neo-β-carotene U.

TABLE I

SPECTRA OF REVERSIBLY FORMED STEREOISOMERS OF β-CAROTENE IN THE SEQUENCE OF DECREASING ADSORPTION AFFINITIES

No.	Extinction maxima (mμ)		
1	481	450	(neo-β-carotene U)
2	472.5	441.5	(neo-β-carotene V)
3	486	454	(β-carotene)
4	469	437.5	(neo-β-carotene A)
5	475.5	444.5	(neo-β-carotene B)
6	465.5	433	(neo-β-carotene C)
7	474.5	441.5	(neo-β-carotene D)
8	477.5	445	(neo-β-carotene E)
9	468.5	437	(No names given)
10	473.5	443	
11	476.5	445.5	
12	471	440	
13	473	444	

Pigment no. 5 is spectroscopically nearly identical with "pseudo-α-carotene."

Some uncertainty exists concerning the pigments 9–13 due to their great lability. In different experiments only one to two isomers appeared and could be differentiated below pigment 8. Because of this lability it was impossible to identify or differentiate two such zones originating from different kinds of experiments by mixed chromatography. In this case the spectral data depend on the time which elapses between elution and optical measurement, and even on the rapidity of the reading, considering the photochemical effect of the light source. Above and including pigment 8 the individuality of the pigments listed is well established in spite of great differences in stability, because in all experiments, using the melt and the hydrochloric acid methods, a series of five to seven zones appeared in this section. Some members of this section must also be investigated rapidly; pigment 6 showed *e. g.*, 6 mμ longer wave length maxima than listed when in another experiment the time factor was not taken into consideration.

For one of the main stereoisomers of β-carotene which is adsorbed above β-carotene in the column, we suggest the name neo-β-carotene U (U for ultra).[10] Depending on the conditions, 10–25% of β-carotene can be converted into this compound and 17% has been actually isolated in crystals.[11] The compound was also observed in extracts of pumpkin, squash, carrots, etc., where it was formed by spontaneous isomerization. A natural occurrence remains to be shown. The tendency for the formation of the U isomer is considerable and the fact that it was isolated only recently requires some explanation. While Gillam's pseudo-α-carotene (neo-β-carotene B) appears below the usually sharp bottom line of unchanged β-carotene in the column and can easily be observed under various conditions, the U isomer (which is spectroscopically not very different from β-carotene) is included in the upper, more blurred part of the β-carotene zone and separates under adequate conditions only. With the brand of calcium hydroxide now in use in this laboratory, developing with petroleum ether which contains some acetone promotes the differentiation and finally produces a colorless interzone between the two stereoisomers.

The following remarks may summarize briefly our present views with regard to the stereochemistry of β-carotene.

(10) A final nomenclature cannot yet be given as the respective configurations must first be established (*cf.* footnote 12).

(11) Our results are in accordance with a short remark of H. H. Strain [THIS JOURNAL, **63**, 3448 (1941)] that under the influence of acid "eschscholtzxanthine, cryptoxanthine and β-carotene were converted slowly into substances that were adsorbed both above and below the native pigments." (In the iodine catalysis no pigment located above β-carotene in the column seems to have been observed.) In unpublished experiments we observed stereoisomers of α-carotene which were adsorbed above the original pigment in the column. It is intended to report later on this subject.

According to Pauling[12] the steric interaction of hydrogen and methyl prevents the assumption of the *cis* configuration for double bonds with C-CH_3 adjacent. Therefore out of the eleven double bonds in β-carotene only five are stereochemically effective, *viz.*, numbers 3, 5, 6, 7 and 9 (see the formula).

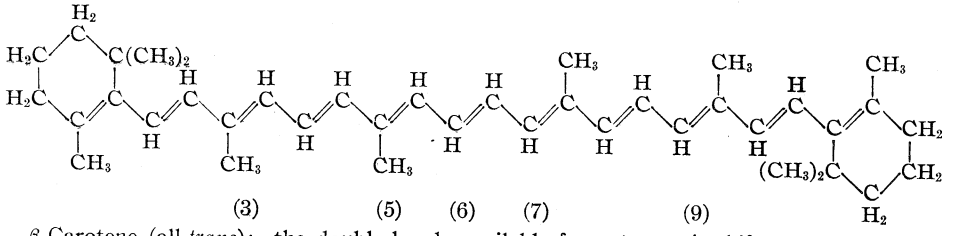
The quantum mechanical treatment of the carotenoid spectra[13] leads to the conclusion that the greatest intensity of light absorption would be shown by the isomer with the all-*trans* configuration and that the shorter *cis* isomers would show decreased intensity. This is in agreement with our experiments, and with the *cis–trans* interpretation of the phenomena studied. Also, according to a private communication from Professor Linus Pauling who is working on the theoretical aspects of the problem discussed, the *cis* configuration for a double bond would be expected to produce a spectral shift in wave length toward the violet, with magnitude dependent on the position of the double bond in the long conjugated system.[7]

The following figures show that the spectral differences between the first maxima of all-*trans* polyene-hydrocarbons and their spectroscopically closest stereoisomers are about 4–6 mμ.

	mμ		mμ
β-Carotene	486	γ-Carotene	496
Neo-β-carotene U	481	Neo-γ-carotene A[14]	489.5

Lycopene 504.5 mμ

Neolycopene A 500.5 mμ



(3) (5) (6) (7) (9)

β-Carotene (all-*trans*); the double bonds available for a *trans–cis* shift are numbered.

We tentatively assume with rough approximation that each *cis* double bond produces a spectral shift of the order of magnitude mentioned.

The stereoisomer so far observed which shows the greatest displacement from the β-carotene maxima has bands at 465.5 and 433 mμ. The position of the first band (Δ = about 20 mμ) indicates the presence of four or five *cis* bonds, that is, all but one or all of the available double bonds have the *cis* form. This stereochemical situation is closely similar to that suggested for prolycopene and pro-γ-carotene.[15] In the present case, however, its lability has prevented the crystallization of the substance.

Gillam's pseudo-α-carotene (Δ = 9 mμ) seems to contain two *cis* bonds while tentatively one such bond could be assigned to neo-β-carotene U (Δ = 5 mμ).

Possibly neo-β-carotene U contains in *cis* form that particular double bond (the central one) which on both sides is farthest from C-CH_3 groups and is attacked by the enzyme carotinase in the liver. It remains to be seen whether the biological formation of vitamin A is or is not preceded by a stereochemical shift. Neo-β-carotene U has no vitamin A activity when tested with rats.

Acknowledgment.—We wish to thank the Rockefeller Foundation for a grant which enabled the members of this Laboratory to carry out the experiments described below and in some previous papers. To Dr. G. Oppenheimer and Mr. G. Swinehart, the authors are indebted for microanalytical assistance, to Merck & Co., Inc. for a vitamin A assay.

Experimental

Methods.—The pigment solutions were chromatographed on calcium hydroxide (Shell Brand lime, chemical hydrate; 98% through 325 mesh). For development petroleum ether (b. p. 60–70°) was used or, depending on the quality of the lime, the same solvent with 1–5% acetone. The figures on the left side of the described chromatograms denote width of the zones, in mm. Petroleum ether–alcohol mixtures are suitable eluents or else ether may be

(12) (a) L. Pauling, *Fortschritte Chem. Organ. Naturstoffe*, **3**, 203 (1939); connected paper, (b) L. Zechmeister, A. L. LeRosen, F. W. Went and L. Pauling, *Proc. Nat. Acad. Sci.*, **27**, 468 (1941).

(13) L. Pauling, see footnote 12b, and *ibid.*, **25**, 577 (1939); R. S. Mulliken, *J. Chem. Phys.*, **7**, 364 (1939).

(14) The denomination "neo-γ-carotene A" is now applied to that stereoisomer which appears immediately below unchanged γ-carotene on the Tswett column. Zones of the same pigment have been mentioned under the name "neo-γ-carotene" by R. F. Hunter and A. D. Scott [*Biochem. J.*, **35**, 31 (1941)] and by the authors [*J. Biol. Chem.*, **139**, 193 (1941)]. Preliminary experiments, using refluxing and iodine catalysis, have revealed the presence of at least one more reversibly formed stereoisomer which is adsorbed below the A compound and is termed neo-γ-carotene B.

(15) Footnote 12(b); A. L. LeRosen and L. Zechmeister, THIS JOURNAL, **64**, 1075 (1942); L. Zechmeister and W. A. Schroeder, *ibid.*, **64**, 1173 (1942).

used if an immediate crystallization is intended. The spectra (in petroleum ether unless otherwise indicated) were determined with an Evaluating Grating Spectroscope (Zeiss, light filter BG-7, 2 mm. thick). For the estimation of the concentrations a Pulfrich Gradation Photometer was used (light filter S 45 or S 47). The necessary data for neo-β-carotene U are given below. Values for β-carotene itself were published by Cholnoky.[16] Relative photometric values of components of a chromatogram are expressed in % of the extinction of the sum of the components.

(a) **Heat Isomerization of β-Carotene Solutions.**—A solution of 25 mg. of chromatographically homogeneous β-carotene crystals (from carrots) in 150 ml. of petroleum ether was refluxed in an all glass apparatus, in a slow carbon dioxide stream for 60 min. The following chromatogram was obtained (28 × 7 cm.):

2 brownish yellow: irreversible layer (heterogeneous, about 485, 453 mμ.)
15 colorless
35 reddish orange: neo-β-carotene U (481, 450)
2 almost colorless
0.5 yellow: irreversible layer[17] (479, 448)
2 almost colorless
85 dark orange: β-carotene (486, 454)
40 dark yellow: neo-β-carotene B (475.5, 443.5)
2 almost colorless
20 pale reddish: neo-β-carotene E (479.5, 447)
2 almost colorless
12 yellow: a labile isomer (473, 443)

Unchanged β-carotene and each stereoisomer (without irreversible zones) was cut out, transferred into petroleum ether and refluxed again. The relative photometric values of the zones thus formed are listed in Table II.

TABLE II

RELATIVE PHOTOMETRIC VALUES OF THE PIGMENTS REVERSIBLY FORMED BY SIXTY MINUTES OF REFLUXING OF β-CAROTENE AND SOME OF ITS STEREOISOMERS

Starting material	Relative photometric values (%) neo U	β-carotene	neo B	neo E	labile isomer
Neo-β-carotene U	31	40	19	10	
β-Carotene	4	86	8	1	1
Neo-β-carotene B	4	50	40	3	3
Neo-β-carotene E	14	49	19	18	
Labile isomer	10	22	24	30	14

(b) **Isomerization of β-Carotene by Iodine Catalysis, at Room Temperature.**—25 mg. of homogeneous β-carotene in 200 ml. of petroleum ether was kept in the presence of 0.5 mg. of iodine for sixty minutes and chromatographed (calcium hydroxide, 28 × 7 cm.). The same pigments as were listed in (a) appeared, except the 0.5-mm. yellow zone. Each zone was again submitted to this catalytic treatment with subsequent adsorption analysis. The relative photometric values of the isomers formed are summarized in Table III.

TABLE III

RELATIVE PHOTOMETRIC VALUES OF β-CAROTENE AND OF SOME OF ITS STEREOISOMERS AS FORMED BY IODINE CATALYSIS AT ROOM TEMPERATURE

Amount of iodine, 2% of the starting material; duration, 60 min.

Starting material	Relative photometric values (%) neo U	β-carotene	neo B	neo E	labile isomer
Neo-β-carotene U	24	47	24	3	2
β-Carotene	22	48	25	3	2
Neo-β-carotene B	21	51	23	3	2
Neo-β-carotene E	20	48	24	4	4
Labile isomer	18	45	16	13	8

(c) **Isomerization of β-Carotene with Hydrochloric Acid.**—25 mg. of homogeneous β-carotene in 200 ml. of petroleum ether was mechanically shaken with 100 ml. of concentrated hydrochloric acid for thirty minutes, then washed free of acid and developed with petroleum ether, containing 1% acetone, on a calcium hydroxide column (24 × 5.5 cm.)

7 orange: irreversible layer (heterogeneous)
4 almost colorless
2 orange-yellow: irreversible (459, 430.5 mμ)
90 reddish orange: neo-β-carotene U (480, 450)
5 almost colorless
40 dark orange: β-carotene (486, 454)
35 dark yellow: neo-β-carotene B (476.5, 444)
12 pale reddish: neo-β-carotene E (479.5, 447)
8 yellow: labile isomer (476.5, 445.5)
5 almost colorless
15 pale yellow: irreversible (479, 448.5)[18]

The relative photometric values of the zones were: β-carotene: neo U: neo B: neo E: labile isomer = 50:23:23:3:1. The chromatogram was subject to minor variations in different experiments. A reversible minor zone appeared on long development in most experiments below the U-isomer: neo-β-carotene V (474, 443 mμ), while in some other cases two isomers (471, 440 and 473, 444 mμ) were observed below neo-β-carotene E, both of which showed a very great tendency for spontaneous reisomerization into β-carotene. If the indicated volume of acid was diminished or the duration of the catalysis shortened, the irreversible bottom layer was missing. In longer exposure to the acid, the amounts of the bottom layer increased; furthermore, two minor stereoisomers of β-carotene appeared, both located above the U-compound.

The irreversible bottom layer has been crystallized. A fresh solution of the crystals did not separate from carrot α-carotene in the mixed chromatogram and will be investigated later.

(d) **Isomerization of β-Carotene by Melting.**—25 mg. of homogeneous β-carotene (m. p. 179.5°, cor.) crystals was melted in a sealed glass tube in carbon dioxide and kept in a bath at 190° for fifteen minutes. The melt was rapidly solidified in ice water, dissolved in petroleum ether and chromatographed. (The loss in the total photometric

(16) L. Cholnoky, *Z. Unters. Lebensm.*, **78**, 157 and 401 (1939); further communication in print.

(17) This minor layer has not been observed when stereoisomers of β-carotene were refluxed. If this pigment is refluxed separately, an irreversible pigment possessing 459, 430.5 mμ appears above it on the column. The same can be obtained from β-carotene by means of hydrochloric acid.

(18) 0.5–1% of the starting material.

value of the starting material amounted to about 60%.) The column (27 × 6.8 cm.) was developed with petroleum ether containing 2% acetone:

15 colorless
1 yellow: irreversible (457.5, 427 mμ)
63 reddish orange: neo-β-carotene U (481, 450)
2 pink: unidentified (very little)
7 yellow: neo-β-carotene V (474, 443)
7 almost colorless
30 dark orange: β-carotene (486, 453.5)
2 almost colorless
15 dark yellow: neo-β-carotene A (469, 437.5)
25 pale orange: neo-β-carotene B (475.5, 444.5)
1 yellow: neo-β-carotene C (471.5, 440.5)
3 colorless
15 pale reddish: neo-β-carotene E (477.5, 445)
5 colorless
10 yellow: labile isomer (468.5, 437)

Filtrate: yellow (432 mμ). This irreversible pigment (2% of the total photometric value of the melt) can be adsorbed on alumina (Alorco). The chromatographic filtrate of the latter contained a colorless substance showing greenish fluorescence in ultraviolet light.

The relative photometric intensities of the reversible zones (the width of which is printed in italics) were from top to bottom: 19:4:33:8:24:8:4.

(e) **Isolation and Properties of Neo-β-carotene U.**—To a solution of 50 mg. chromatographically homogeneous β-carotene (from carrots) in 250 ml. of petroleum ether 1 mg. of iodine (in 1 ml. of the solvent) was added and the liquid kept at room temperature for an hour. The solution was then developed with petroleum ether containing 3–5% acetone on a calcium hydroxide column (28 × 7 cm.) until the following sequence appeared: near the middle of the column the typical deep orange zone of β-carotene was located (about half of the total pigment), and this was followed by a strong zone of neo-β-carotene B and other minor neo-forms. Immediately above the β-carotene zone but well separated from it by a colorless intermediate section the light orange layer of neo-β-carotene U was observed. The latter was cut out, eluted with alcohol and eventually combined with an analogous eluate obtained by a second treatment with iodine of the unchanged β-carotene portion. On addition of water the pigment was transferred into petroleum ether, washed free of alcohol, dried and re-chromatographed on a smaller column. Only minor zones appeared below the main product which was eluted with peroxide free ether. After evaporating the dried solution, the residue was dissolved in the minimum amount of benzene, transferred into a centrifuge tube and crystallized out by cautious addition of several volumes of absolute methanol. The crystallization was almost complete within a few minutes at room temperature and the yield was 12.7 mg., *i. e.*, about 25% of the starting material. If the second treatment of β-carotene is omitted, the yield is reduced by about one third (obtained 41 mg., from 250 mg. of β-carotene).

Neo-β-carotene U was obtained as an orange crystalline powder which did not glitter. The basic microscopic form was a long narrow plate with one tapered end; the individuals were partly grouped in sheaves; m. p. 122–123° (cor., electrically heated Berl block; sealed tube filled with carbon dioxide); a fraction isomerized during the determination.

Anal. Calcd. for $C_{40}H_{56}$: C, 89.48; H, 10.52; mol. wt., 537. Found: C, 89.34; H, 10.58; mol. wt., 486 (in exaltone; a considerable fraction was isomerized).

Neo-β-carotene U is somewhat more soluble than β-carotene, especially in petroleum ether. It shows an epiphasic behavior in the partition test. The spectra, compared with those of β-carotene, are included in Table IV. On addition of iodine the following spectra appear: In carbon disulfide: 516, 481.5 mμ.; in pyridine: 498, 464.5 mμ; in benzene: 495.5, 462 mμ.; in chloroform: 494, 461 mμ.; in carbon tetrachloride: 493.5, 461 mμ.; in dioxane: 490.5, 458 mμ.; in cyclohexane: 486.5, 455 mμ.; in acetone: 485, 453.5 mμ.; in ligroin (b. p. 86–100°): 484, 453 mμ.; in ethanol: 482, 450.5 mμ.; in petroleum ether (b. p. 60–70°): 485, 453 mμ.; in ether: 484, 452 mμ.; in hexane: 483.5, 452.5 mμ., and in methanol: (479), (448) mμ.

A 0.1% benzene solution did not show optical activity in a 2-dm. tube. The concentration of petroleum ether solutions can be determined by means of the Pulfrich Gradation Photometer (k = extinction coefficient, c = mg. of pigment in 100 ml. of solution).

	k	0.2	0.4	0.6	0.8	1.0
Light filter S45	c	0.085	0.18	0.27	0.36	0.45
Light filter S47	c	0.095	0.19	0.29	0.39	0.49

TABLE IV

SPECTRA OF β-CAROTENE AND NEO-β-CAROTENE U IN DIFFERENT SOLVENTS (mμ)[a]

Solvent	β-Carotene		Neo-β-carotene U	
Carbon disulfide	520.5	484	512.5	478.5
Pyridine	503.5	469	498	464.5
Benzene	497.5	463.5	494	461
Chloroform	497.5	464	493.5	461
Carbon tetrachloride	497.5	463	492.5	460
Dioxane	494	462	490	458
Cyclohexane	490	457	485.5	454
Acetone	488.5	456	485	453.5
Ligroin (b. p. 86–100°)	487	455.5	483	452
Ethanol	486.5	453.5	482	450.5
Pet. ether (b. p. 60–70°)	486	453.5	481	450
Ether	485.5	453	481	449.5
Hexane	485	453.5	480	449.5
Methanol	484.5	452.5	480.5	449.5

[a] Gillam and El Ridi gave maxima for their pseudo-α-carotene in carbon disulfide: 507, 477 mμ.; in benzene, 491, 458 mμ.; in chloroform, 486, 456 mμ.; in ethanol, 478, 447 mμ.; and in petroleum ether (b. p. 70–80°), 477, 446 mμ.

Neo-β-carotene U is less easily adsorbed on lime from petroleum ether than pro-γ-carotene, much less than γ-carotene and considerably more strongly than β-carotene. The latter and neo-β-carotene U can be separated by developing with petroleum ether but more easily when 2–5% acetone is added to the solvent, depending on the quality of the adsorbent. On some brands of calcium hydroxide no separation takes place from pure petroleum ether but it occurs in many cases in the presence of 15% benzene.

Isomerization experiments with different methods, which started from crystallized neo-β-carotene U gave, with some variations, the stereoisomers mentioned above. The compound U is comparatively resistant to moderate heating, *e. g.*, a solution of 3 mg. in 25 ml. of petroleum ether, when kept at 60° for one hour, contained about three-fourths of the final pigment in the form of unchanged compound U. In melt experiments the same stereoisomers were obtained as in the corresponding experiments with β-carotene and a further reversible zone was observed (neo-β-carotene D, 474.5, 441.5 mμ). The melt was kept at 135° for fifteen minutes and because of the lower temperature (as compared with the β-carotene melt) and the partial formation of the more intensely colored β-carotene, the total loss in extinction was only one-fourth to one-fifth of the initial value in this case. Of the total photometric value of the melt 40% was caused by unchanged U-isomer, 22% by β-carotene formed and 38% by seven minor stereoisomers. No slightly colored or colorless and fluorescent breakdown products were observed.

Summary

As a contribution to the stereochemistry of polyenes, the isomerization of β-carotene was studied, under the influence of refluxing, iodine catalysis, hydrochloric acid catalysis, and by melting the crystals. The chromatograms showed a number of pigments, nine or ten of which were stereoisomers of β-carotene. Some of them are very labile. On addition of iodine they all yield a preponderant quantity of β-carotene and minor stereoisomers. One of the new isomers, "neo-β-carotene U," has been crystallized in a yield of 17% of the starting material. It is adsorbed above β-carotene and thus does not follow an earlier suggested rule concerning the location of polyene-hydrocarbon isomers on the Tswett column. It is tentatively assumed that the U isomer contains one *cis* double bond, and Gillam's pseudo-α-carotene two such bonds, out of the five stereochemically available double bonds. An observed labile stereoisomer which shows spectral maxima at 20 mμ. shorter wave lengths than β-carotene may possess four or five *cis* bonds in its molecule.

PASADENA, CALIFORNIA RECEIVED APRIL 27, 1942

[FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, NEW YORK]

An Extension of the Acidity Scale

BY L. MICHAELIS AND S. GRANICK

After it had been recognized that the concentration of the hydrogen ion was only to a first approximation a useful concept for an acidity scale, *p*H was then defined as the logarithm of the reciprocal of the activity, instead of concentration, of the hydrogen ion. Because of the essential uncertainty involved in the definition of the activity of a single ionic species such as the hydrogen ion, one may avoid committing oneself to a definition in terms of strictly thermodynamical concepts and adopt the following working definition

$$p\mathrm{H} = \frac{E - E_0}{2.3RT}$$

where E is the e. m. f. of a cell composed of a hydrogen electrode, the solution to be measured, a saturated potassium chloride bridge and a calomel cell. The constant E_0 is chosen either so that in a very dilute solution of hydrochloric acid (say 10^{-4} M) *p*H equals the logarithm of the reciprocal of the concentration of the acid, or so that the *p*H in an equimolecular mixture of acetic acid and sodium acetate of infinitely low ionic strength equals the *p*K of acetic acid, whether this *p*K be determined by a thermodynamical or by a non-thermodynamical method, such as the conductivity method.[1] These two ways of fixing the value of E_0 are, for all practical purposes, compatible with each other.

This working definition is valid only on the assumption that the liquid junction potential of the above galvanic cell is irrelevant, either because it is negligibly small, or because it is constant for such cases of *p*H determinations as practically may occur. This assumption breaks down for solutions of large ionic strength and especially for solutions of very high acidity or alkalinity. Here, the liquid junction potentials can by no means be said to be irrelevant. If one tries to establish a *p*H scale for extremely acid solutions, another working definition of the acidity scale has to be chosen, and, possibly, such that in the region of lower acidities it coincides with the ordinary *p*H scale. One approach to this problem has been made by Hammett,[2] who, by means of colori-

(1) One of the more recent presentations of this much discussed problem is given by MacInnes in "The Principles of Electrochemistry," Reinhold Publishing Corporation, New York, N. Y., 1939.

(2) L. P. Hammett, *Chem. Rev.*, **16**, 67 (1935); "Physical Organic Chemistry," McGraw-Hill Book Company, New York, N. Y., 1940.

metric studies of a suitably chosen set of acidity indicators in the form of dyestuffs, has established an acidity scale in terms of an "acidity function," which in the range of pH, say 12 to 1, coincides with the pH scale.

The writers encountered during their studies on bivalent reversible oxidation–reduction systems an opportunity of establishing an acidity scale on a different basis. The principle of the method is this.[3]

In a bivalent, reversible system one may distinguish three levels of oxidation–reduction: the reduced (R), the semi-oxidized (S), and the totally oxidized (T) form. The normal potential of the R,S system, or the normal potential of the lower step of oxidation, will be designated as E_1; that of the S,T system, or that of the higher step of oxidation, as E_2; and the normal potential of the R,T system, or the mean normal potential, as E_m. These three normal potentials are related to each other as follows

$$E_m = (E_1 + E_2)/2$$

All of these normal potentials depend on pH. Hence, also the difference $E_2 - E_1$ depends on pH. This difference will be referred to as the "spread" of the normal potentials. On plotting E_1 and E_2 against pH, the curves consist to the first approximation of rectilinear sections with slopes of $n \times$ 0.06 volts per pH unit (at 30°), where n is an integer, including 0, and scarcely ever >3 (see, for instance, Fig. 1). From this approximation one arrives at the more correct form of the curves by rounding out the discontinuities. For example, the potential of the true, rounded-out curve at the pH of the intersection of two straight lines (pK) differs from that of the point of intersection by 18 millivolts.[4] This rule is of practical use for rounding out the preliminary discontinuities of the plots. Similarly, the E_m curve, as preliminarily plotted, consists of rectilinear sections with slopes of $n \times 0.03$ volts per pH unit, and here the correction for rounding out the edges is 9 millivolts at the pH of the intersection.

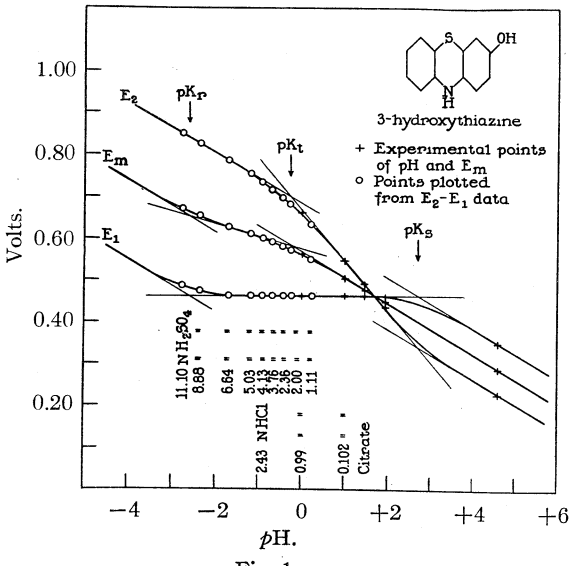


Fig. 1.

A further consequence of these rules is that also the spread, $E_2 - E_1$, depends on pH in a definite manner: in some pH intervals the spread may be independent of pH; in other pH intervals the spread may depend linearly on pH, the slope being either 0.06 or an integer multiple thereof. The transition from a region where the spread is independent of pH to a region where it is 0.06 is, of course, not a discontinuous one, but has to be rounded out according to the same principle as mentioned before. A change of this slope is brought about by a change of acidic ionization of the dye in one of its levels of oxidation–reduction.

Within the range of well definable pH values, plots of the three normal potentials against pH have been previously established for numerous dyestuffs. On working in very acid solutions there are two factors interfering with an unambiguous extension of the plot. First of all, there is no way of measuring pH by the hydrogen electrode. In the second place, there is no way of obtaining absolute values of the oxidation–reduction potential. It is true, that by a method described in a previous paper,[5] the liquid junction potential can be kept constant for all practical purposes during the time of the titration experiment, but the absolute value of the potential[6] cannot be determined. What one can measure is only the change of the potential during the titration. So, neither E_1 nor E_2 nor E_m can be measured, yet the spread, $E_2 - E_1$, can be measured.

(3) The writers are fully aware of the fact that what follows is not quite easy to follow for anybody not thoroughly familiar with the theory of the equilibrium in a reversible two-step oxidation–reduction system. Detailed presentations of this subject are L. Michaelis, *Chem. Rev.*, **16**, 243 (1935); L. Michaelis and M. P. Schubert, *ibid.*, **22**, 437 (1938); L. Michaelis, *Ann. N. Y. Acad. of Sciences*, XL, 39 (1940).

(4) Furthermore, at that pH which equals $pK \pm 1$ the analogous correction is 2.4 mv., and at any pH still further apart from pK this correction is practically negligible.

(5) L. Michaelis, M. P. Schubert and S. Granick, THIS JOURNAL, **62**, 204 (1940).

(6) "Absolute," of course, only in so far as the potential of the normal hydrogen electrode is arbitrarily taken as zero.

Now the spread depends on the acidity, and this functional relationship can be used for an acidity scale which, in the ordinary acidity range, coincides with *p*H. The procedure is best explained by an example. A suitable dyestuff is chosen. 3-Hydroxythiazine[7] is, by far, the best for reasons which will presently be understood. For this dyestuff it is easy to establish a plot of the normal potentials in the *p*H range from alkaline solution to acidities still measurable by the hydrogen electrode, say to *p*H 1 (the right-hand part of Fig. 1). Now the curves, which from *p*H 2 into the more acid region are all linear, can be extended into the region of higher acidity to the left, leaving all slopes unchanged, as long as one can be sure that no acidic ionization constant of the dye in any of its three forms, R, S or T interferes. Hereby one can establish a bridge from what may be called the known region of *p*H into the unknown region.

A series of potentiometric titrations in solutions of sulfuric acid furnishes the data for the spreads of the potentials at various concentrations of the acid (Table I). Thus, one can graphically correlate the spread with the concentration of the acid (Fig. 1). For instance, a titration experiment in 1.11 *N* sulfuric acid gave for the spread, $E_2 - E_1$, the value 174 millivolts. Now we mark that ordinate in the plot where the spread is 174 millivolts, and read on the abscissa that the *p*H here is +0.24. Hence, it is legitimate to ascribe to a 1.11 *N* sulfuric acid, the *p*H value +0.24. In a similar way, the *p*H values of sulfuric acid at other concentrations can be ascertained.

This procedure is legitimate for the extension of the *p*H scale to about 0. From here on, the oxidized form (t-hydroxythiazine) begins to change its state of acidic ionization by attaching a proton. Since the absorption spectra of the two forms of the oxidized dye are different, it is easy to find by a spectrophotometric method, such a concentration of sulfuric acid in which the ratio of the two forms is 1:1. The *p*H of this acid solution may be identified with the *pK* of the dye. The uncertainty involved in this simplified assumption will be discussed later on. To the left-hand side from *p*H 0, the E_2 curve must change its slope from 0.06 to 0.03. Now, one has to find the point of intersection in order to draw the straight line with slope 0.03 at the correct height above the abscissa. This is accomplished as follows. By a potentiometric oxidation–reduction experiment in such a sulfuric acid solution in which the ratio of the two acidic levels of the dye is 1:1, one finds a certain value of the spread for the normal potentials. In order to construct the two intersecting tangents and the correct value of the rounded-out curve at this point of intersection, one utilizes the rules stated above, saying that the normal potential of the T,S system at the point of intersection of the two tangents must be 18 millivolts lower than the point of intersection itself. In this way, the point of intersection is found to lie at *p*H −0.25. This, then, is also the exponent of acidic ionization, *pK*. Now, from the potentiometric oxidative titration experiments at higher acidities and the spreads derived from them, one can correlate the higher concentrations of sulfuric acid each with a definite *p*H value. This procedure can be extended to a *p*H about −2. Here, an acidic dissociation constant of the reduced form of the dye begins to interfere. By studying the ultraviolet absorption spectra of the reduced form, it was possible to obtain a semi-quantitative confirmation of the existence of this constant in the neighborhood of the acidity expected. It is safer to restrict the exploitation of this dye only to that region in which the *pK* of the reduced form of the dye does not yet interfere.

Now we select another dyestuff, 3-aminothiazine, utilizing the *p*H data obtained from oxythiazine. This is shown in Fig. 2. The points obtained within the ordinary *p*H range with aminothiazine are marked +. At higher acidities, up to −2, we can correlate the "spreads" with the *p*H of the acid solutions, as obtained from the first dye (Fig. 1). By optically determining the acidic ionization constant of the new dye in the same fashion as with the first, the plot can be extended up to *p*H −4. Here, again, a dissociation constant of the reduced form begins to interfere. For this reason, we proceed to another dye, 3,9-diaminothiazine (thionine) (Fig. 3) which permits us to extend the *p*H scale to about −6 in an analogous manner. This is as far as it was possible to go as yet.

On extending the *p*H scale by this method to the range of high acidity, there can be no objection to the procedure described, as long as the dye-

(7) As regards the nomenclature of the dyes, we follow our previous suggestion [S. Granick, L. Michaelis and M. P. Schubert, THIS JOURNAL, **62**, 1802 (1940)] of using the name of the leukodye which is always more convenient than that of the quinonoid form. When one of the three levels of oxidation–reduction is to be referred to in a special case, these three levels, then, are distinguished by the prefixes, r-, s- and t-.

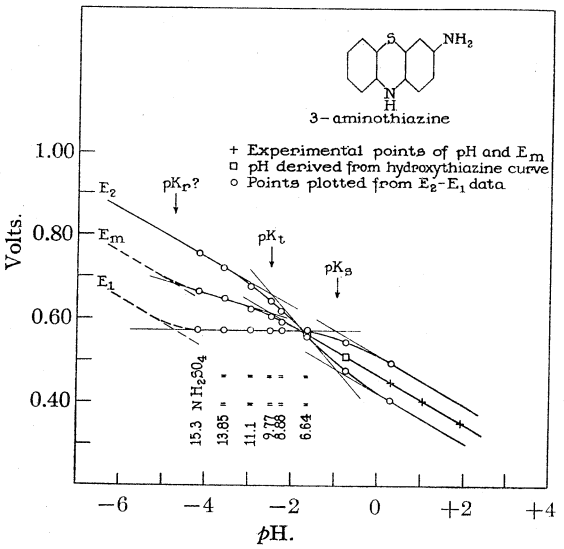


Fig. 2.

stuff in any of its three levels of oxidation–reduction (the R, S and T forms) does not change its state of acidic ionization. As soon as an acidic ionization constant of the dyestuff in one of its three levels of oxidation–reduction becomes noticeable, the following uncertainty begins to interfere. The optical method to be described presently yields that concentration of sulfuric acid where the ratio of the concentrations of the two forms of the dye, in their two levels of acidic ionization, is 1:1. What we want to know, however, is that concentration of the acid in which the ratio of the *activity* of the two forms is 1:1. Since the two forms of acidic ionization of necessity differ with respect to the number of free electric charges, the activity coefficients for the two forms will not be alike. On identifying the apparent ionization constant, as determined optically, with the thermodynamical ionization constant, one commits an error. This is the limitation of the method. Although the direction of the error may be recognizable from theoretical reasoning, there is no way of finding out a reasonable quantitative correction. For this reason, no correction will be applied at all in this paper, leaving any possible refinement for later work. Very likely, in sulfuric acid solutions the error in this procedure is small, and one should not over-emphasize it. The error may be estimated to rise up to a few tenths of a *p*H unit in the worst cases.

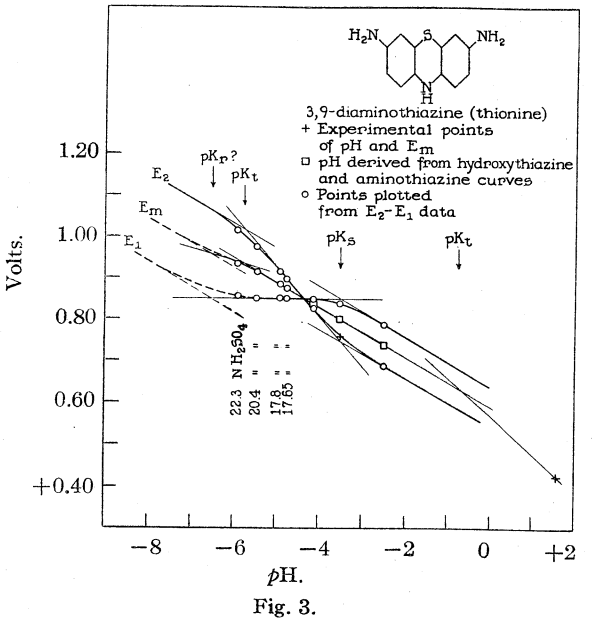


Fig. 3.

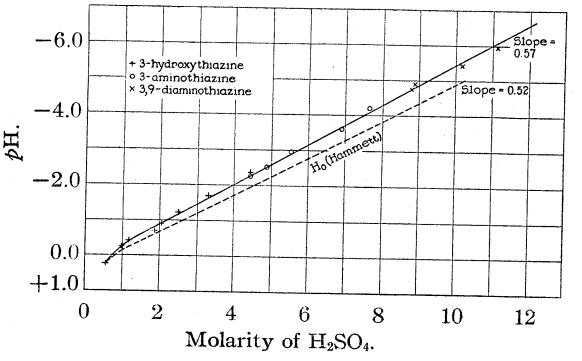


Fig. 4.

The results of the method may be understood, without further comment, from Figs. 1–4. The last of these figures permits of a comparison of this extended *p*H scale with Hammett's acidity function, H_0. It is striking that in both scales there is a linear relationship between *p*H (or acidity function) and the concentration of sulfuric acid above 1 *M* sulfuric acid.[8] Why this should be so is not yet explained. The slopes in the two methods are not quite the same: 0.52 for Hammett's function, 0.57 for ours. The writers are more impressed by the similarity than by the discrepancy between the two scales considering the different approaches used.

Optical Determination of the Ionization Constants.—Only two constants, those of the T forms of hydroxythiazine and aminothiazine, are essential for the plotting of the curves. The others that have been determined are not necessary but serve as a nice confirmation of the theory. For example, the *pK* value for the R form of oxythiazine in acid solution can be approximately es-

(8) N. F. Hall and W. Spengeman, THIS JOURNAL, **62**, 2487 (1940).

TABLE I

3-HYDROXYTHIAZINE

Solvent	pH, directly measured with H_2 electrode	E_m, volts	Index potential E_i, mv.	Spread $E_2 - E_1$, mv.	pH values from spread
Acetate buffer	+4.62	+0.288	14.9, 15.0	−120	
Citrate buffer	+1.96	+ .449	19.4, 19.5	− 22	
Citrate buffer	+1.47	+ .477	26.0, 25.8	+ 24	
0.112 N HCl	+1.02	+ .506	43.6, 43.8	+ 81	
1.11 N H_2SO_4	+0.29	+ .543	87.0, 87.0	+174	+0.24
0.990 N HCl	+0.02	+ .555	99.0, 99.0	+198	− .02
2.00 N H_2SO_4[a]	+0.03	+ .550		+217	− .25
2.36 N H_2SO_4[a]	..	(+ .523)		+233	− .40
3.76 N H_2SO_4				+252	− .70
2.43 N HCl[a]				+270	− .90
4.13 N H_2SO_4[a]				+270	− .90
5.03 N H_2SO_4[a]				+295	−1.20
6.64 N H_2SO_4				+324	−1.68
8.88 N H_2SO_4				+363	−2.35

[a] These experiments are new data. The others are taken from the previous papers by the authors. pK of T–TH$^+$ at 2.00 N H_2SO_4.

TABLE II

3-AMINOTHIAZINE REDUCTION WITH Pd + H_2 AND TITRATION WITH POTASSIUM DICHROMATE IN SAME ACID

Solvent	pH	E_m	E_i, mv.		$E_2 - E_1$, mv.	pH values from spread of $E_2 - E_1$
Acetate buffer	+4.62	+0.293	15.4	15.6		
Citrate buffer	1.91	+ .452	15.4	15.3		
Citrate buffer	1.02	+ .506	15.9	15.8		
1.11 N H_2SO_4	0.29	+ .548	15.6	15.3	− 99	
3.58 N H_2SO_4			16.3	16.4	− 67	
6.64 N H_2SO_4			20.0	19.2	− 19	
8.88 N H_2SO_4			30.5	30.2	+ 42	−2.25
9.77 N H_2SO_4[a]			38.0	38.0	+ 67	−2.50
11.1 N H_2SO_4			54.5	54.0	+106	−2.95
13.85 N H_2SO_4[a]					+148	−3.60
15.3					+188	−4.20

[a] New data. pK of TH$^+$–TH$_2^{++}$ at 10.0 N H_2SO_4.

TABLE III

REDUCTIVE TITRATIONS OF THIONINE WITH $TiCl_3$

H_2SO_4 N	E_i, mv.		$E_2 - E_1$, mv.	pH values from spread $E_2 - E_1$
9.35	15.5	15.3	−99	
12.9	16.0	16.0	−78	
15.0	19.3	19.7	−18.9	
17.65	31.4	32.8	+48	−4.75
17.80	38.0	38.5	+68	−4.90
	39.0	39.0		
20.4	64.0	66.0	+130	−5.45
22.3	78.0	80.0	+158	−5.90

pK of TH$^+$ − TH$_2^+$ at 3.5 N H_2SO_4 (this pK value is only needed to get correct E_m, but is not necessary for the pH determination). pK of TH$_2^{++}$ − TH$_3^{+++}$ at 21.2 N H_2SO_4.

timated from the fact that the $E_2 - E_1$ values increase only slightly above 9 N sulfuric acid.

The pK values of the oxidized forms were determined by means of a Pulfrich photometer. The absorption spectra of the T and TH$^+$ forms of hydroxythiazine overlap. By selecting several suitable filters where the ratios of the absorption of the two components are different, the determination of the ionization constant is made possible. The pK values of aminothiazine TH$^+$ − TH$_2^{++}$ and of thionine TH$_2^{++}$ − TH$_3^{+++}$ are more readily determined, since there is scarcely any overlapping of the absorption spectra. The acid concentration is increased until the extinction is found to be just half the extinction of the dye with one less proton (the dyestuff concentration, of course, remaining constant).

The determination of the ionization constant of the reduced form of oxythiazine is made possible, because the R form has a sharp absorption band at 3100 Å. in contrast to the RH$^+$ form which does not absorb at all in this region. By increasing the acidity in a series of steps, it was found that an absorption curve corresponding to one containing 50% of the concentration of the reduced form was obtained in a region between 8.5–12.0 N sulfuric acid, most probably in the neighborhood of 9.5 N sulfuric acid.

We wish to thank Dr. G. I. Lavin for taking the ultraviolet absorption plates of aminothiazine and Dr. E. G. Pickels for photometering these plates.

Summary

An extension of the pH scale for aqueous solutions of sulfuric acid up to 11 molar is accomplished by utilizing what is defined in the text as the spread of the normal potentials of certain dyestuffs which form large amounts of semiquinone radicals at suitable acidities. The results obtained from the use of three suitable dyes: hydroxythiazine, aminothiazine and thionine, can be compared with the Hammett acidity scale. In spite of the different approaches of Hammett's method and ours, we find a striking similarity between Hammett's results and our own.

NEW YORK, N. Y. RECEIVED APRIL 10, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

The Autoxidation of Manganous Hydroxide

BY AMBROSE R. NICHOLS, JR.,* AND JAMES H. WALTON

The composition of the products obtained in the autoxidation of manganous hydroxide has received the attention of numerous investigators. The contributions of Meyer and Nerlich[1] and of Herman and Lievin[2] are of especial interest in this connection.

Meyer and Nerlich made a very complete study of the reaction in connection with the theories of the nature of trivalent manganese. They found that when manganous chloride, ammonium chloride and ammonium hydroxide were mixed and shaken in air, the product was manganic oxide, as evidenced by both the analysis of the product and the volume of oxygen absorbed. When potassium hydroxide, calcium hydroxide, or barium hydroxide was used, the product was stated to be manganese dioxide, although the volume of oxygen absorbed varied between 81 and 94% of the amount corresponding to the formation of manganese dioxide. According to Meyer and Nerlich, the autoxidation in the ammoniacal solution takes place through a mangano-ammonia complex which is oxidized to a mangani-complex. The latter is subsequently hydrolyzed with the formation of manganic hydroxide or manganic oxide. For the autoxidation of manganous hydroxide precipitated by fixed alkali, these authors accept the mechanism proposed earlier by Meyer.[3] Meyer postulated that the first step is the formation of a moloxide, H_2MnO_4, or $H_2MnO_2(O_2)$, which is not identical with manganic acid. The moloxide easily gives up oxygen to an acceptor such as manganous hydroxide. These authors find that other acceptors such as sodium sulfite and sodium arsenite have no effect. They did not attempt to investigate the rate of the reaction.

Herman and Lievin carried out experiments in which a bulb of manganous sulfate solution was broken within a flask containing potassium hydroxide solution, the flask being connected with a gas buret filled with oxygen. The volume of oxygen absorbed was plotted against time. With an excess of potassium hydroxide the curves obtained appeared to consist of two rectilinear portions connected by a curved portion. The ratio between the velocities indicated by the two sections varied with the amount of excess potassium hydroxide. These authors were unable to observe an absorption of more than 82% of the theoretical volume of oxygen necessary for the formation of manganese dioxide. With an excess of manganous sulfate, they found that there was a rapid absorption lasting about one minute, followed by a slow reaction at constant velocity, ending at a limit corresponding to the formation of manganic oxide. The greater the excess of manganous sulfate, the slower was the reaction, but in each case all of the manganese precipitated was in the form of manganic oxide.

The work described in this paper was undertaken to extend the knowledge of the factors affecting the rate of autoxidation of manganous hydroxide.

Apparatus and Procedure.—The apparatus was essentially that described by Filson and Walton.[4] An indented reaction flask containing a bulb of ammonium hydroxide or sodium hydroxide and the desired amount of manganous chloride solution was placed in a thermostated shaking device and connected with a gas buret. The system was evacuated and filled with oxygen. The reaction flask was rotated rapidly back and forth about a vertical axis which resulted in breaking the bulb and keeping the resulting reaction mixture saturated with oxygen. The volume of solution used was 60 cc. in each case. The reaction was followed by recording the buret readings at the end of definite time intervals. The temperature of the gas buret and the reaction flask was always 25° except as otherwise stated.

Autoxidation in Solutions Containing Manganous Chloride, Ammonium Chloride, and Ammonium Hydroxide.—Since ammonium chloride prevents the precipitation of manganous hydroxide by ammonium hydroxide, the effect of varying the ammonium chloride concentration was first studied. Because the reaction does not follow any ordinary rate law the results have been recorded (Table I) as volumes of oxygen absorbed in definite time intervals. A comparison of these volumes shows the effect of the concentration of ammonium chloride upon the reaction. The total volumes absorbed indicate definite limits. Each trial was continued until the buret level had remained constant for a period of from one-half to one hour.

The final volume of oxygen absorbed varied between 67 and 83% of the volume theoretically required for the formation of manganese dioxide (54.0 cc.). Curves represent-

* Present address: San Diego State College, San Diego, Calif.

(1) J. W. Meyer and R. Nerlich, *Z. anorg. allgem. Chem.*, **116**, 117 (1921).

(2) J. Herman and O. Lievin, *Compt. rend.*, **200**, 1474 (1935); also J. Herman, *ibid.*, **202**, 419 (1936).

(3) J. Meyer, *J. prakt. Chem.*, **72**, 278 (1905).

(4) G. W. Filson and J. H. Walton, *J. Phys. Chem.*, **36**, 740 (1932).

TABLE I

EFFECT OF AMMONIUM CHLORIDE CONCENTRATION

$MnCl_2$, 0.0692; NH_4OH, 0.477 mole per liter

NH_4Cl mole/liter	*p*H	Volume of oxygen, cc., absorbed in 5 min.	10 min.	15 min.	20 min.	Total volume absorbed
0.0	9.59	34.4	35.9	36.6	37.2	41.55
.167		31.5	37.5	38.55	39.1	44.65
.250		21.7	35.7	37.6	38.3	41.75
.333		19.3	26.6	36.1	38.6	42.7
.417	9.12	17.6	21.7	27.9	35.1	41.7
.500		15.4	19.6	23.5	29.45	41.15
.583		13.1	17.9	21.8	26.9	39.7
.750		9.1	14.05	17.65	23.6	36.15
1.35	8.93	2.3	4.95	7.95	11.1	39.7
2.70	8.60	1.7	2.05	2.4	2.9	38.8
4.05	8.36	0.45	0.6	0.7	0.8	37.3

ing duplicate runs varied by not more than 2%. The *p*H values listed were obtained by preparing reaction mixtures identical with those autoxidized and measuring the *p*H immediately by means of the glass electrode. A precipitate of manganous hydroxide was formed immediately in samples of *p*H above 9.3. Samples of *p*H 9.0 precipitated after standing a moment or two, while those of *p*H below 8.8 precipitated only very slowly. In each case the precipitate was white when first formed.

The rate of oxygen uptake decreased at first after the reaction had proceeded for a period, and then increased appreciably before finally decreasing as the reaction approached completion. The possibility of an autocatalytic effect, suggested by this observation, was investigated by adding to the reaction mixture a small amount of the solid oxidation product from previous trials. This resulted in a much more rapid reaction, and the rate was found to decrease continuously. Since the oxidation product was presumably largely manganese dioxide, a pure sample of this substance was tried. It also catalyzed the reaction. The effect of the manganese dioxide was found to depend upon its state of subdivision. Four reaction mixtures of the following composition were prepared: manganous chloride, 0.0692 mole per liter, ammonium hydroxide, 0.477 mole per liter, ammonium chloride, 2.25 moles per liter. The results, expressed in terms of the time required for the absorption of 20 cc. of oxygen when 0.5 g. of manganese dioxide of the indicated fineness was added to the reaction mixture, were: 60–80 mesh, 28 minutes: 120–140 mesh, 15 minutes; 200 mesh, 9 minutes. A similar sample to which no solid material had been added required 82 minutes.

Commercial manganese dioxide, ferric oxide, diatomaceous earth, and ground glass gave effects similar to that of the prepared manganese dioxide. Thus the effect appears to depend upon the surface of the particles rather than upon their chemical composition.

In connection with the study of these solid accelerators, powdered lead dioxide was tried. In this case the autoxidation was found to be completely inhibited. The manganese precipitated from this slightly alkaline solution is in a form which is not affected by oxygen. The reaction may take place through the steps:

$$PbO_2 + Mn^{++} + H_2O \rightleftarrows MnPbO_3 + 2H^+$$
$$MnPbO_3 + Mn^{++} + H_2O \rightleftarrows Mn_2PbO_4 + 2H^+$$

From these equations, the addition of neutral lead dioxide to manganous chloride solutions should result in a noticeable decrease in *p*H. That such a decrease actually occurs is shown by the following test: 1 g. of lead dioxide was added to 60 cc. of distilled water of *p*H 6.30. The *p*H of the supernatant liquid was 6.18. In a similar experiment with 60 cc. of 0.568 molar manganous chloride solution of *p*H 5.85, the *p*H was reduced to 3.20 by the addition of 1 g. of lead dioxide. The X-ray diffraction pattern of the product gave no lines other than those characteristic of lead dioxide, indicating that if a new product is formed, it is either amorphous or present in comparatively small amount. Powdered stannic oxide and red lead oxide had no effect upon the volume of oxygen absorbed; they showed, however, the accelerating effect of the other inert solids.

Since autoxidation reactions are frequently accelerated or retarded by phenols, nitrogen compounds, iodine compounds, etc., the effects of certain examples of these classes of compounds upon the autoxidation of manganous hydroxide were determined. The results may be summarized as follows:

Potassium iodide, urea, thiourea, aniline, β-naphthol, acetamide, ethylene glycol, ammonium thiocyanate, nickel chloride, calcium chloride, sodium chloride, and potassium chloride had no appreciable effect. Ammonium picrate and *m*-nitroaniline accelerated the reaction slightly. Dextrin, glycerol, and iodine retarded the reaction very markedly, but had no effect upon the total volume of oxygen absorbed. These substances perhaps act by being adsorbed at the surface of the oxidation product, thus reducing its catalytic effect. In some cases complex formation may also be a possibility.

Copper chloride, cobalt chloride, and ferric chloride accelerate the reaction, as shown by trials in which reaction mixtures of the following composition were used; manganous chloride, 0.0722 mole per liter, ammonium hydroxide, 0.477 mole per liter, ammonium chloride, 1.35 moles per liter. In each case the concentration of the catalyst used was 0.0018 mole per liter. The times required for the absorption of 20 cc. of oxygen were: cupric chloride, thirty-one minutes; cobaltous chloride, eleven minutes; ferric chloride, eight minutes. A similar sample to which nothing was added required 35.5 minutes. The effect of the ferric chloride is probably due to the large surface of the ferric hydroxide and is similar to that produced by other insoluble substances. The effects of copper and cobalt are probably due to their well-known property of acting as oxygen carriers. In the data recorded above, the concentration of the added salt was one-fortieth of the manganous chloride concentration. In other trials, the salt concentration was reduced to one-two-hundredth, but the accelerating effect was still noticeable.

In connection with the possibility of the formation of an intermediate peroxide in these solutions, it was of interest to determine whether or not the autoxidation of manganous hydroxide was capable of inducing the oxidation of certain acceptors. Dhar[5] and his co-workers have reported that the

(5) N. R. Dhar, *J. Proc. Asiatic Soc. Bengal Proc. 8th India Sci. Cong.*, **17**, CXXX (1921); through *Chem. Abs.*, **17**, 2220 (1923).

oxidation of sodium formate, sodium oxalate, sodium arsenite, sodium nitrite, and ferrous ammonium sulfate are induced by this reaction. In the present work these results were not confirmed. Sodium formate, sodium oxalate, sodium arsenite, sodium nitrite, and allyl alcohol were used as acceptors but in no case was any excess of oxygen absorbed over that required for the manganese alone. In view of these results the formation of a peroxide seems improbable.

When air was used in place of pure oxygen, the absorption was much slower and the total volume of oxygen taken up was much less. The volume absorbed with pure oxygen was about 32 cc., while with air it was about 18 cc. When air was used and the ammonium chloride concentration was varied, the volume of oxygen absorbed remained the same, while the effect of ammonium chloride upon the rate was the same as that observed when oxygen was used. In these trials all of the manganese was precipitated, although the volume of oxygen absorbed was only about 40% of that theoretically required for the formation of manganese dioxide. This surprising result may be explained if it is assumed that a secondary reaction takes place by which manganese is removed from solution without being oxidized. If this secondary reaction does not involve oxygen, it would be expected to continue at an undiminished rate when air is substituted for oxygen. Since the autoxidation reaction is slower in air, a larger proportion of the manganese would be removed by the secondary reaction, and the total volume of oxygen absorbed would be correspondingly reduced. The nature of the secondary reaction will be further discussed in connection with the effect of change in temperature.

Autoxidation of Manganous Hydroxide Precipitated by Sodium Hydroxide.—In the work described, ammonium hydroxide was used in the presence of such amounts of ammonium chloride as would give a conveniently measurable reaction velocity at 25°. It was of interest to determine the effect of temperature, but since the use of ammonium hydroxide did not lend itself satisfactorily to such measurements, a number of experiments were carried out in which sodium hydroxide was used. In all of these experiments the absorption of oxygen was very rapid, but the theoretical volume of oxygen required for the formation of manganese dioxide was never absorbed. However, temperature and the proportions of manganous chloride and sodium hydroxide were found to have a very great effect upon the extent of the reaction as shown by Tables II and III.

TABLE II

EFFECT OF CONCENTRATION OF SODIUM HYDROXIDE AT 45°
$MnCl_2$, 0.0568 mole per liter

NaOH mole/liter	Ratio NaOH/2-$MnCl_2$	Volume of oxygen, cc. absorbed in 5 min.	10 min.	15 min.	Final vol. O_2 abs./theo. vol. for MnO_2
0.100	0.88	13.6	13.6	13.6	0.306[a]
.114	1.00	16.0	16.0	16.0	.360[a]
.128	1.13	22.4	22.5	22.5	.515
.171	1.51	31.0	31.8	32.1	.763
.186	1.63	32.0	32.7	33.2	.798
.200	1.76	34.2	35.0	35.4	.874

[a] See note *a* in Table III.

TABLE III

EFFECT OF CONCENTRATION OF SODIUM HYDROXIDE AT 0°
$MnCl_2$, 0.0568 mole per liter

NaOH mole/liter	Ratio NaOH/2-$MnCl_2$	Volume of oxygen, cc., absorbed in 5 min.	10 min.	15 min.	Final vol. O_2 abs./theo. vol. for MnO_2
0.100	0.88	18.5	20.8	21.8	0.537[a]
.114	1.00	25.0	26.4	26.9	.664[a]
.128	1.13	28.3	29.3	29.8	.722[a]
.143	1.26	35.4	36.3	36.8	.902
.157	1.38	37.3	38.1	38.6	.935
.171	1.51	37.7	38.6	39.1	.948
.186	1.63	38.2	38.9	39.4	.957
.200	1.76	38.4	39.1	39.5	.957

[a] Analysis of solutions remaining after oxygen absorption had ceased indicated that in these trials not all of the manganese had been precipitated.

At the end of each run the samples were removed and filtered. The clear filtrate was tested for manganous ion by treatment with an excess of sodium hydroxide. A solution at 0° which had contained 1.13 times the amount of sodium hydroxide theoretically required to precipitate all of the manganese was found to contain an appreciable amount of manganese in solution; while in the corresponding trial at 45°, all of the manganese had been precipitated. Analysis of the solid oxidation products gave results in agreement with the volumes of oxygen absorbed.

Certain peculiarities in the results of these experiments are worthy of further consideration.

(1) In those trials at 45° in which all of the manganese was not precipitated, the composition of the precipitate was approximately Mn_2O_3, while in similar trials at 0°, the product had a composition intermediate between Mn_2O_3 and MnO_2.

(2) With excess of sodium hydroxide, the degree of oxidation at 45° was never as high as that in corresponding trials at 0°.

(3) Under no circumstances, regardless of tem-

perature or excess of alkali, was the product 100% MnO_2.

(4) At 45° the less sodium hydroxide present, the more abruptly the reaction stopped, while at 0° the reverse was true.

(5) The equivalent amount of sodium hydroxide does not cause complete precipitation of the manganese as manganous hydroxide.

The fact that the composition of the product varies between that corresponding to MnO_2 and a product of lower degree of oxidation than Mn_2O_3 can be explained by either of two mechanisms, represented by the following series of reactions

I

$$6Mn(OH)_2 + O_2 \longrightarrow 2Mn_3O_4 + 6H_2O \quad (1)$$
$$4Mn_3O_4 + O_2 \rightleftarrows 6Mn_2O_3 \quad (2)$$
$$2Mn_2O_3 + O_2 \rightleftarrows 4MnO_2 \quad (3)$$

II

$$2Mn(OH)_2 + O_2 \longrightarrow 2MnO_2 + 2H_2O \quad (4)$$
$$MnO_2 + Mn^{++} + H_2O \rightleftarrows Mn_2O_3 + 2H^+ \quad (5)$$
$$Mn_2O_3 + Mn^{++} + H_2O \rightleftarrows Mn_3O_4 + 2H^+ \quad (6)$$

Series I would account for the results if steps (2) and (3) are equilibria which shift to the left at higher temperatures and to the right at higher sodium hydroxide concentrations. However, experiments showed that steps (2) and (3) do not take place in either direction under conditions comparable with those under which autoxidation was carried out.

Series II would explain the results provided steps (5) and (6) are rapid at high temperatures but almost negligibly slow at 0°. This mechanism also includes the secondary reactions needed to account for the results observed when air is used in place of oxygen. The fact that steps (5) and (6) do actually take place is indicated by the results of other investigators. Tillmans,[6] Hirsch, and Höffner in a very complete study of the reaction between manganese dioxide and manganous ions found that the reaction is favored by high temperature and by increasing *p*H in the range in which manganous hydroxide is not precipitated. They also found free acid is formed as indicated by step (5). The effect of excess alkali in repressing steps (5) and (6) would be expected since it would reduce the manganous ion concentration.

It will be noted that steps (5) and (6) correspond closely to the reactions previously proposed to account for the effect of lead dioxide.

As a further check on the nature of the oxidation product the X-ray diffraction patterns of samples prepared under different conditions were determined and compared with the published patterns of the known manganese oxides. A sample prepared at 90–100° in the presence of excess manganous chloride gave a pattern identical with that of hausmannite, Mn_3O_4. No patterns corresponding to Mn_2O_3 or MnO_2 were obtained from any of the samples prepared. Apparently if such products are formed they are amorphous. The product which approached the composition of MnO_2 most closely showed faint suggestions of a pattern but not enough to permit its definite identification.

Autoxidation in Solutions Containing Triethanolamine.—In order to permit the study of the effect of *p*H without the complicating effect of ammonium ions, triethanolamine was used as the precipitating agent. The oxidation was much slower than under any previously studied conditions, but no induction period was observed, although the *p*H was in the same range as that of the ammonium hydroxide–ammonium chloride solutions previously described. However, when ammonium chloride was added to the triethanolamine solution, the resulting curve did show an induction period. The extreme slowness of the reaction is shown by the following data which give volumes of oxygen absorbed for various time intervals at 25°. The reaction mixture had the following composition: $MnCl_2$, 0.0568; triethanolamine, 0.317 mole per liter.

Minutes	5	15	60	220	366
Gas abs., cc.	12.0	15.2	18.6	24.2	26.7
Minutes	477	605	1320	1440	
Gas abs., cc.	28.0	28.95	47.2	48.2	

The Nature of the Autoxidation Process in Ammoniacal Solution.—In considering the autoxidation of manganous hydroxide in the solutions containing ammonium chloride and ammonium hydroxide, the question arises as to the substances present in the solution and which of these is actually undergoing autoxidation. In addition to the presence of manganous ions, undissociated dissolved manganous hydroxide, and in some cases a precipitate of manganous hydroxide in these solutions, there is a definite possibility that a complex ion of the type $Mn(NH_3)_x^{++}$ is also present. The work of Brezena,[7] who made polarographic and cryoscopic studies of these solutions, has shown that manganous ions and

(6) J. Tillmans, P. Hirsch and J. Höffner, *Gas- u. Wasserfach.*, **70**, 26 (1927).

(7) J. Brezena, *Rec. trav. chim.*, **44**, 520 (1925).

ammonia molecules are both removed from solution with the formation of a complex when ammonium hydroxide is added to a manganous chloride solution containing ammonium chloride. The evidence of the present work seems to favor the existence of a mangano-complex in these solutions. The specific effect of ammonium chloride in producing a different shaped velocity curve from that obtained in triethanolamine solutions of the same *p*H, and the fact that changes in ammonium chloride concentration have no effect upon the composition of the final product may both be explained by the assumption of the existence of such a complex. However, since Brezena's work indicates that the amount of complex increases with increasing ammonium chloride concentration, while the present work has shown that the rate of autoxidation decreases with increasing ammonium chloride concentration, it is unlikely that the complex itself is the substance autoxidized. Undoubtedly precipitated manganous hydroxide is autoxidized, and it is probable that the dissolved undissociated manganous hydroxide behaves similarly. Since neutral solutions show no autoxidation, it is evident that manganous ions are not affected.

Summary

1. The rate of autoxidation of manganous hydroxide in ammoniacal solution has been found to decrease with increasing ammonium chloride concentration. An induction period exists when the ammonium chloride concentration is high.

2. Powdered manganese dioxide, stannic oxide, ferric oxide, red lead oxide, ground glass, and diatomaceous earth accelerate the reaction and eliminate the induction period.

3. In the presence of lead dioxide no autoxidation of divalent manganese occurs.

4. Cobalt chloride and copper chloride accelerate the reaction, while glycerol, dextrin, and iodine retard it. A large number of other substances were found to have no effect.

5. The autoxidation of manganous hydroxide does not induce the oxidation of sodium oxalate, sodium formate, sodium arsenite, sodium nitrite, or allyl alcohol.

6. The autoxidation by air is much slower and less complete than that by pure oxygen.

7. The autoxidation of manganous hydroxide precipitated by fixed alkali is very rapid. The product depends upon the temperature and the proportions of manganous ion and alkali. The X-ray diffraction patterns of the products were studied.

8. The autoxidation of manganous hydroxide precipitated by triethanolamine was found to be very slow. It did not display the induction period observed in ammoniacal solution.

9. A mechanism to account for the above results has been proposed.

MADISON, WISCONSIN RECEIVED JANUARY 24, 1942

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

The Dielectric Investigation of Polypeptides. II. The Dispersion of Simple Amino Acid Polypeptides

BY W. P. CONNER[1] AND C. P. SMYTH

Although important conclusions concerning the nature of polypeptide molecules have been drawn from consideration of their dielectric increments per mole of solute, it is recognized that a more complete picture may be obtained from measurement of the anomalous dispersion of the dielectric constants of their water solutions. The linear increase of increment values of the polypeptides with the number of glycine residues, as suggested by Wyman,[2] lends support to the view that there is almost complete freedom of rotation about the valence bonds which make up the backbone of the peptide chains. Statistical calculations by Kuhn[3] of the polarization of a straight-chain molecule in which there is free rotation about the valence bonds and electrostatic attraction between the oppositely charged ends of the chain show that the polarization as measured by the static dielectric constant would be the same whether the chains underwent orientation polarization or dilation–contraction polarization. Because of the apparent lack of restriction in position of the electrically

(1) Research Assistant on Special Funds from the Rockefeller Foundation.

(2) (a) Wyman, *Chem. Rev.*, **19**, 213 (1936); (b) Wyman, *J. Phys. Chem.*, **43**, 143 (1939).

(3) Kuhn, *Z. physik. Chem.*, **175A**, 1 (1935).

charged end groups of the peptide chains, Wyman suggested[2] that dispersion might not be found for these polypeptide chains inasmuch as they might undergo polarization by stretching rather than orientation. If this were the case, then, size and shape studies from dispersion measurements would be rendered impossible.

Before 1940, no unequivocal data existed in the literature which indicated dispersion in the simpler amino acids and their polypeptides. However, in that year, Bateman and Potapenko[4] reported dispersion measurements at 25.5 cm., for glycine and alanine and their dipeptides. Making use of the energy absorption accompanying dispersion, other investigators[5,6,7] have obtained relaxation times for some amino acid peptides. These data differ widely in the reported relaxation times for the simple peptides.

In this paper, dispersion measurements are reported for the glycine polypeptides and for the simpler di- and tripeptides of alanine, leucine, and glycine in the wave length region of 40 to 80 cm.

Experimental

Method.—For measurement of the static dielectric constant of the aqueous peptide solutions, the Twin-T impedance measuring circuit reported in the first paper of this series[8] was employed. The shortest wave length used was ten meters, which was only just within the region of slight anomalous dispersion for the larger molecules, as indicated by the high frequency measurements. For measurement of the dielectric constants in the dispersion region, approximately 60 cm., the first Drude method was followed. An ultra-high frequency oscillator, similar to that reported by Barrow,[9] was constructed making use of a WE 316-A vacuum tube. Copper was used throughout and catalin rings served for insulation and for mechanical support. To reduce the high frequency loss in the insulation as many holes were drilled in the insulating rings as were possible without lessening the mechanical rigidity. Since the frequency of oscillation is stabilized by the resonant concentric tubes, an attempt was made to increase the Q values of the circuit according to the relations reported by Reukema,[10] in which the influence of the radiative resistance of such transmission lines is fully considered. The tube conductor diameters were: plate, 1.834 and 0.437 inches; filament, 2.00 and 0.187 inches; all three tubes were 20 inches long. The selections were made with the intent to give a maximum Q value to the plate circuit and a maximum impedance to the filament tuned circuit at 50 cm. wave length by the use of copper tubing of standard dimensions. The equations followed were: for maximum Q of a shorted quarter wave length concentric line, $b/a = 4.22$ and $b = 0.0634\ \lambda^{0.9}$, and for maximum impedance, $b/a = 14.3$ and $b = 0.077\ \lambda^{0.9}$, in which a and b are the radii of the inner and outer conductors. A closer approach to the theoretical Q values was attained by the installation of the "standpipe" oscillator on its side, thereby enabling the use of a plunger mechanism for the determination of resonance lengths and thus avoiding slotting the out copper tubes. The theoretical Q value of 3400 at 600 Mc., is considerably less than that reported by Barrow since the equations by which he computed Q values do not consider radiative resistance losses. Since only loose coupling between this oscillator and the detector was desired, a short length of copper wire extending from the coaxial line power output connection into the chamber which contained the vacuum tube was found to be completely adequate. A maximum in the grid current and a minimum in the plate supply indicated oscillation of the instrument. The frequency range of the oscillator was approximately 300–750 Mc.

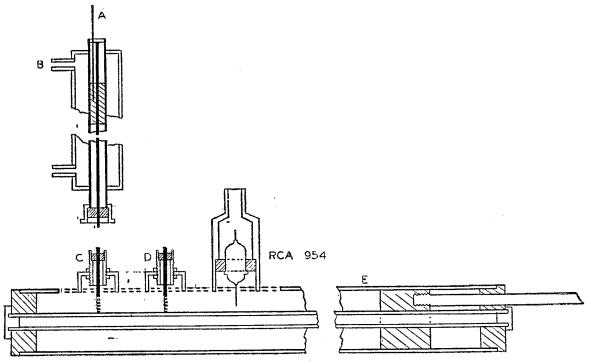


Fig. 1.—Apparatus for the determination of dielectric constants at ultra-high frequencies: A, water resonance chamber; B, water jacket; C, coupling lead to water resonance chamber; D, input lead from oscillator; E, air resonance chamber.

Dielectric measurements required the determination of the wave length of the high frequency oscillation in air and in the water solutions of the polypeptides. For the air measurements (see Fig. 1), standing electric waves were formed in a system of concentric tubes of the same dimensions as those used for the plate tank circuit of the oscillator, the length of which could be varied by means of a shorting plunger. The detector was a simple probe-type voltmeter[11] using an RCA-954 acorn tube capacitatively coupled to the inner tube of the resonance chamber by very short leads. The outer tube of the chamber was slotted so that the voltmeter might be inserted approximately at a voltage antinode. With this arrangement positions of resonance were quite sharp and could be set to ±0.01 cm. A micrometer was attached to the plunger so that the resonance length might be varied by small steps. With close coupling to the oscillator, a rather large decrease in the oscillator grid current was noted as the resonance chamber passed through a point of resonance. The

(4) Bateman and Potapenko, *Phys. Rev.*, **57**, 1185 (1940).
(5) Fricke and Parts, *J. Phys. Chem.*, **42**, 1171 (1938).
(6) Parts, *Pub. Tech. Univ. Estonia Tallin*, Ser. A No. 8, 3 (1940); *C. A.*, **34**, 4952 (1941).
(7) Linhart, *Z. physik. Chem.*, **B38**, 23 (1937).
(8) Conner, Clark and Smyth, THIS JOURNAL, **64**, 1379 (1942).
(9) Barrow, *Rev. Sci. Instr.*, **9**, 170 (1938).
(10) Reukema, *Elec. Eng.*, **56**, 1002 (1937).
(11) Radiotron Division of RCA Manufacturing Co., *Q. S. T.*, **19**, 42 (1935). A one megohm grid leak was added to the grid probe.

coupling was reduced to such an extent that the change in the grid current was less than one-half milliampere, since further loosening of the coupling had been shown to have no effect upon the measured wave length. The wave length was then considered equal to twice the distance between any two positions of the plunger for which the voltmeter indicated a maximum voltage.

The wave length in the water solutions was determined in much the same manner, except that, for this case, the resonance tubes were much smaller, $^3/_8$ and $^1/_8$ inches; and were water-jacketed at 25.00 ± 0.02° for most of the experiments. The smaller size was chosen to reduce the volume of material required for measurement and to gain a higher Q value, since the wave length in these media is one-ninth that in air. The water resonance chamber was coupled to the air chamber rather than directly to the oscillator in order to minimize any change in frequency of the oscillator resulting from interaction between the two circuits. The relative positions of the connective terminals on the air chamber were varied. However, those indicated in Fig. 1 were the most satisfactory. The connections between the instruments were all of $^3/_8$ inch coaxial cable with polystyrene bead insulation. Thus, the apparatus was completely shielded so that the position of the observer did not affect the measurements. This was a great improvement over the customary Lecher wire devices.

In making a measurement, the oscillator was first adjusted to one of its positions of most stable oscillation and the wave length determined with the air chamber. Customarily, the wave length was checked when the plunger in the water chamber was first set at a node and then at an antinode. The positions of resonance in the air chamber were different for these two positions in the water chamber but the actual wave length was not modified. With the plunger in the air chamber at a voltage node and with the consequent maximum in voltage indicated by the voltmeter, the plunger in the water chamber was withdrawn slowly. A minimum in the voltmeter now indicated the presence of standing waves in the water resonance chamber, since maximum power had been transferred from the air chamber to the water chamber. The wave length in the solution was considered equal to twice the distance between any two minima. Because of attenuation, the minima became too broad for accurate settings after about four nodes had been detected. Settings were made readily to ±0.015 cm., and greater accuracy could be attained when the voltage was recorded for each millimeter shift in the plunger and the minima read from the plot of these values. Considerable asymmetry was introduced into these plots of voltage against distance in the water chamber depending on the position of the plunger in the air chamber. If the air chamber was set at resonance when the water chamber was completely out of resonance, the curves were symmetrical except for the exponential absorption due to conductance.

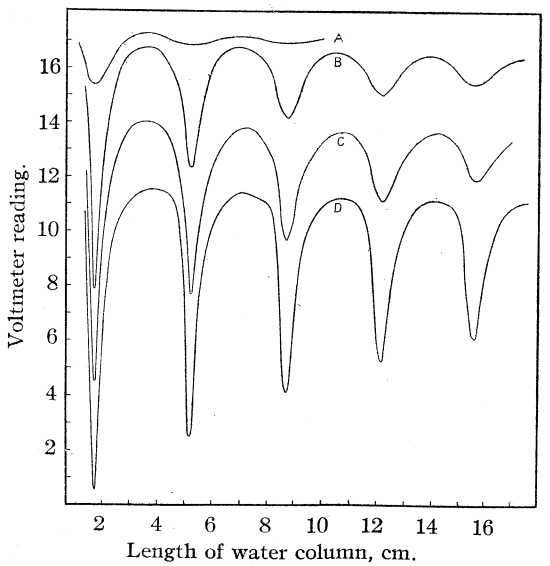


Fig. 2.—Resonance minima in aqueous potassium chloride solutions: specific conductance, A, 0.853 × 10^{-2}; B, 1.67 × 10^{-3}; C, 0.953 × 10^{-3}; D, 1.007 × 10^{-4} mhos. For each curve, the zero point of the voltmeter reading has been shifted arbitrarily to prevent overlapping.

In Fig. 2 is recorded such a plot for water solutions of potassium chloride of varied conductivity. The conductance of these solutions at 25° was measured with a one thousand cycle conductance bridge. Since the Debye–Hückel theory of electrolytes predicts an increase in the dielectric constant of aqueous salt solutions above that of pure water, it was of interest to calculate[12] this increase, $\Delta\epsilon_{DH}$, expected for these solutions (see Table I).

TABLE I

Spec. cond. × 10^3 ohm^{-1} cm.$^{-1}$	$\Delta\epsilon_{DH}$	$\Delta\epsilon_R$	$\epsilon_{obs.}$
0.1077	0.000325	0.0000	78.46 ± 0.13
0.953	.0202	.000	78.57 ± 0.13
1.666	.0529	.006	78.57 ± 0.13
8.53	.548	.157	79.5 ± 0.4

In addition to the increase in the dielectric constant resulting from the polarization of the ionic atmosphere around a central ion, $\Delta\epsilon_{DH}$, there arises an apparent increase, $\Delta\epsilon_R$, in the real dielectric constant resulting from the conduction in the dielectric medium in which the standing electric waves are produced. This effect is comparable with the apparent increase in capacity of a conducting condenser found in low frequency impedance measurements. The dielectric constant increase, $\Delta\epsilon_R$, was calculated according to an approximate treatment of the problem.[13] The dielectric constant values, $\epsilon_{obs.}$, observed for these potassium chloride solutions show small increases with increasing concentration, agreeing within the experimental error with the calculated increases.

(12) Falkenhagen, "Electrolytes," The Clarendon Press, Oxford, 1934, pp. 219–221.

(13) Drake, Pierce and Dow, *Phys. Rev.*, **35**, 613 (1930).

Since the specific conductivities of all peptide solutions were no greater than 1×10^{-4} ohm^{-1} cm.$^{-1}$, an error due to conduction was considered negligible. A slight initial decrease in the dielectric constant of salt solutions as the salt concentration is increased has been reported,[14] although a complete quantitative treatment has not been given. However, it is likely that this effect lies well within the experimental error of these measurements.

Most of the high frequency measurements were performed at 61.42 cm., the minimum being determined by a plot of the voltage against the length of the resonance chamber. For some measurements, a larger range of wave length, 40 to 80 cm., was used. However, because of the tedium involved in the selection of suitable positions of the three plungers of the oscillator from the many positions at which oscillation gave unstable or distorted frequencies, this procedure was discontinued.

Results

In Table II are recorded the dielectric data for the amino acids investigated, from which the dispersion calculation is made. Some of the high frequency measurements were made at room temperature before the thermostat was installed and have been included as taken without a correction to 25°. To correlate the dispersion data taken over a frequency range with solutions of different concentrations, the critical wave lengths, λ_c, have been calculated according to the dispersion equation[15]

$$\frac{\epsilon - \epsilon_\infty}{\epsilon_0 - \epsilon_\infty} = \frac{1}{1 + (\lambda_c/\lambda)^2} \qquad (1)$$

where ϵ is the dielectric constant of the aqueous solution at wave length λ; ϵ_∞ is taken equal to the dielectric constant of water, 78.54, at 25°; and ϵ_0 is the static dielectric constant of the solution considered equal to that measured with the Twin-T apparatus at approximately 10 meters. The critical wave length is related to the relaxation time by the expression

$$\lambda_c = 2\pi c\tau$$

in which c is the velocity of light in cm./sec., and τ is the relaxation time in seconds.

Viscosity corrections for different concentrations of solute and temperature of solution were applied by multiplying the critical wave length determined by Eq. (1) by the factor $\eta_{H_2O}/\eta_{solution}$. An Ostwald viscometer, with an efflux time for water of 24 sec., was used for the viscosity determinations listed in Table II and the viscosity of water at 25° was taken as 8.94 millipoises. The substances are represented in Tables II and III by abbreviations: A for alanine, L for leucine, G_1 for glycine, G_2 for diglycine, etc. All preparations were racemic mixtures.

Since both measuring cells were constructed of copper, there was a slight formation of the copper complex of the amino acids in solution. Except for those of high glycine content, the solutions were only faintly tinted after the measurements were completed. In view of the excellent agreement with reported data for the measurements at low frequencies, it was considered that, for this case, the formation of the copper complex was negligible. However, inasmuch as the solutions were left in contact with a larger surface of copper for a longer time during the high frequency measurements, the low frequency increments were always determined after the high frequency experiments on the same solutions. Thus the decrease in the dielectric constant of the solution resulting from the formation of the complex was not counted as dispersion of the dielectric constant.

The spread of the calculated results is large for glycine since λ_c in Eq. (1) is very sensitive to slight changes in ϵ when the difference $\epsilon - \epsilon_\infty$ is small, as it is when the measuring wave length is remote from the critical wave length. Thus the apparent trend with increasing concentration of glycine is not held to be significant. Equation (1) is a very much simplified description of the dielectric constants of these aqueous solutions, since it implies the presence of a kinetic unit having only one relaxation time. However, no well-defined trend in the critical frequencies calculated in this manner was noticeable as the viscosity and frequency were varied for any single compound. Since all measurements were made on the low frequency side of the complete dispersion curve, it is unlikely that the effect of a second smaller relaxation time would be greater than the error of the dielectric measurements.

Also the choice of ϵ_∞, the dielectric constant of the solution at a frequency sufficiently great so that dispersion due to the solute molecule has been completed and yet sufficiently small so that dispersion of the solvent has not begun, is some-

(14) Grubb and Hunt, THIS JOURNAL, **61**, 565 (1939).

(15) Williams and Oncley, *Physics*, **3**, 314 (1932); Williams, *Trans. Faraday Soc.*, **30**, 723 (1934); Elliott and Williams, THIS JOURNAL, **61**, 718 (1939).

what arbitrary. Actually ϵ_∞ should be less than the dielectric constant of water, since, at frequencies sufficiently high to eliminate the contribution of the polar solute molecules to the dielectric con-

TABLE II

DISPERSION DATA FOR AMINO ACID PEPTIDES

Substance	t, °C.	Concn., m	ϵ_0	ϵ	λ	η (0.001 c. g. s.)	λ_c
H_2O	25		(78.54)	78.46	61.56	(8.94)	
				78.51	61.42		
				78.55	61.42		
G_1	25	0.6895	93.77	93.67	61.42	9.74	4.6
		0.6950	93.98	93.85	61.42	9.74	5.2
		1.900	118.6	117.4	78.02	11.65	10.5
		2.041	121.3	118.7	60.26	11.84	11.6
		2.264	125.7	122.5	75.88	12.2	15.0
							9.4±3.6
G_2	21	0.1020	87.20	84.94	75.26	10.3	23.5
	25	.3136	100.61	98.06	62.30	9.74	20.7
				98.01	61.04		20.5
				98.20	61.40		19.8
				98.10	62.20		20.5
				97.61	62.22		22.7
	25	.4918	113.20	108.63	62.70	10.18	21.4
				109.01	62.50		20.4
				108.40	62.64		22.1
				108.60	60.72		20.9
							21.0±0.3
G_3	19.6	.0437	85.52	83.02	39.70	10.30	34.6
				84.58	76.24		31.8
				83.02	39.64		34.4
	21.6	.0617	86.84	83.30	38.96	9.92	35.2
				84.93	62.32		34.3
				85.20	71.82		35.7
				85.42	76.40		34.6
							34.3±0.3
G_4	25	.0531	87.77	84.19	61.42	9.17	47.8
			87.55	84.04	62.41		47.8
		.0566	88.40	84.98	57.86	9.20	41.0
				84.18	59.86		50.4
				85.68	75.40		43.1
		.0638	89.66	85.53	62.44	9.30	46.1
		.0938	94.70	88.03	61.50	9.48	48.8
							46.6±0.8
G_5	25	.01890	82.30	80.23	61.42	9.02	66.0
			82.12	80.02	61.42		72.5
							68.6±2.6
A	25	1.4372	109.3	106.3	59.80	12.21	14.7
		1.5782	111.9	109.2	57.32	12.56	9.5
							12.1±2.6
LG	25	.1270	86.89	84.68	62.24	9.81	34.0±3.0
LA	25	.06361	81.88	80.63	61.42	9.10	46.6±0.5
AGG	23.2	.05127	85.21	82.01	38.42	9.65	38.0
				83.15	64.80		43.3
				83.53	68.20		39.4
				83.41	71.24		43.1
				83.96	75.12		35.7
				83.89	75.28		37.1
							39.4±1.1

TABLE II (*Concluded*)

Substance	t, °C.	Concn., m	ϵ_0	ϵ	λ	η (0.001 c. g. s.)	λ_c
LGG	24	.06095	86.24	81.32	38.20	9.75	50.0
				83.06	62.20		49.8
				82.90	62.20		52.2
				82.36	62.86		61.0
				83.32	72.36		53.8
							53.4±1.5
ALG	25	.08208	88.50	83.89	61.42	9.64	52.9
	21.0	.0787		82.06	38.82	10.43	64.6
				85.27	69.90		55.4
				86.10	72.22		48.2
				86.16	76.06		50.1
				86.92	79.44		43.8
							52.5±2.1

stant of the solution, the solution should behave as if non-polar molecules of the same total volume were dissolved in it. In this case of water acting as the solute, the presence of non-polar molecules would reduce the number of dipolar water molecules per cubic centimeter and thus reduce the dielectric constant of the solution. An estimation of this volume correction for the increment values is recorded in the preceding paper.[8]

In Table III are recorded the average values of the critical wave lengths taken from Table II and the critical wave lengths after the volume correction has been applied. Inasmuch as dispersion has been found for these polypeptides, it is of interest to compare the measured critical wave lengths with those calculated on the assumption that the rotating units are spheres of volumes equal to those of the dissolved molecules and moving according to the laws of hydrodynamics. For this case, the Debye equation

$$\lambda_0 = 2\pi c\tau = 2\pi c\frac{3\eta}{RT}v$$

applies in which η is the viscosity of the solvent and v is the partial molar volume of the solute. In Table III are listed the critical wave lengths, λ_0, thus calculated. The volume v was taken equal to the apparent molar volume plus the electrostriction. For those compounds for which v has not been measured, use was made of the additivity of atomic volumes[16] for their calculation. In addition, there is listed the shape factor a/b, the ratio of major to minor axis of the assumed molecular ellipsoid of revolution, as determined by the quotient of the observed and calculated critical wave lengths in the manner described by Perrin.[17] This calculation assumes, of course, a rigid particle undergoing orientation polarization. Inasmuch as the mechanism of polarization is not definitely known, these calculations must be regarded as tentative. Also, it must be emphasized that, in view of the error involved in the determinations of λ_c, small differences in a/b are not significant. Correction of the dielectric constant values for the effect of the volume occupied by the solute molecules according to the method previously employed[8] gave slightly smaller values λ_c' for the critical wave lengths and larger values $(a/b)'$ for the axis ratios.

TABLE III

DISPERSION OF AMINO ACIDS

Substance	λ_c (obs.), cm.	λ_0	λ_c/λ_0	a/b	λ_c'	λ_c'/λ_0	$(a/b)'$
G_1	9.4 ± 3.6	11.7	0.803		8.9	0.76	
G_2	21.3 ± 0.3	19.1	1.12	1.40	20.2	1.085	1.27
G_3	34.3 ± 0.3	26.5	1.295	1.68	32.8	1.240	1.58
G_4	46.6 ± 0.8	32.0	1.46	1.92	44.5	1.390	1.83
G_5	68.6 ± 2.6	41.4	1.65	2.15	64.3	1.55	2.06
A	12.1 ± 2.6	14.9	0.812		11.1	0.94	
LG	34.0 ± 1.0	32.4	1.05	1.18	33.6	1.038	1.14
LA	46.5 ± 1.0	35.5	1.31	1.71	40.7	1.146	1.40
AGG	39.4 ± 1.1	29.8	1.32	1.71	37.1	1.243	1.57
LGG	53.4 ± 1.5	39.8	1.34	1.77	49.3	1.238	1.57
ALG	52.5 ± 2.1	43.1	1.22	0.52	48.6	1.126	1.33

Discussion of Results

The agreement of the ratio of the critical wave lengths listed here and those reported elsewhere is satisfactory in the cases of glycine and alanine. Bateman and Potapenko[4] reported ratios of 0.39 and 0.77, whereas Fricke and Parts[5] reported 0.55 and 0.63 as calculated from absorption measurements. For the higher peptides, Bateman and Potapenko listed ratios of 1.38, 1.60 and 1.67 for diglycine, glycylalanine, and alanylglycine, indicating shape factors of 1.8 to 2.2. However, Fricke and Parts reported ratios less than unity for such large molecules as α-aminobutyric acid, γ-aminobutyric acid, and ϵ-aminocaproic acid;

(16) Cohn, McMeekin, Edsall and Blanchard, THIS JOURNAL, **56**, 784 (1934).

(17) Perrin, *J. Physique*, **5**, 497 (1934).

and later Parts[6] reported ratios from 0.7 to 1 for the large molecules of *d,l*-phenylalanine, diglycine, and ϵ-aminocaproic acid. On the other hand, Linhart[7] found that the critical wave lengths for glycine, diglycine, and leucylglycylglycine lay between 80 and 100 cm., depending upon the concentration of the solute. It would appear that the results of Bateman and Potapenko are the most trustworthy since they were determined at 25.5 cm., where dispersion is most pronounced. In addition, a relaxation time of 1.29×10^{-10} sec., $\lambda_c = 24.4$ cm., for triglycine has just been reported by Wyman[18] from absorption measurements at 2.61 meters. For the two smallest molecules, glycine and alanine, the observed values for λ_c are less than the values calculated for a spherical model. This discrepancy is customary for investigations of this sort for small molecules of size comparable with those of the solvent, and has led to the suggestion that the inner viscosity is of smaller magnitude than the macroscopic viscosity.

Another approach to the whole process of dielectric relaxation may be obtained by considering it as a rate process involving the rotation of the molecule between two equilibrium positions separated by a potential barrier.[19,20,21] Following Eyring's treatment of relaxation times in general, one may calculate the free energy of activation for rotation, $\Delta F^{\ddagger}$, for these polypeptides from the equation

$$\tau = \frac{h}{kT} e^{\Delta F^{\ddagger}/kT}$$

Values of $\Delta F^{\ddagger}$ so determined are listed in Table IV, together with those of the apparent molar volume φ of the solute corrected by adding the electrostriction E. The ratio $\Delta F^{\ddagger}/(\varphi + E)$ is given to show that the increase of free energy of activation with increase of molecular volume becomes less as the molecules increase in size.

These $\Delta F^{\ddagger}$ values may be compared with the free energies of activation for viscous flow by the application of the equation

$$\eta = \frac{Nh}{V} e^{\Delta F^{\ddagger}/RT}$$

where V is the molar volume of the liquid in question. The heat content change $\Delta H^{\ddagger}$ for the same process may be determined from the slope of a log η against $1/T$ plot since

$$\Delta H^{\ddagger} = R \frac{\mathrm{d} \ln \eta}{\mathrm{d}(1/T)}$$

Unfortunately, this curve is not linear, and hence $\Delta H^{\ddagger}$ varies with the temperature. This temperature variation probably indicates a structural change in the flow process.[22] The results of such a calculation for water are listed below.

	$\Delta F^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
Viscous Flow			
H_2O	2.21	4.058	6.0
Dipole Rotation			
H_2O	2.38		
40% H_2O (in dioxane)	2.57		

Since the temperature dependence of the relaxation time for water has not been determined, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ cannot be calculated explicitly. In all likelihood, the temperature dependence is the same as that for viscosity, as is the case for many small dipole molecules. If this be so, then the entropy change is the same for both processes and requires the breaking of a somewhat organized structure in the formation of a more random system. Undoubtedly, the directed hydrogen bonds are fractured. Thus, the mechanisms of dipole rotation and viscous flow for water are equivalent.

The $\Delta F^{\ddagger}$ for the dipole rotation of the zwitterions increases but very slowly with increasing molecular volume except in the cases of smaller

TABLE IV

FREE ENERGY OF ACTIVATION FOR ROTATION OF POLYPEPTIDES

Substance	λ_c	$\tau \times 10^{12}$	$\Delta F^{\ddagger}$ (kcal.)	$\varphi + E$	$\frac{\Delta F^{\ddagger}}{(\varphi + E)}$
G_1	9.4	48.7	3.34	57	0.0585
G_2	21.3	114.3	3.96	93.3	.0425
G_3	34.3	181.3	4.23	129.6	.0326
G_4	46.6	247	4.40	166.6	.0265
G_5	68.6	363	4.63	202.6	.0228
A	12.1	64.0	3.58	73.3	.0488
LG	34.0	180.0	4.24	158.5	.0267
LA	46.5	246	4.40	173.7	.0253
AGG	39.4	206	4.32	145.7	.0296
LGG	53.4	282	4.48	194.8	.0230
ALG	52.5	278	4.48	210.9	.0213
Water[a]	1.60	8.52	2.38	18	.1323
40% Water (in dioxane)	2.27	12.04	2.57		

[a] Hackel and Wien, *Physik. Z.*, **38**, 767 (1937); Esau and Bäz [*ibid.*, **38**, 774 (1937)] report λ_c for water equal to 1.85 cm. Slevogt [*Ann. Physik*, **36**, 141 (1939)] reports $\lambda_c = 2.1$ cm. Fricke and Parts [*J. Phys. Chem.*, **42**, 1171 (1939)] report $\lambda_c = 1.85 \pm 10\%$.

(18) Marcy and Wyman, THIS JOURNAL, **63**, 3388 (1941).

(19) Eyring, *J. Chem. Phys.*, **4**, 283 (1936).

(20) Glasstone, Laidler and Eyring, "The Theory of Rate Processes," McGraw-Hill Book Company, Inc., New York, N. Y., 1941.

(21) Powell, to be published shortly.

(22) Ewell and Eyring, *J. Chem. Phys.*, **5**, 726 (1937).

molecules. Thus, in contrast to the linear viscous flow of pure liquids, a cavity proportional to the volume of the moving molecule need not be formed for this rotational motion. The temperature coefficient is probably that of water, as it is in the case of the larger protein molecules. Thus, the entropy change in this case is almost zero, perhaps slightly negative. Since the mechanism is basically the same as that of viscous flow in the pure solvent, *i. e.*, movement of one molecule of solvent over the same potential barrier to a second rest position, the entropy change is the sum of an increase due to the breaking of directed valence bonds of the solvent and a decrease which measures the number of molecules which must be organized in the flow process to permit rotary diffusion of the dipole molecule. This decrease in entropy is dependent upon the size and shape of the molecule in solution, and causes the rather large relaxation times found for large protein molecules.

The smallness of the variation of the $\Delta F^{\pm}$ values with change in the size of the molecules results from the fact that the range of relaxation times is extremely short. However, it is noted for both glycine and alanine that the free energy of activation is approaching that for water. From this fact it would appear that the number of solvent molecules which must coöperate in the rotary diffusion of these dipole ions is becoming smaller with the decrease in size of these ions and is approaching unity as it is for the rotary diffusion of water in water.

That the Debye equation for relaxation time fails for these small particles is evident in the fact that λ_c/λ_0 is less than unity. However, the reaction rate hypothesis affords a complete picture of this region of small molecules in which it has been customary to assume a difference between the macroscopic and microscopic viscosities. For large particles the reaction rate calculation and the Debye equation must agree, but the details of the transition have not been worked out.

The mere presence of dispersion in the half meter range of wave length does not completely prove the rigidity of these dipolar molecules. Since the heats of activation have not been determined, the actual mechanism of polarization is still in doubt. The free energies of activation are of such a magnitude that the slow process may be the movement of a water molecule over the potential barrier for viscous flow to create a space to be occupied by a part of the rotating dipolar molecule, or it may be the crossing of the potential barrier for rotation around the valence bonds within the dipolar molecule in polarization by stretching. Since $\Delta H^{\pm}$ for viscous flow changes with temperature and $\Delta H^{\pm}$ for rotation about a single bond does not, one might differentiate between the two processes from the temperature coefficient of the relaxation times. However, since in the stretching of a valence chain possessing free rotation, the rate of change of stress on its ends with the change in its elongation is inversely proportional to the number of chain links,[23] it becomes increasingly easier to stretch the chain as its length increases. Thus, one would expect that the relaxation time for this process would decrease with increasing chain length since the entropy change decreases. This view may be applied to a chain-stretching mechanism in which a potential barrier must be crossed if the barrier height does not change with chain length. It would appear, then, in view of the experimentally found increase in relaxation times with the chain length of the polypeptides, that stretching of the tangled backbone chain alone is not the slow process. If the slow process is that of the viscous flow of water, then the mechanism is still in doubt for a hole of some sort must be created about the dipolar molecule whether it occupies the new space by expansion and contraction or by orientation in the direction of the field.

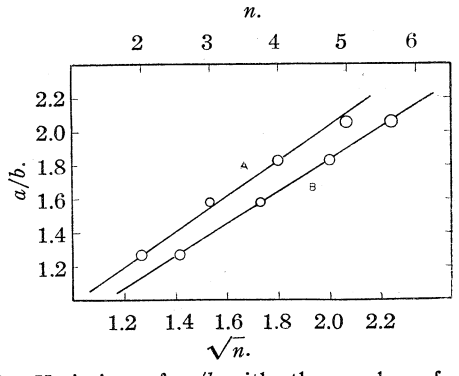


Fig. 3.—Variation of a/b with the number of glycine residues, n: A, variation with n; B, variation with $\sqrt{n}$.

However, it is evident that the orientation hypothesis gives reasonable values for the molecular shapes of the peptides. The shape factors of the glycine peptides appear to increase linearly with the square root of the number of glycine

(23) Mark, "Physical Chemistry of High Polymeric Systems," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1940, p. 75.

residues (see Fig. 3). Although the accuracy of the determinations is not sufficient to exclude the possibility of a linear increase with the first power, the apparent linear dependence upon the square root of the number of glycine residues is what one would expect from a statistical consideration of rigid molecules randomly distributed in all possible configurations resulting from potential minima symmetrically distributed about the valence bonds of the backbone chain. The triglycines appear to have approximately the same shapes, except for alanylleucylglycine which appears somewhat more spherical as would be expected since the large isobutyl group has been attached to the middle of the chain. Leucylglycine is more spherical than would be predicted. Perhaps in this case the Perrin equation fails since the assumed ellipsoid of revolution is a poor approximation for this molecule. The dipolar part of the molecule may undergo motion with very little change in the position of the hydrocarbon chain at one end of the molecule. Undoubtedly a more satisfactory picture would be obtained for these small irregular molecules if it were possible to discard the hydrodynamic view-point and the prolate spheroid model in favor of more accurate knowledge of the nature of the process of rotation.

Other complicating factors which have not been considered are the change in the volume of the rotating unit due to hydration resulting from hydrogen bonding of the dipolar molecule with water, and, second, hydrogen bonding within the peptide chain, which must occur to stabilize the structures of protein molecules. The second factor is probably of little importance since these peptide chains act as denatured proteins.

The writers wish to express their gratitude to Professor Eugene Pacsu for his helpful discussions relating to the polypeptides used in this investigation.

Summary

An apparatus has been constructed for the measurement of the dielectric constants of liquids at wave lengths from 40 to 80 cm. by the first Drude method. The dielectric constants of aqueous solutions of ten amino acid peptides in this region of anomalous dispersion have been measured, as have the viscosities of the solutions. The mechanism of dispersion has been discussed and the results have been combined with previous dielectric constant measurements at 10 meters in this Laboratory to calculate the relaxation times and shape factors for the solute molecules. Although the results are not inexplicable in terms of internal rotation around valence bonds in the molecules, the values and their trend are consistent with the simple picture of rotation of the molecule as a whole.

PRINCETON, NEW JERSEY RECEIVED APRIL 3, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Apparent Molal Volumes of Aqueous Solutions of Sulfuric Acid at 25°

BY IRVING M. KLOTZ AND CHARLES F. ECKERT

It has been known for some time that the apparent molal volume of a strong electrolyte may be expressed as a linear function of the square root of its volume concentration. For aqueous solutions of sulfuric acid, however, the apparent molal volumes show an unusual dependence on the concentration. In contrast to most electrolytes, the volumes rise very rapidly in the dilute range but approach a linear function of the square root of the concentration at high molarities. This behavior has been explained qualitatively as being due to the ionization of bisulfate ion.[1] With data on the dissociation constants of bisulfate ion a quantitative explanation of the observed volume changes in terms of the apparent molal volumes of the component ions is also possible. We have determined the densities of solutions of sulfuric acid from 0 to 3 molar, and have calculated, by a method of successive approximations, the apparent molal volumes of $H^+ + HSO_4^-$ ions.

Experimental.—The solutions were placed in Pyrex containers immersed in a thermostat at 25° (±0.001°). The density of each solution was measured by means of the sinker method described by Wirth.[2] The method was sensitive to differences of less than one part per million in the density.

(1) Geffcken and Price, *Z. physik. Chem.*, **26B**, 81 (1934).

(2) Wirth, THIS JOURNAL, **59**, 2549 (1937).

TABLE I[a]

APPARENT MOLAL VOLUMES OF $(H^+)_2(SO_4^=)$ AND $(H^+)(HSO_4^-)$

Concn. H_2SO_4, moles/liter	$(d_3 - d_0)$ 1000	ϕ_3, cc.	K_c	μ	ϕ_2	ϕ_1
0.01432	1.038	25.68	0.0185	0.0277	15.74	34.49
.02708	1.901	27.96	.0208	.0466	15.98	34.73
.04053	2.771	29.80	.0226	.0648	16.16	35.67
.05933	3.986	30.99	.0241	.0885	16.35	35.77
.0839	5.544	32.09	.0266	.1188	16.58	36.18
.0900	5.929	32.29	.0270	.1260	16.63	36.20
.1157	7.567	32.77	.0289	.1562	16.83	36.16
.3493	22.057	35.03	(.03)	.401	17.96	36.39
.6833	42.383	36.15	(.03)	.739	19.02	36.88
1.275	78.013	37.01	(.03)	1.332	20.43	37.40
2.030	122.214	37.99	(.03)	2.090	21.79	38.23
3.194	188.318	39.23	(.03)	3.244	23.45	39.35

[a] d_3 is the density of the sulfuric acid solution and d_0 is that of pure water.

Concentrations were determined by titration against sodium hydroxide which had been standardized with potassium acid phthalate.

The Apparent Molal Volumes of $(H^+)(HSO_4^-)$.—To interpret our data we have assumed that a solution of sulfuric acid may be considered as a mixture of two components, $(H^+)_2(SO_4^=)$ and $(H^+)(HSO_4^-)$. For a concentration of c_3 moles per liter of sulfuric acid we should have c_1 moles per liter of $(H^+)_2(SO_4^=)$ and $c_3 - c_1$ moles per liter of $(H^+)(HSO_4^-)$ where c_1 is determined by c_3 and by K_c, the classical ionization constant of bisulfate ion. If the volume change due to the addition of N_3 moles of sulfuric acid to the quantity of water necessary to give the concentration c_3 is ΔV, then

$$\phi_3 = \Delta V/N_3 = (c_1/c_3)\phi_2 + [(c_3 - c_1)/c_3]\phi_1 \quad (1)$$

where ϕ_1 is the apparent molal volume of $(H^+)(HSO_4^-)$, ϕ_2 that of $(H^+)_2(SO_4^=)$ and ϕ_3 the observed value. Consequently

$$\phi_1 = [\phi_3 - (c_1/c_3)\phi_2]/(1 - c_1/c_3) \quad (2)$$

The classical ionization constant of bisulfate ion, K_c, is a function of the ionic strength, μ, and has been determined up to $\mu \sim 0.14$.[3] Since c_1 is a function of K_c and K_c is a function of μ, and consequently of c_1, it has been necessary to use a series of successive approximations to establish the value of c_1. For the dilute range the value of K_c for $\mu = 0$ was used to obtain the first provisional value of c_1. Then μ was estimated from this value of c_1, K_c interpolated from an appropriate graph, and a second value of c_1 determined. This process was continued until two successive evaluations of K_c agreed within the experimental error in the determination of this constant. At high concentrations no reliable data on K_c are available. In this range, however, the correction due to the ionization of bisulfate ion is small and not very sensitive to the value chosen for K_c. We have computed this correction for three different values of K_c, 0.01, 0.03 and 0.09, and have found only small differences in the results obtained for ϕ_1. The constant of 0.03, however, gave the best agreement with the molal volumes in the dilute region.

An alternative procedure for calculating ϕ_1 in concentrated solutions of sulfuric acid is to compute values of K_c from the data given by Harned and Hamer[4] combined with the ionization constant of bisulfate ion at infinite dilution determined by Hamer[5] or by Klotz.[3] This method, however, involves extensive computations, and since a precise value of K_c is unnecessary in the concentrated region, this alternative procedure was not adopted.

The apparent molal volumes of $(H^+)_2(SO_4^=)$ were calculated from the appropriate data for potassium chloride, hydrochloric acid and potassium sulfate[2,6] with the added assumption that the respective volumes are linear functions of the square root of the total ionic strength. Such a behavior is not fulfilled by hydrochloric acid or potassium sulfate[2,6] but the errors so introduced occur mainly in concentrated solutions where the correction of ϕ_3 for the ionization of bisulfate ion is small.

Knowing c_1 and ϕ_2 we can calculate the apparent molal volumes of $(H^+)(HSO_4^-)$ by entering the appropriate quantities in equation (2). The significant steps in the calculation are outlined in Table I.

(3) Klotz, Ph.D. Dissertation, University of Chicago, 1940.

(4) Harned and Hamer, THIS JOURNAL, **57**, 27 (1935).

(5) Hamer, *ibid.*, **56**, 860 (1934).

(6) Wirth, *ibid.*, **62**, 1128 (1940).

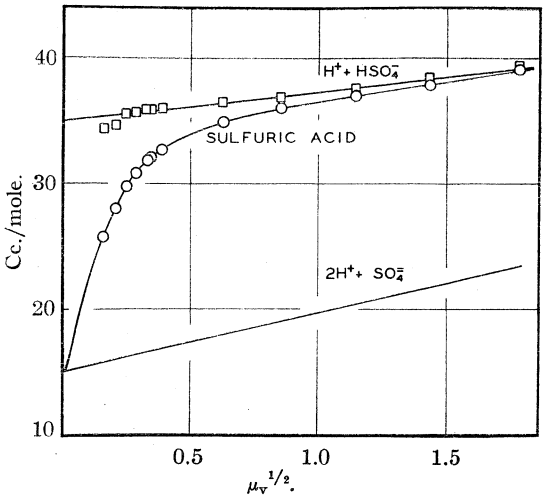


Fig. 1.—Apparent molal volumes of sulfuric acid and its constituents: O, observed volumes; □, calculated volumes.

Figure 1 shows the results for the calculated volumes of the constituents of sulfuric acid solutions as well as the experimental data. The curve for sulfuric acid in the very dilute range (up to $\mu^{1/2} = 0.15$) was calculated from the volumes of the ionic components and shows a definite cusp just beyond $\mu^{1/2} = 0$. The observed apparent molal volume rises very rapidly as the concentration is further increased because more and more bisulfate ion is formed. As we reach concentrated solutions ($\mu^{1/2} > 0.5$) the proportion of sulfate ions becomes progressively smaller and the observed volumes become, very nearly, those calculated for $(H^+)(HSO_4^-)$. Thus the observed volumes of sulfuric acid from 0 to 3 molar can be interpreted quantitatively in terms of the respective contributions of the constituent ions.

The Volume Change on Ionization of Bisulfate Ion.—Extrapolation to infinite dilution yields a value of 35.1 cc./mole for $\overline{V}^0$ of $(H^+)(HSO_4^-)$. Combining this figure with that for $(H^+)_2(SO_4^=)$ we find the volume change upon ionization of bisulfate ion at infinite dilution to be −20.2 cc./mole:

$$HSO_4^- = H^+ + SO_4^= \qquad \Delta\overline{V}_2^0 = -20.2 \text{ cc./mole}$$

Acknowledgment.—We are indebted to Professor Frank T. Gucker, Jr., and to Professor T. F. Young of the University of Chicago for a number of suggestions concerning the presentation of this material.

Summary

The densities of solutions of sulfuric acid have been determined over the concentration range of 0 to 3 molar and the apparent molal volumes interpreted in terms of the volumes of the hydrogen, sulfate and bisulfate ions.

The apparent molal volumes of hydrogen and bisulfate ions have been calculated by a series of successive approximations.

EVANSTON, ILLINOIS RECEIVED APRIL 21, 1942

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

The Kinetics of the Thermal Reaction between Hydrogen and Cyanogen

BY N. C. ROBERTSON AND R. N. PEASE

Since the reactions of hydrogen with the various halogens have had such an important role in the development of chemical kinetics, it was thought that an investigation of the reaction with cyanogen might be profitable. The only reference to such a reaction is a report by Berthelot[1] that heating hydrogen and cyanogen in glass vessels in the neighborhood of 550° results in the formation of hydrogen cyanide together with a considerable amount of a polymer assumed to be paracyanogen.

The object of the present research was to establish the mechanism of this reaction in its relation to the other familiar reactions of hydrogen.

(1) M. Berthelot, *Compt. rend.*, **89**, 63 (1878).

Experimental Procedure

The reaction was studied in a static system employing a silica vessel for most of the runs. This bulb, which was spherical and of some 550-cc. capacity, was placed at the center of a large electrically heated furnace which was provided with an auxiliary winding for the reaction chamber by means of which the temperature of the chamber was controlled to ±0.1° by a photoelectric potentiometer device connected to control thermocouples. The temperature was measured by means of two thermocouples immediately adjacent to the reaction vessel, heat losses and temperature gradient being minimized by packing the space for 10 inches above and below the reaction chamber with asbestos fiber. Apiezon was found to be satisfactory for stopcock lubrication.

Tank hydrogen was purified by passage over platinized

asbestos at 350° and dried by condensing the water vapor in a trap surrounded by liquid air. Cyanogen was prepared by slowly dropping a concentrated solution of C. P. sodium cyanide onto powdered copper sulfate in a 500-cc. flask which was provided with a ground glass joint for the dropping funnel. The cyanogen was dried by passage through calcium chloride and was repeatedly fractionated from dry-ice and ether in an all glass system. Finally after admission to the storage vessel attached to the main vacuum system it was condensed several times in liquid air and the non-condensable gases evacuated with a mercury vapor pump. Cyanogen prepared by this method was found to contain only traces of hydrogen cyanide as shown by analysis, and the vapor pressure over dry-ice was that observed by Perry and Bardwell;[2] moreover, the consistency of the results obtained with a number of different preparations was considered good evidence for a reasonable degree of purity.

The hydrogen cyanide used in the experiments on inhibition was kindly furnished by Dr. J. Holmes of this Laboratory and was prepared by the action of sulfuric acid on sodium cyanide with subsequent drying and fractionation.

In making a run hydrogen as the lighter gas was first admitted to the thoroughly evacuated reaction chamber up to the desired pressure as indicated by a mercury manometer; then cyanogen was rapidly admitted from the storage bulb to give the desired total pressure. At the end of the run a sample amounting to approximately 60% of the reaction mixture was admitted to a previously evacuated analysis bulb of known volume, which was attached to the apparatus by a ground glass joint, the exact amount of the sample being determined by the pressure difference.

Since it soon became apparent that, aside from a small quantity of polymer, hydrogen cyanide was the only product formed in any substantial amount, the analytical procedure was designed to determine hydrogen and hydrogen cyanide. In order to determine hydrogen the cyanogen and hydrogen cyanide were condensed by surrounding the analysis bulb with liquid air and the hydrogen rapidly pumped off. The difference in pressure when the contents of the bulb had been allowed to return to room temperature was a measure of the hydrogen present since several experiments showed that no appreciable quantity of hydrogen dissolves in the condensed phase.

The determination of hydrogen cyanide in the presence of cyanogen was based on the method of Rhodes[3] and involves the rapid and quantitative reaction of hydrogen cyanide with a slightly acidified solution of silver nitrate with no interference by cyanogen. The analysis bulb was removed from the apparatus and inverted in a beaker containing a measured quantity of 0.025 *N* solution of silver nitrate to which one drop of dilute nitric acid per 5 cc. of solution had been added. By momentarily opening a stopcock a portion of this solution was allowed to flow up into the analysis bulb containing the cyanogen and hydrogen cyanide. The bulb was then shaken vigorously, opened, and the contents, consisting of precipitated silver cyanide and unreacted solution, washed out into the beaker with distilled water. The solution was then filtered and the remaining silver nitrate determined by titration with standard potassium thiocyanate using an indicator solution of ferric ammonium sulfate. From the silver nitrate neutralized by the hydrogen cyanide it was possible to calculate the pressure of hydrogen cyanide in the reaction vessel. Analysis of known mixtures and the consistent checks with the analysis for hydrogen showed this method to be accurate to 1%.

(2) J. H. Perry and D. C. Bardwell, THIS JOURNAL, **47**, 2629 (1925).

(3) F. H. Rhodes, *J. Ind. Eng. Chem.*, **4**, 652 (1912).

Results

The reaction was studied over the temperature range 550–675°; however, it proceeds at a very convenient rate at 625°, and the kinetic results were obtained at this temperature.

In order to show experimentally that equilibrium in the system

$$H_2 + (CN)_2 \rightleftarrows 2HCN$$

is far to the right, 0.5 atmosphere of hydrogen cyanide was allowed to stand for forty-eight hours at 625°. No decomposition could be detected on analysis although polymerization amounted to about 3%. It was concluded that the reaction as written is at least 98% complete.

About thirty runs were made in the silica vessel at temperatures of 500–600° before any attempt at accurate kinetic measurements. In view of the tendency of both cyanogen and hydrogen cyanide to polymerize in this region, it is probable that some polymer accumulated on the surface of the bulb. In a single run at any temperature above 600°, however, the pressure decrease was only of the order of magnitude of 0.5%. About sixty runs were made in this "aged" bulb, each series being bracketed by standard runs of 215 mm. of each reactant for a sixty-minute period at 625°. Typical kinetic results at this temperature are summarized in Table I-A.

The most prominent feature of the reaction is the emphasis upon the concentration of hydrogen. Constants for a three halves order and for a "Bodenstein–Lind" expression were calculated and are given in the table. The temperature coefficient in this bulb was determined over the range 575–675° (Table I-C) and corresponded to an over-all activation energy of 72 kcal. (Fig. 1).

Although the reaction appeared to be of low order as far as total pressure is concerned, the rate decreased rather rapidly with time, which suggested an inhibiting action by the product, hydrogen cyanide. To test this, pure hydrogen cyanide was added at the beginning of several runs with results recorded in Table I-B. Not

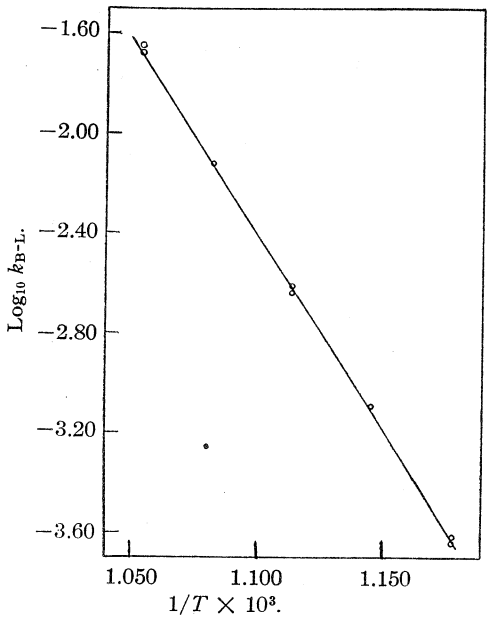


Fig. 1.—Activation energy in aged bulb.

only was the inhibiting action confirmed, but it was shown to be significantly greater when the ratio of the initial concentration of hydrogen to that of cyanogen was high.

TABLE I

KINETIC RESULTS IN AGED BULB

A. Time and pressure dependence

Run no.	Time, min.	Mm. H_2 in	Mm. $(CN)_2$ in	Mm. HCN out	$k_{s/2}$ × 10⁴	k_{B-L} × 10³[a]
	Approximately 100 mm. H_2–100 mm. $(CN)_2$					
93	30	103	105	39	6.94	3.00
72	60	100	105	67	7.33	3.17
77	120	100	100	96	6.46	2.82
	Approximately 205 mm. H_2–225 mm. $(CN)_2$					
40	2	204	249	(24)	(19.0)	(7.7)
37	15	195	224	63	(8.05)	(3.29)
38	30	208	230	102	6.39	2.70
79	60	206	225	150	5.50	2.29
66	120	207	226	223	5.00	2.25
41	240	207	238	293	4.27	2.27
	Approximately 305 mm. H_2–325 mm. $(CN)_2$					
55	30	304	319	162	6.19	2.29
56	60	302	335	249	5.84	2.33
57	120	305	337	360	5.03	2.33
	Approximately 310 mm. H_2–110 mm. $(CN)_2$					
51	2	312	106	(16)	(12.8)	(5.18)
91	30	305	111	74	4.51	1.91
90	60	307	110	132	4.98	2.27
76	120	320	112	180	3.68	1.98
75	180	319	105	188	2.95	2.10
	Approximately 105 mm. H_2–320 mm. $(CN)_2$					
50	2	101	311	(22)	(32.8)	(13.2)
92	30	104	325	59	6.45	2.60
89	60	107	319	84	4.88	2.10
43	120	103	329	136	5.30	2.21
74	180	106	320	160	4.64	1.80

[a] *k*'s are for the units millimeters and minutes.

B. Inhibition by hydrogen cyanide. All runs for 60 minutes at 625°

Run no.	Mm. H_2 in	Mm. $(CN)_2$ in	Mm. HCN in	Mm. HCN produced
86	223	221	0	158
85	220	225	100	143
87	218	227	196	134
90	307	110	0	132
81	309	111	98	113
89	107	319	0	84
80	105	311	98	81
72	100	105	0	67
94	103	101	203	57

C. Temperature dependence

Run no.	Temp., °C.	Time, min.	Mm. H_2 in	Mm. $(CN)_2$ in	Mm. HCN out	k_{B-L} × 10³[a]
62	575	720	205	228	168	0.230
64	575	921	204	222	189	0.225
61	600	360	205	242	236	0.797
65	625	60	207	230	157	2.41
66	625	120	207	226	223	2.25
59	650	35	206	234	226	7.51
58	675	10	203	230	209	23.5
63	675	10	207	241	202	21.2

D. Precision of measurements. Bracket runs at 625° for 60 min.

Run no.	Mm. H_2 in	Mm. $(CN)_2$ in	Mm. HCN out	k_{B-L} × 10³[a]
36	206	226	148	2.25
42	217	210	156	2.41
49	208	225	150	2.34
60	208	217	154	2.46
65	207	230	157	2.41
70	207	238	152	2.22
79	206	225	150	2.29
88	206	231	154	2.34
95	204	223	148	2.29

[a] *k*'s are expressed in the units millimeters and minutes.

In several experiments 1–2 mm. of oxygen was added to the reaction mixture, in which instance the rate was observed to increase by about 75%; however, no evidence for catalysis by minute traces of oxygen, such as characterizes the vapor phase reactions of many organic substances, was obtained.

An early observation that the rate in Pyrex at 550° is some 50% higher than in clean silica indicated a qualitative effect of surface. In order to study the quantitative influence, the reaction vessel was removed, treated with concentrated nitric acid to cleanse the surface of any film of polymer, washed with distilled water and packed with clear silica tubing of 10-mm. diameter which had been cleaned by prolonged treatment with hot nitric acid. This packing increased the surface–volume ratio by a factor of 3.5–4, and its surface was considered to be the best obtainable duplication of that of the blown silica vessel. Since it developed that cleaning the surface causes some alteration in the rate and temperature coefficient of the

process, a series of runs was made in the acid-cleaned unpacked bulb for purposes of comparison.

Although preliminary results in the packed bulb were erratic and somewhat high, the rates quickly settled down and became reproducible. A puzzling complication was encountered in that after raising the temperature from 550 to 625° or higher, it was necessary to make several runs followed by periods of extended pumping before the rate at the higher temperatures rose to a consistent value. On account of the greater pressure decrease during low temperature runs, it may be possible to attribute this to the formation of paracyanogen on the walls since this is said to occur in the range 500–600°. The consistent rates are given in Table II-A for standard runs at several temperatures in comparison with runs in the empty vessel after the packing had been removed. It is apparent that packing increases the rate at low temperatures somewhat, while causing no appreciable change at 650 or 675°. This makes it highly improbable that the reaction is entirely a surface process; however, it would seem to indicate either that at the lower temperatures there is a concurrent reaction proceeding on the surface or that the wall participates in some step of a gas phase process.

Since the nature of the surface is obviously of considerable importance to the kinetics, a means of treating it so that its function could be studied to better advantage was sought. It had been observed that treating the aged bulb with oxygen caused no substantial change in the rate; however, when the packed bulb was treated at 675° for two hours with an atmosphere of pure oxygen and then thoroughly evacuated, the rate was very decisively decreased at all temperatures, as may be seen from Table II-B. When the packing was removed, this procedure had no effect on the rates in the empty bulb. This seeming anomaly may be due to a qualitative difference between the surface of the packing and that of the bulb itself, but the fact that the rate in the packed bulb after oxygen treatment is less than in the unpacked bulb is considered most significant. It is plausible that oxygen at such high temperatures would strip any adsorbed film from the surface although this may not be its sole action.

A few runs with varying initial pressures of reactants were made in the unpacked bulb following oxygen treatment. The kinetics at 625° (Table II-C), although not markedly different from those in the aged bulb seem to require a somewhat lower power of the cyanogen concentration (see Discussion). The fact that the temperature coefficient is lower than in the aged bulb may be taken to indicate increased participation by the surface in some phase of the reaction.

TABLE II

EFFECT OF SURFACE

A. Comparison of rates in packed and unpacked bulbs. All runs with approximately 205 mm. H_2–225 mm. $(CN)_2$

Temp. °C.	Time, min.	Packed Bulb (b) Mm. H_2 in	Mm. $(CN)_2$ in	Mm. HCN out	Unpacked Bulb (b) Mm. H_2 in	Mm. $(CN)_2$ in	Mm. HCN out
550	1140	206	230	234	206	228	178
625	60	208	227	238	209	231	216
	60	206	228	241	206	245	214
650	20	206	230	191	208	230	183
675	10	207	235	170	206	232	180
					207	235	187

B.

		Oxygen treated packed bulb			Oxygen treated unpacked bulb		
550	1140	205	232	53	206	228	178
625	60	207	235	78	210	233	210
650	20	206	242	40	207	240	172
	20	206	235	28			

C. Pressure dependence in unpacked bulb[b]

Run no.	Temp., °C.	Time, min.	Mm. H_2 in	Mm. $(CN)_2$ in	Mm. HCN out	$k_{B\text{-}L} \times 10^3$	$k' \times 10^{2a}$
137	625	60	103	107	103	6.18	1.251
148	625	60	209	231	216	3.89	1.217
149	625	60	310	313	300	3.31	1.222
135	625	60	312	108	187	4.89	0.811
136	625	60	103	320	109	3.03	1.290
145	675	10	102	108	82	18.5	...
144	675	10	206	235	187	15.3	...
146	675	10	316	328	305	14.3	...

[a] k's are expressed in the units millimeters and minutes.
[b] After nitric acid treatment.

Discussion of Results

With regard to the reaction kinetics, the following facts are outstanding: the existence of a brief period of rapid reaction when the gases are first introduced, the greater dependence upon the hydrogen concentration during the further course of the reaction, the inhibiting effect of the product, and the low order of the reaction with respect to total pressure.

A second-order expression of the hydrogen–iodine type was implausible on account of the low order of the reaction and the necessary dominance of the hydrogen concentration in any kinetic expression.

Constants for a three halves order equation involving the square root of the cyanogen concentration (Table I-A, Column 6) fall sharply with time when the ratio of hydrogen to cyanogen is high. This, together with the inhibition by hy-

drogen cyanide, pointed to the well-known Bodenstein–Lind[4] type of expression developed for the reaction of hydrogen and bromine

$$\frac{d[HCN]/2}{dt} = \frac{k_{B\text{-}L}\,[H_2][(CN)_2]^{1/2}}{1 + m\,\dfrac{([HCN]/2)}{[(CN)_2]}}$$

The constants, calculated for $m = 0.25$ and expressed in millimeters and minutes, are listed in column 7 of Table I-A, the values of the constants for some fifty runs falling within the range shown. This expression is the simplest one which fits the kinetics in the aged bulb reasonably well. Aside from its neglect of the period of initial acceleration, it is deficient only in the high values of the constants for runs with low total pressures. Quite possibly this may be attributed to a surface reaction of very low order; for, if 5–10 mm. of product per hour were formed by a zero-order reaction, the constants for runs with 100 mm. of each reactant would become compatible with those for higher pressures. For runs at low pressures or for high ratios of one reactant to the other the integrated expression is extremely sensitive, and this accounts for most of the observed fluctuations.

Since the packing experiments showed that the reaction is not heterogeneous, the applicability of the Bodenstein–Lind equation, the inhibition by product, and the strong inhibition by the packing in the oxygen-treated bulb are cogent arguments for a reaction involving chains propagated by free radicals and atoms. The acceleration by a small concentration of oxygen is also a type of phenomenon frequently encountered when chain processes are involved.

The most elementary mechanism, by analogy with the hydrogen–bromine reaction, is

$$(CN)_2 \longrightarrow 2CN \qquad (1)$$
$$CN + H_2 \longrightarrow HCN + H \qquad (2)$$
$$H + (CN)_2 \longrightarrow HCN + CN \qquad (3)$$
$$H + HCN \longrightarrow H_2 + CN \qquad (4)$$
$$CN + CN \longrightarrow (CN)_2 \qquad (5)$$

which leads by the familiar steady state solution to the equation

$$\frac{d[HCN]/2}{dt} = \frac{2k_2\sqrt{k_1/k_5}\,[H_2][(CN)_2^{1/2}}{1 + \dfrac{k_4}{k_3}\,\dfrac{[HCN]}{[(CN)_2]}}$$

The propagation of the chains almost certainly centers around reactions 2, 3 and 4, and the necessity for introducing the one-half power of the cyanogen concentration is good evidence for chain ending by a recombination of two CN radicals. The feasibility of chain initiation by the dissociation of cyanogen molecules into free radicals as in equation 1, however, must be determined by other considerations; for, if this is the case, the maximum concentration of cyanide radicals is that attained when the reversible dissociation of cyanogen has reached equilibrium. In order to determine whether this equilibrium concentration is sufficient to give the observed absolute rate of reaction the simple collision theory treatment used by Morris and Pease[5] in considering the thermal hydrogen–chlorine reaction may be employed. The rate of formation of hydrogen cyanide, neglecting the inhibiting action by the product through reaction 4, is calculated as

$$dn_{HCN}/dt = 2k_2\sqrt{K_{eq.}}\sqrt{n_{(CN)_2}}\,n_{H_2}$$

where the n's are the numbers of hydrogen and cyanogen molecules, k_2 is the rate of the reaction

$$CN + H_2 \longrightarrow HCN + H \qquad (2)$$

and $K_{eq.}$ is the equilibrium constant for the dissociation

$$(CN)_2 \rightleftarrows 2CN$$

According to collision theory k_2 is given by

$$k_2 = 2\left[2\pi R\,\frac{M_1 + M_2}{M_1M_2}\right]^{1/2}\sigma_{12}^2\,T^{1/2}\,e^{-E/RT}$$

A value of 7 kcal. for E, the activation energy of reaction 2, has been reported by Hartel and Polanyi[6] from their studies of highly dilute flames. The radius of hydrogen is taken from viscosity data as 1.09 Å. and that of the CN radical as 1.50 Å. or slightly less than that of the nitrogen molecule[7] which should occasion no serious error. Substitution of these values gives $k_2 = 1.34 \times 10^{-11}$ in cc. per molecule per second at 900°K.

Unfortunately, reports of the heat of dissociation of cyanogen into radicals are contradictory. The value 77 kcal. was determined by Kistiakowsky and Gershinowitz.[8] More recently White[9] has assigned 137 kcal. as a minimum value with a probable value of 146 kcal. White has also calculated the entropy change in the dissociation as a function of temperature making use of the best available spectroscopic data; and from this the free energy change and equilibrium constant at

(4) (a) M. Bodenstein and S. C. Lind, *Z. physik. Chem.*, **57**, 168 (1907); (b) C. N. Hinshelwood, "Kinetics of Chemical Change," Oxford Press, New York, N. Y., 1940, p. 102.

(5) J. C. Morris and R. N. Pease, THIS JOURNAL, **61**, 391, 396 (1939).

(6) H. v. Hartel and M. Polanyi, *Z. physik. Chem.*, **B11**, 97 (1930).

(7) Landolt–Börnstein, "Tabellen," Erg. I, 1927, p. 69.

(8) G. B. Kistiakowsky and H. Gershinowitz, *J. Chem. Phys.*, **1**, 432 (1933).

(9) J. U. White, *ibid.*, **8**, 79, 459 (1940).

any temperature not far from 1200°K. may be evaluated if the heat of dissociation is known.

Using the value 77 kcal., which is almost certainly too low, and calculating the equilibrium constant by means of White's equation, dn_{HCN}/dt is 5.4×10^6 mm./min. for a reaction mixture of 215 mm. each of hydrogen and cyanogen at 900° K. With White's value of 137 kcal. the rate is calculated as 0.30 mm./min. These calculated rates, whose validity depends upon the 7 kcal. activation energy for reaction 2, bracket the observed "steady" rate, the rate after the period of initial acceleration, of 2 mm./min.

It is possible that White's value may be somewhat high. Hogness and T'sai[10] concluded from their studies on the photochemical polymerization of cyanogen that 2240 Å., corresponding to 127 kcal., is the longest wave length of a cyanogen absorption band and is sufficient to give dissociation into CN radicals. If this value is taken, the equilibrium rate of formation of hydrogen cyanide, assuming again that reaction 2 requires 7 kcal. activation energy, becomes 4.5 mm./min. in better agreement with experiment.

It is also noteworthy that on the assumption of chain starting by dissociation of cyanogen it should be possible to obtain the over-all activation energy as the sum of half the heat of dissociation plus the activation energy of step 2. With the values 127 kcal. and 7 kcal., respectively, the over-all activation energy should be 71 kcal., in good agreement with the observed value of 72 kcal. From another standpoint, however, this is most significant in that it shows the experimental activation energy to be consistent with the proposed mechanism. Thus if the activation energy for step 2 as observed by Hartel and Polanyi is too high by several kilocalories, a larger heat of dissociation could be admitted; if it is too low, a value of even less than 127 kcal. would be necessary to account for the observed over-all activation energy and rate.

If the heat of dissociation of cyanogen is very large, the question of why the reaction does not proceed by the initial dissociation of hydrogen, which requires only 103 kcal., arises. Using White's equation for the entropy change, the equilibrium concentration of CN radicals would be equal to that of hydrogen atoms only if the heat of dissociation of cyanogen were as low as 114 kcal. If the starting involved the dissociation of hydrogen, however, the rate of reaction 3 would determine the absolute rate of formation of hydrogen cyanide; and this, for an equilibrium concentration of hydrogen atoms, may be so low compared to that of reaction 2, for an equilibrium concentration of CN radicals, that the hydrogen dissociation would be of minor importance in the conversion. This would imply that the activation energy of reaction 3 is larger than that of reaction 2, which is reasonable when the large energy of the carbon–carbon bond in cyanogen is considered.

It must be emphasized that these considerations show only that chain initiation by the direct dissociation of cyanogen into cyanide radicals is well within the realm of possibility. The final decision must wait upon the clarification of the uncertainties already mentioned when new data become available.

If chains are initiated by the dissociation of cyanogen molecules, then they must certainly start on the walls of the vessel since an elementary collision theory calculation shows that the time required to attain an equilibrium concentration of CN radicals by gas phase dissociation is of the order of magnitude of several days; furthermore if the walls act as a catalyst for the dissociation, they must also catalyze the chain ending process of recombination.

In view of the complexity of the reaction, however, chain initiation by some process other than the direct dissociation of cyanogen, by means of which a concentration of radicals greater than the equilibrium concentration could be furnished, must not be ruled out. Such a process might be a reaction between cyanogen and adsorbed hydrogen similiar to a mechanism suggested by Morris and Pease for chain starting in the hydrogen–chlorine reaction in one of their Pyrex bulbs.

$$WH_2 + (CN)_2 \longrightarrow WHCN + H + CN$$

For strong adsorption of hydrogen this leads to a Bodenstein–Lind type of expression.

Too few runs in which there were wide variations in the initial pressures were made in the oxygen treated empty bulb to warrant broad generalizations with regard to the kinetics. The expression

$$\frac{d[HCN]/2}{dt} = \frac{k'[H_2]}{1 + m\dfrac{([HCN]/2)}{[(CN)_2]}}$$

seems to fit the data at 625°, the constants for $m = 0.25$ and again expressed in terms of milli-

(10) T. R. Hogness and Liu-Sheng T'sai, THIS JOURNAL, **54**, 123 (1932).

meters and minutes appearing in column 7 of Table II-C. The low value for the one run with a 3–1 initial ratio of hydrogen to cyanogen is understandable since by the end of the run practically all the cyanogen has reacted. Bodenstein–Lind constants, however, fit the variation with respect to total pressure at 675°, and the fit would be better if a lower value of m were taken for this temperature; but they are totally unsatisfactory at 625°.

Since there is no reason to suppose that the steps in chain propagation are any different in the clean bulb, the increased rate at low temperatures along with the lower temperature coefficient argues for a different method of chain starting on the surface. The possibility

$$WH_2 + W(CN)_2 \longrightarrow WHCN + H + CN$$

which results in the foregoing kinetic expression suggests itself since Hadow and Hinshelwood[11] obtained evidence of strong adsorption of cyanogen on clean silica in their oxidation studies.

Hogness and T'sai[10] found that CN radicals disappear at room temperature by addition to cyanogen molecules to form a postulated $(CN)_3$ which acts as a nucleus for further polymerization with the ultimate formation of paracyanogen. White[9] concluded that the radicals formed during an electric discharge combine with complex ions simultaneously produced in the discharge as a first step in polymerization. In the present investigation at temperatures of 625° or higher such an addition reaction was not indicated by kinetic analysis of the results in the aged bulb, nor was any extensive polymerization observed. This must mean that the reactions

$$CN + H_2 \longrightarrow HCN + H$$

and

$$CN + CN + W \longrightarrow (CN)_2 + W$$

are much faster than the addition of radical to molecule. It may well be that the $(CN)_3$ complex is unstable at these temperatures since it is known that cyanogen does not polymerize at elevated temperatures and that paracyanogen begins to regenerate cyanogen in the region 700–800°.

(11) H. J. Hadow and C. N. Hinshelwood, *Proc. Roy. Soc.* (London), **A132**, 375 (1931).

Summary

The thermal reaction of hydrogen and cyanogen to yield hydrogen cyanide has been studied in a silica vessel over the temperature range 550–675°. The reaction proceeds without undue complications, but the nature of the surface of the reaction bulb has some influence on the rate. The product, hydrogen cyanide, inhibits the reaction. Packing increases the rate at low temperatures but has little effect above 625°.

The simplest expression which fits the kinetics at 625° reasonably well is that developed by Bodenstein and Lind for the combination of hydrogen and bromine. Evidence is presented which favors a radical chain mechanism involving gas phase propagation by hydrogen atoms and cyanide radicals with chains starting and breaking on the walls. The steps in this process would be analogous to those in the hydrogen–bromine reaction with the cyanogen assuming the role of bromine.

PRINCETON, NEW JERSEY RECEIVED MAY 6, 1942

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

The Ternary Systems Involving Cyclohexane, Water, and Isopropyl and Normal Propyl Alcohols

BY E. ROGER WASHBURN, CHARLES E. BROCKWAY, C. LOREN GRAHAM AND PHILIP DEMING

The ternary systems[1] made up of cyclohexane, water, and[1a] methyl and[1b] ethyl alcohols have been described previously.

The systems[2] involving water, isopropyl alcohol and[2a] benzene,[2b] toluene and[2c] cyclohexene have been described.

This report adds normal propyl and isopropyl alcohols to the first group and cyclohexane to the second group.

Materials.—Cyclohexane from Eastman Kodak Company was carefully fractionated, dried with sodium and recrystallized several times. The alcohols were the best grades obtainable from the same company. They were dried with active lime and carefully fractionated. Some physical

(1) E. R. Washburn, *et al.*, THIS JOURNAL, (a) **56**, 361 (1934); (b) **54**, 4217 (1932).

(2) E. R. Washburn, *et al.*, *ibid.*, (a) **57**, 303 (1935); (b) **62**, 579 (1940); (c) **62**, 1454 (1940).

constants for the materials used in this investigation are recorded in Table I.

TABLE I

Material	Specific gravity, d^{25}_4	Refractive index, $n^{25}D$	Freezing point, °C.
Cyclohexane	0.7746	1.4232	6.1[a]
n-Propyl alcohol	.8000	1.3838	..
Isopropyl alcohol	.7808	1.3749	..

[a] A small amount of cyclohexane resulting from many recrystallizations had a freezing point of 6.33° and a specific gravity, d^{25}_4 of 0.7744, and a refractive index not measurably different from that recorded above. This more highly purified material was employed in four solubility measurements with *n*-propyl alcohol and water at 35°. The differences in the results obtained with the 6.1° and the 6.33° cyclohexane, both for the solubility determinations and the refractive index–composition relationships, were well within the experimental errors.

Procedure and Results.—The experimental procedures were essentially the same as those which have been described.[1,2] The results are presented in the following tables and graphs. Since the concentrations are presented in weight per cent., it will be enlightening to state that in each solubility determination and in each distribution study the total weight of liquids employed was of the order of 13 to 15 g.

TABLE II

n-PROPYL ALCOHOL, CYCLOHEXANE AND WATER AT 25.0°

Cyclohexane, wt. %	*n*-Propyl alcohol, wt. %	Refractive index	Cyclohexane, wt. %	*n*-Propyl alcohol, wt. %	Refractive index
92.41	7.30	1.4192	17.77	58.73	1.3825
84.09	14.98	1.4152	12.91	57.60	1.3788
75.60	22.55	1.4114	6.56	49.52	1.3708
66.73	29.87	1.4071	4.29[a]	43.01	1.3660
56.64	37.94	1.4027	2.16[a]	35.63	1.3608
46.57	45.22	1.3974	0.72[a]	27.42	1.3550
36.81	51.50	1.3930	0.08[a]	18.49	1.3488
26.95	56.68	1.3880	0.06[a]	9.40	1.3408
		Water saturated with cyclohexane			1.3322
		Cyclohexane saturated with water			1.4233

[a] Mixtures of *n*-propyl alcohol and water were titrated with cyclohexane.

TABLE III

n-PROPYL ALCOHOL, CYCLOHEXANE AND WATER AT 35.0°

Cyclohexane, wt. %	*n*-Propyl alcohol, wt. %	Refractive index	Cyclohexane, wt. %	*n*-Propyl alcohol, wt. %	Refractive index
92.06	7.62	1.4137	18.05	58.91	1.3792
84.21	14.86	1.4101	13.14	57.99	1.3758
75.60	22.54	1.4062	7.42[a]	51.60	1.3692
67.04	29.81	1.4026	4.19[a]	42.96	1.3692
57.29	37.48	1.3982	2.21[a]	34.87	1.3579
46.54	45.27	1.3937	0.85[a]	27.46	1.3528
37.31	51.40	1.3893	0.11[a]	18.40	1.3467
26.96	56.68	1.3844	0.07[a]	9.21	1.3392
		Water saturated with cyclohexane			1.3311
		Cyclohexane saturated with water			1.4177

[a] Mixtures of *n*-propyl alcohol and water were titrated with cyclohexane.

TABLE IV

ISOPROPYL ALCOHOL, CYCLOHEXANE AND WATER AT 25.0°

Cyclohexane, wt. %	Isopropyl alcohol, wt. %	Refractive index	Cyclohexane, wt. %	Isopropyl alcohol, wt. %	Refractive index
0.14	8.80	1.3400	18.97	55.74	1.3778
0.32	23.88	1.3531	26.85	53.53	1.3848
1.08	36.80	1.3616	35.97	49.29	1.3897
4.81	48.29	1.3687	43.56	45.08	1.3936
10.46	53.88	1.3739	55.02	37.86	1.3995
16.27	55.57	1.3777	71.40	25.78	1.4066
			86.98	12.82	1.4144

TABLE V

CONJUGATE SOLUTIONS CONTAINING *n*-PROPYL ALCOHOL AT 25.0°

Water layer			Cyclohexane layer		
Refractive index	Alcohol, wt. %	Water, wt. %	Refractive index	Alcohol, wt. %	Water, wt. %
1.3377	5.8	94.1	1.4228	0.9	0.0
1.3403	8.6	91.1	1.4225	1.4	0.0
1.3450	13.9	85.6	1.4208	4.4	0.0
1.3480	17.5	81.9	1.4167	12.1	0.7
1.3494	19.3	79.9	1.4120	21.3	1.7
1.3505	20.8	78.5	1.4002	41.6	6.7
1.3513	21.9	77.3	1.3922	52.6	12.4
1.3521	23.0	75.9	1.3862	57.8	18.5
1.3636	39.6	57.2	1.3680	45.7	49.2

TABLE VI

CONJUGATE SOLUTIONS CONTAINING *n*-PROPYL ALCOHOL AT 35.0°

Water layer			Cyclohexane layer		
Refractive index	Alcohol, wt. %	Water, wt. %	Refractive index	Alcohol, wt. %	Water, wt. %
1.3365	6.2	93.7	1.4172	1.1	0.0
1.3384	8.3	91.6	1.4168	1.8	0.1
1.3426	13.3	86.7	1.4142	6.7	0.2
1.3448	16.1	84.0	1.4105	14.1	0.8
1.3460	17.7	82.4	1.4050	25.0	2.3
1.3470	19.0	81.0	1.3954	42.6	6.8
1.3480	20.3	79.6	1.3875	53.6	13.0
1.3494	22.3	77.4	1.3812	58.6	20.3
1.3588	36.4	61.2	1.3664	48.0	46.5

TABLE VII

CONJUGATE SOLUTIONS CONTAINING *i*-PROPYL ALCOHOL AT 25.0°

Water layer			Cyclohexane layer		
Refractive index	Alcohol, wt. %	Water, wt. %	Refractive index	Alcohol, wt. %	Water, wt. %
1.3356	4.4	95.4	1.4233	0.0	0.0
1.3383	7.1	92.8	1.4231	0.2	0.0
1.3465	15.4	84.1	1.4223	1.3	0.1
1.3545	25.9	73.9	1.4190	5.9	0.2
1.3590	32.6	66.5	1.4154	11.2	0.3
1.3647	41.6	55.7	1.4117	17.2	1.0
1.3718	52.1	39.9	1.4066	25.8	2.8
1.3789	55.5	26.7	1.4021	33.5	5.4

The earlier investigations[2] of ternary systems containing isopropyl alcohol, water and the hydrocarbons benzene, toluene and cyclohexene showed

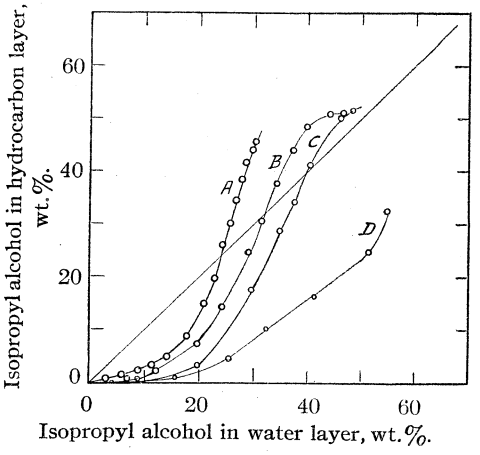


Fig. 1.—A, Benzene; B, toluene; C, cyclohexene; D, cyclohexane.

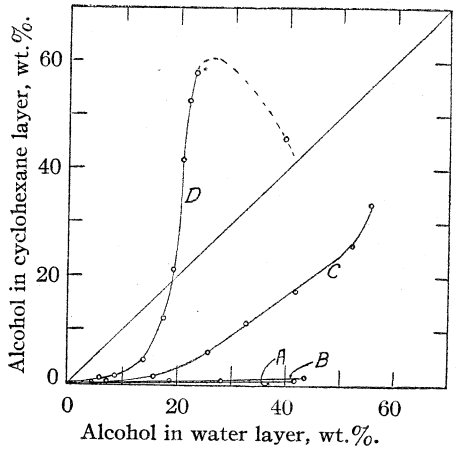


Fig. 2.—A, Methyl alcohol; B, ethyl alcohol; C, isopropyl alcohol; D, *n*-propyl alcohol.

that the greatly increasing proportions in which the alcohol entered the hydrocarbon layer as the total amount of alcohol in the system was increased caused a change in the direction of slope of the tie lines. It will be noted in the present study that, while the proportion of alcohol in the cyclohexane layer increases as the total amount of alcohol increases, it does not ever become equal to the proportion of alcohol in the conjugate layer which is rich in water. The tie lines never become horizontal and the plait point is some distance down on the cyclohexane branch of the binodal solubility curve. Experimental difficulties prevented a very close approach to the plait point and a study of the conjugation curves[3] did not greatly improve the situation. It is probably not far from 48% alcohol on the cyclohexane arm of the curve.

It should be mentioned that extensions of the tie lines for this system do not converge at a single point. Attention has been called to the fact that in several ternary systems such convergence is to be observed.[4] The system methyl alcohol–cyclohexane and water when studied at 25.0°[1a] not only shows such convergence but the point at which the tie lines converge is practically the cyclohexane vertex of the ternary diagram. The solubility of methyl alcohol in cyclohexane is not only limited but very small. As would be expected, ethyl alcohol[1b] is between methyl alcohol and the propyl alcohols in its distribution. It is not much different from methyl alcohol.

The systems in which the tie lines change direction of slope represent extreme cases of non-convergence. In one of the earlier studies the distribution of isopropyl alcohol between water and cyclohexene[2c] was investigated at three different temperatures, 15, 25 and 35°. The slopes of the tie lines and the positions of the plait points changed to a marked extent with the change in temperature. Larger proportions of the alcohol entered the hydrocarbon layer at the higher temperatures. If the present system behaves in a similar manner it might be expected that a change in direction of slope of the tie lines would be observed at a temperature somewhat higher than 25°.

The other system, described in this report, involving *n*-propyl alcohol shows such a change in the direction of slope of the tie lines at 25 and 35°. The change causes the plait point to appear on the opposite branch of the binodal curve from that which would be predicted by the tie lines obtained with the smaller total proportions of the alcohol. It was possible to determine the plait point quite accurately with this system; it appeared at about 42% alcohol on the water branch at 25°. The change of temperature to 35° did not cause as large a change in plait point as was observed in the former system.

The proportions in which these alcohols are distributed between the water and the hydrocarbon layers for these and related systems are clearly shown in Figs. 1 and 2.

Summary

The solubility relationships for the ternary system containing water, cyclohexane and isopropyl alcohol have been determined at 25°. The system containing water, cyclohexane and *n*-propyl alcohol has been studied at 25 and 35°.

LINCOLN, NEBRASKA RECEIVED JUNE 3, 1942

(3) "International Critical Tables," Vol. III, p. 398.

(4) A. V. Brancker, T. G. Hunter and A. W. Nash, *Ind. Eng. Chem., Anal. Ed.*, **12**, 35 (1940).

[CONTRIBUTION FROM ALLERGEN INVESTIGATIONS, BUREAU OF AGRICULTURAL CHEMISTRY AND ENGINEERING, U. S. DEPARTMENT OF AGRICULTURE, AND THE ALLERGY CLINIC OF PROVIDENCE HOSPITAL, WASHINGTON, D. C.]

The Chemistry of Allergens. VI. Chemical Composition and Properties of an Active Carbohydrate-free Protein from Cottonseed*,[1]

BY JOSEPH R. SPIES AND ERNEST J. UMBERGER

The importance of the role of carbohydrates in immunological specificity has increased since Heidelberger and Avery[2] first showed that polysaccharides determine the specificity of the pneumococcus organism. The possible analogous relationship of polysaccharides to allergenic specificity has made it seem worth while to record properties characterizing a carbohydrate-free allergenic protein fraction from cottonseed.[3]

Allergenic protein-polysaccharidic fractions containing less than 1% carbohydrate were described in a previous paper.[4] Some of these fractions which contained 0.9 to 3.0% carbohydrate were subjected to further electrophoresis to remove the carbohydrate. The material which migrated toward the cathode was used as starting product in three successive electrophoretic fractionations. The final cathodic fraction, CS-60C, was essentially free from carbohydrate as shown by chemical tests.[5]

Experimental

Apparatus.—Electrophoresis apparatus similar to that described and illustrated (Fig. 1) in the fourth article of this series[4] was employed, except that 125, 50 or 25 ml. cells were used, depending on the quantity of material to be fractionated. Side tubes were 10 mm. in outside diameter. Connection between cells was made with gum rubber tubing having 3 mm. wall thickness. *Danger of the current becoming grounded between the glass side-arm and the rubber connection was eliminated by coating the glass with petrolatum before sliding on the rubber tubing.*

Preparation of CS-60C.—Preliminary electrophoresis of previously described fractions[4] consisting of 1.0 g. of CS-51R, 1.5 g. CS-52R and 7.0 g. of CS-53R, which contained 0.9, 0.9, and 3.0 per cent. carbohydrate, respectively, was made in a 7-cell apparatus. The allergenic solution was placed in the center cell and an equal volume of distilled water was placed in each of the other cells. Electrophoresis was conducted with voltages ranging from 2500 to 5000 for six days. A general technique similar to that previously detailed[4] was used. The final *p*H in the cells ranged from 2.8 at the anode to 11.0 at the cathode. The substance which collected in cathodic cells having *p*H values higher than 6.5 was separated and isolated, as previously described, by alcohol precipitation. A combined total of 2.68 g. of solid was obtained in the first run. This solid was dissolved in 25 ml. of water and the solution was filtered from a slight amount of insoluble precipitate. The solution was placed in cell 2+ (25-ml. vol.) of a 6-cell apparatus and subjected to a second electrophoresis, using from 2500 to 5000 v. for five days. The *p*H in the cells ranged from 5.28 at the anode to 11.2 at the cathode. The substance which collected in cathodic cells having *p*H values from 7.69 to 11.0 was isolated by alcohol precipitation. The 563 mg. of solid thus obtained was dissolved in 25 ml. of distilled water and the solution (*p*H 9.4) was placed in cell 2+ of the 6-cell (25-ml. vol.) apparatus. After electrophoresis at 2500 v. for one day the solution in cell − was replaced with 25 ml. of distilled water. Electrophoresis was continued at 5000 v. for three days. The *p*H in the cells ranged from 4.49 at the anode to 10.6 at the cathode. Solutions in cells −, 1−, and 2− (*p*H, 7.52, 8.81 and 10.6, respectively) were combined and concentrated to 30 ml. in a vacuum desiccator over phosphorus

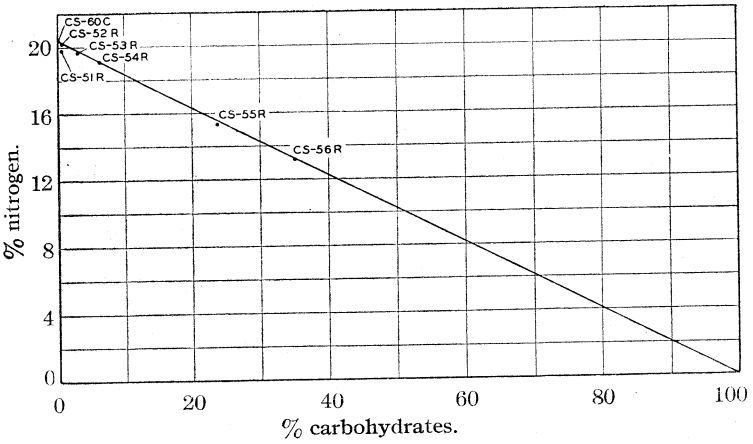


Fig. 1.—Curve showing the relationship between carbohydrate and nitrogen contents of allergenic fractions obtained by the electrophoretic fractionation of CS-1A.[4]

* Not copyrighted.

(1) For Paper V of this series see Spies, THIS JOURNAL, **63**, 2994 (1941).

(2) Heidelberger and Avery, *J. Exptl. Med.*, **38**, 73 (1923).

(3) The possible non-protein nature of allergens is discussed by Coca, Walzer and Thommen, "Asthma and Hay Fever in Theory and Practice," Charles C. Thomas, Baltimore, 1931, pp. 734 *et seq.*; also Vaughan, "Practice of Allergy," C. V. Mosby Co., St. Louis, Mo., 1939, p. 607.

(4) Spies, Bernton and Stevens, THIS JOURNAL, **63**, 2163 (1941).

(5) A Molisch test made on a 1% solution of CS-60C was negative. A control test using an equal volume of a 0.002% solution of galactose was distinctly positive by comparison. Using the orcinol method [Heidelberger and Kendall, *J. Immunol.*, **30**, 267 (1936)] 0.2% carbohydrate was indicated in CS-60C. This value is so near the lower limit of the method that it is indecisive and may be due to "blank."

pentoxide. The clear solution was then filtered through a porous platinum filter to avoid contamination with filter paper hairs. The colorless solution was then frozen in a 250-ml. conical centrifuge cup. After freezing the ice was dissolved by addition of 120 ml. of absolute ethanol and the suspension was stirred gently. This procedure eliminated the *p*H adjustment required to effect precipitation of the protein when its solution was poured into alcohol. The suspension was then centrifuged and the solid was washed with two 25-ml. portions of cold 80% ethanol. The white solid, designated as CS-60C, was dried in a vacuum over phosphorus pentoxide. A yield of 204 mg. was obtained. CS-60C was ground to a powder and equilibrated with air before analysis. CS-60C was completely soluble in water and gave protein color tests like those described in previous publications for the precursor fractions.

Discussion

The chemical composition and some properties of CS-60C are shown in Table I. Carbon and hydrogen content were of the usual order of magnitude encountered in proteins. The nitrogen content of CS-60C was higher than that found in most proteins, owing to the relatively large proportion of arginine present in cottonseed allergenic fractions.[1] Fraction CS-60C had a levo optical rotation of 140.

Substantiating evidence for the absence of carbohydrate in fraction CS-60C is contained in Fig. 1 where carbohydrate contents of the previously described[4] electrophoretic fractions CS-51R, CS-52R, CS-53R, CS-54R, CS-55R, and CS-56R are plotted as abscissas against their nitrogen contents as ordinates. A straight line starting on the abscissa at 100% carbohydrate passed through these points and intersected the ordinate representing zero per cent. carbohydrate at 20.4 which is the percentage of nitrogen actually found in CS-60C.

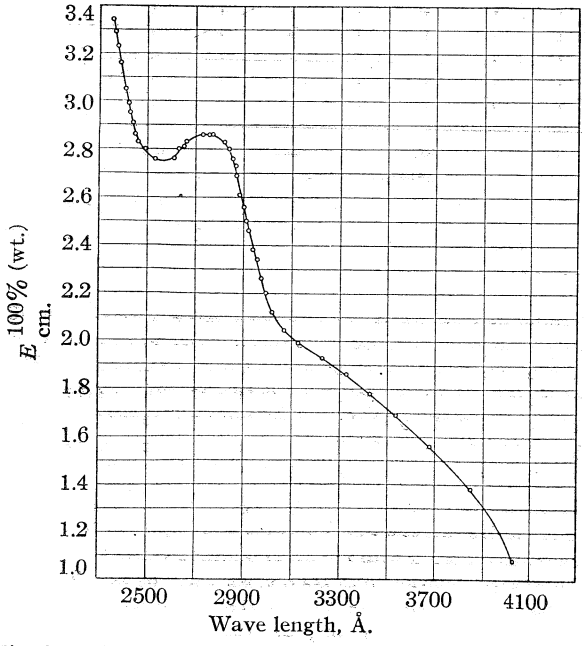


Fig. 2.—Ultraviolet absorption curve of CS-60C in water (concentration 0.413%).

TABLE I

CHEMICAL COMPOSITION AND PROPERTIES OF CS-60C[a]

Nitrogen	20.4
Nitrogen pptd. by 5% trichloroacetic acid [20 ± 0.1°][b]	86.6
Carbon	48.2
Hydrogen	6.58
Sulfur	2.35
$[\alpha]^{20}D$ 1% water solution	−140[c]
$[\alpha]^{20}D$ 2% water solution	−135

[a] All analyses are expressed on an ash and water-free percentage basis. CS-60C contained 0.58% ash and 7.94% water. Analyses were made by the micro methods of Pregl. [b] *Cf.* Paper IV, of this series, Table I.[4] [c] Optical rotation was kindly determined by Dr. E. Yanovsky of the Bureau of Agricultural Chemistry and Engineering.

CS-60C was further characterized by determination of the ultraviolet absorption curve,[6] Fig. 2. An absorption maximum occurred at 2750 Å. which coincides with that found for tyrosine.[7] The fractions from which CS-60C was obtained contained approximately 5% tyrosine.[1] No absorption maximum corresponding to that of phenylalanine was found.[7] The ultraviolet absorption of CS-60C corresponds in general to that which would be predicted from its composition.[1,8]

The solubility curve of CS-60C, Fig. 3, indicated that it was a solid solution.[9]

Whether this protein fraction was a mixture of allergenic components, closely related structurally, or consisted of a single active constituent associated with inactive contaminant cannot be decided from present evidence. However, in view of the variety and drastic nature of the processes used to isolate CS-60C, it seemed unlikely that a small proportion of active substance could have persistently remained associated with a preponderance of inactive material. It seemed more probable that CS-60C represented a mixture of proteins whose structural variations were too slight to permit effective chemical fractionation

(6) The authors are indebted to Dr. P. A. Cole of the National Institute of Health for determination of the ultraviolet absorption curve.

(7) Smith, *Proc. Roy. Soc.* (London), **B104**, 198 1929).

(8) *Cf.* Schmidt, "Chemistry of Amino Acids and Proteins," Charles C. Thomas, Baltimore, Md., 1938, pp. 552 *et seq.*

(9) For comparison the solubility curve of a precursor fraction CS-51R, is included in Fig. 3.

or perhaps too slight to impart immunological identity even if they could be separated.

Fraction CS-60C was antigenic as demonstrated by the property of producing anaphylactic sensitivity and shock in guinea pigs.[10]

The threshold quantity of CS-60C required to incite passive transfer reactions is shown in Table II. These results show that 1×10^{-9} g. of CS-60C was capable of producing positive reactions using a serum of moderate potency.[11]

TABLE II

THRESHOLD QUANTITY OF CS-60C REQUIRED TO PRODUCE POSITIVE PASSIVE TRANSFER REACTIONS WITH SERUM FROM A COTTONSEED SENSITIVE PATIENT[a]

CS-60C Injected,[b] micrograms	Recipients[c] T.W.	N.W.	H.B.
1	19 × 17		
0.1	15 × 15	15 × 13	12 × 15
.01	12 × 14	11 × 11	9 × 11
.001	6 × 7	10 × 10	0
.0001	0	±	0
.00001	..	0	..

[a] This serum (E.S.) gave positive passive transfer reactions to cottonseed allergen when diluted 1:10 and in one case 1:10². *Cf.* Coca and Grove, *J. Immunol.*, **10**, 445 (1925); also Levine and Coca, *ibid.*, **11**, 411, 435 and 449 (1926). [b] Quantity of CS-60C (contained in 0.025 ml. of sterile physiological salt solution) injected into each sensitive site. [c] Recipients were uniformly sensitized on the upper arms with 0.05 ml. of serum in each of five sites. The tests of each series were conducted simultaneously. The numbers refer to the diameter (in mm.) of the wheals which formed within fifteen to thirty minutes. CS-60C produced no non-specific reactions in normal skin. Qualitatively similar results were obtained using serum from another cottonseed sensitive patient (G.W.).

(10) The authors are indebted to Dr. E. J. Coulson for immunological tests: *cf.* Coulson, Spies and Stevens, *J. Immunol.*, **41**, 375 (1941).

(11) The authors wish to acknowledge their indebtedness to Dr. Harry S. Bernton for clinical facilities and to Dorris C. Chambers for assistance in conducting the tests. The clinical evidence showing that CS-1A and fractions derived from it are immunologically distinct from other allergens present in cottonseed has been described by Bernton, Spies and Stevens, *J. Allergy*, **13**, 289 (1942).

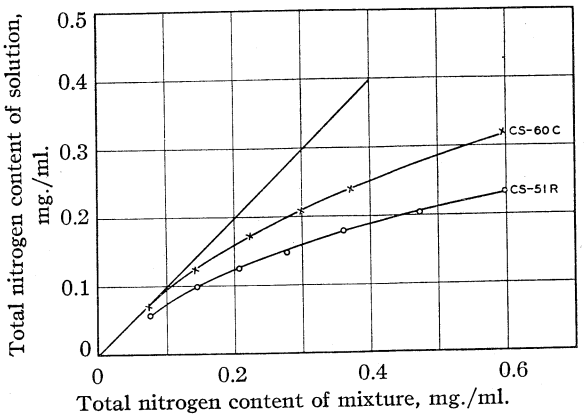


Fig. 3.—Solubility curves of CS-51R and CS-60C: weighed quantities of the protein fractions were placed in glass-stoppered tubes and then dissolved in 1.5 ml. of 0.05 *M* acid potassium phthalate solution buffered at *p*H 5.0. One ml. of absolute ethanol was added to the solution. The suspension was equilibrated by slowly rotating the tubes at 5 ± 0.1° for at least eighteen hours. The excess solid collected on the walls of the tubes during equilibration, leaving a clear supernatant solution which was analyzed for total nitrogen.

Summary

1. A carbohydrate-free allergenic protein, CS-60C, has been isolated from previously described protein-polysaccharidic fractions from cottonseed. Its chemical composition, optical rotation and ultraviolet absorption curve were determined. Solubility data indicated that CS-60C was not homogeneous but probably represented a mixture of active proteins whose structural variations were too slight to permit effective chemical separation.

2. Fraction CS-60C was antigenic as shown by tests on guinea pigs. Positive passive transfer reactions were produced with 1×10^{-9} g. of CS-60C.

WASHINGTON, D. C. RECEIVED JUNE 6, 1942

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

Erythrina Alkaloids. XII. Chromatographic Analyses of Erysodine, Erysovine and "Erysocine" and Technique for Preparative Isolation[1]

BY KARL FOLKERS AND JOHN SHAVEL, JR.

The isolation and characterization of erysopine, erysodine, erysovine[2] and erysonine[3] from various species of *Erythrina* have been described. These four alkaloids were obtained by appropriate techniques subsequent to their liberation by the acid hydrolysis of their aqueous solutions after complete removal of the free alkaloids. Difficulties in isolating homogeneous alkaloids from species of *Erythrina* have been observed frequently in published[4] and unpublished studies. It is to be emphasized again that special care should be given to establishing the homogeneity of any new free *Erythrina* alkaloid. Chromatographic analyses have been applied to alkaloids,[5] and preliminary experiments on erysonine[3] confirmed the purity of samples obtained by crystallization technique. This paper describes the results of further chromatographic analyses on pure eryso- alkaloids as a further check on purity and application of such adsorption methods for actual preparative separation of *Erythrina* alkaloidal mixtures.

The melting point and specific rotation of standard samples of erysodine and erysovine were not altered by chromatographic analyses over aluminum oxide. Pure erysopine was not sufficiently soluble in the ordinary solvents to make this analysis feasible. It was soluble in morpholine, as was erysonine,[3] but it was unstable in this solvent, the solution becoming dark green in color, probably because of oxidation due to its two ortho phenolic hydroxyl groups.[2] It was strongly adsorbed and was badly decomposed after elution. However, it is not so essential to confirm the purity of erysopine or isolate it by this technique, since the normal solvent isolation and purification is dependable because of the low solubility of this alkaloid.

"Erysocine" was described[2] as an alkaloid of apparently constant melting point, specific rotation and elementary analyses as isolated from four species of *Erythrina*, and from six other species of *Erythrina* listed in Table II. Gentile and Labriola recently isolated[6] "erysocine," besides erysodine and erysopine, from *E. falcata* Benth. in Argentina. A standard sample of "erysocine" was found to be separated into approximately equal parts of erysodine and erysovine by analysis over alumina. Since these two substances have identical empirical formulas, $C_{18}H_{21}NO_3$, elementary analyses were not significant. "Erysocine," from *E. sandwicensis* Deg.,[2] *E. flabelliformis* Kearney,[2] and *E. costaricensis* Micheli,[3] and from the six species in Table II of this paper, was separated into the two components. Only erysovine was obtained from the "erysocine" of *E. Poeppigiana* (Walp.) O. F. Cook[2] because of the paucity of the sample. Thus, sufficient samples of "erysocine" have been resolved into erysodine and erysovine to show that it is not a single alkaloidal entity.

"Erysocine" might be a molecular complex of erysodine and erysovine obtainable from ether or ethanol, the solvents used for crystallization. Erysodine and erysovine have similar solubilities in ether and it would be expected that their separation in this solvent would be difficult. Conclusive proof as to whether "erysocine" is just a mixture of erysodine and erysovine, mixed crystals or a complex of the two, remains to be settled.[7] Alkaloidal complexes are not unknown; for example, the ergot alkaloidal product, erygoclavine, was shown[8] to be an equimolecular mixture of ergosine and ergosinine. Stoll[9] found sensibamine to be a similar complex of ergotamine and ergotaminine.

Because of the curare-like action of so many species of *Erythrina*,[10] it was of interest to charac-

(1) Presented in part before the Division of Organic Chemistry at the Meeting of the American Chemical Society in Atlantic City, N. J., September 10, 1941.

(2) Folkers and Koniuszy, THIS JOURNAL, **62**, 1677 (1940).

(3) Folkers, Shavel and Koniuszy, *ibid.*, **63**, 1544 (1941).

(4) Folkers and Koniuszy, *ibid.*, **61**, 1232 (1939); **62**, 436 (1940)

(5) Zechmeister and Cholnoky, "Principles and Practice of Chromatography," John Wiley and Sons, New York, N. Y., 1941, p. 233. Strain, "Chromatographic Adsorption Analyses," Interscience Publishers, Inc., New York, N. Y., 1942, p. 101; see also Ruzicka, Dalma and Scott, *Helv. Chim. Acta*, **24**, 63 (1941).

(6) Gentile and Labriola, *J. Org. Chem.*, **7**, 136 (1942).

(7) Preliminary determination of an equilibrium diagram, based on melting points in a capillary, indicated such a complex. Molecular weight determination of "erysocine" by the freezing point depression of dioxane showed negligible association in this solvent. Determination of freezing points of molten erysovine and "erysocine" for plotting cooling curves was not satisfactory because of the decomposition of the molten alkaloids.

(8) Smith and Timmis, *J. Chem. Soc.*, 396 (1937); Köfler, *Arch. Pharm.*, [276] **40**, 61 (1938).

(9) Stoll and Schweiz, *Med. Woch.*, **65**, 1077 (1935); Köfler *Arch. Pharm.*, **275**, 455 (1937).

(10) Folkers and Unna, *J. Am. Pharm. Assoc.*, **28**, 1019 (1939).

terize the liberated alkaloidal fraction of certain other species of the genus for possible isolation of new physiologically active alkaloids. The data on seven such species are in the Experimental Part and the alkaloids isolated are indicated in Table I by positive signs. Widespread occurrence of the liberated alkaloids, erysodine, erysovine and erysopine, is observed[2,3] and is in contrast to the more limited range of occurrence of the free *Erythrina* alkaloids such as erythraline or erythramine.

TABLE I

ISOLATION OF ALKALOIDS

Plant	Alkaloids Erysodine	Erysovine	Erysopine
E. cubensis Wright	+	+	+
E. pallida Britton & Rose	+	+	+
E. arborescens Roxb.	+	+	+
E. Folkersii Kruk.	+	+	
E. velutina Willd.	+	+	
E. excelsa Baker	+	+	+ (?)
E. Berteroana Urb.	+	+	

The ether extraction technique previously described[2] for the isolation and separation of erysovine and erysodine, which also resulted in "erysocine" for some species, has been abandoned in favor of the chromatographic technique. Actually, the isolation of pure erysovine in quantity was quite unsatisfactory, and the chromatographic method described herein has been a desirable improvement.

Experimental Part

Isolation of Alkaloids.—The data on the generalized part of the procedures have been recorded in Table II, Parts A and B. The details of the procedures were analogous to those of the isolations described in paper IX.[2] Reference to the General Remarks to the Experimental Part of Paper IX[2] and X[3] should also be made for additional information which is not repeated here. Those details which cannot be tabulated satisfactorily, concern the fractional crystallizations of the liberated alkaloids and their identification. These data are described briefly as expanded notes to Part B of Table II. For the hydrolyses, after removal of the free alkaloidal fraction, the aqueous solutions were acidified as described in note *c*. For exploratory work, successive hydrolyses have proved helpful for examination of the alkaloids because of the different rates of hydrolysis of the combined alkaloids, but for subsequent preparative work, single prolonged hydrolyses have been used. The numbers of the specimens were assigned by Mr. B. A. Krukoff to the botanical specimens taken from the same plants as the seeds.[11] These specimens are deposited with the New York Botanical Garden.

General Procedure for the Chromatographic Analyses.—For 100–300 mg. of alkaloid, a 15 × 1 cm. column of aluminum oxide Merck (according to Brockmann) was found to be satisfactory. For 1 g. of alkaloid, a 30 × 1.9 cm. column was used.

For chromatographing erysovine and "erysocine," chloroform was preferred as the initial solvent and developing agent. For erysodine, chloroform was preferred for the solution, but ethanol was a better developing solvent.

It was found that when ethanol, morpholine or water solutions were passed over alumina, fine particles of alumina were dispersed which were not removed from the eluate by filter paper. The solutions were cloudy and, on standing, slowly deposited a fine sediment of alumina. Consequently, such eluates were concentrated *in vacuo*, and the residue was dissolved in chloroform and passed through a 2–3 cm. column of alumina. A sufficient amount of chloroform was used to elute the alkaloids.

During development, the column was examined under ultraviolet light, and occasional fluorescent bands were marked with a crayon and followed. Erysodine exhibited a weak yellow–green fluorescence, whereas erysovine seemed to exhibit even less fluorescence. In general, these weak bands were of little help. At the top of the column, there was always a light to dark brown band of decomposition products which had a vivid green fluorescence under ultraviolet light. These top bands remained there during the development and were discarded when the alumina was taken out for elution.

When the amount of alkaloid being eluted by washing the column decreased to a small value it was desirable to elute the remaining material by other means. The method used has been to put the alumina in a glass thimble of a continuous extractor shown in Fig. 1, and extract for several hours with chloroform. This procedure consistently gave almost quantitative recovery of the residual alkaloid. When alkaloid samples were adsorbed so strongly that only very small eluated residues were obtained, the column of adsorbant was divided into several parts, each of which was eluted in the continuous extractor.[12]

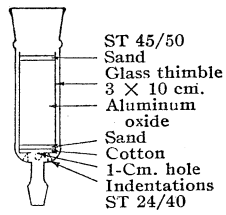


Fig. 1.[12]

Chromatographic Analysis of Erysodine.—The erysodine used was from *E. flabelliformis* Kearney (Jones 9485) and showed m. p. 200–201°, $[\alpha]^{25}D$ +251°, 75.8 mg./10 ml. ethanol, $l = 1$. The 3.66 g. was dissolved in 100 ml. of chloroform and passed into a 45 × 2.3 cm. column. There was a 5-mm. light brown top band which represented decomposition products. The tube under ultraviolet light showed a 5-mm. band of a light yellow–green fluorescence located 10 cm. from the top. The column was then developed with absolute ethanol. After collection of five fractions of the filtrate, the alumina was eluted with chloroform in the continuous extractor. The data are in Table III. Rotations were taken in ethanol at 30–60 mg./10 ml. concentration.

(11) Krukoff, *Brittonia*, **3**, 205 (1939); *Am. J. Botany*, **28**, 683 (1941).

(12) The sand at the bottom of the thimble prevented passage of the alumina, and the sand at the top prevented splattering of the adsorbent and its being washed down into the flask, causing "bumping." This extractor was used for a 30 × 1.9 cm. column of alumina.

TABLE II

DATA ON THE ISOLATION OF ALKALOIDS FROM SPECIES OF ERYTHRINA

PART A. FREE ALKALOIDAL FRACTION

Line	Plant	Collectors' names and specimen numbers	Amount seeds, g.	Fatty fraction, %	Alcohol[a] extractives, %	Free alkaloidal fraction,[b] %	Hypaphorine hydrochloride,[e] %
1	*E. cubensis* Wright	Acuna 9626	106.0	16.0	18.1	0.6	[f]
2	*E. cubensis* Wright	Acuna 9234	9.5	14.1	19.8	.7	..
3	*E. pallida* Britton & Rose	Wortley 9257	785.0	15.2	13.6	.41	..
4	*E. pallida* Britton & Rose	Wortley 9257	1030.0	11.7	14.5	.40	..
5	*E. pallida* Britton & Rose	Wortley 9257	705.0	13.0	15.3	.49	6.7
6	*E. arborescens* Roxb.	Ghose 9228	707.0	14.3	22.1	.27	[f]
7	*E. Folkersii* Kruk. & Mold.	Kinloch 9167	650.0	15.4	16.3	.07	[f]
8	*E. velutina* Willd.	Vasconcellos 9263 Sobrinho	650.0	9.2	20.0	.32	2.0
9	*E. velutina forma aurantiaca* (Ridl.) Kruk.	Rocha 9272	50.0	15.2	22.4	.25	..
10	*E. excelsa* Baker	Thomas 9342	347.0	9.6	25.6	.34[n]	2.4

PART B. LIBERATED ALKALOIDAL FRACTION

		Acid hydrolyses[c] First T.	First Y.	Second T.	Second Y.	Third T.	Third Y.	Total liberated alkaloidal fraction,[d] %	Alkaloids
1	*E. cubensis* Wright	10	0.78	75	2.05	90	0.06	2.89	[h]
4	*E. pallida* Britton & Rose	20	0.32	60	1.09	60	.50	1.96[j]	[i]
5	*E. pallida* Britton & Rose	10	1.28	60	0.95	60	.05	2.28	..
6	*E. arborescens* Roxb.	45	0.32	90	.49	120	.62	1.43	[k]
7	*E. Folkersii* Kruk. & Mold.	60	.22	120	.06			0.28	[l]
8	*E. velutina* Willd.	10	.93	20	.17	30	.20	1.30	[m]
9	*E. velutina forma aurantiaca* (Ridl.) Kruk.	15	1.2					1.2	..
10	*E. excelsa* Baker	15	1.01	60[g]	.85	60[g]	.54	2.40	[o]

[a] Methanol was used. [b] The free alkaloidal fraction was removed by the preferred procedure as described in paper IX. [c] The hydrolyses were made on aqueous solutions acidified with hydrochloric acid to about *p*H 2–2.3 except in a few cases where the solutions were acidified to *p*H 1 as indicated. T. = time in minutes, Y. = % yield of crude liberated bases after removal of the chloroform solvent. [d] The total yield of chloroform residues. [e] The hypaphorine was removed by the alternative procedure as described in paper IX. Further remarks on the isolation of hypaphorine are found in paper III. [f] Examination for hypaphorine was not made. [g] Hydrolysis was made at *p*H 1.

[h] **Erysovine, Erysodine and Erysopine from E. cubensis Wright.**—The 830 mg. of chloroform residue obtained from the first hydrolysis did not give a green color test with ferric chloride, showing the absence of erysopine. When treated with 1 ml. of ethanol, crystallization took place and 548 mg. of crystals, m. p. 154–157°, was obtained. Ether fractionation and recrystallization gave 223 mg. of "erysocine," m. p. 160–161°. A 162-mg. quantity of this fraction was dissolved in 5 ml. of chloroform and passed into a 1.5 × 1 cm. column. On developing with 40 ml. of chloroform, the first eluate gave 56 mg. of erysovine, which after crystallization from ether, showed m. p. 178–178.5°, $[\alpha]^{25}D$ +230°. Elution of the alumina in the extractor gave 108 mg. of alkaloid which gave 12 mg. of erysodine, after one recrystallization from ethanol, m. p. 200–201°, $[\alpha]^{25}D$ +248°. The second hydrolysis yielded 2.175 g. of alkaloids which gave a green color test with ferric chloride, showing the presence of erysopine. Treatment with 4 ml. of ethanol and refrigeration yielded 1.154 g. of m. p. 168–172°. When this material was heated with about 12 ml. of hot ethanol and filtered, 423 mg. of insoluble bases (A) of m. p. 197–198° was obtained. After refrigeration of the filtrate, 431 mg. of crystals (B) of m. p. 198–199° was obtained, which yielded 351 mg. of pure erysodine, m. p. 201–202°, $[\alpha]^{25}D$ +248°, after recrystallization from ethanol. When the crystals (A) were heated with about 4 ml. of hot ethanol and filtered, 51 mg. of crystals (C) of m. p. 214° was obtained. These were recrystallized twice from ethanol to yield 25 mg. of pure erysopine, m. p. 242–243°, $[\alpha]^{25}D$ +265.5° in 40% glycerol and 60% ethanol.

[i] **Erysovine and Erysodine from E. pallida Britton and Rose.**—The 3.271 g. of residue (negative green color test with ferric chloride) from the first hydrolysis was extracted with 300 ml. of boiling ether. There was 96 mg. of insoluble material of m. p. 143–146°. The ether solution yielded 2.245 g. of crystals of m. p. 146–150°. Three recrystallizations of this crop yielded 810 mg. of "erysocine," m. p. 161–162°. A 544-mg. quantity of "erysocine" was dissolved in 50 ml. of chloroform and passed into a 30 × 1.9 cm. column. On developing with 100 ml. of chloroform, the first eluate yielded 431 mg. of gum which, after two recrystallizations from ether, gave 123 mg. of pure erysovine showing m. p. 178–179°, $[\alpha]^{25}D$ +234°. The remaining erysodine adsorbed on the alumina was not sought. The 11.237 g. of residue from the second hydrolysis was combined with the 5.186 g. of residue from the third hydrolysis. Only the latter material gave a slight green color test with ferric chloride for erysopine. The com-

bined bases were extracted with 800 ml. of boiling ether. There was 3.206 g. of insoluble bases of m. p. 193–195°, and the ether extract yielded 4.476 g. of m. p. 157–159°, which corresponded to the material chromatographed before. The insoluble bases were recrystallized twice from ethanol to give 1.5916 g. of erysodine of m. p. 198–199° and $[\alpha]^{25}D$ +250°.

[j] **Erysopine from E. pallida Britton and Rose.**—A fourth hydrolysis of sixty minutes yielded 309 mg. of solid bases, which gave a positive color test with ferric chloride for erysopine. Treatment with 1 ml. of ethanol yielded 131 mg. of crystals of m. p. 186–188°. Five recrystallizations from ethanol gave 8 mg. of erysopine, m. p. 242–243°, $[\alpha]^{25}D$ +262.5°, in 40% glycerol and 60% ethanol. A fifth hydrolysis for sixty minutes at *p*H 1 yielded only 259 mg. of brown semi-crystalline residue which gave a positive color test for erysopine.

[k] **Erysovine, Erysodine, and Erysopine from E. arborescens Roxb.**—The 2.227 g. of bases from the first hydrolysis was triturated with 3 ml. of ethanol at 25° and the insoluble portion, 994 mg., m. p. 160–178°, was extracted with 50 ml. of boiling ether. The insoluble portion (A) was 311 mg., m. p. 164–190°, and the filtrate was concentrated to give a second crop (B), 413 mg., m. p. 163–164°. The portion (B) was recrystallized from ether to give 335 mg. of "erysocine," m. p. 162–163°. A quantity of 327 mg. of this fraction was then dissolved in 5 ml. of chloroform and passed into a 15 × 1 cm. column. On developing with 15 ml. of chloroform, the first eluate gave 139 mg. of erysovine, which after one recrystallization from ether showed m. p. 178–178.5°, $[\alpha]^{25}D$ +235°. The second eluate was added to the extract from the continuous elution of the adsorbent and, after distillation, it gave 184 mg. of residue which after one recrystallization from ethanol gave 35 mg. of pure erysodine, m. p. 199–200°, $[\alpha]^{25}D$ +250°. The portion (A) was triturated twice on the filter with ethanol and the insoluble portion left was 197 mg., m. p. 164–195–197°. This crop was recrystallized from ethanol to give 116 mg. of erysodine, m. p. 199–200°, $[\alpha]^{25}D$ +249°.

The second hydrolysis gave 3.429 g. of bases, which, after trituration with 5 ml. of ethanol, gave 1.367 g. of erysodine, m. p. (and mixed) 201–203°. The second crop was fairly pure erysodine, m. p. 197–200°. During the chloroform extraction after the third hydrolysis, 1.466 g. of erysopine separated from the aqueous solution and was filtered, m. p. (and mixed) 240–242°. Recrystallization from ethanol gave pure erysopine, m. p. 240–242°, $[\alpha]^{25}D$ +264°. The chloroform extraction residue amounted to 2.948 g. and yielded 1.105 g. of erysodine by crystallization.

[l] **Erysovine and Erysodine from E. Folkersii Kruk. and Mold.**—The 1.412 g. of bases from the first hydrolysis did not give a green color test with ferric chloride. It was triturated with 1 ml. of ethanol and the insoluble portion was 684 mg. (A). The filtrate was combined with the similar filtrate from the second hydrolysis, and after concentration the 811 mg. of residue was dissolved in aqueous sodium hydroxide solution and extracted six times with chloroform. The 402 mg. of solvent residue was triturated with 0.4 ml. of ethanol to give 127 mg. of insoluble material, m. p. 159–161° (B). The mother liquor on standing yielded large crystals which were fairly pure erysovine, m. p. 173.5–175°. The insoluble portion (B) was recrystallized once from ethanol and once from ether to give 23 mg. of "erysocine," m. p. 161–162°. A 15-mg. portion of this complex was dissolved in 1 ml. of chloroform and passed into a 3 × 1 cm. column to give 3 mg. of base, m. p. 160–161°. The second development gave 5 mg., m. p. 161–162° (clear at 178°) and on recrystallization from ether yielded 2 mg. of erysovine, m. p. 175–176° (clear, 180°, indicating presence of some erysodine). Elution of the alumina gave 5 mg. of base, m. p. 170–174° (clear at 190°). On recrystallization from ethanol, it yielded 2 mg. of erysodine, m. p. 197–198°, $[\alpha]^{25}D$ +244°. The insoluble portion (A) was recrystallized from ethanol to give 438 mg. of pure erysodine, m. p. (and mixed) 202–203°. The second hydrolysis gave 395 mg. of bases which was triturated with 0.4 ml. of ethanol to give 103 mg. of solid of m. p. 199–201°. After two recrystallizations from ethanol, pure erysodine was obtained, 10 mg., m. p. 200–201°, $[\alpha]^{25}D$ +249°.

[m] **Erysovine and Erysodine from E. velutina Willd.**—The 6.039 g. of bases from the first hydrolysis gave a negative green color test with ferric chloride. Trituration with ethanol, and subsequent recrystallization from ether of the solvent insoluble residue yielded 1.991 g. of "erysocine," m. p. 162–163°. A 1.108-g. quantity of this substance was dissolved in 25 ml. of chloroform and passed into a 30 × 1.9 cm. column. On developing with 400 ml. of chloroform, the first eluate yielded 377 mg. of gum which on recrystallization from ether gave 277 mg. of pure erysovine, m. p. 178–178.5°, $[\alpha]^{25}D$ +230°. Elution of the adsorbent in the extractor yielded 716 mg. of residue which after one recrystallization from ethanol gave pure erysodine, m. p. 200–201°, $[\alpha]^{25}D$ +247°.

The second hydrolysis gave 1.152 g. and the third gave 1.295 g. of bases. Neither product gave the green color test with ferric chloride. Both gave crude erysodine on trituration with ethanol, which, on combination and recrystallization, gave 564 mg. of pure erysodine, m. p. 200–201°, $[\alpha]^{25}D$ +249°.

[n] **Erysodine from the Free Alkaloidal Fraction of E. excelsa Baker.**—The 1.184 g. of the free alkaloidal fraction gave 474 mg. of crude erysodine, m. p. 196–200°, after trituration with 1 ml. of ethanol. Three recrystallizations gave pure erysodine, m. p. 201–202°, $[\alpha]^{25}D$ +245°.

[o] **Erysodine and Erysovine from E. excelsa Baker.**—The 2.033 g. of bases, m. p. 148–150°, from the first hydrolysis was extracted with 50 ml. of boiling ether. There was 460 mg. of insoluble bases (A), m. p. 174–194°, and the filtrate yielded 569 mg. of bases (B), m. p. 158–175°, after concentration. Three recrystallizations of (A) from ethanol yielded 161 mg. of pure erysodine, m. p. 201–202.5°, $[\alpha]^{25}D$ +246°. Recrystallization of (B) from ether gave 403 mg. of "erysocine," m. p. 161–162°. This was dissolved in 5 ml. of chloroform and passed into a 15 × 1 cm. column. It was developed with 25 ml. of chloroform. There was obtained 43 mg. of erysovine, m. p. 178–178.5°, $[\alpha]^{25}D$ +235°, after one recrystallization from ether of the 94 mg. of residue. Elution of the alumina in the extractor yielded 67 mg. of erysodine which showed, after one recrystallization from ethanol, m. p. 200–201°, $[\alpha]^{25}D$ +250°.

The 1.760 g. of bases from the second hydrolysis was triturated with 2 ml. of ethanol, and the 785 mg. of insoluble bases, m. p. 197–200°, showed the presence of erysopine by the ferric chloride color test. Two recrystal-

lizations from ethanol gave pure erysodine, m. p. 201–202°, $[\alpha]^{25}D$ +246°. The third hydrolysis gave 1.084 g. of liquid bases which was deeply fluorescent in chloroform solution.

TABLE III

DATA ON ERYSODINE

Filtrate	Vol., ml.	Residue, g.	M. p., °C.	$[\alpha]^{25}D$
1	200	None		
2	100	1.119	199–200	+247
3	100	0.290	200–201	+243
4	200	.458	197–198	+252
5	200	.323	200–201	+245
Continuous eluate	(*ca.* 6 hr.)	.906	197–198	+245

The residues were not recrystallized before taking the constants. The eluates were slightly cloudy and on standing slowly deposited a slight, fine sediment of alumina; this might account for the slight variations in the constants of the fractions. This chromatographic analysis did not yield erysodine of significantly altered constants when compared to the starting material.

Chromatographic Analysis of Erysovine.—The specific rotation of erysovine has been redetermined on larger and purer samples and found to be $[\alpha]^{25}D$ +232–234° as compared to the original value, $[\alpha]^{25}D$ +252°.[2] The erysovine used was from *E. glauca* Willd.[2] (Wortley 9242) and showed m. p. 177–178°, $[\alpha]^{25}D$ +232°, 49.0 mg./10 ml. ethanol, $l = 1$. A quantity of 1.045 g. was dissolved in 20 ml. of chloroform and passed into a 30 × 1.9 cm. column. Fresh solvent was added and 50-ml. fractions of filtrate were collected. The data are in Table IV. The specific rotations were in ethanol at 10 to 28 mg./2 ml. concentration.

TABLE IV

DATA ON ERYSOVINE

Filtrate	Residue, mg.	M. p., °C.	$[\alpha]^{25}D$
1	None		
2	None		
3	83	177–178	+235
4	192	178–179	+232
5	142	178–179	
6	77	178–179	
7	55	176–177	
8	67	175–176	
Continuous eluate	423	178–179	+233

None of the fractions showed significantly different constants.

Chromatographic Resolution of "Erysocine" into Erysodine and Erysovine.—When a chloroform solution of erysocine was passed into a column of alumina and developed with chloroform, the first eluate was found to contain pure erysovine. An intermediate eluate containing erysovine and erysodine followed, after which the erysodine was slowly eluted. To effect almost quantitative removal of erysodine, the alumina was extracted continuously with chloroform. After removal of the solvent recrystallization of the residue from ethanol gave pure erysodine.

When a solution of erysovine in chloroform was quickly concentrated to dryness *in vacuo* at 50–60°, the residue was an amorphous fluff which was easily soluble in ether. The addition of a little ether followed by warming, quickly dissolved the fluff, and pure erysovine started to crystallize after a minute or two. This procedure was found to be the most efficient for giving pure erysovine with the minimum amount of recrystallizations.

The details on the obtaining of erysodine and erysovine from "erysocine" are described in the footnotes to Table II.

Preparative Isolation of Erysovine by Chromatographic Technique.—The crude alkaloids obtained from the first hydrolysis of an extract from *E. Berteroana* Urb. (Armstrong 9304) on several recrystallizations from ethanol yielded "erysocine," m. p. 159–161°, indicating the presence of erysovine and erysodine. Mr. Frank Koniuszy found that another similar extract yielded on hydrolysis two crops of alkaloidal mixtures. The first crop of 43 g., m. p. 169–172°, was dissolved in 150 ml. of chloroform and passed through a 92 × 4 cm. column, and was developed with chloroform. The data are in Table V. The weight of crystals represents the yield obtained after the gum remaining, after distillation of the chloroform eluant, was recrystallized from ether. The second crop of 24 g., m. p. 177–178°, was treated similarly and pure erysovine obtained.

TABLE V

ISOLATION OF ERYSOVINE

Filtrate	Volume, ml.	Crystals, g.	M. p., °C.	$[\alpha]^{25}D$
1	500	14	178	+236.9
2	1000	12	178	+236.7
3	2000	4.5	178	

Acknowledgment.—We wish to express our gratitude to Mr. B. A. Krukoff of the New York Botanical Garden for obtaining the plant materials and for his coöperation on botanical matters. We are indebted to the many people who aided in the collection of plant material. The technical assistance of Messrs. Michael Kasha and W. B. Wright was very valuable.

Summary

Chromatographic analyses of standard samples did not significantly alter the constants of erysodine and erysovine. All samples of "erysocine" were chromatographically resolved into approximately equal parts of erysodine and erysovine. The chromatographic technique is more satisfactory for the isolation and separation of pure erysovine from erysodine than the previously used ether extraction process.

Erysodine and erysovine have been isolated for the first time from *E. cubensis* Wright, *E. pallida* Britton and Rose, *E. arborescens* Roxb., *E. Folkersii* Kruk. and Mold., *E. velutina* Willd. and *E. excelsa* Baker. Erysopine was isolated anew from the first three mentioned species, and erysodine was isolated from *E. Berteroana* Urb. These three eryso- alkaloids have a very wide distribution in the seeds of species of the genus *Erythrina*.

RAHWAY, NEW JERSEY RECEIVED MARCH 23, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Utilization of Alkoxy Ketones in the Synthesis of Quinolines by the Pfitzinger Reaction. II[1]

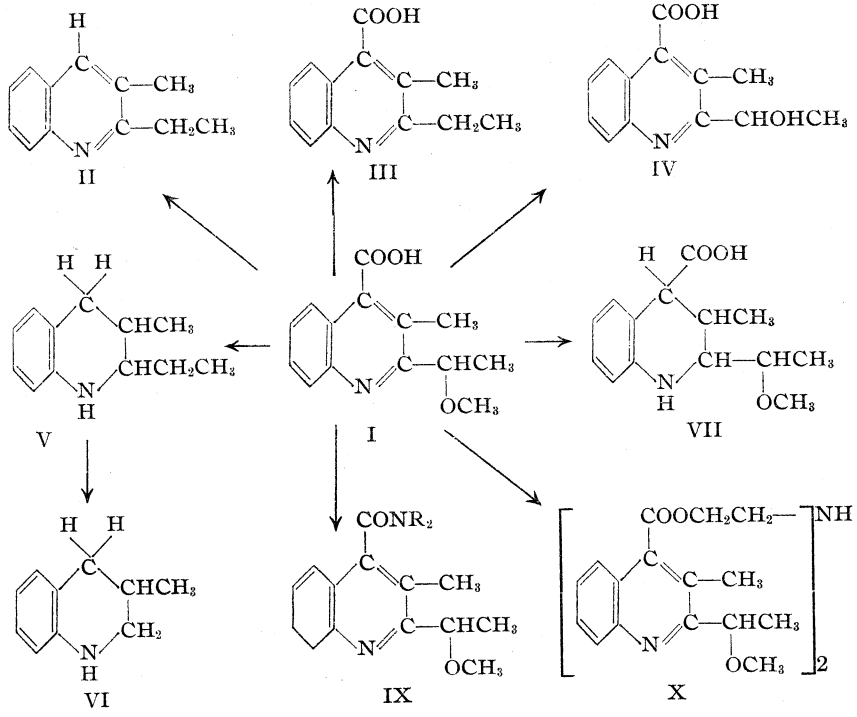
BY SHERMAN D. LESESNE[2,3] WITH HENRY R. HENZE

It has been shown recently in this Laboratory that keto ethers[4] can be employed in the synthesis of quinoline derivatives by the Pfitzinger reaction. Thus,[4b] ethoxyacetone and ethoxymethyl ethyl ketone, respectively, were condensed with isatin to produce the corresponding 2-methyl- (or 2-ethyl)-3-ethoxycinchoninic acid. A survey of the literature revealed no record of the preparation of any 2-alkoxyalkylcinchoninic acids.

In the present investigation the Pfitzinger reaction has been extended to include the utilization of alkoxy ketones in the synthesis of 2-alkoxyalkyl and 2-alkoxyalkyl-3-alkylcinchoninic acids. For example, isatin and 1-methoxydiethyl ketone were condensed in potassium hydroxide solution to form 2-(1-methoxyethyl)-3-methylcinchoninic acid (I). Proof of the structure of I was obtained by conversion into 2-ethyl-3-methylquinoline (II)[5] by heating at the melting point of the acid. The decarboxylation which occurred thus was anticipated but the cleavage of the ether linkage and reduction of the carbinol to alkyl was unexpected. Cleavage and reduction without decarboxylation of I to form III was accomplished by heating with hydriodic acid and red phosphorus for six hours. In contrast, when I was heated with concentrated hydrochloric acid only the ether grouping underwent fission and 2-(1-hydroxyethyl)-3-methylcinchoninic acid (IV) resulted. However, by heating for seven days with hydriodic acid and red phosphorus, I was converted into 2-ethyl-1,2,3,4-tetrahydro-3-methylquinoline (V). In turn, V, by action of hydrochloric acid and tin, yielded 1,2,3,4-tetrahydro-3-methylquinoline (VI).[6] Reduction without cleavage was effected by catalytic hydrogenation of I in the preparation of 2-(1-methoxyethyl)-1,2,3,4-tetrahydro-3-methylcinchoninic acid (VII).

By treatment of I with thionyl chloride and subsequent interaction with appropriate secondary amines, three substituted amides (IX) were produced; diethanolamine reacted with the acid chloride of I to form the dicarbethoxyamine (X) rather than an hydroxyethyl amide. 2-(1-Methoxyethyl)-cinchoninic acid (XV) reacted in an analogous manner with the same amines.

In view of the fact that some 2-substituted-cinchoninic acid derivatives are useful as antimalarials,[7] it was thought desirable to include, in this study, the synthesis of bis-2-cinchoninic acid (XI) and 2-phenyl-3-ethylcinchoninic acid (XIII).



(1) Presented before the Division of Organic Chemistry of the American Chemical Society at Memphis, Tenn., April 19–24, 1942.

(2) From the Ph.D. dissertation of S. D. Lesesne, June, 1939.

(3) Present address, Oklahoma City University, Oklahoma City, Okla.

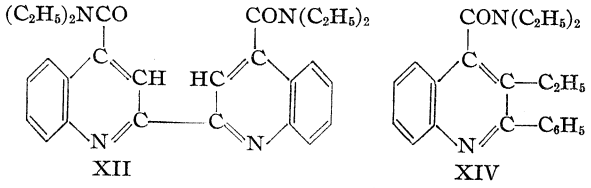
(4) (a) Calaway with Henze, THIS JOURNAL, **61**, 1355 (1939); (b) Cross with Henze, *ibid.*, 2730.

(5) Doebner and v. Miller, *Ber.*, **17**, 1714 (1884).

(6) Braun, Gmelin and Schultheiss, *ibid.*, **56**, 1343 (1923).

(7) von Oettingen, "Therapeutic Agents of the Quinoline Group," Reinhold Publishing Corporation, New York, N. Y., 1935.

Finally, XI and XIII were converted into the corresponding diethylamides, XII and XIV, respectively.



XII XIV

Through the courtesy of Parke, Davis and Company, preliminary pharmacological testing of ten of the new derivatives of cinchoninic acid has been made. The study was made by daily oral treatment for three days of canaries infested with *Plasmodium cathemerium* and led to negative results as far as the antimalarial activity of I, III, XI, XIII, XIV and XVI are concerned. Likewise, against avian malaria compounds XIII and the diethylamides of I and III are inactive. Finally, the diethylamide of bis-2-cinchoninic acid (XII) was found to have no action orally on *Streptococcus viridans* in mice.

Experimental

2-(1-Methoxyethyl)-3-methylcinchoninic Acid (I).—Sixty grams (0.41 mole) of isatin was dissolved in 300 g. of 33% potassium hydroxide solution; 42 g. (0.42 mole) of 1-methoxydiethyl ketone[8] was added and the mixture was heated under a reflux condenser on a steam cone for twenty-four hours. The reaction mixture was diluted with water to a volume of 750 cc., partially decolorized with Norite and filtered while hot. The filtrate was cooled and acidified by addition of 250 cc. of 50% acetic acid solution. After standing in an ice-bath a light cream-colored solid separated. The acid was recrystallized from water in colorless needles melting at 234° (cor.) with decomposition; yield 74 g. (74%). This cinchoninic acid is soluble in alcohol, moderately soluble in acetone, and insoluble in ether and benzene. It readily formed a picrate which melts at 201° (cor.).

Anal. Calcd. for $C_{14}H_{15}NO_3$: neut. equiv., 245.3; C, 68.55; H, 6.16; N, 5.71. Found: neut. equiv., 244.0; C, 68.92; H, 6.17; N, 5.77.

Effect of Heating I.—Fifteen grams of I was heated in a distilling flask in an oil-bath at 250°; the solid first melted, then carbon dioxide was evolved. At the end of twenty minutes gas evolution had ceased and the residual, black liquid was distilled under diminished pressure. There was obtained about 1.5 g. (14% yield) of a clear yellow oil (II) which readily yielded a bright yellow picrate. The latter, after recrystallization from diluted alcohol, melted at 191° (cor.)[9].

Anal. Calcd. for picrate, $C_{18}H_{16}N_4O_7$: C, 54.00; H, 4.03; N, 14.00. Found: C, 53.98; H, 4.03; N, 13.48.

Action of Hydrochloric Acid on I.—Five grams of I was heated with 10 cc. of concentrated hydrochloric acid for forty-eight hours at 100°. Upon neutralization with sodium hydroxide a light cream-colored precipitate formed, which was purified through resolution in alkaline solution and reprecipitation with acetic acid. Thus was obtained 2.7 g. (55% yield) of the mono-hydrate of **2-(1-hydroxyethyl)-3-methylcinchoninic acid** (IV) melting at 265° (cor.). The picrate of this compound has a melting point (explosive!) above 310°.

Anal. Calcd. for $C_{13}H_{13}NO_3 \cdot H_2O$: C, 62.61; H, 6.06; N, 5.62. Found: C, 62.76; H, 5.94; N, 5.50.

Action of Hydriodic Acid on I.—(A) Twelve grams of I, 50 cc. of hydriodic acid (57% strength), and 5 g. of red phosphorus were heated together under a reflux condenser for six hours at 150°. The mixture was made basic with sodium hydroxide and filtered to remove phosphorus. The filtrate was acidified with acetic acid causing precipitation of a white solid, which was filtered, washed with cold water, and after drying weighed 8 g. (78% yield). **2-Ethyl-3-methylcinchoninic acid** (III) melts at 279° (cor.) and is soluble in alcohol, moderately soluble in acetone, and insoluble in ether and benzene. It readily forms a picrate melting at 198° (cor.).

Anal. Calcd. for $C_{13}H_{13}NO_2$: neut. equiv., 215.2; C, 72.54; H, 6.09; N, 6.51. Found: neut. equiv., 213.3; C, 72.52; H, 6.04; N, 6.66.

(B) Twenty grams of I, 100 cc. of hydriodic acid (57% strength), and 5 g. of red phosphorus were heated together for *seven days* at 140–150°. The reaction mixture was made alkaline and subjected to steam distillation. The colorless oil in the distillate was extracted with ether, dried over sodium sulfate and fractionated. Ten grams (70% yield) of **2-ethyl-1,2,3,4-tetrahydro-3-methylquinoline** (V) was obtained; b. p. 253° (716 mm.); $n^{20}D$ 1.5902; d^{20}_4 1.0423; *MR* calcd. 56.51; *MR* found 56.78; picrate (from alcohol) m. p. 188° (cor.).

Anal. Calcd. for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.10; H, 9.45; N, 8.03.

Action of Tin and Hydrochloric Acid on V.—Seven grams of V, 40 g. of granulated tin, and 150 cc. of concentrated hydrochloric acid were heated on a steam-bath for twelve hours. At intervals, 50-cc. portions of acid were added to maintain reaction. The reaction mixture was made alkaline and steam-distilled; the distillate was ether extracted, the extract dried and fractionated; 4 g. (68% yield) of **1,2,3,4-tetrahydro-3-methylquinoline** (VI) was collected; b. p. 117° (15 mm.);[10] $n^{20}D$ 1.5536; d^{20}_4 0.9931; *MR* calcd. 47.27; *MR* found 47.50; picrate (from ether) m. p. 159° (cor.).[11]

Catalytic Reduction of I.—Two grams of I in 30 cc. of ethanol was shaken for two hours with 0.05 g. of the Adams catalyst and hydrogen at atmospheric pressure. After filtration from the catalyst, spontaneous evaporation of the filtrate of the solvent yielded **2-(1-methoxyethyl)-1,2,3,4-tetrahydro-3-methylcinchoninic acid** (VII) melting with

(8) (a) Gauthier [*Ann. chim. phys.*, (8) **16**, 322 (1909)] reported only b. p. 133° (729 mm.); (b) Wallace [M.A. thesis, University of Texas, 1936] reported b. p. 154–155° (746 mm.); $n^{20}D$ 0.8913; semicarbazone m. p. 120.5° (cor.).

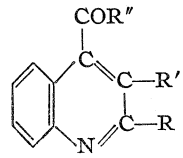
(9) Doebner and v. Miller, ref. 5, recorded m. p. 193° for the picrate of 2-ethyl-3-methylquinoline.

(10) Braun, Gmelin and Schultheiss, ref. 6, reported b. p. 117° (17 mm.).

(11) Braun, Gmelin and Schultheiss, ref. 6, reported m. p. 155°.

TABLE I

AMIDES AND ESTERS OF CERTAIN SUBSTITUTED CINCHONINIC ACIDS



R	R′	R″	Yield, %	M. p., °C. (cor.)	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Picrate m. p., °C. (cor.)
$CH(OCH_3)CH_3$	CH_3	$N(C_2H_5)_2$	55	94	71.95	72.06	8.05	8.13	9.33	9.54	179
$CH(OCH_3)CH_3$	CH_3	$N(CH_2CH_2CH(CH_3)_2)_2$	32	190	74.96	75.22	9.44	9.67	7.29	7.72	200
$CH(OCH_3)CH_3$	CH_3	$N(CH_2CH{=}CH_2)_2$	61	112	74.04	73.68	7.46	7.39	8.64	8.62	146
$CH(OCH_3)CH_3$	CH_3	$(—OCH_2CH_2)_2NH$	52	200	68.67	68.42	6.66	6.60	7.51	7.54	201
C_2H_5	CH_3	$N(C_2H_5)_2$	22	100	75.52	75.68	8.20	8.23	10.36	10.52	174
C_2H_5	CH_3	$N(CH_2CH_2CH(CH_3)_2)_2$	12	132	77.92	78.01	9.67	9.57	7.90	7.83	
C_2H_5	CH_3	$N(CH_2CH=CH_2)_2$	36	liq.	77.52	77.15	7.53	7.70	9.52	9.53	159
C_2H_5	CH_3	$(—OCH_2CH_2)_2NH$	26	295	72.12	71.86	6.66	6.71	8.41	8.49	209
C_6H_5	C_2H_5	$N(C_2H_5)_2$	50	244	79.48	79.53	7.28	7.32	8.43	8.45	179
Diethylamide of bis-2-cinchoninic acid			34	257	73.98	74.04	6.65	6.68	12.33	11.46	

decomposition at 232° (cor.). This acid is soluble in alcohol and acetone, but only moderately so in ether and water. The picrate (from ether) melts at 201° (cor.).

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.20; H, 7.86; N, 5.50.

Methyl Ester of I.—Five grams of I was heated with 10 cc. of dimethyl sulfate for eight hours at 100°. Upon neutralization of the reaction mixture with sodium hydroxide, a viscous liquid separated and was extracted with petroleum ether. Upon evaporation of the solvent at 0°, **methyl 2-(1-methoxyethyl)-3-methylcinchoninate** crystallized (4.5 g. or 85% yield); m. p. 57° (cor.); picrate (from alcohol) m. p. 179° (cor.).

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.85; H, 6.49; N, 5.64.

Substituted Amides of I.—In general, 0.02–0.05 mole of I was dissolved in 0.12–0.18 mole of purified thionyl chloride, the mixture was allowed to stand at 0° for thirty minutes, then poured into a mixture of 0.025–0.07 mole of a secondary amine, 0.11–0.26 mole of potassium carbonate and 200–300 cc. of crushed ice. After reaction had ceased the mixture was placed in a separator with 200–300 cc. of ethyl ether and allowed to stand for six hours. The ether layer was removed and dried over sodium sulfate before being concentrated to a small volume by impact of a jet of dry air at 0°. Then 100–200 cc. of petroleum ether was added and evaporation continued until the amide crystallized. Amides were thus prepared from interaction of diethylamine, diisoamylamine and diallylamine, respectively. The compounds are moderately soluble in alcohol and acetone, but insoluble in benzene and water. The melting point of each of these amides, as well as that of the corresponding picrate, is listed in Table I.

In the same manner were prepared three analogous amides from 2-ethyl-3-methylcinchoninic acid (III) and the diethyl amide from bis-2-cinchoninic acid (XI) and 2-phenyl-3-ethylcinchoninic acid (XIII), respectively. Likewise, interaction of diethanolamine and the acid chloride of I and III, respectively, yielded the corresponding dicarbethoxyamines. The melting point data for these amides and ester amines are also included in Table I.

2-(1-Methoxyethyl)-cinchoninic Acid (XV).—This acid was prepared in a manner wholly similar to that of its 3-methyl homolog by interaction of 47 g. of isatin, 34 g. of 1-methoxyethyl methyl ketone,[12] and 200 g. of 33% potassium hydroxide solution. Forty-four grams (60% yield) of the acid was obtained; m. p. 186° (cor.) dec.; a picrate was not produced.

Anal. Calcd. for $C_{13}H_{13}NO_3$: neut. equiv., 231.2; C, 67.52; H, 5.67; N, 6.06. Found: neut. equiv., 229.1; C, 67.35; H, 5.70; N, 6.24.

Twelve grams of XV, 5 g. of red phosphorus and 50 cc. of hydriodic acid (sp. gr. 1.7) were heated at 150° for six hours. Using the procedure for preparation of III, there was obtained 8.2 g. (80% yield) of **2-ethylcinchoninic acid** (XVI) melting at 180° (cor.); a picrate of XII was not obtained.

Anal. Calcd. for $C_{12}H_{11}NO_2$: neut. equiv., 201.2; C, 71.61; H, 5.51; N, 6.96. Found: neut. equiv., 201.2; C, 71.68; H, 5.43; N, 7.13.

When 17 g. of XV was heated at 200° the solid first melted, then decomposed with evolution of carbon dioxide. After twenty minutes the residual black oil was fractionated yielding but 1.5 g. (13% yield) of liquid. The latter was converted into a picrate which melted at 148° (cor.). This temperature compares well with that of the anticipated product of decarboxylation, namely, **2-ethylquinoline.**[13]

Anal. Calcd. for picrate, $C_{17}H_{14}N_4O_7$: C, 52.85; H, 3.65; N, 14.50. Found: C, 52.30; H, 3.62; N, 14.02.

Bis-2-cinchoninic Acid (XI).—A mixture of 40 g. (0.27 mole) of isatin, 12.5 g. (0.14 mole) of acetoin, and 200 g. of 33% potassium hydroxide solution was heated for twenty-four hours at 100°. On cooling the sodium salt of the acid separated and was filtered, redissolved in hot water and acidified with acetic acid. When dry the crude material weighed 28 g. (58% yield) and was purified by dissolution in sodium hydroxide solution and reprecipitation with

(12) Gauthier, ref. 8a, reported only b. p. 114° (727 mm.); Wallace, ref. 8b, reported b. p. 115–116° (739 mm.); $n^{20}D$ 1.3936; d^{20}_4 0.9014; semicarbazone m. p. 141°.

(13) Reher [*Ber.*, **19**, 2997 (1886)] recorded m. p. 147° (cor.).

acetic acid; m. p. 367° (cor.). This acid is insoluble in water and in the common organic solvents; attempts to form a picrate failed.

Anal. Calcd. for $C_{20}H_{12}N_2O_4$: neut. equiv., 172.16; C, 69.76; H, 3.51; N, 8.14. Found: neut. equiv., 174.4; C, 69.64; H, 3.61; N, 8.14.

2-Phenyl-3-ethylcinchoninic Acid (XIII).[14]—In a similar manner, from 40 g. (0.27 mole) of isatin, 43 g. (0.27 mole) of phenyl *n*-propyl ketone, and 200 g. of 33% potassium hydroxide solution, was obtained 40 g. (55% yield) of crude acid. After recrystallization from acetone this compound melts at 286° (cor.); the picrate melts at 147° (cor.).

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.41; H, 5.59; N, 5.04.

(14) Listed by von Oettingen, ref. 7, page 92.

Summary

1. The Pfitzinger reaction has been extended to include the production of two cinchoninic acid derivatives containing an alkoxyalkyl substituent at the 2-position through utilization of alkoxyalkyl ketones of type $CH_3OCH(CH_3)COR$.

2. These acids suffer cleavage of their ether linkage by action of concentrated hydriodic acid and red phosphorus, yet resist reduction.

3. The acids are decarboxylated by heating above their melting points, and, by action of tin with hydrochloric acid, undergo reduction of the pyridine nucleus and dealkylation of the ether group.

4. Bis-2-cinchoninic acid and 2-phenyl-3-ethylcinchoninic acid have been prepared and converted into their diethylamides.

5. Several substituted amides of these cinchoninic acids have been prepared and shown elsewhere not to possess antimalarial activity.

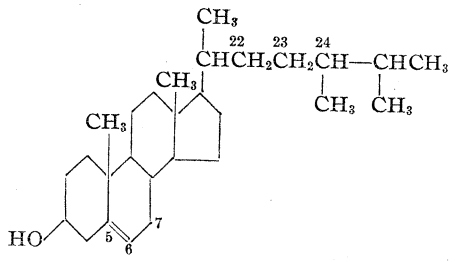
AUSTIN, TEXAS RECEIVED MAY 18, 1942

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH, DIVISION OF ORGANIC CHEMISTRY]

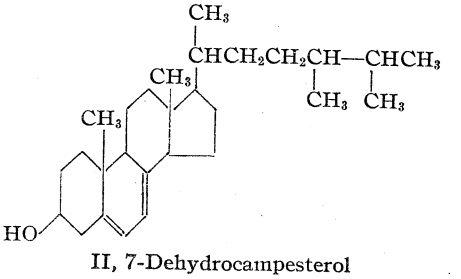
7-Dehydrocampesterol, a New Provitamin D

BY WILLIAM L. RUIGH

The relationship between the structure of the side chain of the D vitamins and their antirachitic activity has been the subject of a number of investigations. The isolation[1] of a new phytosterol, campesterol (I), and the determination of its structure[2] as the C-24 epimer of Δ^5-ergostenol, suggested a new approach to the problem.



I, Campesterol



II, 7-Dehydrocampesterol

(1) Fernholz and MacPhillamy, THIS JOURNAL, **63**, 1155 (1941).
(2) Fernholz and Ruigh, *ibid.*, **63**, 1157 (1941).

Campesteryl acetate was converted by the conventional method[3] via the 7-keto compound into 7(α)-benzoxycampesteryl benzoate. The usual method of preparing 7-dehydrosterols was modified at this point by selectively hydrolyzing the dibenzoate to the 7-monobenzoate and cleaving the latter into benzoic acid and free 7-dehydrocampesterol[4] II. Irradiation of this compound with ultraviolet light gave a resin, the antirachitic activity of which determined by the line test on rats was 725,000 international units per gram. The product obtained from ergosterol under identical conditions assayed at 7,000,000 I. U. per gram corresponding to a yield of 17.5% vitamin D_2 (40,000,000 I. U. per gram). Assuming the same extent of conversion in both cases the potency of the vitamin from 7-dehydrocampesterol is estimated to be 4,100,000 I. U. per gram, which is thus only 10% of the potency of vitamin D_2. Due to lack of sufficient material no attempt was made to isolate the new vitamin in crystalline form.

Vitamin D_4, prepared from 22,23-dihydroergosterol by Windaus and Trautmann,[5] was reported to have from 20,000,000 to 30,000,000

(3) Windaus, Lettré and Schenck, *Ann.*, **520**, 98 (1935).
(4) Wintersteiner and Ruigh, THIS JOURNAL, **64**, 1177 (1942).
(5) Windaus and Trautmann, *Z. physiol. Chem.*, **247**, 185 (1937).

international units per gram. On the basis of the comparative data available, the antirachitic substance from 7-dehydrocampesterol has only one-sixth the activity of vitamin D_4. The two vitamins are stereoisomers differing only in the configuration of carbon atom twenty-four in the side-chain. It is thus apparent that the difference in antirachitic activity due to stereoisomerism on C-24 is considerably greater than the comparatively slight difference (25–50%) caused by the presence or absence of the side chain double bond in vitamins D_2 and D_4, respectively.

The demonstration that 7-dehydrocampesterol can function as a provitamin is also of interest in connection with the claim advanced by Wunderlich[6] and later by Bills[7] that 7-dehydrositosterol can be activated by ultraviolet light. The starting material employed by Wunderlich for the preparation of the 7-dehydrositosterol was the sterol fraction from soy-bean which remained after the removal of the stigmasterol as the tetrabromide. From a similar fraction 3% of pure campesterol was later isolated in this Laboratory[1] and has served as the starting material for the present work. It seems reasonable to assume that Wunderlich's sitosterol contained 3% or more campesterol and possibly other as yet unisolated C-28 sterols such as 22,23-dihydrobrassicasterol.[8] It is, therefore, probable that a part of the antirachitic activity possessed by Wunderlich's product from sitosterol was due to the presence of vitamin derived from campesterol. In view of the fact that irradiated 7-dehydrostigmasterol is practically devoid of vitamin D activity,[9,10,11] the possibility will now have to be considered that the same may be true of pure 7-dehydrositosterol and of C-29 sterols in general. It is clear that this question cannot be unequivocally answered until Wunderlich's work has been repeated with a sitosterol entirely free from C-28 sterols.

The author wishes to thank Dr. O. Wintersteiner for his interest and encouragement during the course of this work, Dr. A. Black of the Squibb Vitamin Research Laboratory for the biological assays and the benefit of his experience on the irradiation of 7-dehydrosterols, Dr. N. H. Coy of the same laboratory for absorption spectra and assays and Mr. Karl Reinhardt for his efficient technical assistance. All microanalyses were performed by Mr. J. F. Alicino, Fordham University.

(6) Wunderlich, *J. physiol. Chem.*, **241**, 116 (1936).
(7) Bills, *J. Am. Med. Assoc.*, **108**, 13 (1937).
(8) Fernholz and Ruigh, THIS JOURNAL, **62**, 3346 (1940).
(9) Linsert, *Z. physiol. Chem.*, **241**, 125 (1936).
(10) Grab, *ibid.*, **243**, 63 (1936).
(11) Haslewood, *Biochem. J.*, **33**, 454 (1939).

Experimental

7-Ketocampesteryl Acetate.—Forty grams of campesterol, m. p. 156.5–158°, isolated from soy-bean oil[1] was converted to the acetate, m. p. 137–138°. The acetate was oxidized with chromic acid in glacial acetic acid following the method of Windaus, Lettré and Schenck[3] for the preparation of 7-ketocholesterol acetate. Fourteen grams of crude product, m. p. 168–80°, was obtained which on repeated recrystallization from alcohol yielded 7.4 g. of pure 7-ketocampesteryl acetate, needles, m. p. 177–178°; $[\alpha]^{24}D$ −88.6° (1.18% in chloroform).

Anal. Calcd. for $C_{30}H_{48}O_3$: C, 78.90; H, 10.59. Found: C, 78.72, 78.80; H, 10.47, 10.60.

7(α)-Benzoxycampesteryl Benzoate.—The reduction with aluminum isopropylate and isopropyl alcohol of 7 g. of 7-ketocampesteryl acetate yielded 4.7 g. of crude hexane-precipitable diol. Benzoylation in pyridine gave 3.8 g. of crude dibenzoate, m. p. 171–172°, from which was obtained pure benzoxycampesteryl benzoate by repeated recrystallization from acetone, needles, m. p. 176.5–177.5°; $[\alpha]^{23}D$ +96.6° (0.81% in chloroform).

Anal. Calcd. for $C_{42}H_{56}O_4$: C, 80.72; H, 9.03. Found: C, 80.90; H, 9.38.

7(α)-Benzoxycampesterol.—To 2 g. of the dibenzoate dissolved in 40 cc. of benzene a solution of 1.33 g. of sodium methylate in 66 cc. of dry methanol was added. The mixture was allowed to stand at room temperature for sixteen hours and worked up as described before[4] for the corresponding cholesterol derivative. The chromatographed product, 1.60 g., crystallized from benzene–hexane in filamentous needles. 7(α)-Benzoxycampesterol melts at 143–145° after sintering to a glassy solid at 126–130°; $[\alpha]^{26}D$ +115.0° (1.16% in chloroform). The analytical sample on drying for two hours at 108° in a high vacuum showed a loss in weight of 2.07%.

Anal. Calcd. for $C_{35}H_{52}O_3$: C, 80.72; H, 10.07. Found: C, 80.40, 80.38; H, 9.87, 9.94.

7-Dehydrocampesteryl Benzoate.—One gram of 7(α)-benzoxycampesterol was refluxed with dimethylaniline and worked up as previously described.[4] The digitonide on decomposition by pyridine–ether yielded 564 mg. of impure 7-dehydrocampesterol; leaflets from acetone, m. p. 148–149.5°[12] $[\alpha]^{23}D$ −91.0°, ϵ_{282} = 9350, corresponding to 81% of the absorption at 282 mμ given by ergosterol. The crude dehydrocampesterol (475 mg.) was benzoylated in pyridine and after seven recrystallizations from benzene–alcohol 229 mg. of 7-dehydrocampesteryl benzoate was obtained in the form of fine needles. The compound melted at 156–157° to a cloudy liquid which cleared sharply at 164°. This degree of purity was actually attained on the fourth crystallization and three further crystallizations did not change the melting point behavior. The compound gave positive Tortelli–Jaffé and Rosenheim trichloroacetic acid reactions, $[\alpha]^{23}D$ −50.2 (1.0% in chloroform).

(12) All melting points of dehydro derivatives were taken in sealed evacuated tubes after drying for half an hour under a high vacuum at 107°.

Anal. Calcd. for $C_{35}H_{50}O_2$: C, 83.61; H, 10.03. Found: C, 83.43; H, 10.02.

7-Dehydrocampesterol.—A solution of 150 mg. of dehydrocampesteryl benzoate in 5 cc. of benzene was added to 10 cc. of 5% methanolic potassium hydroxide. After boiling for two hours, the hydrolyzed product was obtained by ether extraction and crystallized from acetone–methanol. 7-Dehydrocampesterol formed shining irregular plates, m. p. 164–165°, $[\alpha]^{25}D$ −109.0° (0.96% in chloroform). The sample for analysis was dried for two and one-half hours at 107° in a high vacuum.

Anal. Calcd. for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.81; H, 11.58.

The absorption spectrum in ether exhibited the maxima at 272 mμ and 282 mμ characteristic of 7-dehydrosterols; $\epsilon_{282\ m\mu}$ = 10,600.

Irradiation with Ultraviolet Light.—The light source used in this work was a 125-watt air-cooled quartz mercury vapor lamp. For each run 63 cc. of a 0.1% solution of the sterol in peroxide-free ether was taken, and after displacing the dissolved air with a stream of carbon dioxide, irradiation commenced with the preheated lamp. After irradiation the solution was evaporated to dryness, taken up in a few drops of alcohol and then made up to 6.3 cc. with corn oil for assay. Preliminary experiments with ergosterol showed that four minutes was the optimal time for irradiation. Under these conditions ergosterol gave a product the activity of which assayed by the U. S. P. XI line test on rats was found to be 7,000,000 international units of vitamin D per gram of original ergosterol. This corresponds to a conversion of 17.5%. 7-Dehydrocampesterol irradiated under identical conditions assayed 725,000 international units per gram of original substance.[13]

Summary

The preparation and properties of 7-dehydrocampesterol are described. 7-Dehydrocampesterol on irradiation with ultraviolet light yields an antirachitically active product. By comparison with ergosterol irradiated under the same conditions the antirachitic potency of the vitamin derived from 7-dehydrocampesterol has been estimated as 4,100,000 international units per gram.

(13) Preliminary results indicated that the vitamin from 7-dehydrocampesterol resembles vitamin D_2 rather than vitamin D_3 in that it is relatively less active when assayed by the chick test.

NEW BRUNSWICK, N. J. RECEIVED JUNE 6, 1942

[CONTRIBUTION FROM THE SHELLAC RESEARCH BUREAU OF THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

Nature and Constitution of Shellac. XVI. Preparation of 8,9,15-Trihydroxypentadecylamine from Aleuritic Acid by the Naegeli–Curtius Series of Reactions[1]

BY ARTHUR L. DAVIS[2] AND WM. HOWLETT GARDNER

Introduction

Aliphatic polyhydroxyamines have many interesting properties.[3] They should be valuable intermediates in the synthesis of several new compounds which would be useful in the paint and other fields. Such hydroxyamines might be prepared from polyhydroxy acids which have been obtained from shellac.[4,5] The hydroxyl groups of such acids, however, have a tendency to react intermolecularly when subjected to elevated temperatures of 100° or higher, such as are employed in a number of common methods for obtaining amines from carboxylic acids. This was what apparently occurred in attempts to prepare the amide when using the Hofmann procedure.[5] The Lossen method involving the formation of a substituted hydroxamic acid also gives very poor results. The Curtius method[6] likewise has proved unsatisfactory. Nagel obtained only a mixture of partially chlorinated amines when he attempted to prepare 8,9,15-trihydroxypentadecylamine from aleuritic acid by this method. His failure can be traced to the use of concentrated hydrochloric acid in hydrolyzing the relatively stable trihydroxypentadecylurethan. Other strong mineral acids lead to like difficulties.[6] Naegeli[7] had similar trouble in attempting to synthesize the amine from chaulmoogric acid. Hence he was led to prepare the isocyanate from the azide instead of the urethan. Isocyanates generally can be hydrolyzed to the amines in the presence of aqueous solutions of alkali without affecting the hydroxyl groups. These series of reactions can be expressed as follows wherein the group $C_{15}H_{31}O_3$ may be rep-

(1) This communication is part of a thesis for the degree of Master of Science in Chemistry presented by Arthur L. Davis to the Graduate Faculty of Polytechnic Institute of Brooklyn, June, 1941.

(2) Shellac Research Fellow, 1939–1942.

(3) (a) B. M. Vanderbilt and H. B. Hass, *Ind. Eng. Chem.*, **32**, 35–36 (1940); (b) M. M. Sprung, THIS JOURNAL, **61**, 3381 (1939).

(4) (a) B. B. Schaeffer and W. H. Gardner, *Ind. Eng. Chem.*, **30**, 333 (1938); (b) H. Weinberger and W. H. Gardner, *ibid.*, **30**, 454 (1938); (c) P. M. Kirk, P. Spoerri and W. H. Gardner, THIS JOURNAL, **63**, 1243 (1941).

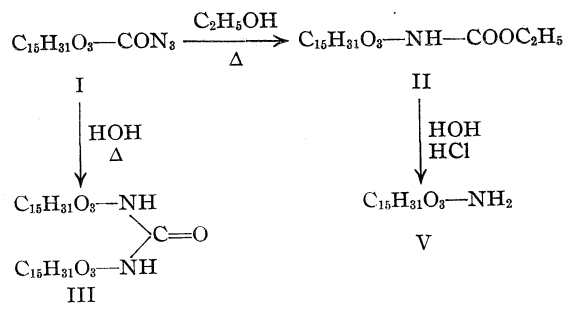
(5) A. L. Davis, Master's Dissertation, Polytechnic Inst. of Brooklyn, Brooklyn, N. Y., June, 1941.

(6) Th. Curtius, *Ber.*, **27**, 779 (1894).

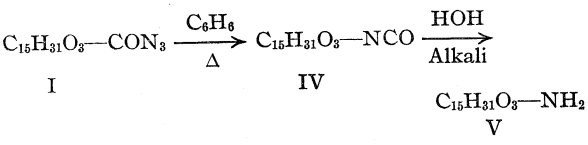
(7) C. Naegeli, L. Grüntuch and P. Lendorff, *Helv. Chim. Acta*, **12**, 227 (1929).

resented as, $CH_2OH—(CH_2)_5—CHOH—CHOH—(CH_2)_7—$.

CURTIUS SERIES OF REACTIONS



NAEGELI MODIFICATION



This article describes how 8,9,15-trihydroxypentadecylamine was prepared from aleuritic acid by such a method. Kirk has already suggested how such a procedure might be employed in the study of shellac acids of unknown structure, such as shellolic acid.[4c,8] This study of shellolic acid will be described in a later communication.

In an attempt to prepare the amine corresponding to aleuritic acid (9,10,16-trihydroxypalmitic acid) with the aid of the Curtius series of degradation reactions, the acid was esterified directly with anhydrous methyl alcoholic hydrogen chloride. The product, methyl aleuritate, was converted to the acid hydrazide, by the action of hydrazine hydrate on an alcoholic solution of the ester. This conversion was practically quantitative when highly purified samples of the ester were used. Nitrosation, at temperatures approaching 0°, converted the hydrazide into aleurityl azide I, an unstable, hygroscopic solid. When I was heated in water for three hours, N,N′-bis-8,9,15-trihydroxypentadecyl urea III was formed, while when I was refluxed with anhydrous ethyl alcohol for one and one-half hours, 8,9,15-trihydroxypentadecylurethan II was the resulting product. Inasmuch as hydrolytic action failed to convert either II or III into the corresponding amine, the Naegeli modification was resorted to. When I was decomposed by heating in anhydrous benzene for one hour, the corresponding isocyanate was formed.

(8) P. M. Kirk, Doctor's dissertation, Polytechnic Institute of Brooklyn, Brooklyn, N. Y., June, 1939.

Pure 8,9,15-trihydroxypentadecyl isocyanate IV which was prepared for the first time, was a colorless, crystalline solid melting at 103.5–104.5°. It was soluble in alcohol and dioxane but practically insoluble in diethyl ether, petroleum ether and water. The isocyanate reacted with water and alcohol to produce N,N′-bis-8,9,15-trihydroxypentadecylurea III and 8,9,15-trihydroxypentadecylurethan II, respectively. These compounds were identical with those obtained previously by Nagel[9,10] from aleurityl azide except that the urethan was more highly purified.

Hydrolysis of the isocyanate IV with hot aqueous alkali produced 8,9,15-trihydroxypentadecylamine V which was obtained as minute colorless crystals melting at 146–147°. This product was soluble in aqueous solutions of mineral acids and gave the characteristic qualitative tests for primary aliphatic amines.[11] The picrate of the amine was a yellow powder melting at 118–119°.

Experimental Part

Aleuritic Acid.—A suspension of 100 g. of crude zinc salt in a liter of hot (90°) 20% sulfuric acid was stirred mechanically for thirty minutes, filtered and cooled quickly with ice cubes and the precipitated acid removed by filtration. This was dissolved in ethanol, decolorized with Norit, repeated if necessary, precipitated with water, recrystallized from hot water and dried at 41°; m. p. 101–101.5°. *Anal.* Calcd. for $C_{16}H_{32}O_5$: C, 63.15; H, 10.53. Found: C, 63.09, 63.27; H, 10.98, 10.79.

Methyl Aleuritate.—A solution of 10 g. of aleuritic acid in 80 ml. of 5% hydrogen chloride in absolute methanol, was allowed to stand for three days, then was neutralized with a solution of sodium hydroxide in absolute methanol, the precipitated sodium chloride filtered off and the filtrate poured into a large excess of cold (10°) water. The solid was filtered, washed with 10% aqueous sodium carbonate, stirred for thirty minutes, filtered, the precipitate washed with water, dried on a porous plate, and recrystallized from alcohol, yield 86.5%; m. p. 73°. *Anal.* Calcd. for $C_{17}H_{34}O_5$: C, 64.15; H, 10.69. Found: C, 63.99, 64.07; H, 10.81, 10.90.

Aleurityl Hydrazide.—A solution of 10 g. of highly purified methyl aleuritate in 100 ml. of 30% hydrazine hydrate in methanol was refluxed for forty minutes on a water-bath and then filtered through fluted paper, while still hot, to remove any insoluble impurities. The solution, in cooling, deposited crystals of the hydrazide, which were removed by means of a Büchner funnel with the aid of partial vacuum. The filtrate was then concentrated under reduced pressure so as to yield more crude aleurityl hydrazide, which was recrystallized thrice from hot (90°) water, yield 98%; m. p. 139–139.5°. *Anal.* Calcd. for

(9) W. Nagel, *Ber.*, **60**, 605 (1927).

(10) W. Nagel, *Wiss. Veroffentl. Siemens-Konzern*, **10**, 108 (1931).

(11) O. Kamm, "Qualitative Organic Analysis," John Wiley and Sons, New York, N. Y., 2nd ed., 1932, p. 158.

$C_{16}H_{34}O_4N_2$: C, 60.38; H, 10.69; N, 8.81. Found: C, 60.16, 60.40; H, 10.95, 10.61; N, 8.81, 8.88.

Aleurityl Azide.—A solution of 3 g. of pure aleurityl hydrazide in 600 ml. of hot (90°) water was carefully and slowly cooled to below 5° to produce supercooling. Despite the low solubility of the hydrazide in water, no precipitate formed under these conditions.

51 ml. of an aqueous solution (2%) of sodium nitrite at 0° was cautiously added with gentle stirring, before acidification of the system with 12 ml. of an iced (0°) 25% solution of acetic acid. On stirring, the white flocculent azide separated spontaneously.

The azide was filtered with the aid of gentle suction, washed with water and, finally, dried in an evacuated vacuum desiccator containing solid sodium hydroxide which was maintained at 10°, by placing in a refrigerator, yield 90%; decomp. 52°. The azide was soluble in chloroform and ethyl alcohol, partially soluble in ether and benzene, and completely insoluble in water and petroleum ether. It reacted rapidly with hot water (60°) evolving nitrogen, while a similar decomposition occurred when it was heated on a porcelain spatula. It did not explode when struck sharply with a hammer, on an iron plate.

8,9,15-Trihydroxypentadecyl Isocyanate.—A suspension of 3 g. of the azide in 150 ml. of anhydrous benzene was heated slowly under a reflux condenser for one hour. When decomposition of the azide had been completed and a clear solution remained, the insolubles were removed by filtration and the solution allowed to come to room temperature in a desiccator. Sufficient anhydrous petroleum ether (b. p. 28–38°) was added to the cold filtrate to precipitate the isocyanate completely. The coagulated precipitate was filtered, washed, dried on an unglazed plate and recrystallized from anhydrous dioxane, yield 92%; m. p. 103.5–104.5°. *Anal.* Calcd. for $C_{16}H_{31}O_4N$: C, 63.78; H, 10.29; N, 4.65. Found: C, 63.65, 63.91; H, 10.37, 10.59; N, 4.30, 4.42. The pure isocyanate was soluble in alcohol and dioxane, but insoluble in ether, petroleum ether, and water.

N,N'-Bis-8,9,15-trihydroxypentadecyl Urea. Method I.—A suspension of 3 g. of pure aleurityl azide in 200 ml. of water was refluxed for three hours over a small flame. When cool, the urea was filtered from the solution, dried on an unglazed plate and recrystallized from ethyl alcohol; m. p. 122.5–123°. *Anal.* Calcd. for $C_{31}H_{64}O_7N_2$: C, 64.58; H, 11.11; N, 4.86. Found: C, 64.50, 64.38; H, 11.27, 11.19; N, 4.73, 4.79. **Method II.**—A suspension of 0.2 g. of pure 8,9,15-trihydroxypentadecylisocyanate in 100 ml. of water was refluxed, at 100° for three hours. The system was cooled, the precipitate filtered, dried on an unglazed plate and recrystallized from ethyl alcohol; m. p. 122.5–123°.

Mixtures of various proportions of this product with that obtained by Method I, showed no lowering of the melting point. It was only slightly soluble in cold ethyl alcohol, but dissolved easily at temperatures approaching the boiling point.

8,9,15-Trihydroxypentadecyurethane. Method I.—A solution of 3 g. of pure aleurityl azide in 60 ml. of absolute ethyl alcohol was refluxed for one hour on a water-bath. The resulting solution, when cold, was filtered, added to an excess of anhydrous diethyl ether and the solid filtered, dried and recrystallized thrice from hot anhydrous ethyl acetate; m. p. 78–79°. *Anal.* Calcd. for $C_{18}H_{37}O_5N$: C, 62.25; H, 10.66; N, 5.03. Found: C, 62.37, 62.39; H, 10.89, 10.79; N, 5.03, 5.06. The pure product melted sharply at 78–79°, while slightly contaminated products melted at 73–74°, as reported by Nagel.[9,10] **Method II.**—. 0.2 g. of the pure isocyanate was suspended in 100 ml. of water, and refluxed at 100° for three hours. The solution was then allowed to cool to room temperature, filtered and the crude urethan thus obtained was purified as above. Fractional crystallization from ethyl acetate yielded a product melting at 78–79°, which showed no lowering in melting point when mixed with different proportions of the urethan prepared from the azide.

8,9,15-Trihydroxypentadecyl Amine.—A suspension of one gram of the pure isocyanate in 100 ml. of a 50% aqueous sodium hydroxide solution was refluxed for four hours on a hot plate. The solution was then cooled to room temperature and filtered through a sintered glass funnel. The residue was washed free of all adhering alkali with water, dried on an unglazed plate and fractionally crystallized from hot ethyl alcohol, yield 65%; m. p. 146–147°. *Anal.* Calcd. for $C_{15}H_{33}O_3N$: C, 65.45; H, 12.00; N, 5.09. Found: C, 65.39, 65.20; H, 11.66, 11.68; N, 5.29, 5.21. The purified product was completely soluble in hydrochloric acid and ethyl alcohol, but was insoluble in ether, petroleum ether, ethyl acetate and water.

Picrate of 8,9,15-Trihydroxypentadecyl Amine.—A solution of 1 g. of the purified amine dissolved in a 10% alcoholic solution of picric acid was evaporated to dryness on a water-bath. The solid product was extracted with hot benzene until a test portion of the extract showed the absence of even traces of the acid. The picrate was then thrice crystallized from ethyl alcohol and the purified product found to melt with decomposition at 118–119°. *Anal.* Calcd. for $C_{21}H_{36}O_{10}N_4$: C, 50.00; H, 7.14; N, 11.11. Found: C, 49.74, 49.83; H, 7.32, 7.39; N, 10.98, 10.89.

Summary

1. This investigation has demonstrated that it is possible to prepare a polyhydroxyamine from a polyhydroxycarboxylic acid by means of the Naegeli–Curtius series of reactions. The method has many possibilities of use in the further study of the chemical structure of shellac acids.

2. 8,9,15-Trihydroxypentadecyl isocyanate and 8,9,15-trihydroxypentadecylamine were prepared for the first time. These compounds are colorless solids which melt at 103.5–104.5° and 146–147°, respectively.

3. The isocyanate reacts with water to produce N,N'-bis-8,9,15-trihydroxypentadecylurea, and with alcohol, 8,9,15-trihydroxypentadecylurethan. Both of these compounds were identical with those obtained by Nagel who prepared them from the azide. The pure urethan has a melting point of 78–79° instead of 73–74° as previously reported.

4. Aleurityl azide is relatively stable at room

temperature when obtained pure. It decomposes at 52° as compared with the crude product which explodes if heated rapidly to 50°. The pure azide does not readily detonate when attacked with a hammer.

BROOKLYN, NEW YORK RECEIVED MARCH 20, 1942

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY No. 873]

A Method for Standardization of Chromatographic Analysis[1]

BY ARTHUR L. LEROSEN

The chromatographic method of Tswett has been applied to many problems of the chemist with great success, making possible separations which could not be attained satisfactorily by any other means. As the use of this method increases it is desirable to obtain quantitative data for the comparison of adsorbents and the behavior of the adsorbed substances on these materials. A quantitive treatment of chromatography should be helpful in determining the best conditions for a given operation and in standardizing the properties of adsorbents.

Good books on chromatography are now available (Zechmeister,[2] Strain[3]). Theories of chromatography have been developed by Wilson[4] and by Martin and Synge,[5] and measurements of a quantitative nature have been made by Cassidy.[6,7] Brockmann and Schodder[8] have suggested a method of standardizing the adsorption affinity of certain alumina samples, using azo dye mixtures.

The investigations herein recorded were undertaken primarily with the purpose of ascertaining how far it is possible to determine the relative position of carotenoids on the adsorbent column by separate measurements of the rate of movement for each pigment.

It was first necessary to investigate the flow of the developing solvent through the adsorbent. The velocity of flow was found to vary directly with the pressure difference between the ends of the column, inversely with the length of the column and to be essentially independent of the diameter of the tube (tubes of diameter 17, 43, and 70 mm. gave almost equal rates for columns of the same length). The exact nature of each of these dependencies has not been thoroughly studied.

The change of rate of flow with time was of more importance. Table I illustrates the behavior of calcium hydroxide columns. It is evident that the flow becomes constant after an initial decrease, a uniform rate being obtained soon after the solvent has reached the bottom of the column.

Three terms will now be introduced to simplify the following discussion: S = length of adsorbent column containing one unit volume of solvent/length of tube required to contain the same volume of solvent; V_c = rate of flow of developing solvent through the column when a state of constant flow has been reached (mm./min.); R = rate of movement of adsorbate zone (mm./min.)/rate of flow of developing solvent (V_c).

The ratio S may be of importance in characterizing the packing of the column, and, moreover, it gives the percentage of the tube volume occupied by the adsorbent (% volume adsorbent = $100(S-1)/S$). There is a variation in the degree of packing throughout the column; S was found to vary

TABLE I

RATE OF BENZENE FLOW THROUGH CALCIUM HYDROXIDE COLUMNS (17 MM. IN DIAMETER AND 150 ± 5 MM. LONG).

The data given indicate flow in mm. column length/min. Time was measured from the instant the solvent was poured on the column.[a]

Column no.	Time, min. 1	5	10	15	20	25	30	35	40
1	32.0	14.5	9.0	7.1	6.4	6.3	6.3	...	...
2	43.0	15.5	9.8	7.1	7.0	7.0	7.0	...	...
3	36.0	13.5	7.8	...	7.6	7.5	7.5	7.5	...
4	42.0	15.3	...	...	7.6	7.7	7.7	7.7	7.7
5	43.0	13.8	8.8	...	8.4	8.2	8.2	8.2	8.2
6	42.0	16.0	13.0	...	...	8.1	8.1	8.1	8.1

[a] The solvent reached the bottom of the column in about twelve minutes.

(1) Presented before the Division of Analytical and Micro Chemistry of the American Chemical Society at the Memphis meeting, April, 1942.

(2) L. Zechmeister and L. Cholnoky, "Principles and Practice of Chromatography," John Wiley and Sons, Inc., New York, N. Y., 1941.

(3) H. H. Strain, "Chromatographic Adsorption Analysis," Interscience Publishers, Inc., New York, N. Y., 1941.

(4) J. N. Wilson, THIS JOURNAL, **62**, 1583 (1940).

(5) A. J. P. Martin and R. L. M. Synge, *Biochem. J.*, **35**, 1358 (1941).

(6) H. G. Cassidy and S. E. Wood, THIS JOURNAL, **63**, 2628 (1941).

(7) H. G. Cassidy, *ibid.*, **63**, 2735 (1941).

(8) H. Brockmann and H. Schodder, *Ber.*, **74**, 73 (1941).

on the average from 1.97 for the top third to 1.79 for the bottom third of the calcium hydroxide columns used. No consistent relation has been observed between S and V_c, probably due to the greater importance of local variations in the column packing.

The rate of solvent flow, V_c, varies from column to column packed with the same adsorbent under similar conditions, but the variation is within reasonable limits; for example, in 14 of 15 cases considered, V_c was between 6.3 and 8.2, while in one instance it was much higher, 10.3.

V_c itself depends on such variables as particle size, shape, surface character, solvent, etc., but it is beyond the scope of this paper to discuss these factors.

The "strength" or adsorption affinity of a material may be best determined by measuring the adsorption isotherm, but this is not always practical, as Brockmann and Schodder have pointed out. The same end can be attained with somewhat less precision by measuring R, the relative rate of movement of an adsorbate zone with respect to the developing solvent. Table II gives the values of R for certain carotenoids. Table III shows the agreement of the relative positions of carotenoid zones, calculated from R, and positions observed when a mixture was separated chromatographically.

There should be a relation between the adsorption isotherm and R. Let us consider the element of volume of any adsorbent column which contains in its interstitial spaces one unit volume of solution of uniform concentration c/unit volume. The adsorbent in equilibrium with this unit volume contains $f(c) = A$ concentration units of the solute. The use of volume here rather than length or weight has an advantage in dealing with rates, because, after the relation is obtained for an adsorbent, it is independent of tube radius. In the case of lycopene, $C_{40}H_{56}$, the relation was approximately linear over the concentration range studied for the system lycopene–benzene–calcium hydroxide; the value $A = 8c$ was found for the calcium hydroxide columns studied.

Eight units of solution would have to pass through an element of column, as defined above, before it reached saturation; therefore, the front edge of the solvent moves through nine elements, while the pigment moves through one. R should, therefore, be equal to 0.111. The value observed for lycopene, 0.125, is in reasonably good agreement.

Martin and Synge,[5] in discussing the theory of a certain type of chromatogram, have used a term, R,[10] for the relative rate of movement of a chromatographic zone. Their definition differs slightly from that proposed above.

Dr. W. T. Stewart has suggested[11] an alternative procedure, namely, the measurement of rates of movement relative to some standard dye, for the determination of the relative positions of chromatographic zones.

From measurements of R certain inversions of the relative positions of pairs of carotenoids on different adsorbents were predicted. The first example was the case of kryptoxanthin–lycopene;

TABLE II

RATES OF MOVEMENT OF CHROMATOGRAPHIC ZONES RELATIVE TO THAT OF THE DEVELOPING SOLVENT, ON CALCIUM HYDROXIDE AND DEVELOPED WITH BENZENE. MEASUREMENTS APPLY TO BOTTOM EDGE OF ZONE

Substance	R	Substance	R
Capsanthin	0.007	Lycopene	0.125
Celaxanthin[a]	.150	Kryptoxanthin	.340
β-Carotenone	.030	Physalien	.590
Zeaxanthin	.040	γ-Carotene	.790
Lutein	.070	Prolycopene[9]	.885
Hydroxy-γ-carotene[a]	.070	β-Carotene	1.000

[a] Obtained from the fruits of *Celastrus scandens* (unpublished).

TABLE III

CALCULATED AND OBSERVED RELATIVE POSITIONS OF THE COMPONENTS OF A MIXTURE SEPARATED ON CALCIUM HYDROXIDE, DEVELOPED WITH BENZENE. ZONES WERE IDENTIFIED SPECTROSCOPICALLY

	Calculated		Observed[c] Position mm. from the top relative to lycopene	
Substance	R	$R/R_{lycopene}$	I	II
Capsanthin	0.007	0.056	0.04	0.04
Celaxanthin[a]	.015	.12	.13	.11
β-Carotenone	.030	.24	.24	.19
Zeaxanthin	.040	.32	.35	.30
Lutein	.070	.56	.62[b]	.55
Hydroxy-γ-carotene[a]	.070	.56		
Lycopene	.125	1.00	1.00	1.00

[a] Obtained from the fruits of *Celastrus scandens*. [b] Not separated; rechromatographing on calcium carbonate showed the presence of both pigments in this zone. [c] Two readings were taken at different stages in the development of the chromatogram.

(9) L. Zechmeister, A. L. LeRosen, F. W. Went and L. Pauling, *Proc. Nat. Acad. Sci.*, **27**, 236 (1941).

(10) The use of a somewhat different R in this paper is not only due to a delay in receiving the journal containing the work of Martin and Synge (received May 12, 1942), but also for convenience in measurement.

(11) W. T. Stewart, Thesis, California Institute of Technology, 1941.

kryptoxanthin is adsorbed above lycopene on calcium carbonate or alumina but below it on calcium hydroxide. Several other cases of this type have been observed. This phenomenon has already been noticed, *e. g.* by Duschinsky and Lederer.[12]

It has been found in this Laboratory that measurements of V_c of adsorbents led to the acquirement of better materials than before its use. For ordinary laboratory work a range of from about 5 to 15 mm./min. is desirable; this seems to be associated with an average particle size of 5 to 15 microns. If the adsorption affinity of a material shows much variation, as in the case of alumina, measurements of R for the substances to be separated should allow standardization. The most suitable value for R seems to be between 0.2 and 0.3. The values given for R in the tables are subject to correction as the measurement technique is improved.

Experimental

Determination of V_c.—For all the experimental work, except that concerning the influence of diameter, chromatographic tubes 250 by 17 mm. were used (obtainable from Scientific Glass Apparatus Co., Bloomfield, N. J.). The adsorbent was "Shell" brand lime, chemical hydrate, 325 mesh, obtained from the Braun Chemical Company in Los Angeles.

For the determination, the tubes were filled with the absorbent while suction was applied (about 25 mm. vacuum) and the absorbent slowly poured into the tube, the sides of which were then vigorously tapped in order to allow the absorbent to settle. The top of the column was pressed down firmly with a stamper, and the absorbent was removed from the walls above the column. Three successive 5-cc. portions of solvent were then pipetted onto the top of the column. Just as each portion disappeared into the absorbent the next one was introduced. At the same time, the position of the bottom edge of the solvent was noted. In this manner it was possible to determine the number of mm. column length equivalent to 1 cc. of solution. Next a buret was attached to the top of the absorption tube by a stopper provided with an outlet which could be closed when the air space above the column was filled with solvent. The buret stopcock was then opened, the tube filled with solvent and the outlet closed. It was then possible to determine the velocity of solvent in the column from the flow in cc. per minute shown by the buret.

Determination of R.—The procedure was the same as described above except that the initial portion of solvent (ligroin or ligroin–benzene) contained the carotenoid pigment, while all succeeding portions were pure benzene. The pigment was poured on the column in a solution containing ligroin, from which it is more strongly absorbed than benzene, in order to obtain a concentrated zone. The ligroin is immediately washed through the column by the benzene and, consequently, does not interfere with the determination. The buret reading and carotenoid position on the column were recorded at ten-minute intervals by a stop watch. The values, recorded in Table II, were obtained when V_c was reached.

All measurements were made with fresh solutions of pure crystals since the rates of movement may be profoundly influenced by impurities. It remains to be seen how far, even in very crude solutions, the relative rates remain proportional to those found with pure materials.

Summary

1. Some terms of importance to quantitative chromatography have been suggested; these are S, which indicates the average packing of the column, V_c, the rate of solvent flow when the velocity has become constant, and R, the rate of movement of an absorbate zone relative to that of the developing solvent.

2. Evidence has been given to show that the above mentioned quantities are of value in characterizing and standardizing absorbents, as well as predicting the relative positions of chromatographic zones.

3. Inversion of the sequence of some carotenoid pairs on different absorbents has been predicted and observed.

PASADENA, CALIFORNIA RECEIVED MAY 6, 1942

(12) R. Duschinsky and E. Lederer, *Bull. soc. chim. biol.*, **17**, 1534 (1935); see also Strain, "Chromatographic Analysis" (ref. 3), page 6.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SYRACUSE UNIVERSITY]

Effect of Strong Electric Fields on the Radiochemical Decomposition of Gaseous Ammonia[1]

BY MICHAEL J. MCGUINNESS, JR.,[2] AND HARRY ESSEX

A paper by Essex and Smith[3] presented the results of ion yields in the alpha ray decomposition of ammonia in electric fields. This work has been continued with measurements at lower pressure and at higher field strength. The effects of these changes on the ion yield are significant as regards the mechanism of the alpha ray decomposition and on the products of the reactions between electrons and ammonia molecules.

The ion yields were determined by the saturation current method, the rate of ion production being determined from the saturation current across the ionized gas and the rate of decomposition of the gas by the increase in pressure of the gases, nitrogen and hydrogen, uncondensed by liquid air. Previous papers from this Laboratory have shown that the saturation current method gives ion yields which, when account is taken of the effect of the difference in intensity of irradiation, agree with the ion yields determined by the more indirect methods of "homogeneous irradiation" and "central irradiation" used by others.

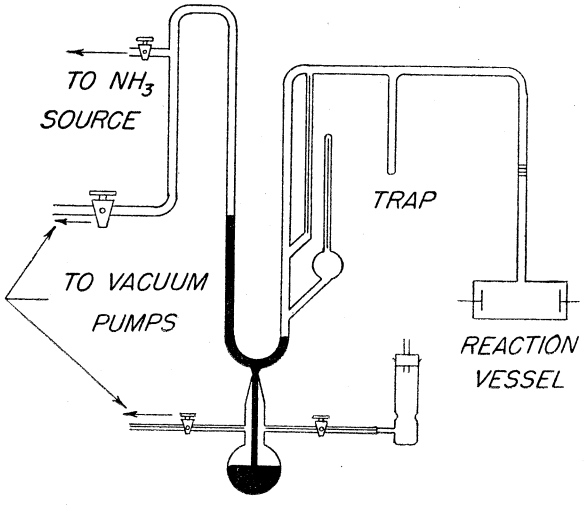


Fig. 1.

Experimental

The apparatus is shown in Fig. 1. The radioactive material, mesothorium, was placed in a small depression in the reaction vessel. The vessel was fitted with platinum electrodes as shown. Ammonia, guaranteed by the manufacturers to be not less than 99.95% NH_3, was dispensed from a solution in ammonium thiocyanate, dried over metallic sodium and purified by repeated condensation in the indicated trap at liquid-air temperature, followed each time by evacuation of uncondensed gases. The ammonia gas at about 20 cm. was finally enclosed by the mercury seal. The reaction vessel was surrounded by an air-bath maintained at $24.7 \pm 0.2°$.

Circular thin copper shields were cemented to the outside of each end of the reaction vessel with a nitrocellulose cement containing silver filings to improve electrical contact. The shield at the low potential end was electrically insulated from the lead to the electrode. Currents to electrode and shield were measured separately. At the highest potentials the current to the shield was about 2% of that to the plate and was included in the ion current since preliminary experiments showed the conductivity through and over this glass to be negligible. The shields prevented sparking between glass and electrode edges.

During a run the field strength was kept constant except that at intervals of about twenty-four hours the saturation current was measured and the residual pressure ($N_2 + 3H_2$) determined with the McLeod gage after freezing out ammonia in the trap. At the end of a run the ammonia was frozen out, the system evacuated, the mercury seal closed and a new run started at another field strength. In many of the runs the field strengths were far higher than necessary for saturation.

The results are presented in Table I and the ion yields (M/N) are plotted *vs.* field strength in Fig. 2. The experi-

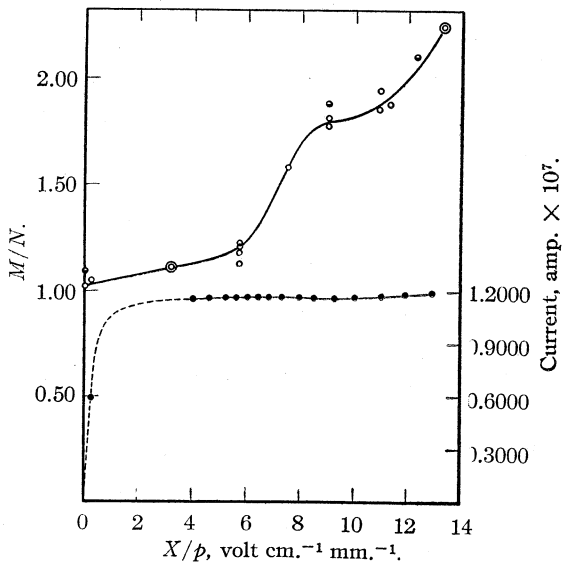


Fig. 2.—Comparison of ion yield with plate current: ○, ion yield; ◒, short run; ●, plate current.

(1) This paper is from the doctoral dissertation of Michael J. McGuinness, Jr., Syracuse University, 1941, and was presented at the Atlantic City meeting of the American Chemical Society, September, 1941.

(2) Present address: Battelle Memorial Institute, Columbus, Ohio.

(3) Essex and Smith. *J. Chem. Phys.*, **6**, 188 (1938).

TABLE I

ION YIELDS IN AMMONIA

Temperature 24.7°, pressure 20 cm.

Duration, hours	Residual pressure change, mm.	Saturation current, amp. × 10^8	M/N	Potential diff. between electrodes, kv.	X/P, volt, cm.$^{-1}$ mm.$^{-1}$
23.62	0.00763	12.03	1.09	0	0
304.15	.0905	11.90	1.02	0	0
175.73	.0537	11.82	1.05	0.5	0.25[a]
210.4	.0677	11.68	1.12	6.4	3.2
185.5	.0608	11.88	1.12	6.4	3.2
43.08	.01436	11.70	1.16	11.4	5.7
43.70	.01398	11.81	1.10	11.4	5.7
		Average, for last two runs	1.13	11.4	5.7
162.22	.0579	11.73	1.23	11.4	5.7
91.38	.0319	11.67	1.21	11.4	5.7
29.23	.0092	11.69	1.09	11.4	5.7
		Average, for last two runs	1.18	11.4	5.7
34.92	.0135	11.59	1.35	11.4	5.7
170.00	.0578	11.68	1.18	11.4	5.7
		Average, for last two runs	1.21	11.4	5.7
76.92	.0363	11.84	1.62	15.0	7.5
63.43	.0287	11.80	1.56	15.0	7.5
		Average, for last two runs	1.59	15.0	7.5
191.4	.0980	11.69	1.78	18.0	9.0
47.27	.0260	11.81	1.89	18.0	9.0
364.3	.193	11.83	1.82	18.0	9.0
96.17	.0524	11.90	1.86	21.8	10.9
169.55	.0961	11.81	1.95	21.8	10.9
55.27	.02703	10.93	1.81	22.6	11.3
193.00	.1052	11.50	1.92	22.6	11.3
		Average, for last two runs	1.90	22.6	11.3
43.65	.0261	11.78	2.11	24.6	12.3
62.2	.0405	11.80	2.24	26.6	13.3
91.8	.0600	11.84	2.24	26.6	13.3
		Average, for last two runs	2.24	26.6	13.3
138.47	.0903	11.80	2.24	26.6	13.3

[a] Current to plate during this run equal to one-half of saturation current.

mental errors are naturally greater in the shorter runs. Figure 2 also shows a typical current *vs.* field strength curve. The ion yields reported here were obtained at intensities of ionization similar to those in the experiments carried out in this Laboratory[3] on ammonia at pressures in the neighborhood of one atmosphere. The nature of the method, depending upon saturation current measurements, precludes the use of higher intensities of irradiation where saturation is obtainable only at extremely high voltages, if at all. The ion yield 1.03 (weighted) obtained in the absence of a field at 20 cm. may be compared with the value 1.37 previously obtained[3] at 62 cm. and 30°. Luyckx[4] also observed a decrease in ion yield with decrease in pressure in the alpha ray decomposition of ammonia. He found that the effect was greater the lower the intensity of irradiation. Since the lowest intensity of irradiation he used was greater than that employed in these experiments, quantitative comparison is not possible.

(4) Luyckx, *Bull. soc. chim. belg.*, **43**, 117 (1934).

Discussion

Effect of Pressure.—It frequently has been assumed that alpha ray induced decompositions are entirely the result of recombination of ions. By measuring the ion yield at constant pressure and temperature as a function of field strength, it is possible to calculate the fraction of the decomposition which in the absence of a field is consequent on recombination of ions and the fraction of the decomposition due to other mechanisms. At field strengths sufficient for saturation, recombination cannot occur. But practical saturation is obtained only at such high fields that, as our previous work has shown, decomposition by a new mechanism, probably by electron collisions, has begun. However, half saturation is obtained

at field strengths only a small fraction, often about one-tenth of those necessary for saturation and the ion yield due to ion recombination should be twice the difference between the ion yield in no field and at half saturation. The ion yield due to other mechanisms is obtained by difference.

In this way Essex and Smith[3] calculated in the decomposition of ammonia at 30° and 62 cm. that 30% of the decomposition is consequent on ion recombination. But the data here presented show that at 24.7° and 20 cm. pressure and under very similar conditions as regards vessel size and intensity of irradiation, the ion yield at no field is 1.03 and at half saturation 1.05. These yields are identical within the experimental error and show that at this lower pressure, none of the alpha ray decomposition is consequent on ion recombination, *i. e.*, that the decomposition is entirely due to other mechanisms. It seems probable that at the lower pressure all of the ions reach the walls by diffusion and are there discharged. The only effect of low fields is to change the location of ion discharge from the walls to the electrodes. Assuming that recombination takes place entirely in alpha ray tracks which extend completely across the vessel at all pressures and that the diameter of the track and the rate of diffusion of ions show the pressure dependence to be expected, it is easily shown that the fraction of the ions recombining in the gas is proportional to the $^5/_2$ power of the pressure. Comparing the fraction of the ions which combine at 20 cm. and 62 cm. pressure

$$\frac{\text{fraction combining at 20 cm.}}{\text{fraction combining at 62 cm.}} = \frac{20^{5/2}}{62^{5/2}} = \frac{1}{17}$$

which makes plausible the implications of these experiments that at 20 cm. in a vessel of this shape and size, most of the ions are neutralized at the walls.

At 30° and 62 cm. pressure the total ion yield in the absence of a field was 1.37, the ion yield due to recombination of ions 0.40 and that due to other mechanisms 0.97. Comparing the latter figure with 1.03 it is seen that pressure has little or no effect on that portion of the reaction due to mechanisms other than ion combination.

Effect of Electric Field.—The first effect of increasing the field strength across ionized ammonia is to remove ions before they recombine, which often results in decomposition, or reach the walls by diffusion. The increase in ion yield at higher field strength is due to collisions of electrons with ammonia molecules as, at the pressures of these experiments, the energy of molecular ions is increased by the field but slightly above the thermal energy of the molecules. The ion yield curve (Fig. 2) is therefore an electron yield curve but with the electron yield scale undetermined since the ratio of electrons to molecular negative ions is unknown. High energy electrons are known to split the ammonia molecule with attachment of the electron to one or the other fragment.

Bradbury[5] passed electrons through ammonia at pressures from 3 to 97 mm. Negative molecular ions appeared at $X/p = 7.5$ at which value he estimated the average energy of the electrons to be 4 volts. A gas uncondensable by liquid air was formed upon the appearance of negative ions. Four volts is approximately the energy of dissociation of NH_3 either to NH_2 and H or NH and H_2. Bradbury postulated one or the other of the reactions

$$NH_3 \longrightarrow NH_2^- + H$$
$$NH_3 \longrightarrow NH^- + H_2$$

Mann, Hustrulid and Tate[6] analyzed with the mass spectrograph the ions formed in ammonia at very low pressures by electrons of controlled energies. The only negative ions found were NH_2^- and H^-. The onset of formation of both ions occurred at electron energies very close to the excitation potential, 6 e. v. The disagreement between Bradbury and Tate as to the minimum energy necessary for electron attachment (4 and 6 e. v., respectively) may be inherent in their methods of attack. Bradbury's method was excellent for detecting ions at small probability of formation due to the fact that he was using much higher pressures than are possible in mass spectrometric methods. His calculations provided the average energy of the electrons, but, regarding the actual energies of the individual electrons, little information is available since the distribution function has not been satisfactorily determined. Therefore, as Bradbury has stated,[7] his results do not show convincingly that electrons of energies less than 6 e. v. do become attached. Tate and his co-workers,[6] on the other hand, were operating at such low pressures that although the energy of the electrons could be known accurately, attachment would not be detectable if the probability of attachment were small.

The ion yield curve (Fig. 2) exhibits two poten-

(5) Bradbury, *J. Chem. Phys.*, **2**, 827 (1934).
(6) Mann, Hustrulid and Tate, *Phys. Rev.*, **58**, 340 (1940).
(7) Private communication.

tial ranges in which the rise in ion yield is rapid, the first of which is followed by a potential range in which the ion yield increases more gradually. It seems plausible to assume that non-resonant splitting and resonant splitting occur successively with increasing field, *e. g.*

$$(1)\quad NH_3 + e \begin{cases} \nearrow NH_2^- + H \\ \searrow NH_2 + H + e \end{cases}$$

and

$$(2)\quad NH_3 + e \longrightarrow NH_3^* + e \begin{cases} \nearrow NH_2^- + H \\ \searrow NH_2 + H + e \end{cases}$$

in which are included the possibility of failure of a molecular fragment to capture the electron. After an electron is captured by either mechanism, no further decomposition is possible by the ion (thereafter molecular) in its progress toward the electrode, which may explain the nearly horizontal portion of the curve. That the first increase in ion yield occurs at a value of X/p less than that ($X/p = 7.5$) at which Bradbury first observed negative ions is probably due to the fact that in these experiments no special precautions were taken to maintain the field uniform. Under such conditions as obtained in these experiments the field strength is considerably above the average in the neighborhood of the electrodes, especially at the cathode and at low potentials.

That considerable splitting of ammonia molecules without electron attachment occurs is apparent from the magnitude of the increase in ion yield with increase in field strength, from 1.03 to 2.24. Splitting with attachment could only result in an increase in ion yield of 1 unit if all negative ions were initially electrons and if no ammonia resulted from the recombination of the fragments. The work of Melville and Birse[8] indicates that only 43% of ammonia molecules which are split into NH_2 and H finally result in nitrogen and hydrogen. It would therefore appear that in the collisions of electrons with ammonia molecules approximately 2 molecules are split without attachment for each split with attachment; more than 2 in so far as negative molecular ions are produced by the action of the alpha rays, less than 2 to the extent that resonance splitting occurs by the second Tate mechanism

$$NH_3 + e \longrightarrow NH_3^* + e \longrightarrow N + H_2 + H^-$$

That no positive ions are produced by accelerated electrons in our experiments is evidenced by the appearance of the current–field strength curve which remains flat above the saturation voltage. Maximum energy of the electrons is therefore less than 10.5 e. v., the ionization potential of ammonia.

The reactions occurring in a field are also operative in the ordinary radiochemical decomposition (in the absence of a field) where energetic electrons are also present. The direct splitting reaction postulated by Bradbury would account for little of the decomposition since Mann, Hustrulid and Tate have shown it to be an improbable one. That portion of the reaction not consequent on recombination of ions probably results, largely, from resonance splitting (*e. g.* (2)).

Acknowledgment.—The liquid air used in this investigation was provided by the General Electric Company of Schenectady, New York, through the courtesy of Dr. L. M. Willey, to whom the authors wish to express their gratitude.

Summary

Ion yields in the alpha ray decomposition of gaseous ammonia at 25° and a pressure of 20 cm. have been determined over a wide range of field strengths. In the absence of a field none of the reaction is consequent on ion recombination under these experimental conditions. The increase in ion yield at high field strengths has been attributed to electron collisions. The electron collisions have been assumed to result in direct and resonance splitting of the ammonia molecule. The splitting of an ammonia molecule on collision with an electron does not involve electron attachment in the majority of such collisions.

SYRACUSE, N. Y. RECEIVED APRIL 8, 1942

(8) Melville and Birse, *Proc. Roy. Soc.* (London), **A175**, 164 (1939).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BRITISH COLUMBIA]

The Viscosity of *cis* and *trans* Decahydronaphthalene

BY WM. F. SEYER AND JOHN D. LESLIE[1]

Considerable work has been done in these Laboratories during the last few years on the properties of the cyclic and dicyclic naphthene hydrocarbons. The present paper deals with viscosity measurements on the *cis*- and *trans*-forms of decahydronaphthalene over a range of temperature from −30 to 180°.

Experimental Procedure

The materials used for this work had been specially purified. The *cis*-isomer after eight recrystallizations had a freezing point of −43.25°. In the case of the *trans*-compound the freezing point, −31.16°, obtained after twenty recrystallizations, was slightly higher than had previously been recorded, *viz.*, −31.47°.

The viscometers available were modifications of the Ostwald type. They were made in accordance with British Standards Specification No. 188–1937, and were specially designed to reduce deviations from Poiseuille's law to a minimum. For a given viscometer and constant volume of liquid where no external pressure is used the equation

$$\eta = \frac{\pi g H r^4 t}{8V(l+\lambda)} - \frac{mV\rho}{8\pi(l+\lambda)t}$$

is recommended by various authorities.[2] Here the symbols have the following meaning

- η = viscosity in absolute units
- r = radius of tube
- l = length of tube
- H = average acting hydrostatic head
- V = volume of fluid
- λ = a fictitious amount added to length of tube to correct for the extremities
- m = a constant which is here taken as 1.12
- ρ = density of fluid
- t = time of efflux

Where the tube is to be calibrated with liquids of known viscosity the above equation can be expressed in the simple form $\eta = C\rho t - c\rho/t$. The constants C and c can then be determined by experiment. It can be shown from the above equation that the second term is less than 2.5% of the first provided the efflux time is greater than one-hundred seconds. Hence it is clear that the kinetic energy correction can be kept small by selecting a viscometer which will give a sufficiently long efflux time.

Loading errors did not arise in this work since the same liquid was used throughout each series of measurements. Furthermore the liquid levels were kept constant at all temperatures, thus ensuring that the mean liquid head remained constant over the entire range. Again, the dimensions of the viscometer were such as to make errors due to drainage and surface tension differences negligible. Another possible source of error lies in the fact that the viscometer may not always be vertical. The error is proportional to $(1 - \cos\theta)$, where θ is the angular deviation from the vertical, and hence is about 0.1% for $\theta = 2.5°$. Such a deviation was easily detected by means of a small plum-bob.

A very important question is whether or not the constants of the instrument remain truly constant throughout the series of experiments. One possible effect is that of temperature. Although, as stated above, special pains were taken to ensure that the same apparent efflux volume, V, was used at all temperatures, there might still have been an error caused by expansion of the glass. Taking the mean coefficient of expansion of glass as 0.1×10^{-4}, and considering a range of 200°, we can show readily that C will increase by 0.2%, and c by 0.4%. The latter error will obviously have a negligible effect on the final results. Since the calibration covered the range from 20 to 100° the constants are probably correct near 60°, and hence the maximum error due to a variation in C would not likely exceed 0.1%. Some workers think that the constants may also vary because of continuous changes in the capillary bore owing to solvent action of the liquids and cleaning solutions used. In the present work it was considered very unlikely that the decalin would act on the glass, and care was taken not to leave strong cleaning solutions in the viscometer over long periods of time.

The viscometer was cleaned with concentrated dichromate solution, water, alcohol and ether in turn. Before each series of measurements the instrument was rinsed and left in contact with the test liquid for several hours.

The constant temperature bath consisted of a cylindrical Pyrex jar of about 11-liters capacity (45 cm. deep and 20

(1) Standard Oil Company of British Columbia Research Fellow, 1940–1941.

(2) E. C. Bingham, "Plasticity and Fluidity," McGraw-Hill Book Co., Inc., New York, N. Y., 1922.

cm. in diameter). It was lagged with asbestos and cotton batting, and was filled with a medium, clear petrolatum oil, which was circulated by a triple propeller. Some trouble resulted at high temperatures from the oil charring and becoming opaque; a lubricating oil, Marvelube 40, was tried but was found to be even less satisfactory. The bath was heated electrically by two Cenco immersion knives and a small nichrome coil (1 inch in diameter), the latter being hooked up to a precision thermo-regulator. A switchboard with suitable resistances enabled any temperature between 20 and 180° to be obtained. For the measurements below room temperature a double-walled, evacuated, Pyrex flask (25 cm. deep by 7 cm. in diameter) was found convenient. Acetone served as a bath liquid and the temperature was lowered and kept constant by dropping in small pieces of dry-ice. Except at the extremes, the temperature could be kept constant within ±0.02°, and even at the highest and lowest temperatures the variation was less than ±0.05°.

The temperature was measured with a Leeds and Northrup platinum resistance thermometer, No. 169,314, which had recently been checked by the Bureau of Standards in Washington and whose ice point had been determined several times in this Laboratory. Temperatures were calculated by means of Callendar's equations.

A Meylan stop watch, reading to 0.2 second, served as timing device. Checking against several reliable timepieces indicated a loss of 0.02 sec. per min., and while this is well within the limit of error required by Bingham,[2] a suitable correction was applied to all readings. Since the viscometer was designed for an efflux time of not less than one hundred seconds, and since the final results were always averages of from five to fifteen readings, the mean error in the stop watch reading was probably less than 0.1%. Care was taken always to run the stopwatch in a horizontal position.

Calibration.—To cover the viscosity range of the decalin isomers and to keep the efflux times greater than one hundred seconds, it was necessary to choose an uncalibrated viscometer. The instrument was calibrated by measuring the efflux times of pure water at several temperatures and from the resulting equations the constants of the viscometer were calculated by the method of least squares. The absolute viscosities of water were taken from the data of Bingham and Jackson[3] and the relative densities from the Smithsonian Tables. The calibration was later checked with a sample of oil, of which the kinematic viscosity had been accurately determined at 20, 40, and 100°, from the Bureau of Standards. The constants were redetermined, using the two sets of data together, and the final equation was

$$\nu = \eta/\rho = 0.004043t - 1.52/t$$

For the measurements below 0° another viscometer of larger bore was calibrated to avoid excessively long efflux times. *cis*-Decalin was used this time, as values for its viscosity above 0° were already known. The resulting equation for this instrument was

$$\nu = \eta/\rho = 0.05737t - 1.16/t$$

The final standard for all these measurements is the absolute viscosity of water (η = 1.005 at 20.00°), and this, according to Cannon and Fenske,[4] may be in error by ± 0.5%. Relative to this value, however, we believe our measurements to be correct within ± 0.3 %, except perhaps at the lower extreme of temperature where the error may be ± 0.5%.

Procedure.—The kinematic viscosities of first the *cis*- and then the *trans*-isomer were measured at 10° intervals between −30 and 180°, and from these data and the densities as given by Seyer and Davenport,[5] the absolute viscosities were calculated as explained above. Each temperature was maintained for at least two or three hours and in some cases from twelve to twenty-four hours. In all cases the averages of numerous readings were taken. At one time it was thought that the vibration from the stirring apparatus might affect the results, and a few runs were made with the motor turned off to see if any difference could be detected. No difference was found.

Then, for reasons given below, the measurements on *cis*-decalin were repeated between 110 and 180°. With both the *cis*- and the *trans*-decalin the measurements were repeated at intervals coming down the scale of temperature after the upper limit had been reached. In all cases these latter gave slightly higher results. The cause of this phenomenon has not yet been determined.

Discussion of Results

The curves obtained (Fig. 1) when log η is plotted against $1/T$ are not linear, but they are quite smooth and there appears to be no evidence to support the claims of discontinuities in various temperature ranges as suggested by Seyer and Davenport in the proceedings of the Petroleum Division of the A. C. S. (Boston Meeting, 1939). In the case of the *cis*-isomer, however, a considerable deviation begins to show itself at 110°. This deviation increased as the temperature went higher, and, furthermore, the longer the hydrocarbon was kept at any one temperature in this interval the greater its viscosity became. This is similiar to the results stated by the above authors who found an increase not only in the viscosity but also in the density, and surface tension. Additional measurements on these latter properties suggested an irreversible change in the *cis*-isomer possibly due to some chemical reaction or to the formation of a structural isomer. No definite

(3) Bingham and Jackson, *Bureau Stds. Bull.*, **14**, 75 (1918).

(4) M. R. Cannon and M. R. Fenske, *Ind. Eng. Chem., Anal. Ed.*, **10**, 297 (1938).

(5) Seyer and Davenport, THIS JOURNAL, **63**, 2425 (1941).

VISCOSITY IN CENTIPOISES

Temp., °C.	*cis-*	*trans-*
−30.00	15.761	7.310
−20.00	10.677	5.394
−10.00	7.582	4.094
00.00	5.620	3.233
10.00	4.300	2.588
20.00	3.381	2.128
30.00	2.723	1.774
40.00	2.239	1.493
50.00	1.867	1.282
60.00	1.588	1.114
70.00	1.363	0.978
80.00	1.188	.865
90.00	1.045	.772
100.00	0.920	.692
110.00	.819	.626
120.00	.752	.572
130.00	.684	.521
140.00	.622	.476
150.00	.569	.438
160.00	.521	.406
170.00	.479	.375
180.00	.439	.350

evidence of oxidation or of the formation of unsaturated compounds could be found. The surface tension measurements mentioned above, and more recently measurements on the specific heats and refractive indices indicate further irregularity in the behavior of the *cis*-isomer in the region 50–52° but, as can be seen, this is not supported by the present work.

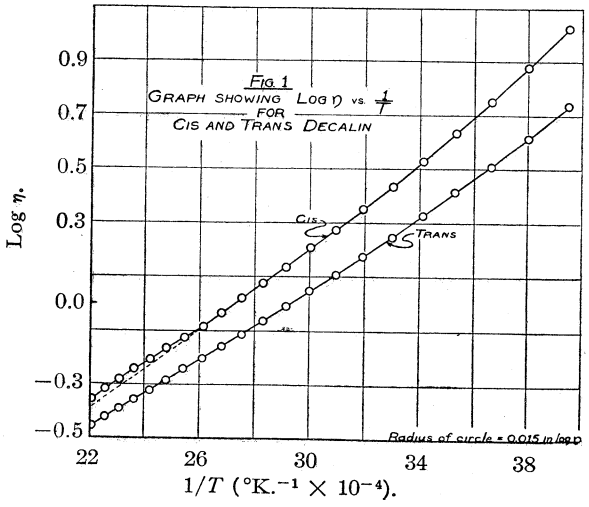


Fig. 1.

Many equations other than the simple exponential law, $\eta = Be^{A/T}$, have been proposed to express the temperature variation of viscosity, and several of these, including Batschinski's[6] relationship $\eta = B/(v-c)$ where v is the specific volume and B and c are constants, were tried on the present data. The results were, in general, the same, none gave linear curves and all indicated the abnormality discussed above.

The curves are sufficiently straight for their slopes to be of possible significance. If the assumed equation is $\eta = Be^{E_{vis}/RT}$, then the slopes, m, of our curves are given by $m = \frac{E_{vis}}{R} = \frac{\ln(\eta_2/\eta_1)}{1/T_2 - 1/T_1}$, where E_{vis} is the average molar activation energy for viscous flow. E_{vis} is given in the table below for the decalin isomers and also for a few other hydrocarbons of comparable size or structure. The data for these latter were taken from the work of E. B. Evans,[7] and from a compilation of physical data by The Texas Co.[8]

Hydrocarbon		η_0° (cp)	η_{100}° (cp)	m	E_{vis}, cal./mole
n-Hexane	C_6H_{14}	0.398	0.167	880	1750
n-Decane	$C_{10}H_{22}$	1.298	.357	1315	2615
Cyclohexane	C_6H_{12}	1.455	.572 (50°)	1650	3285
trans-Decalin	$C_{10}H_{18}$	3.233	.692	1570	3125
cis-Decalin	$C_{10}H_{18}$	5.620	.920	1845	3670
Cyclodecane	$C_{10}H_{20}$	4.48 (20°)	1.76 (60°)	2280	4535

It is apparent that for a given number of carbon atoms, cyclization increases both the viscosity and the activation energy. It is interesting, to note that although *trans*-decalin has a higher viscosity than cyclohexane E_{vis} is about the same for both, and again that although the single ringed compound, cyclodecane, has a higher viscosity than either *cis*- or *trans*-decalin at low temperatures, its E_{vis} is also much greater, which means that at more elevated temperatures the viscosity curves will cross. The same argument applies to the two decalin isomers themselves, and a rough calculation shows that if no structural changes took place the two would have the same viscosity at about 300°.

So far we have assumed that $dE_{vis}/dT = 0$. The curves show that this condition definitely does not hold for the decalin isomers, and this fact suggests the possibility that from the standpoint of viscosity they may be regarded as abnormal liquids. In a general discussion on liquids held by the Faraday Society,[9] A. G. Ward classifies the various types of liquids and then attempts to explain departures from the simple exponential equation for viscosity in terms of structure and forces. He states that E_{vis} will vary with the tem-

(6) A. Batschinski, *Z. physik. Chem.*, **84**, 643 (1913).

(7) E. B. Evans, *J. Inst. of Pet. Technologists*, **24**, 38, 321, 537 (1938).

(8) The Texas Co., "Physical Constants of the Principal Hydrocarbons," 2nd edition, New York, N. Y., 1939.

(9) "Structure and Molecular Forces in (a) Pure Liquids and (b) Solutions," *Trans. Faraday Soc.*, **33**, 189 (1937).

TABLE I

Hydrocarbon		B. p. (760 mm.), °C.	Sp. gr. (d^{20}_4)	η (cp)$_{15°}$	η (cp)$_{30°}$	E_{vis}, cal./mole	E_{cis}/E_{trans}
1-Methyl-2-propyl-cyclopentane	*cis*	152.5	0.7921	0.941	0.753	2575	
	trans	146.3	.7774	.750	.622	2170	1.18
1,2-Diethylcyclopentane	*cis*	153.5	.7959	.815	.669	2290	
	trans	147.5	.7831	.723	.605	2050	1.12
1,2-Dimethylcyclohexane	*cis*	130.0	.7962	1.188	.925	2885	
	trans	123.7	.7760	0.863	.697	2270	1.27
1,3-Dimethylcyclohexane	*cis*	124.9	.7835	.888	.722	2390	
	trans	120.4	.7663	.665	.556	2050	1.17
1,4-Dimethylcyclohexane	*cis*	124.6	.7827	.933	.749	2535	
	trans	119.6	.7626	.749	.614	2300	1.10
Decalin	*cis*	194.6	.8967	3.792	2.723	3810	
	trans	185.4	.8700	2.342	1.774	3215	1.18

perature if the coördination of the molecules changes and further that a negative dE_{vis}/dT, as in the case of both *cis*- and *trans*-decalin, indicates increasing coördination, and hence directional forces. The same author goes on to say that high values of E_{vis} and of the viscosity at the freezing point characterize ionic liquids and those containing polar groups. In the latter he claims the high values indicate a possible bond rupture.

Eyring and his co-workers[10] show, also, that the above characteristics in a liquid may indicate association, by supposing that at the lower temperatures an extra "structure activation energy" is necessary to break the association bonds before the activated state for flow can be brought about. It should be pointed out[11] that even the simplest liquid must show a slightly decreasing activation energy with increasing temperature, if a sufficiently accurate analysis is made. This is because a liquid becomes more gas-like with increasing temperature and new equilibrium positions for the molecules to flow into become more plentiful. It can be shown, however, that this normal change in the activation energy, E_{vis}, is sufficiently small to make the simple exponential law quite accurate for most liquids. We may therefore conclude that the variations in E_{vis} for the decalin isomers indicate abnormality in structure.

Since decalin is a saturated dicyclic hydrocarbon we would not expect it to be markedly dipolar, and it certainly does not fall into the latter classes discussed by Ward. Hence, the present authors suggest that in such liquids as decalin there may be not single molecules, but molecular aggregates or macromolecules, these being naturally more plentiful at low temperatures, with a gradually increasing degree of dissociation as the temperature rises.

The differences between the viscosities and the activation energies of the decalin isomers themselves are not easy to explain because little is definitely known about the space configurations of these two compounds. A little enlightenment is to be had, however, from an examination of the data for several other naphthenic hydrocarbons which show *cis–trans* isomerism. These data are from the Texas Co. publication mentioned above, and are given in the following table along with the corresponding data for the decalin isomers.

In each compound the *cis*-isomer has a higher boiling point, a higher specific gravity, a higher viscosity and a higher E_{vis} than the *trans*. This would suggest that the differences in these properties are characteristic of the *cis–trans* isomerism itself and do not depend upon the number, sizes or complexity of the rings. The values are much higher for the decalin isomers but the ratio of the E_{vis} for the two isomers is about the same for all the hydrocarbons shown. In view of the discussion above a possible interpretation of these results is that directional forces are more pronounced in the *cis*-isomer and hence that there is closer packing of the molecules and a greater proportion of "macromolecules."

Eyring, *et al.*,[10] have developed a number of relationships between E_{vis}, $\Delta F^{\ddagger}$ and $\Delta E_{vap.}$ where $\Delta F^{\ddagger}$ is the molar free energy of activation for viscous flow and $\Delta E_{vap.}$ the molar energy of activation for evaporation. Lack of reliable vapor pressure data for decalin prevents us from making use of these relationships at the present time, but we hope to do so in a future paper.

Summary

1. The viscosities of *cis*- and *trans*-decahydro-

(10) Glasstone, Laidler and Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 505.

(11) Private communication from H. Eyring and R. E. Powell.

naphthalene have been measured from −30 to 180°.

2. When log η is plotted against $1/T$ straight lines are not obtained and there is evidence that the *cis*-form undergoes some change at 110°.

3. An attempt is made to explain the high values of η and E_{vis}, and also the effect of *cis–trans* isomerism on these.

VANCOUVER, B. C. RECEIVED JUNE 10, 1942

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

The Electromagnetic Mechanism of the Beta Phosphorescence of Fluorescein in Acid Solution

BY S. I. WEISSMAN[1] AND DAVID LIPKIN

Introduction

The peculiar nature of the beta phosphorescence of fluorescein in acid solution, investigated recently by Lewis, Lipkin and Magel,[2] suggested to us the desirability of studying the mechanism of this emission process. The peculiarities made themselves evident in several ways. Firstly, the luminescence is of unusually long duration. Secondly, no absorption band corresponding to a transition from the normal to the phosphorescent state has been found.[3] Thirdly, although the fluorescein molecules in the phosphorescent state have been found to be oriented when excited to that state by polarized light, the beta phosphorescence from such molecules is but little polarized.[2]

It is possible to describe the radiation processes from a source which is small compared with the wave length of the emitted waves in terms of the electric and magnetic multipole moments of the source. In the case of most of the familiar sources the only significant contribution to the radiation arises from an oscillating electric dipole. Indeed, most of the selection rules used in interpreting atomic and molecular spectra are not applicable in the case of transitions other than those involving electric dipoles. Thus, many spectral lines have been observed which appear to arise from processes which are forbidden by these selection rules. Two explanations may be advanced for the occurrence of these processes. In the first place, as we have just indicated, these seeming violations may occur because a given transition involves a multipole other than an electric dipole. Secondly, they may occur because of the invalidation of the rules by external perturbations of the emitting system. The $^2S_{1/2}$–$^2D_{3/2,\,5/2}$ doublet of potassium studied by Segrè and Bakker,[4] the $^1S_0$–$^3P_2$ and $^1D_2$–$^3P_0$ transitions of lead studied by Jenkins and Mrozowski,[5] and the $^1S_0$–$^1D_2$ transition of oxygen studied by Frerichs and Campbell[6] may be cited as examples of breakdowns of the first type. On the other hand, the 6^3P_2–7^3P_2 transition of mercury,[7] which is induced by external electric fields, may be cited as an example of a breakdown of the second type.

In the case of the transitions just mentioned, the investigators were able to determine the nature of the emission mechanism (magnetic dipole, electric dipole and electric quadrupole) by a study of the Zeeman effect. Obviously, this method cannot be used to study broad spectral bands such as those of large organic molecules. In this case it becomes necessary to use the wide-angle interference method of Selényi.[8] This method, the interpretation of which depends on characteristic differences in directional distribution of radiation about the various elementary multipoles,[9] involves the study of the coherence properties of rays issuing in widely diverging directions from small sources.

Experimental

In order to obtain interference between two beams of light issuing at a wide angle from a source, it must be of such dimensions that the interference patterns from different parts of the source do not obliterate each other. The most critical requirement as to the size of the source is that one dimension be not more than about one-twentieth of the wave length of the light. The other dimensions may be much larger and are determined by various optical characteristics of the interference apparatus. Selényi[8] has devised a simple experimental set-up which admirably fulfills the above requirements. We have used essentially

(1) National Research Council Fellow, 1941–1942.

(2) Lewis, Lipkin and Magel, THIS JOURNAL, **63**, 3005 (1941).

(3) These last two observations are, of course, interrelated.

(4) Segrè and Bakker, *Naturwiss.*, **19**, 738 (1931); *Z. Physik*, **72**, 724 (1931).

(5) Jenkins and Mrozowski, *Phys. Rev.*, **59**, 808 (1941).

(6) Frerichs and Campbell, *ibid.*, **36**, 151 (1930); **36**, 1460 (1930).

(7) Segré and Bakker, *Nature*, **128**, 1076 (1931).

(8) Selényi, *Ann. Physik*, **35**, 444 (1911); *Z. Physik*, **108**, 401 (1938); *Phys. Rev.*, **56**, 477 (1939).

(9) Halpern and Doermann, *ibid.*, **52**, 937 (1937); Doermann, *ibid.*, **53**, 420 (1938); Doermann and Halpern, *ibid.*, **55**, 486 (1939).

his set-up, but have adapted it so that the emitting source could be examined at liquid air temperatures.

A saturated solution of fluorescein in a phosphoric acid approximating metaphosphoric acid in composition was found satisfactory for preparing the small source necessary for the wide-angle interference study.[10] This source was obtained by placing a droplet (*ca.* 10^{-4} ml.) of the solution on the hypotenuse of a right angle prism and covering with a freshly split sheet of mica 0.005–0.010 mm. thick. The prism was maintained at a temperature of 110° until the film spread to the required thickness. The other dimensions of the source were determined by a pinhole in a sheet of black paper placed in contact with the mica (see Fig. 1B).

The experimental arrangement for the excitation and examination of the phosphorescence of the fluorescein film is depicted schematically in Fig. 1A. Light from a high-pressure mercury arc (1) was focused on the pinhole by means of a large aperture lens (2). The right angle prism (5)[11] was suspended in an unsilvered dewar (4) fitted with a balsa wood cover (7). The interfering beams of phosphorescent light from the film passed through a glass window in the cover (6). The fringe system was focused on the slit of the spectrograph (13) by means of a lens (9) and totally reflecting prism (11). The polarization of the fringe system was studied with the aid of a Polaroid disk (12) placed before the slit of the spectrograph.[12]

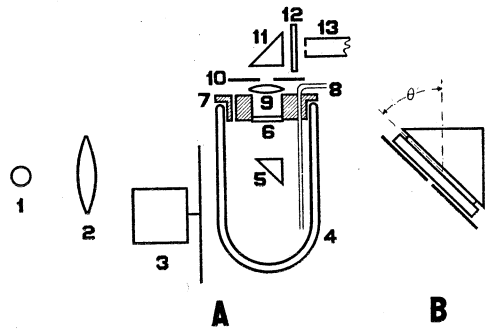


Fig. 1.—Schematic representation of the apparatus used for wide-angle interference studies at low temperatures.

The fluorescein film which served as the source of phosphorescent light was maintained at the desired temperature (95°K.) by a stream of cold air produced by boiling the liquid air contained in the dewar. This method of cooling was found necessary in preference to the usual method of immersion in liquid air in order to prevent disturbance of the exciting and emitted light beams.

In order that only phosphorescent light might enter the spectrograph a phosphoroscope was used which consisted of two synchronized shutters A disk (3) with a 50° sector of an annulus cut out of it, rotating at the rate of one revolution per second, served as the shutter for the exciting beam. A Packard Ideal shutter (10) placed in the phosphorescent beam was operated in synchronism with the first shutter by means of electrical contacts placed at properly spaced intervals on the disk.

The fringes arising from the broad band of wave lengths contained in the phosphorescent light were separated and photographed in the spectrograph (13), which was a small Bausch and Lomb constant deviation spectrometer fitted with a camera.

The Nature of the Emission Process

Observations of the interference patterns formed by pairs of rays diverging at angles of 90° and 45° sufficed for an unambiguous assignment of the multipole nature of the source. At an angle of divergence $2\theta = 90°$ (see Fig. 1B) and with the Polaroid set to transmit light polarized with its electric vector perpendicular to the plane of the two interfering beams, we obtained a picture of the emission spectrum crossed by interference fringes of high visibility. The photograph showing these fringes is reproduced in Fig. 2(a). At the same angle of divergence, but with the Polaroid turned through 90° from its first position, interference fringes no longer appeared in the photograph of the emission spectrum (Fig. 2(b)). These results, when interpreted in the light of the theoretical

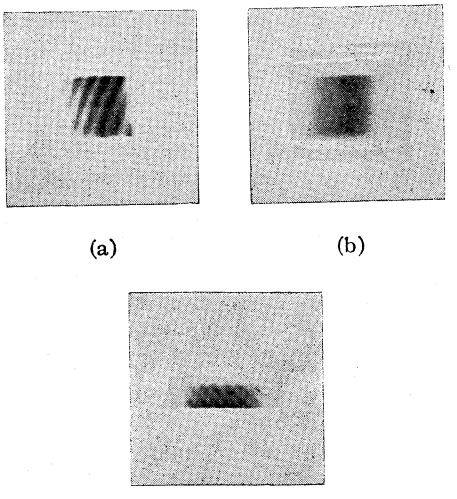


Fig. 2.—Phosphorescence (5400–6200 Å.) of fluorescein in phosphoric acid at 95°K. (a) $2\theta = 90°$, electric vector perpendicular to plane of interfering beams. (b) $2\theta = 90°$, electric vector parallel to plane of interfering beams. (c) $2\theta = 45°$, electric vector perpendicular to plane of interfering beams. The photograph obtained with $2\theta = 45°$ and the electric vector parallel to plane of interfering beams is indistinguishable from this one.

(10) It was necessary to use such a concentrated solution of fluorescein in order to obtain phosphorescence of sufficient intensity. The low intensity of the phosphorescence as compared with the fluorescence is accounted for by the fact that the fluorescein molecules spend such a long time in the phosphorescent state.

(11) For observations at an angle of $2\theta = 90°$ (Fig. 1B) the 45° prism was used. At $2\theta = 45°$ a glass half cylinder was used such as the one described by Freed and Weissman [*Phys. Rev.*, **60**, 440 (1941)].

12) Since the only polarizations studied were perpendicular and parallel to the plane of incidence of the totally reflecting prism (11), it was permissible to place the Polaroid disk in this position.

investigations of Doermann and Halpern,[9] show that the emission process involved in the beta phosphorescence may be either an electric dipole or magnetic quadrupole transition. Furthermore, the theory definitely excluded transitions involving magnetic dipoles, electric quadrupoles, electric octopoles and magnetic octopoles. Detailed predictions of the interference properties of still higher multipoles have not as yet been made and, therefore, we cannot definitely exclude these on the basis of our photographs. However, these can be excluded on the basis of reasoning involving the lifetime of the phosphorescent state and the intensity of the emission.

In order to decide between the two alternatives allowed us by the results described above, *i. e.*, electric dipole and magnetic quadrupole, it was but necessary to observe the interference patterns at an angle of divergence $2\theta = 45°$. At this angle of divergence we again made observations with the Polaroid set to transmit light polarized with its electric vector perpendicular to, and parallel with, the plane of the two interfering beams. In each case we obtained photographs of the spectrum crossed with fringes of high visibility (Fig. 2(c)). These photographs definitely show the emission process to be electric dipole in nature.[13]

Had our wide-angle interference experiments shown that the transition giving rise to the beta phosphorescence involved a multipole of higher order than a dipole, there would have been no great difficulty in explaining the long lifetime and small polarization of this process.[14] However, the unambiguous results of these experiments confront us with this question: how can the long-lived beta dipole process occur with only slightly preferred directional properties in the same oriented molecule which gives rise to highly selective directional properties for the short-lived dipole fluorescence? Let us suppose that the two states involved in the beta transition resemble non-degenerate states of zero total electronic angular momentum encountered in atomic spectra. Transitions of any multipole order between such highly symmetrical states are forbidden. However, a perturbation possessing sufficiently low symmetry may induce an electric dipole transition between such states. In the case here being considered such a perturbation may arise from zero point fluctuations in the medium or the molecule, as suggested by Lewis, Lipkin and Magel.[2] The direction of the oscillating moment associated with such an induced transition would be determined principally by the direction of the perturbation and little by the molecular axes, giving rise to phosphorescence with little polarization. On the other hand, in the fluorescence the upper state may be thought of as arising from a degenerate electronic state. Presumably there would be no prohibition against an electric dipole transition between this state and the ground state, and the observed lifetime of the fluorescence[15] is actually found to be in good agreement with this presumption. Furthermore, such a state would partake of the symmetry of the molecule and the oscillating dipole moment associated with the transitions in which it is involved would be expected to be oriented with respect to the molecular axes. This would readily account for the high degree of polarization observed in the fluorescence and alpha phosphorescence.

We wish to thank Professor Gilbert N. Lewis for many helpful discussions of the results of this investigation.

Summary

A wide-angle interference study of the beta phosphorescence of fluorescein in phosphoric acid at 95°K. has shown that the process involves an electric dipole transition.

BERKELEY, CALIFORNIA RECEIVED MAY 26, 1942

(13) The results of Doermann and Halpern are applicable to isotropic sources. Our source fulfilled this requirement of isotropy for two reasons. In the first place, a highly convergent beam of exciting light was used. Second, almost complete saturation of the source was achieved and, therefore, even molecules whose axes approach parallelism with the axis of the exciting light beam are activated.

(14) It has been shown by means of electromagnetic theory that the lifetime of an oscillator increases markedly with increase in the order of the multipole. Thus, the ratio of the lifetimes of two successive multipoles, *i. e.*, dipole and quadrupole, is approximately equal to $(\lambda/a)^2$, where λ is equal to the wave length of the emitted radiation and a is equal to the amplitude of the oscillation.

(15) Gaviola, *Z. Physik*, **42**, 853 (1927).

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, PASADENA, NO. 890]

Separation of *cis* and *trans* Stilbenes by Application of the Chromatographic Brush Method

BY L. ZECHMEISTER AND W. H. MCNEELY

In the stilbene series the *cis*-isomers are usually prepared either by irradiation of the stable *trans*-compound[1] or by direct synthesis.[2] The stereoisomers have been separated or differentiated by fractional crystallization, distillation and hydrogenation methods, and use has also been made of molecular addition compounds. For the determination of the *cis* and *trans* components in mixtures among other methods use has been made of spectrophotometric measurements and the study of melting point curves.[3]

We find that a convenient and rapid procedure for the detection, purification, separation and estimation of stereoisomeric stilbenes is to be found in the so-called chromatographic brush method.[4] After extrusion of the column, containing the invisible chromatogram, a narrow streak is made down the column with a brush which has been dipped into a 1% permanganate solution. Whenever the reagent crosses a zone containing *cis*- or *trans*-stilbenes it turns brown almost instantaneously. The zones thus located can be cut out and the isomers eluted after the streak has been shaved off.

In the present paper the application of this principle to stilbene, *p*-methylstilbene and *p*-methoxystilbene is described. In each case the *trans*-isomer possesses stronger adsorption affinity than the *cis*-form and is located near the top of the alumina column. After adequate development the two isomers are separated by a wide interzone. The procedure can be completed in ten to sixty minutes, with a total recovery of more than 90% when carried out with a quantity of starting material in a range of 10–500 mg. If the experiment is performed at room temperature no measurable isomerization of the *cis*-compound seems to take place.

By this method samples of *cis*- or *trans*-stilbenes can be tested for possible contamination by the other isomer. If 30–100 mg. of a mixture is analyzed the limit of detection is 1–2%. The method may also prove useful for the study of *cis–trans* shifts under the influence of light[5] and of other factors.

Finally, we may remark that the use of chromatography has revealed the presence of minor contaminants in commercial and in some recrystallized samples of stilbenes. These impurities are retained near the top of an activated alumina column where the adsorbate shows visible fluorescence in ultraviolet light. The main compound is easily washed into the filtrate by petroleum ether–benzene mixtures or by pure benzene. If the filtrate is sent through a fresh column, no fluorescing adsorbate appears. A great difference between the fluorescing power of non-chromatographed and chromatographed *p*-methyl- and *p*-methoxystilbene was observed when the crystals or 0.1% benzene solutions were inspected in ultraviolet light. The fluorescence of the purified samples was much weaker. No such difference was noticed in the case of stilbene except on the Tswett column. A preliminary chromatographic test of samples may be advisable if fluorescence spectra are to be studied.[6]

Acknowledgment.—The authors wish to thank Dr. G. Oppenheimer and Mr. G. Swinehart for microanalyses.

Experimental

The following adsorbents were used: for the purification of commercial *trans*-stilbene, activated alumina ("Alorco," 150–200 mesh or minus 80 mesh); for the purification of synthesized *p*-methoxy- and *p*-methylstilbene, Super Filtrol (Filtrol Corporation, Los Angeles) and activated alumina, and for the separation of *cis-trans* pairs, activated alumina. The petroleum ether had a boiling range 60–70°.

(1) R. Stoermer, *Ber.*, **42**, 4865 (1909); R. Stoermer and L. Prigge, *Ann. Chem.*, **409**, 20 (1915); A. Smakula, *Z. physik. Chem.*, **B25**, 90 (1934); G. N. Lewis, T. T. Magel and D. Lipkin, THIS JOURNAL, **62**, 2973 (1940).

(2) *Cf. e. g.*, E. Späth and K. Kromp, *Ber.*, **74**, 189 (1941); P. Ruggli and A. Staub, *Helv. Chim. Acta*, **19**, 1288 (1936); **20**, 37 (1937).

(3) G. B. Kistiakowsky and W. R. Smith, THIS JOURNAL, **56**, 638 (1934); C. Paal and H. Schiedewitz, *Ber.*, **63**, 766 (1930); T. W. J. Taylor and A. R. Murray, *J. Chem. Soc.*, 2078 (1938); Ch. C. Price and M. Meister, THIS JOURNAL, **61**, 1595 (1939); C. Weygand and Th. Siebenmark, *Ber.*, **73**, 765 (1940); C. Weygand and I. Rettberg, *ibid.*, **73**, 771 (1940); G. N. Lewis, *et al.*, see footnote 1.

(4) L. Zechmeister, L. Cholnoky and E. Ujhelyi, *Bull. soc. chim. biol.*, **18**. 1885 (1936); L. Zechmeister and O. Frehden, *ibid.*, **22**, 458 (1940).

(5) J. Wislicenus, *Chem. Zentr.*, **72**, I, 463 (1901).

(6) B. Arends, *Ber.*, **64**, 1936 (1931), observed fluorescing contaminants in some of his *p*-methylstilbene samples. These were not removed by crystallization. No chromatographic treatment is mentioned.

All melting points are corrected and were taken in an electrically heated Berl block. The capillaries were introduced 10° below the melting point. The rise of temperature was 1–2° per minute.

For the inspection of chromatograms during development, a small portable ultraviolet lamp was used (light was excluded by covering the tube and the head of the observer with a black cloth), and for solutions or solids an Examalite Quartz Lamp, (Hanovia, Newark, N. J.). Irradiations were carried out by a mercury arc quartz lamp (4 amp. d. c., voltage drop 32 v.) in a hood cooled by ventilation. The distance between the lamp and the quartz test-tubes was 10 cm. Irradiations were discontinued at night.

cis- **and** *trans-***Stilbene.**—The starting material was stilbene (Eastman Kodak Co.), m. p. 124–125°, from which a small quantity (<0.1%) of strongly fluorescent contaminants can be eliminated by filtering the benzene–petroleum ether (1:1) solution through activated alumina. The impurities are retained near the top while stilbene is washed into the filtrate. The melting point remained unchanged. The adsorbates[7] of *trans-* or *cis*-stilbene purified in this way showed no visible fluorescence in ultraviolet light.[8] For the preparation of the *cis*-compound 2.5 g. of stilbene in 35 ml. of benzene was irradiated for 200 hours. The pale yellow solution was kept in a cold room and samples were taken when needed.

A portion of this solution, containing 160 mg. of substance, was evaporated *in vacuo* at 35°, and in order to eliminate traces of benzene the evaporation was repeated twice after the addition of some petroleum ether. The residue (except for traces of yellow solids) was dissolved in 25 ml. of petroleum ether and poured onto an alumina column (17.5 × 1.7 cm.); the chromatogram was developed with 90 ml. of the solvent. Near the top a yellow by-product was retained, closely followed in some experiments by a minor fluorescent layer.[9] The main section of the column was colorless and did not fluoresce visibly in ultraviolet light. The permanganate brush located a *trans*-stilbene zone (42 mm. broad) and below it, separated by a 6-mm. empty section, the *cis*-zone (48 mm. broad). The streak turned light brown within two seconds where it crossed the zones while the nearly empty interzones began to react after several minutes.[10] Each isomer was eluted with dry ether and evaporated *in vacuo*.

The yield was 99.1 mg. of *trans*-stilbene (m. p. 123.5–124.5°, after one recrystallization from ethanol) and 51.8 mg. of *cis*-stilbene, the total recovery being 94% of the starting material. Before analysis the colorless, oily *cis*-compound (which can be crystallized at a lower temperature) was rechromatographed. Both samples were dried at 45° in high vacuum.

Anal. Calcd. for $C_{14}H_{12}$: C, 93.28; H, 6.72. Found (*cis*): C, 93.36; H, 6.65. Found (*trans*): C, 93.28; H, 6.78.

(7) We suggest that the term "Adsorbate" should designate the substance-adsorbent complex and not the adsorbed substance alone. (This nomenclature is now accepted in the German literature.)

(8) *Cf.* A. Winterstein and K. Schön, *Z. physiol. Chem.*, **230**, 146 (1934); K. W. Hausser, R. Kuhn and E. Kuhn, *Z. physik. Chem.*, **B29**, 417 (1935).

(9) On fluorescing of stilbenes *cf.* G. N. Lewis, *et al.*, footnote 1; H. Ley and H. Specker, *Z. wiss. Phot.*, **38**, 13 (1939).

(10) In blank experiments the column began to show a reaction with permanganate in several minutes.

The *cis* compound was further identified by addition of a trace of iodine and exposure to sunshine for a few hours. By this treatment it crystallized almost completely. A chromatographic analysis showed only a minor zone of unchanged *cis*-isomer while pure *trans*-stilbene was isolated in a yield of 78%.

In order to establish the limits of detection by brushing, artificial mixtures of *cis-* and *trans*-stilbene were chromatographed. It is possible to detect 2 mg. of *cis* in 75 mg. of *trans* on alumina (17.5 × 1.7 cm.) or 0.5 mg. of *trans* in 30 mg. of *cis* by using a smaller column (10.5 × 0.9 cm.). If the quantity of one of the isomers is below these limits, its location may be established roughly from that of the other isomer. By elution of the proper region with ether and analytical recovery by evaporation, an extension of the limits of detection can be obtained. The procedure is applicable to *p*-methyl and *p*-methoxy stilbene.

cis- **and** *trans-p-***Methylstilbene.**—The *trans*-compound was prepared according to Meerwein and his associates,[11] however, the crude product was purified by chromatography instead of by tedious sublimations in high vacuum. The hydrochloric acid solution of 13.4 g. of *p*-toluidine was added, after diazotization, to 18.5 g. of cinnamic acid in 150 ml. of acetone. After the addition of 27.5 g. of sodium acetate and a solution of 6.7 g. of crystallized cupric chloride, the liquid was stirred at 20° until the evolution of gases ceased (about five hours). The volatile components were then removed by steam distillation, and the dark residue was extracted with 150 ml. of benzene. After filtration and removal of unchanged cinnamic acid by extraction with ammonia containing ammonium chloride, the solution was dried with sodium sulfate. It was diluted with 400 ml. of petroleum ether and filtered through a Superfiltrol column (27 × 7 cm.) which was washed with about 1 liter of a benzene–petroleum ether mixture (1:1) until a pale blue fluorescing zone reached the filtrate. The column showed numerous intensely colored layers which were discarded. The evaporation residue of the filtrate yielded 6.0 g. of *trans-p*-methylstilbene, m. p. 118.5–119.5°, on crystallization from alcohol.

Such a sample may be used directly for the preparation of the *cis*-isomer by irradiation, or it can first be rechromatographed on activated alumina in order to remove the fluorescing contaminant mentioned which appears near the top on developing with benzene–petroleum ether. After this treatment practically no visible fluorescence of the *cis-* or *trans*-form was observed in petroleum ether on the column.

For the preparation of *cis-p*-methylstilbene 450 mg. of the *trans*-isomer in 90 ml. of petroleum ether was irradiated for seventy-five hours and then developed on alumina (22.5 × 4.3 cm.) with 700 ml. of the solvent. On inspection and brushing the presence of the following zones was revealed (the figures on the left denote the width of the zones in millimeters)

5 by-product (yellow before brushing)
12 empty interzone
30 *trans-p*-methylstilbene (located by permanganate)
55 empty interzone
50 *cis-p*-methylstilbene (located by permanganate)
73 empty bottom zone

(11) H. Meerwein, E. Büchner and K. van Emster, *J. prakt. Chem.*, **152**, 237 (1939).

The isomers were isolated by eluting with dry ether, evaporating and drying *in vacuo*. The yields were 160 mg. of *trans*- and 268 mg. of oily *cis*-*p*-methylstilbene, the total recovery being 95%. For analysis the *trans*-compound was recrystallized from alcohol (m. p. 119.5–120°) and the *cis*-isomer rechromatographed as described. The samples were dried in high vacuum at 20°.

Anal. Calcd. for $C_{15}H_{14}$: C, 92.73; H, 7.27. Found (*cis*): C, 92.98; H, 7.50. Found (*trans*): C, 93.06; H, 7.33.

Eighteen mg. of oily *cis*-*p*-methylstilbene was isomerized in the sunshine with iodine. Crystallization began after fifteen min. but the exposure was continued for a few hours. On brushing the column did not reveal any unchanged *cis*-isomer while 16.4 mg. of the *trans*-form was recovered (m. p. 119.5–120° after one recrystallization). The yield was 91%.

The solution of an artificial mixture of 70.3 mg. of *trans*- and 56.2 mg. of *cis*-*p*-methylstilbene in 10 ml. of petroleum ether was developed on alumina (17.5 × 1.7 cm.) with 60 ml. of the solvent. This washing was completed in twenty-five min. Ten mm. below the top the *trans*-zone appeared (55 mm. wide), and after an empty section (30 mm.) the *cis*-zone followed (50 mm. wide). Elution with 65 ml. of ether and evaporation yielded 68.6 mg. of the *trans*-isomer (m. p. 118–119°, without recrystallization) and 54.4 mg. of the *cis*-compound. The total recovery was 97%. The samples were chromatographically homogeneous.

On an alumina column (10.5 × 0.9 cm.) 0.3 mg. of *trans*-*p*-methylstilbene can easily be detected in admixture with 25.3 mg. of the *cis*-form or on a larger column (17.5 × 1.7 cm.) 1.8 mg. of the *cis*-form in 98.8 mg. of the *trans*-compound.

***cis*- and *trans*-*p*-Methoxystilbene.**—The synthesis of the *trans*-compound from diazotized *p*-anisidine and cinnamic acid was carried out according to Meerwein, *et al.*,[9] the product was purified chromatographically as described for *p*-methylstilbene. By filtering a benzene solution through activated alumina a by-product can be removed, the adsorbate of which fluoresces much stronger than that of the methoxystilbene. The pure compound melted at 135–136° after recrystallization from methanol. For the preparation of the *cis*-isomer a solution of 730 mg. in 35 ml. of benzene was irradiated for 160 hours (shorter irradiation is also satisfactory). A portion of the solution containing 161 mg. of substance was evaporated. The residue was taken up with 2.5 ml. of chloroform and, after the addition of an equal volume of petroleum ether, chromatographed on alumina (17.5 × 1.7 cm.). On developing with 70 ml. of a petroleum ether–benzene mixture (3:1) the following chromatogram appeared

0.5 brownish top layer (visible before brushing)
5 empty interzone
1 bright yellow by-product (visible before brushing)
6 empty interzone
40 *trans*-*p*-methoxystilbene (located by permanganate)
15 empty interzone
47 *cis*-*p*-methoxystilbene (located by permanganate)
60 empty bottom zone

Each main zone was eluted with 65 ml. of ether and treated as described for the *p*-methyl compound. The yield was 58.5 mg. of the *trans*-isomer (m. p. 135–136°, after recrystallization from methanol) and 79.1 mg. of the *cis*-form (colorless oil), the recovery being 86%. The oil was rechromatographed before analysis.

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.67; H, 6.72. Found: (*cis*) C, 85.76; H, 6.66; (*trans*) C, 85.31; H, 7.07.

2.2 mg. of the *cis*-isomer was detected in the presence of 95.4 mg. of the *trans*-form on alumina (17.5 × 1.7 cm.), and 1.5 mg. of *trans* in admixture with 86.6 mg. of *cis*-*p*-methoxystilbene.

Summary

The chromatographic brush method, with permanganate, has been used for the detection, separation and estimation of the *cis*- and *trans*-forms of stilbene, *p*-methylstilbene and *p*-methoxystilbene. In a mixture composed of two stereoisomeric compounds 1–2% of either form can be detected. The method can be used for the study of the interconversion of stilbene *cis*- and *trans*-isomers. Fluorescing contaminants can be removed by chromatography in ultraviolet light.

PASADENA, CALIF. RECEIVED MAY 5, 1942

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 891]

Chromatography of *cis* and *trans* Benzoin and Anisoin Oximes with Application of the Brush Method

BY L. ZECHMEISTER, W. H. MCNEELY AND G. SÓLYOM

It was shown recently that the brushing of a chromatographic column with a suitable color reagent[1] can be used for the detection, separation and estimation of *cis*- and *trans*-stilbenes.[2] This was made possible by the differences in adsorption affinities of stereoisomers which have been observed in various classes of compounds.[3] The present paper describes the application of the same principle to an investigation of the chromatographic behavior of some *cis*- and *trans*-oximes. According to Feigl,[4] a solution of *trans*-benzoin oxime (α or *anti*), $C_6H_5CHOHC(:NOH)C_6H_5$, gives a stable deep-green complex when treated with ammoniacal copper sulfate, while, according to Meisenheimer and Theilacker,[5] the complex obtained with the *cis*-isomer (β, *syn*) is brown. It is this behavior which has been made a basis for the application of the brush method. If two stereoisomeric oximes capable of complex formation are present in a solution, chromatography on a Neutrol Filtrol column shows that the *trans*-form is adsorbed near the top and gives a green brush reaction while the *cis*-isomer is located in a lower section and turns brown where the brush crosses it. Between the two layers an interzone is found, free of substance or containing only very little; no such interzone appears on any other adsorbent tested, including Floridin.[6]

The behavior of the two anisoin oximes, $CH_3O\text{-}C_6H_4CHOHC(:NOH)C_6H_4OCH_3$ is analogous.

If 40–200 mg. of a mixture of two stereoisomers is analyzed by the procedure described, 1–2% of either form can be detected. This allows a study of their interconversion under the influence of different factors. It was known that *cis*-benzoin oxime is isomerized by refluxing an alcoholic solution,[7] but our chromatographic experiments demonstrate that the *trans*-compound also isomerizes to a slight extent.

The analytical applicability is somewhat limited by the catalytic action of Neutrol Filtrol on some *cis*-oximes. If the rate of the chromatographic filtration is low and the duration of the experiment too long, the interzone which separates the *cis*- and *trans*-fractions contains small amounts of the *trans*-isomer formed on the column itself. The latter appears during the slow migration of the *cis*-oxime and is retained near the place of the conversion. In such a case the brush streak does not remain blue where it crosses the interzone, but takes on a slightly greenish tint within several minutes. In contrast, the main portion of the *trans*-compound which was present in the original solution and is adsorbed near the top, instantaneously gives a well-defined dark green color on brushing. This difference allows quantitative experiments to be carried out.

Under the conditions applied, the "column isomerization" amounts to less than 5% of the original quantity of *cis*-benzoin oxime and less than 1% of *cis*-anisoin oxime.

Acknowledgment.—The authors are indebted to Dr. G. Oppenheimer and Mr. G. Swinehart for microanalyses.

Experimental

Neutrol Filtrol (Filtrol Corp., Los Angeles) was used as an adsorbent. A trace of oil was removed either by hot extractions with benzene and then acetone, or by numerous extractions with benzene and alcohol–ether (1:1) at room temperature, with mechanical shaking. The adsorbent was dried at 90° for four hours. These operations increase the adsorptive power, but decrease the rate of filtration. Therefore, 17% Celite (no. 535) or Hyflo Super-Cel (Johns–Manville Co.) was used as a filter aid.

The color reagent was prepared by diluting 0.15 mole of copper sulfate and 4 moles of ammonia to one liter. The

(1) L. Zechmeister, L. Cholnoky and E. Ujhelyi, *Bull. soc. chim. biol.*, **18**, 1885 (1936); L. Zechmeister and O. Frehden, *ibid.*, **22**, 458 (1940).

(2) L. Zechmeister and W. H. McNeely, THIS JOURNAL, **64**, 1919 (1942).

(3) A. Winterstein and G. Stein, *Z. physiol. Chem.*, **220**, 247 (1933); A. H. Cook, *J. Chem. Soc.*, 876 (1938); A. H. Cook and D. G. Jones, *ibid.*, 1309 (1939); A. H. Cook, D. G. Jones and J. B. Polya, *ibid.*, 1315 (1939); L. Zechmeister, O. Frehden and P. Fischer Jörgensen, *Naturwiss.*, **26**, 495 (1938); L. Zechmeister and P. Tuzson, *Ber.*, **72**, 1340 (1939); L. Zechmeister, L. Cholnoky and A. Polgár, *ibid.*, **72**, 1678 and 2039 (1939); L. Zechmeister, A. L. Le Rosen, F. W. Went and L. Pauling, *Proc. Nat. Acad. Sciences*, **27**, 468 (1941); H. H. Strain, THIS JOURNAL, **63**, 3448 (1941); H. H. Strain, "Leaf Xanthophylls," Carnegie Inst. of Washington, No. 490 (1938).

(4) F. Feigl, *Ber.*, **56**, 2083 (1923); F. Feigl, G. Sicher and O. Singer, *Ber.*, **58**, 2294 (1925).

(5) J. Meisenheimer and W. Theilacker, in K. Freudenberg's "Stereochemie," F. Deuticke, Leipsig, 1933, p. 1019.

(6) A series of experiments with Floridin has been described by G. Sólyom in his Thesis (Univ. Pécs, 1940). This adsorbent has been now abandoned as the use of Neutrol Filtrol is far more satisfactory. The earlier experiments were carried out in collaboration with Dr. O. Frehden.

(7) A. Werner, *Ber.*, **23**, 2333 (1890).

melting points are corrected and were taken in an electrically heated Berl block.

***cis*- and *trans*-Benzoin Oxime.**—The oximes were prepared according to the data of Werner and Detscheff.[8] In repeated experiments, however, we were unable to obtain chromatographically homogeneous samples. Adsorption analysis revealed the presence of, for example, 1% of the *cis*-isomer in the *trans*-compound and 30% or more of the *trans*-isomer in the *cis*-compound. The latter when purified in this way showed the m. p. 99° as given by the authors mentioned. The *trans*-compound melted at 151°.

In order to purify *cis*-benzoin oxime, a solution of 1 g. in 100 ml. of a chloroform–benzene mixture (1:1) was poured on a column (19 × 3.2 cm.) and developed within thirty min. with 160 ml. of benzene containing 2% alcohol. After brushing with the reagent, the presence of the following zones was revealed (the colors given refer to the streak,[9] the figures on the left denote the width of the zones in millimeters)

5 sky blue (empty top section)
16 dark green (*trans*-benzoin oxime)
50 bluish green (small amounts of *trans*)
54 dark brown (*cis*-benzoin oxime)
65 sky blue (empty bottom section)

After cutting out the three zones and shaving off the streak, each of the two *trans*-fractions was eluted with 100 ml. of alcohol–ether (1:1) and the *cis*-fraction with the same volume of dry ether. The adsorbent was removed on a sintered glass funnel. Evaporation and analytical weighing indicated the presence of 181 mg. and 43 mg. of *trans*- and 722 mg. of *cis*-benzoin oxime, the total recovery being 95%. The melting point of the *trans*-compound was 147–148° after recrystallization from 2 ml. of ethanol. The oily *cis* fraction was dissolved in a few ml. of dry ether and evaporated in a carbon dioxide current at 25°. On scratching, it crystallized out (m. p. 99–99.5°).

Anal. Calcd. for $C_{14}H_{13}O_2N$: N, 6.17. Found: (*cis*) N, 6.38. Found: (*trans*) N, 6.15.

(a) An artificial mixture of equal parts (75 mg.) of *cis*- and *trans*-benzoin oxime was dissolved in 20 ml. of chloroform–benzene (2:1) and developed with 40 ml. of benzene containing 2% ethanol on a column (17.5 × 1.7 cm.) within twenty min.

2 sky blue (empty top section)
17 dark green (*trans*-benzoin oxime)
42 blue (trace of *trans*)
26 dark brown (*cis*-benzoin oxime)
88 sky blue (empty bottom section)

Fifty ml. of dry alcohol–ether (1:1) was used for the elution of the *trans*-zone, 40 ml. of the same mixture for the interzone and 40 ml. of ether for the *cis*-compound. The recovery was 74.5 mg. and 1.7 mg. of *trans*- and 70.1 mg. of *cis*-benzoin oxime; the melting points were correct.

(b) The limits of detection were established by experiments of the type (a). In the presence of 40 mg. of *trans*-benzoin oxime 0.4 mg. of the *cis*-isomer can be detected by washing with 12 ml. of benzene plus 2% ethanol (column: 10.5 × 0.9 cm.). In the presence of 100 mg. of *cis*-, 2 mg. of the *trans*-compound was detected on a larger column (17.5 × 1.7 cm.). Each experiment required twenty to twenty-five minutes.

(c) A solution of 50 mg. of chromatographed *cis*-benzoin oxime was refluxed in 25 ml. of alcohol for two hours, evaporated and taken up in 10 ml. of chloroform–benzene (1:1). The adsorption analysis showed two equally broad oxime zones from which 11.2 mg. of the *trans*- and 29.3 mg. of unchanged *cis*-compound were isolated in pure state. A similar experiment with *trans*-benzoin oxime showed only 1% isomerization.

(d) Two 125-mg. samples of chromatographically pure *cis*-benzoin oxime were dissolved in 10 ml. of chloroform–benzene (1:1). Each solution was developed on a column (17.5 × 1.7 cm.) with 50 ml. of benzene containing 2% alcohol. The development in one experiment was completed in twenty-two minutes using full suction. The development of the other column, carried out with very little suction, required three and one-fourth hours. In the first case the chromatogram showed a 66-mm. section (above the unchanged *cis* zone) which gave a very weak reaction for *trans* and contained 5.9 mg. of this isomer; 114.4 mg. of *cis*-compound was recovered.

In the slow experiment the 67-mm. upper zone gave a definite brush reaction for the *trans*-oxime and yielded 34.6 mg. of this compound formed by isomerization; 82.3 mg. of the starting material was recovered unchanged. The extent of isomerization during chromatography was 5 and 28%, respectively, in the rapid and slow experiment.

***cis*- and *trans*-Anisoin Oxime.**—Anisaldehyde (Eastman Kodak Co.) was fractioned *in vacuo;* it was then condensed to anisoin in the presence of potassium cyanide.[10] In spite of the correct melting point (112–113°) of the recrystallized product it proved to be chromatographically heterogeneous. For purification, 20 g. was dissolved in 0.8 liter of chloroform–benzene (1:1) and developed on a column (27 × 7 cm.) with 2.5 liters of benzene containing 0.5% ethanol. On brushing with 1% permanganate the anisoin was located in a 90-mm. zone near the top while a minor compound adsorbed below was discarded. The anisoin was eluted with 2 liters of alcohol–ether (10:1) and the solution concentrated in a carbon dioxide stream to 50 ml. The product was recrystallized from alcohol (17 g., m. p. 112–113°).

Anal. Calcd. for $C_{16}H_{16}O_4$: OCH_3, 22.79. Found: OCH_3, 22.68.

The oximation carried out as described by Werner and Detscheff[8] for benzoin oxime gave a mixture of both stereoisomers. For example, 2.3 g. of aqueous hydroxylamine hydrochloride (neutralized against litmus) was added to 4.5 g. of anisoin in 20 ml. of ethanol. After one and one-half hours of refluxing, the liquid was diluted with 150 ml. of water and allowed to stand overnight. The oil was dissolved in 300 ml. of benzene, dried with sodium sulfate, developed with 500 ml. of benzene containing 3% alcohol on a column (22.5 × 4.3 cm.) and brushed[9]

12 sky blue (empty top section)
73 dark green (*trans*-anisoin oxime)
56 bluish green (traces of *trans*)
1 pink without brushing (unknown)
35 dark brown (*cis*-anisoin oxime)
48 sky blue (empty bottom section)

(8) A. Werner and Th. Detscheff, *Ber.*, **38**, 69 (1905); *cf.* L. Malatesta, *Gazz. chim. ital.*, **68**, 319 (1938).

(9) In some cases the *cis*-zone showed a pale yellow color before brushing. This color darkens in air.

(10) M. Bösler, *Ber.*, **14**, 323 (1881); R. Stierlin, *ibid.*, **22**, 376 (1889).

The *trans*-compound was eluted with 450 ml. of anhydrous alcohol–ether (1:1) and the *cis*-isomer with 250 ml. of dry ether. The solvents were removed *in vacuo*.

The *trans*-oxime appeared as an oil and was crystallized by dissolving it in about 50 ml. of benzene at 25° and scratching. The yield was 1.9 g.; the colorless, short, quadrangular plates melted at 125.5°. The *cis*-compound came out in the form of crystals which contained ether. These were dissolved in 6 ml. of acetone at room temperature and rapidly evaporated with a carbon dioxide stream at 25°. The oily residue was evaporated with 2 ml. of benzene, dissolved in 10 ml. of cold benzene and scratched. Thin, elongated, colorless prisms appeared (1.2 g., m. p. 121–122°).

Anal. Calcd. for $C_{16}H_{17}O_4N$: N, 4.88. Found: (*cis*) N, 5.08; (*trans*) N, 4.99.

The difference in the melting points of the two isomers is remarkably small. The configurations, however, are given by the location on the column and by the color reactions. Chromatography showed the presence of less than 1% of the *cis*-compound in the *trans*-sample and *vice versa*.

(a) A mixture of 75 mg. of each isomer was dissolved in 35 ml. of benzene by slight warming, developed on a column (14 × 1.7 cm.) with 50 ml. of benzene containing 3% abs. alcohol, and brushed:

10 sky blue (empty top section)
21 dark green (*trans*-anisoin oxime)
37 blue (interzone)
7 dark brown (*cis*-anisoin oxime)
65 sky blue (bottom section containing a faint yellow line)

After elution with 55 ml. of the solvent mentioned, 69.2 mg. of *trans*-oxime (m. p. 125–125.5°, after crystallization from cold benzene) and 68.3 mg. of *cis*-oxime (m. p. 122.5–123.5°, after crystallization) were isolated, the total recovery being 92%. The interzone yielded 0.8 mg. of the *trans*-compound.

(b) It was found in similar adsorption experiments that 1.6 mg. of *cis*-anisoin oxime can be detected in the presence of 200 mg. of the *trans*-isomer or 1.2 mg. of *trans*- in the presence of 135 mg. of the *cis*-compound. The limit is 0.5–1%.

(c) A solution of 140 mg. of *cis*-anisoin oxime in 40 ml. of ethyl alcohol was refluxed for one and one-half hours. After removing the solvent and chromatographing as described in expt. (a), a 6-mm. zone was located above the main zone by brushing. This contained 11.5 mg. (8%) of the *trans*-compound, formed by isomerization. A parallel experiment carried out with *trans*-anisoin oxime yielded 2.5% of formed *cis*-isomer.

(d) A solution of 125 mg. of pure *cis*-anisoin oxime in 30 ml. of benzene was developed in three and one-fourth hours on a column (17.5 × 1 cm.) with 50 ml. of benzene containing 3% absolute alcohol. From the interzone 13.7 mg. of the *trans*-isomer was isolated. The extent of the "column isomerization" amounted to 11% in this case while the corresponding figure for a short experiment is about 1%.

Summary

The chromatographic brush method, with an ammoniacal copper solution as color reagent, has been used for the detection and separation of *cis*- and *trans*-benzoin and anisoin oximes on Neutrol Filtrol columns. In a mixture composed of two stereoisomers, 1–2% of either form can be rapidly detected in the presence of the other. Some data concerning the interconversion of stereoisomeric oximes are given, and the influence of the adsorbent on the *cis-trans* shift is discussed.

PASADENA, CALIFORNIA RECEIVED MAY 18, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WELLESLEY COLLEGE]

The Configuration of Organic Coördination Compounds of Nickel, with Especial Reference to Bis-formylcamphor-ethylenediamine-nickel

BY H. S. FRENCH, M. Z. MAGEE[1] AND E. SHEFFIELD[1]

Evidence is accumulating from various groups of investigators which may ultimately furnish an answer to the question implied in Pauling's[2] statement that "factors which determine whether the diamagnetic square or the paramagnetic tetrahedral configurations will be assumed by a nickel complex cannot be stated precisely." The present paper seeks to add to the evidence results of three different types: first, the magnetic susceptibilities of nine compounds; second, the absorption spectra of four of these compounds; and third, the *relation between* the adsorption spectrum and rotatory dispersion of a single one of the compounds.

Magnetic Susceptibility.—Determination of magnetic susceptibility is probably the most generally used method for the study of the configuration of the quadricovalent nickel complexes, since diamagnetism is associated with the square coplanar configuration and no unpaired electrons, while paramagnetism is associated with the tetrahedral configuration and two unpaired electrons. Pauling[3] has given the most satisfactory explanation for this change in the number

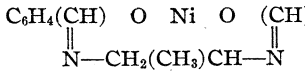
(1) Taken in part from the M.A. Thesis of M. Z. Magee and from the Honors Thesis of E. Sheffield.

(2) Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, p. 112.

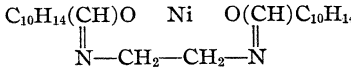
(3) Pauling, *ibid.*, p. 111.

of unpaired electrons by his theory of the hybridization of bond orbitals. The nine compounds chosen for this study of magnetic susceptibility are the following

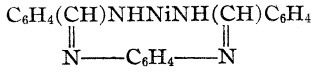
(I) bis-salicylaldehyde nickel $(C_6H_4(CHO)O)_2Ni$
(II) bis-*o*-hydroxyacetophenone nickel $(CH_3COC_6H_4O)_2Ni$
(III) bis-formylcamphor nickel $(C_{10}H_{14}(CHO)O)_2Ni$
(IV) bis-salicylaldimine nickel $(C_6H_4(CH{=}NH)O)_2Ni$
(V) bis-*o*-hydroxyacetophenoneimine nickel $(CH_3C{=}NHC_6H_4O)_2Ni$
(VI) bis-salicylaldehyde-propylenediamine nickel



(VII) bis-formyl camphor ethylenediamine nickel



(VIII) bis-*o*-aminobenzalimine nickel $(C_6H_4(CH{=}NH)NH)_2Ni$
(IX) bis-*o*-aminobenzaldehyde phenylenediamine nickel



Since no new methods of preparation were used for any of the compounds studied, we refer to the original directions by footnotes in Table I. We include also in Table I, the results of the analyses for nickel, and of the magnetic susceptibility determinations. Magnetic susceptibilities were measured by the Gouy[4] method and from these the magnetic moments in Bohr magnetons were calculated in the usual way.[5] The analyses for nickel were carried out on the micro-scale by igniting the compound to the oxides of nickel, and reducing the oxides to nickel in a stream of hydrogen.

TABLE I

Compound		% Ni Calcd.	% Ni Found	$\chi_{mol.} \times 10^6$	μ
A	I[a,b]	17.43	17.47	4265	3.2
	II[c]	12.06	11.97	3884	3.1
	III[d]	12.96	12.94	4857	3.4
B	IV[a]	19.65	19.69	Diamagnetic	
	V[e]	17.96	17.84	Diamagnetic	
	VI[e]	17.33	17.27	Diamagnetic	
	VII[f]	13.31	13.27	1522 (diamagnetic solid)	1.9
C	VIII[e]	19.87	19.68	Diamagnetic	
	IX[g]	15.83	15.61	Diamagnetic	

[a] Adams and Tyson, THIS JOURNAL, **62**, 1228 (1940). Their values for %Ni, $\chi_m \times 10^6$, and μ are 17.53, 3851, and 3.1 for I, and 19.70, diamagnetic for IV.

[b] Mellor and Craig, *J. Proc. Roy. Soc. N. S. Wales*, **74**, 478 (1941). Their values for $\chi_m \times 10^6$ and μ are 4230 and 3.2 for I.

[c] Pfeiffer, Buchholz and Bauer, *J. prakt. Chem.*, **129**, 172 (1931).

[d] French and Corbett, THIS JOURNAL, **62**, 3221 (1940).

[e] Pfeiffer, Hesse, Pfitzner, Scholl and Thielert, *J. prakt. Chem.*, **149**, 255 (1937).

[f] Pfeiffer, Christelheit, Hesse, Pfitzner and Thielert, *ibid.*, **150**, 261 (1938).

[g] Pfeiffer, Breith, Lübbe and Tsumaki, *Ann.*, **503**, 101 (1933).

Absorption Spectra.—The absorption spectra of the two pairs of compounds, I and VI, III[d] and VII were investigated in both the visible and ultraviolet regions. The method used in the ultraviolet region is the same as in previous com-

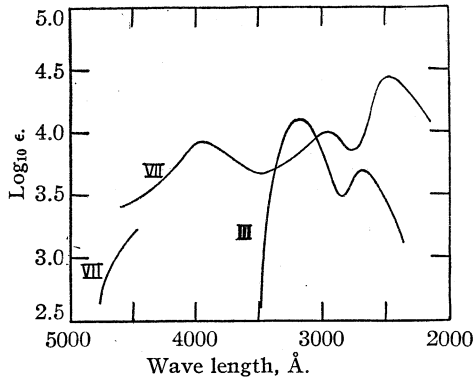


Fig. 1.—Curve III: absorption spectrum of bis-formyl camphor nickel in methyl alcohol[d]; curve VII, absorption spectrum of bis-formyl camphor ethylenediamine nickel in methyl alcohol.

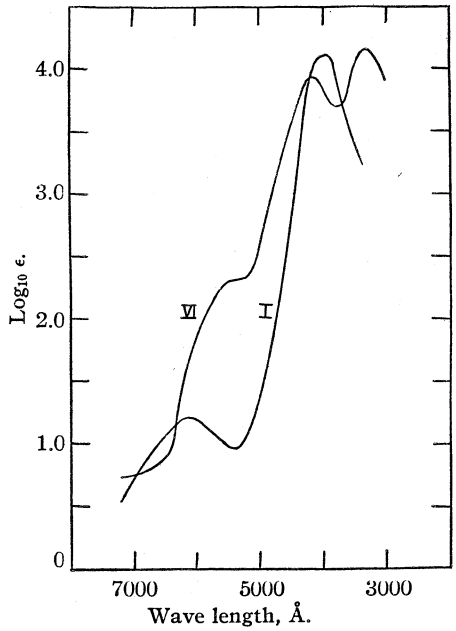


Fig. 2.—Curve I, absorption spectrum of bis-salicylaldehyde nickel in pyridine; curve VI, absorption spectrum of bis-salicylaldehyde propylenediamine nickel in pyridine.

(4) Gouy, *Compt. rend.*, **109**, 935 (1889).
(5) Pauling, *loc. cit.*, pp. 105–106.

munications from this Laboratory.[d] The method used in the visible region has already been described.[6] The results are shown in Figs. 1, 2 and curve AB in Fig. 3.

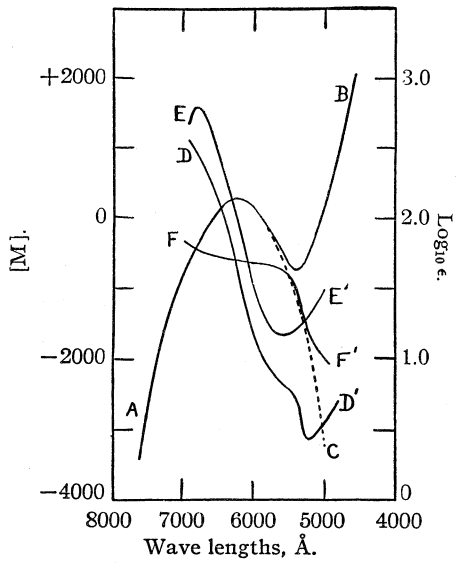


Fig. 3.—Bis-formyl camphor ethylenediamine nickel: AB, observed absorption spectrum; AC, calculated absorption band; DD′, observed rotatory dispersion[f]; EE′, calculated rotatory dispersion; FF′, residual rotatory dispersion.

Analysis of Rotatory Dispersion and Absorption Spectra.—Our third method of investigation was described in detail in a recent communication[d] from this Laboratory. This method has now been applied to compound VII. The experimental rotatory dispersion curve is drawn from Pfeiffer's[f] data. The absorption spectrum in both the visible and ultraviolet regions is here shown for the first time.[7] The results of the analysis are shown in Fig. 3 and in Tables II, III and IV.

TABLE II

CALCULATED POINTS FOR THE THEORETICAL ABSORPTION BAND OF BIS-FORMYLCAMPHOR-ETHYLENEDIAMINE-NICKEL

$(\text{Log}_{10}\ \epsilon)_{max.} = 2.13$ at 6250 Å.; $\theta = 654.55$ Å.

λ		$\text{Log}_{10}\ \epsilon$	λ		$\text{Log}_{10}\ \epsilon$
6250		2.13	6750	5750	1.88
6300	6200	2.12	7000	5500	1.56
6400	6100	2.11	7250	5250	1.12
6500	6000	2.07	7500	5000	0.55

Discussion

Mellor and Craig[b] have suggested a useful classification of nickel compounds according merely to the four atoms joined to the nickel.

(6) French and Lowry, *Proc. Roy. Soc.* (London), **106A**, 511 (1924).

(7) Mills and Mellor, THIS JOURNAL, **64**, 181 (1942), mention a general maximum for such compounds at 385 mμ, but give no further details.

TABLE III

CALCULATED POINTS FOR THE ROTATORY DISPERSION GOVERNED BY THE ABSORPTION BAND AT 6250 Å. OF BIS-FORMYLCAMPHOR-ETHYLENEDIAMINE-NICKEL

λ	[M]	λ	[M]
6900	1485	5750	−1576
6750	1520	5600	−1659
6600	1293	5500	−1621
6400	702	5300	−1414
6250	0	5150	−1227
6100	− 579	5000	−1056
5900	−1284		

TABLE IV

CALCULATED POINTS FOR THE RESIDUAL ROTATORY DISPERSION OF BIS-FORMYLCAMPHOR-ETHYLENEDIAMINE-NICKEL

[M]	λ	1/[M]	λ^2
− 480	6800	20.83×10^{-4}	46.24×10^6
520	6600	19.23	43.55
550	6400	18.18	40.97
600	6200	16.66	38.49
620	6000	16.13	36.00
650	5800	15.40	33.64
720	5600	12.90	31.37
840	5500	11.90	30.25
1090	5400	9.18	29.16
1350	5300	7.41	28.09
1640	5200	6.10	27.04
1960	5000	5.10	25.00

We believe that it will be necessary in any final interpretation to subdivide these classes according to the chelate rings involved, as suggested by Diehl[8] or by Pfeiffer.[9] Our compounds I, II and III fall under Mellor and Craig's class A, in which nickel is joined to four oxygen atoms. Table I shows paramagnetic susceptibility for all three compounds, corresponding to two unpaired electrons and tetrahedral configuration. So far as we know, all class A compounds studied by other investigators are also paramagnetic. Class B includes compounds in which nickel is joined to two oxygen and two nitrogen atoms and it is in such compounds that previous investigators have failed to find any uniformity in magnetic susceptibility. Our compounds IV, V, VI and VII fall in this class. Table I shows diamagnetic susceptibility for all four compounds, corresponding to no unpaired electrons and square co-planar configuration. Compound VII offers the interesting peculiarity, however, that it is diamagnetic in the solid state, but paramagnetic in methyl alcohol solution. This peculiarity will be discussed later. Class C includes compounds in which nickel is joined to four nitrogen atoms. Table I shows our compounds VIII and IX in this

(8) Diehl, *Chem. Rev.*, **21**, 39–42 (1937).

(9) Pfeiffer, *Z. angew. Chem.*, **53**, 93–98 (1940).

class to be diamagnetic, and this fact is in accord with the results of other investigators for compounds in class C.

The absorption spectra studies have thus far been applied to too limited a number of compounds for reliable generalizations. In the four curves shown here it may be noted that the change of two oxygen atoms to two nitrogen atoms in otherwise similar nickel complexes has in each case (1) increased the number of absorption maxima, (2) moved the ultraviolet maxima to longer wave lengths, and (3) moved the visible maximum to shorter wave lengths. The last two effects result in the long-wave length bands approaching each other so closely that one may become merely a step-out in the nitrogen-containing complex. It must remain for further investigation to prove whether *many* absorption bands, including one poorly defined step-out, are always characteristic of diamagnetic, square co-planar nickel complexes, and whether such a phenomenon may serve as one criterion for configuration. Incidentally, it should be added that the substitution of nitrogen for oxygen in metallic coördination compounds frequently moves the visible absorption band characteristic of the metal to shorter wave lengths,[10] and also that the formation of a Schiff base from an ortho (or para) hydroxy aldehyde or ketone causes an additional band to appear in the absorption spectrum.[11] In general, the color in the solid state of the nitrogen-containing compounds of class B is reddish or yellowish, while that of the paramagnetic compounds of class A is green or blue.[7] The few exceptions to this statement thus far found emphasize the necessity for the complete absorption spectra investigations, which alone can show the responsibility for the apparent color being borne by the usual *two* nickel absorption bands.[12]

An earlier paper[d] from this Laboratory has already shown by the method of rotatory dispersion analysis that the nickel center in compound III (class A) has the tetrahedral configuration. The argument was there based on the fact that the rotatory dispersion of the molecule was governed almost entirely by the absorption band of the nickel center, and that only the tetrahedral nickel configuration could result in optical activity. The conclusion was confirmed by finding the compound strongly paramagnetic.

This method has now been applied to compound VII (class B). We find that a logical analysis of the rotatory dispersion (Fig. 3) is given by attributing a considerable degree of optical activity to the absorption band at 6250 Å., due to the nickel center of the molecule. Only by such an assumption is a curve of residual rotation obtained with no inflection within that absorption band. We have already noted that this compound is paramagnetic in methyl alcohol solution, and this fact confirms the conclusion from the rotational dispersion and absorption spectrum. Yet, in the solid state it is diamagnetic. Mellor and Craig[b] suggest two conditions for paramagnetism in class B: first, that the oxygen atom joined to the nickel was *not* previously an hydroxyl oxygen; second, that even if the oxygen atom was previously an hydroxyl oxygen (as in their bis-8-hydroxy-quinoline nickel and presumably in our tautomeric compound) steric effects function to force the bonds out of coplanar positions. Porter[13] similarly explains the unexpected paramagnetism of the nickel complex of 3,3′,5,5′-tetramethylpyrromethane-4,4′-dicarboxylate by steric interference of the substituted groups. Pfeiffer[9] states that only a slight displacement of the four bonds out of the plane is enough to give asymmetry of the metallic center. In our bis-formyl camphor ethylenediamine nickel the oxygen atoms joined to the nickel were at least in an enolic hydroxyl group, so that diamagnetism would be expected. The presence of the ethylenediamine ring would tend to preserve the coplanarity of the molecule rather than force the bonds toward the tetrahedral configuration. A determining factor working in the opposite direction, however, is the presence of asymmetric centers in the camphor rings. That such an asymmetric center induces asymmetry in the carbonyl group of camphor was shown by Kuhn and Gore[14] and is explained by Kuhn's[15] vicinal effect. Such induction might easily go further, after rendering the aldimine bonds asymmetric and cause sufficient strain at the nickel center for the slight "twist" necessary for asymmetry (and ionization ultimately). Such "twist" might not occur in the solid state (hence diamagnetism) but

(10) French and Lowry, *Proc. Roy. Soc.* (London), **106**, 502 (1924).

(11) This conclusion is drawn from a study of the absorption spectra of Schiff bases from Varga, *Magyar Chem. Folyoirat*, **45**, 83 (1939).

(12) Datta and Deb, *Phil. Mag.*, **20**, 1121 (1935); Bäckström, *Arkiv. Kemi, Mineral. Geol.*, **13A**, No. 24, 16 (1940); Bhagwat, *J. Indian Chem. Soc.*, **17**, 53 (1940).

(13) Porter, *J. Chem. Soc.*, 368 (1938).

(14) Kuhn and Gore, *Z. physik. Chem.*, **12**, 389 (1931).

(15) Kuhn and Braun, *ibid.*, **8**, 281 (1930).

might be made possible under the influence of the solvent methyl alcohol. The fact that the change is not complete but that an equilibrium exists in methyl alcohol is indicated both (1) by the low value of the magnetic susceptibility and (2) by the effect of dilution on the absorption spectrum, especially in the region governed by the nickel aldimine complex band (step-out) at about 4500 Å.

We might go further and suggest that this equilibrium in methyl alcohol solution consists of approximately one-third of the paramagnetic form and two-thirds of the diamagnetic form of the molecules, since the observed value of the magnetic susceptibility is approximately one-third as great as the value to be expected for a paramagnetic compound of this type.

Confirmation of the interpretation just given for our results comes from further consideration of the curve for residual rotatory dispersion. When the values of $1/M$ are plotted against λ^2 for this curve, the points do not yet lie on a straight line, showing that at least two other absorption bands are optically active. It is possible, but not advisable without further experimental data, to analyze further the residual curve into two others, one governed by the band at 4500, due probably to the nickel aldimine complex, and the second by the far distant band of the camphor radical itself.

Summary

New data are presented on the visible and ultraviolet absorption spectrum of the nickel complex of formylcamphor-ethylenediamine and on its magnetic susceptibility in the solid state and in methyl alcohol solution. From an analysis of the relation between its rotatory dispersion and its absorption spectrum, and from the magnetic susceptibilities, the conclusion is drawn that the configuration of the nickel complex is square coplanar in the solid state, but strained and twisted under the influence of the asymmetric camphor to such an extent that the nickel center in methyl alcohol solution also is asymmetric and tends toward the tetrahedral configuration. New data are also presented for the magnetic susceptibilities of five other organic coördination compounds of nickel: with *o*-hydroxyacetophenone, *o*-hydroxyacetophenone imine, salicylic aldehyde propylenediamine, *o*-amino-benzalimine, and *o*-aminobenzaldehyde phenylenediamine. New data are given for the absorption spectra in the visible and ultraviolet of bis-salicylaldehyde nickel and bis-salicylaldehyde-propylenediamine-nickel. Tentative conclusions are drawn concerning the difference in absorption spectra of paramagnetic and diamagnetic compounds of the types studied.

WELLESLEY, MASS. RECEIVED MARCH 27, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Rate and Mechanism in the Reactions of *t*-Butyl Nitrate and of Benzyl Nitrate with Water and with Hydroxyl Ion[1]

BY GLENNARD R. LUCAS AND LOUIS P. HAMMETT

We have investigated kinetically the reactions with water and hydroxyl ion of two alkyl nitrates which illustrate the two kinds of reactions other than hydrolysis which such substances undergo in the presence of water.[2]

In the case of tertiary butyl nitrate the only reactions are the two solvolytic ones producing alcohol (A) and olefin (B).

$$C_4H_9ONO_2 + 2H_2O \xrightarrow{k_1} C_4H_9OH + H_3O^+ + NO_3^- \quad (A)$$

$$C_4H_9ONO_2 + H_2O \xrightarrow{k_2} C_4H_8 + H_3O^+ + NO_3^- \quad (B)$$

In the case of benzyl nitrate no olefin is produced but the solvolysis to benzyl alcohol and nitric acid (C) is accompanied by a likewise first order formation of benzaldehyde and nitrous acid (D).

$$C_6H_5CH_2ONO_2 + 2H_2O \xrightarrow{k_3} C_6H_5CH_2OH + H_3O^+ + NO_3^- \quad (C)$$

$$C_6H_5CH_2ONO_2 \xrightarrow[(H_2O)]{k_4} C_6H_5CHO + HNO_2 \quad (D)$$

These first order reactions are accompanied by second order reactions with hydroxyl ion leading to the same products.

$$C_6H_5CH_2ONO_2 + OH^- \xrightarrow{k_5} C_6H_5CH_2OH + NO_3^- \quad (E)$$

$$C_6H_5CH_2ONO_2 + OH^- \xrightarrow{k_6} C_6H_5CHO + H_2O + NO_2^- \quad (F)$$

(1) Dissertation submitted by Glennard Ralph Lucas in partial fulfilment of the requirements of the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

(2) Klason and Carlson, *Ber.*, **39**, 2752 (1906); **40**, 4183 (1907); Carlson, *ibid.*, **40**, 4191 (1907).

Experimental

Apparatus.—Only calibrated weights and volumetric apparatus were used. The temperatures were determined by thermometers calibrated by the Bureau of Standards. The thermostats used at 25 and 50° were of the conventional type; that employed at 0.3 and 10° was the one previously described.[3] The timing of the very fast runs was done with an A. R. & J. E. Meylan one-fifth second split timer.

Tertiary Butyl Nitrate.—Following the procedure of Michael and Carlson,[4] *t*-butyl nitrate was prepared from tertiary butyl alcohol (Eastman Kodak Co. best grade) and 98.6% nitric acid. The product was separated by distillation under vacuum through a 20-in. jacketed column with reflux ratio kept high by means of a cold-tip finger condenser; b. p. 22–23° at 4 mm. The last traces of methylene chloride and nitric acid were removed by repeated partial crystallization without solvent. The crystals were allowed to form slowly until approximately three-fourths was crystallized and the remaining liquid removed through a sintered glass filter. The degree of purity was tested in an air-jacketed test-tube cooled by solid carbon dioxide at a rate of one degree per minute. The material accepted as pure gave a constant freezing point out to half crystallization, was colorless and free from acid; m. p. −34 to −35°. Titration of the acid formed on complete hydrolysis indicated 99.9% purity. For further test 5.00 g. of the *t*-butyl nitrate was added to 8.0 g. of dimethylaniline and warmed. The nitrate salt which crystallized on cooling was washed free of dimethylaniline with dry ether, yielding 7.21 g.; calcd. 7.23; m. p. 82–83°.

In some preparations the ester was colorless but not free from acid after the above recrystallization procedure. Rate measurements on this ester agree within experimental error with those made on the pure material when allowance is made for the effect of electrolyte. The purified ester was sealed in amber ampoules and kept frozen in dry-ice until used.

Benzyl Nitrate.—Following the procedure of Nef,[5] benzyl nitrate was prepared from powdered silver nitrate and benzyl chloride (Mallinckrodt Analytical grade) in dry ether. For complete conversion it was found desirable to add fresh silver nitrate from time to time. After twenty hours at room temperature the ether was distilled off and the product held at 70–75° for five hours. After cooling, the liquid was decanted and the residue extracted with ether and dried over calcium chloride. Fresh silver nitrate was added to the filtered ether solution, the ether removed and the benzyl nitrate distilled directly from silver nitrate. The main fraction (b. p. 72.5–73.5° at 4–5 mm.) was found by refluxing with alcoholic silver nitrate to be chloride free, $n^{25}D$ 1.5180. Redistillation gave fractions with the same constant refractive index. *Anal.* Calcd. for $C_7H_7NO_3$: C, 54.9; H, 4.61. Found: C, 55.2; H, 4.63. The purified ester was kept in a dark bottle in a desiccator over phosphorus pentoxide.

Other Materials.—1,4-Dioxane (Carbide and Carbon Chemical Co.) was purified in 3–4 liter quantities as described by Beste and Hammett.[6]

Sodium perchlorate solution was prepared from Mallinckrodt A. C. S. grade perchloric acid 99.8% neutralized with carbon dioxide-free sodium hydroxide solution. Tests on this solution showed no detectable traces of chloride. The perchloric acid solution that was added to runs was made from the same stock acid.

The potassium bromide and potassium bromate used for the olefin determination and the potassium nitrate and lithium nitrate used in the runs were A. C. S. grade, recrystallized from water and dried over phosphorus pentoxide. Anhydrous lithium nitrate is so hygroscopic that the concentration was probably lower than that indicated because of water absorbed in the weighing process.

The primary standard for titration was Bureau of Standards acid potassium phthalate.

Method.—The solvent in all kinetic experiments was a mixture of dioxane and water in the proportions indicated; that is, in an experiment in "60% dioxane" the proportions of dioxane and water were 60 to 40 by weight. In the case of experiments containing sodium hydroxide, sodium perchlorate or perchloric acid, these solutes were introduced as solutions at the time the solvent was prepared, and correction was made for the amount of water displaced by these solutes. All other solutes were weighed out and added directly.

In starting experiments the reaction bottle with all solutes except the ester was placed in the thermostat to reach temperature equilibrium. In the case of *t*-butyl nitrate, the ester was then removed from the dewar where it was stored, allowed to melt and the approximate amount transferred by means of a graduated pipet, the bottle was shaken and the initial time taken. The exact initial ester concentration was determined by delivering duplicate samples into 40% dioxane at room temperature. The hydrolysis in this medium is complete in a few minutes and the total ester concentration was found by titration of the acid produced. Samples for analysis were withdrawn at convenient intervals using a 5-ml. pipet and delivered into cold dioxane of such volume that in the following titration the dioxane composition always exceeded 80%. In the runs at 0 and 10° the pipet was kept in a well in the thermostat between samples.

In the case of benzyl nitrate, after the mixture had reached temperature equilibrium in the thermostat, the ester was weighed in and the initial time taken. At convenient intervals 10-ml. samples were withdrawn for analysis. In the runs at 50° the dried pipet, initially at room temperature, delivered reproducible volumes of the reaction solution if the sampling was done rapidly. The water reaction was arrested by pipetting the samples into dioxane at room temperature. The hydroxide reaction was stopped by pipetting the samples into an excess of standard nitric acid and dioxane. To reduce further reaction to a negligible level and to prevent the unreacted benzyl nitrate from separating, the dioxane was kept above 50% in the titrating flask. In the solvolytic runs where the percentage benzaldehyde was determined the solvent containing all solutes except the ester was cooled to ice temperature, the ester added and portions of this reaction mixture were placed in 10-ml. ampoules. After freezing solid in a dry-ice bath the ampoules were evacuated and sealed. The initial time was taken when the ampoules were placed in the thermostat.

(3) Price and Hammett, THIS JOURNAL, **63**, 2389 (1941).
(4) Michael and Carlson, *ibid.*, **57**, 1268 (1935).
(5) Nef, *Ann.*, **309**, 171 (1899).
(6) Beste and Hammett, THIS JOURNAL, **62**, 2481 (1940).

Isobutene was determined by a modification of the method of Lucas and Eberz[7] using a standard bromide–bromate solution to liberate bromine and back-titrating with thiosulfate after conversion to iodine. The sample was delivered into glass-stoppered iodine flasks containing a five-fold excess of the neutral bromide-bromate solution; 5 ml. of 6 *N* sulfuric acid was quickly added and the walls washed down with 15 ml. of water. After tightly stoppering, the flask was kept in the dark and shaken frequently for five minutes. The flask was then chilled under running water and saturated, freshly-prepared potassium iodide solution was allowed to be sucked in by carefully lifting the stopper slightly. When a few cc. had been admitted, the stopper was replaced and the flask thoroughly shaken. The stopper was washed free of iodine and removed, and the excess iodine was titrated with thiosulfate. The blank depends slightly on the volume of dioxane in the sample and is reproducible. A correction must be made for the olefin produced by the nearly instantaneous hydrolysis of the unreacted *t*-butyl nitrate. Using the above procedure with *t*-butyl nitrate in 100% dioxane, four blank experiments showed that 2.99 ± 0.01% of the ester was converted to isobutene durings its rapid hydrolysis.

Benzaldehyde was determined by the method of Eitel and Lock,[8] by producing the 2,4-dinitrophenylhydrazone of benzaldehyde and determining it gravimetrically. For small samples drying to constant weight in a vacuum desiccator over phosphorus pentoxide was found more satisfactory than heating in the oven. To prevent the separation of unreacted benzyl nitrate the samples of solution tested had to be kept small. Somewhat larger samples could be added where the precipitating medium for the hydrazone was 50% cold alcohol. The two methods gave consistent results when used in the runs or with standard solutions of benzaldehyde to which benzyl nitrate had been added.

In following the acid production, phenolphthalein is unsatisfactory where much dioxane is present. Brom cresol purple gave a sharp end-point in media containing about 50% dioxane and was consequently used in titrations of the benzyl nitrate runs. Brom phenol blue gave a very sharp end-point in 80–90% dioxane and was used in the *t*-butyl nitrate runs.

Rate Calculations.—The following abbreviations will be used in this section: a is the initial concentration of tertiary butyl nitrate, b initial concentration of hydroxide, c initial concentration of benzyl nitrate, x concentration of acid produced at time t, t time in seconds. The *t*-butyl group will be written Bu, the benzyl group Bz and the phenyl group Ph.

Data for the water reactions (A) and (B) were calculated according to the equation $\ln a/(a - x) = kt$ where $k = k_1 + k_2$; $a = [H^+]_\infty$ or $\{[H]^+_\infty - [H^+]_t\}_0$ in the cases where $[H^+]_0 \neq 0$ and $(a - x) = [H^+]_\infty - [H^+]_t$. The slope of the plot of $\ln (a - x)$ against t increases slightly during the course of a given experiment. For purposes of comparison the initial value of k was obtained from the empirical equation $-\ln (a - x) = -\ln a + (k)_0 t + Kt^2$; the coefficients of this equation were calculated by the method of averages,[9] whereby adjacent experimental points were used to obtain each of the three simultaneous equations. The values of k_1 and k_2 were established by determination of the per cent. olefin produced.

In the runs in the presence of sodium chloride and sodium toluenesulfonate the curve follows too complicated a course to be satisfied by this three constant equation. This is probably because the nitrate ester is gradually being replaced by chloride or toluenesulfonate ester which have slower rates of hydrolysis. Here the initial rates were determined by means of graphical differentiation.

Data for the water reactions of benzyl nitrate (C) and (D) were calculated according to the equation $\ln c/(c - x) = k't$ where $k' = k_3 + k_4$. Here again the plot of $ln\ (c - x)$ against time gave an increasing slope and the initial value was found by the method of averages. The respective values of k_3 and k_4 were established by determination of the per cent. benzaldehyde produced.

In the presence of hydroxyl ion we are concerned with reactions (C), (D), (E) and (F). The rate of disappearance of nitrate ester is given by

$$-\mathrm{d}[BzNO_3]/dt = k_3[BzNO_3] + k_4[BzNO_3] + k_5[BzNO_3][OH^-] + k_6[BzNO_3][OH^-] \quad (1)$$

which may be written

$$-\mathrm{d}[BzNO_3]/dt = k'[BzNO_3] + k''[BzNO_3][OH^-] \quad (2)$$

where

$$k' = k_3 + k_4 \text{ and} \quad (3)$$

$$k'' = k_5 + k_6 \quad (4)$$

The above equation is best solved by writing in the form

$$-\mathrm{d}[BzNO_3]/dt = k'''[BzNO_3][OH^-] \quad (5)$$

where

$$k''' = k'' + (k'/[OH^-]) \quad (6)$$

The value of k''' may be obtained by a plot of $\frac{1}{c - b} \ln \frac{c - x}{b - x}$ against time. The method of averages is again used to determine the initial value of the slope. The value of $(k'')_0$ may then be evaluated from equation (6) using the $(k')_0$ independently determined from hydrolysis measurements. Some uncertainty exists concerning the value of $(k')_0$ to be used. Those independently

(7) Lucas and Eberz, *ibid.*, **56**, 461 (1934).

(8) Eitel and Lock, *Monatsh.*, **72**, 385 (1939).

(9) Daniels, "Mathematical Preparation for Physical Chemistry," McGraw Hill Book Co., Inc., New York, N. Y., 1928, p. 235.

measured were of necessity obtained in the absence of hydroxyl ion. The data on *t*-butyl nitrate indicated that a solvolysis reaction may proceed more slowly in the presence of hydroxyl ion than in the solvent alone and at a much slower rate than in the presence of a corresponding concentration of sodium perchlorate. The rate constants were therefore evaluated on the assumption that $(k')_0$ is not changed by the addition of sodium hydroxide.

Examination of these four equations shows that the rate of benzaldehyde production is given by

$$d[PhCHO]/dt = k_4[BzNO_3] + k_6[BzNO_3][OH^-] \quad (7)$$

and combining equations (5) and (7), we obtain

$$\text{Fraction PhCHO formed in reaction} = \frac{k_4[BzNO_3] + k_6[BzNO_3][OH^-]}{k'''[BzNO_3][OH^-]} \quad (8)$$

Solving for k_6

$$k_6 = k''' x \text{ (fraction PhCHO)} - (k_4/[OH^-]) \quad (9)$$

and using this value of k_6 we obtain k_5

$$k_5 = k'' - k_6 \quad (10)$$

Errors.—Since the results of this research are based on the determination of initial slopes of curves, it is difficult to estimate the precision with which specific rates are known. In general it involves a consideration of duplicate experiments and of the deviation of the individual points of the run from the empirical equation which best fits the data. Careful examination of the data indicates a probable error of 1.5% in $(k)_0$ and $(k')_0$ each of which is the sum of two solvolytic reactions. The percentage of olefin produced is the average of two or three independent determinations and the precision varies from 1 part in 50 to 1 part in 400 as the proportion of olefin increases. Consequently the precision of the constant k_2 varies in the same way. The error in k_1 will be about the same as that in k. The reported percentage of benzaldehyde is also the average of two or more determinations and the precision varies from 1 part in 5 to 1 part in 60 according to the proportion of benzaldehyde. The initial specific rate constants $(k''')_0$ in the hydroxide reaction have a probable error of 2.0 to 2.5% but the lack of precision in the benzaldehyde determination increases the probable error of $(k_5)_0$ and $(k_6)_0$ to 3–5%.

Sample Data.—For the sake of uniformity the constants reported in the tables of results are those at the initial time. It is, however, of some importance to indicate how the specific rate changes during the course of a reaction; a skeleton record is therefore given for a typical experiment on each of the reactions studied (Tables I, II and III).

In Table I the values of k were calculated from the empirical equation

$$-\ln (a - x) = 2.3497 + (3.33_5 \times 10^{-5})t + (8.92 \times 10^{-11})t^2$$

This equation was obtained from the experimental points of Table I by grouping the first three, the second three and the last three to obtain three simultaneous equations according to the method of averages mentioned above. For the olefin determination the ester concentration was found by solving the above equation for $(a - x)$ at the given time. Applying the correction for the olefin produced by the unreacted butyl nitrate, the percentage of x, or moles reacted, going to olefin is determined. The isobutene concentration given in quotation marks is the indicated olefin concentration from the thiosulfate titer, before the correction is made.

TABLE I

TYPICAL EXPERIMENTAL RECORD FOR THE WATER REACTION OF *t*-BUTYL NITRATE, TIME IN SECONDS

Expt. 63: 85% dioxane at 25°; initial concn. $BuNO_3$ = 0.09543

t, sec.	Acid titer[a]	$[H_3O^+]$	$-\ln[BuNO_3]$	$(k) \times 10^5$
0		0.00490	2.3497	3.335
300	1.11	.00589	2.3601	3.340
4080	3.24	.01719	2.4876	3.407
5640	4.04	.02144	2.5400	3.435
7680	5.05	.02680	2.6104	3.472
10140	6.20	.03290	2.6970	3.515
11580	6.84	.03629	2.7487	3.542
16920	8.96	.04754	2.9419	3.637
19860	10.00	.05306	3.0523	3.688
25260	11.59	.06123	3.2420	3.785

t, sec.	*x*	Thiosulfate titer[b]	"$[C_4H_8]$"	$[C_4H_8]$	% Olefin
26400	0.05828	2.38	0.01012	0.00901	15.46
28260	.06080	2.39	.01017	.00913	15.02
623000	.09543	3.49	.01484	.01484	15.53
				Av.	15.35

[a] In ml. of 0.02652 *N* NaOH per 4.998 ml. sample.
[b] In ml. of 0.04251 *M* $Na_2S_2O_3$ per 4.998 ml. sample.

In Table II the values of (k') were calculated from the empirical equation

$$-\ln (c - x) = 2.2562 + (1.57_1 \times 10^{-6})\,t + (2.16 \times 10^{-13})t^2.$$

This equation was obtained like the one for Table I by grouping the points in threes to make three simultaneous equations. The amount of benzal-

dehyde was determined gravimetrically in the way indicated and converted to molar concentration of aldehyde.

TABLE II

TYPICAL EXPERIMENTAL RECORD FOR THE WATER REACTION OF BENZYL NITRATE, TIME IN SECONDS

Expt. 151: 60% dioxane at 50°; initial concn. $BzNO_3$ = 0.10530.

t, sec.	Acid titer[a]	$[H_3O^+]$	$-\ln[BzNO_3]$	$(k') \times 10^6$
0	0	0	2.2562	1.571
10872	0.86	0.00227	2.2731	1.576
52524	3.36	.00887	2.3393	1.594
77436	4.79	.01264	2.3793	1.604
104184	6.28	.01658	2.4226	1.616
143712	8.35	.02204	2.4862	1.633
169200	9.64	.02545	2.5280	1.644
229608	12.50	.03300	2.6273	1.670
256320	13.75	.03629	2.6740	1.682

t, sec.	x	2,4-Dinitrophenylhydrazone,[b] g.	[PhCHO]	% PhCHO
400068	0.05131	0.0098	0.003351	6.5
582912	.06633	.0116	.003966	6.0
			Av.	6.25

[a] In ml. of 0.02652 N NaOH per 10.047 ml. sample.
[b] From 10.222 ml. sample.

In Table III the values of (k''') were calculated from the empirical equation

$$\frac{1}{b-c}\ln\frac{b-x}{c-x} = 10.959 + (4.69_3 \times 10^{-4})t + (3.97 \times 10^{-9})t^2$$

This equation was obtained from the experimental points by grouping as before. The value of x was obtained from this equation for the calculation of the per cent. benzaldehyde produced. While in this experiment the percentage converted to benzaldehyde appears to increase slightly during the course of the reaction, this effect was not reproducible and in calculation of (k_5) and (k_6) by equations (9) and (10) the average value was used.

Results

Data for tertiary butyl nitrate solvolysis in the presence and in the absence of various salts are given in Tables IV and V, the data being subdivided according to the medium and temperature indicated. In the experiments listed in Table IV only the total rate constant $(k)_0$ was determined, while in those in Table V $(k)_0$ is divided into $(k_1)_0$ and $(k_2)_0$ and the percentage olefin produced is indicated. By comparison of Table I and Table IV it may be seen that the values of k in a given reaction mixture drift upward as the reaction proceeds approximately as one would predict from the changing ester concentration and the increasing concentration of nitrate ion.

Data for benzyl nitrate solvolysis in 60% dioxane at two temperatures are given in Table VI, the constants listed being $(k')_0$ the sum in each case of $(k_3)_0$ and $(k_4)_0$; in Table VII experiments where the percentage benzaldehyde produced was determined are listed and the corresponding values of $(k_3)_0$ and $(k_4)_0$ are indicated. In Table VIII are listed data showing $(k_5)_0$ and $(k_6)_0$ for the benzyl nitrate–hydroxyl ion reaction.

In Table IX are listed the energies of activation of the various reactions.

TABLE III

TYPICAL EXPERIMENTAL RECORD FOR HYDROXYL ION REACTION OF BENZYL NITRATE, TIME IN SECONDS

Expt. 138: 60% dioxane 50°; initial concn. $BzNO_3$ = 0.07499; NaOH = 0.10961

t, sec.	$[OH^-]$	$[BzNO_3]$	$k''' \times 10^4$	$k'' \times 10^4$	$k_6 \times 10^4$	$k_5 \times 10^4$
0	0.10961	0.07499	4.693	4.546	1.594	2.952
804	.10709	.07247	4.757	4.606	1.616	2.990
2208	.10194	.06732	4.878	4.719	1.656	3.063
3450	.09727	.06265	4.967	4.799	1.687	3.112
4692	.09373	.05911	5.066	4.891	1.720	3.171
7530	.08674	.05212	5.291	5.101	1.796	3.305
9876	.08175	.04713	5.477	5.274	1.858	3.416
11790	.07768	.04306	5.629	5.415	1.909	3.506
15078	.07248	.03786	5.890	5.659	1.997	3.662
17712	.06770	.03308	6.09	5.851	2.067	3.784

t, sec.	x	2,4-Dinitrophenylhydrazone,[a] g.	[PhCHO]	% PhCHO
7608	0.02306	0.0223	0.00776	33.7
17604	.04260	.0426	.01482	34.8
			Av.	34.2

[a] From 10.047 ml. sample.

TABLE IV

INITIAL SPECIFIC RATES OF SOLVOLYSIS OF TERTIARY BUTYL NITRATE, TIME IN SECONDS

t, °C.	% Dioxane in solvent	Initial concn. $BuNO_3$	Added solutes concn. mole/l.		$(k)_0 \times 10^4$
25	95	0.12784	HNO_3	0.0230	0.01099
25	95	.11711	HNO_3	.0185	.01140
25	85	.12527	HNO_3	.0159	.3589
25	85	.12410	HNO_3	.0190	.3644
25	75	.13282	HNO_3	.0136	2.029
25	75	.12966	HNO_3	.0168	2.033
25	75	.10751	$NaClO_4$	.1109	2.793
25	75	.10688	$LiNO_3$	.1062	2.263
25	75	.10673	KNO_3	.1060	2.318
25	75	.10530	NaTs	.1053	2.217
25	75	.10390	$NaClO_4$	.1111	2.735
25	75	.10351	None		2.017
25	75	.10331	KNO_3	.1060	2.350
25	75	.10246	NaCl	.1065	2.214
25	75	.10172	$HClO_4$	.1158	2.746
25	75	.10083	NaCl	.1064	2.220
25	75	.09834	$NaClO_4$	.0840	3.137
			NaOH	.0280	
25	75	.09047	None		2.002
25	60	.14325	HNO_3	.0112	14.18
25	60	.13922	HNO_3	.0080	14.56
25	60	.05111	None		16.53
10	60	.07251	NaOH	.1096	2.218
10	60	.06975	$NaClO_4$	.1128	2.712
10	60	.06540	None		2.375
0.3	75	.14937	HNO_3	.0174	.06003
0.3	60	.14263	HNO_3	.0129	.4889
0.3	60	.13952	HNO_3	.0129	.4714
0.3	60	.06918	None		.5560
0.3	60	.06818	$NaClO_4$	.1133	.6660

thoroughly studied reactions of tertiary butyl halides, which likewise lead partly to alcohol and partly to olefin.[11]

Like benzyl chloride in a similar medium[6] benzyl nitrate shows a solvolytic reaction which predominates in neutral or acid media and a hydroxyl ion displacement which predominates in alkaline media. These reactions are accompanied by an oxidation–reduction reaction producing benzaldehyde which is both solvolytic and hydroxyl ion catalyzed.

Our data show that none of these reactions are catalyzed by acids in dilute solution.

Salt and Medium Effects.—As has been observed previously with other esters,[6,12] the specific rates of the solvolytic reactions (A) and (C) decrease with increasing concentration of ester. Table IV shows the sensitivity of such reactions to the composition of the medium, the rate increasing somewhat more than a thousand-fold in going from 95% to 60% dioxane, the temperature remaining constant. Table X shows for a 0.1 *M* solution of ester the percentage changes in specific rate produced by the addition of various solutes in the same concentration.

Similar but even larger effects are observed in the second order displacement reaction of benzyl nitrate with hydroxyl ion. At 25° $(k_6)_0$ is essentially unaffected by variations in concentration of ester and of hydroxyl ion. However, at 50°

TABLE V

INITIAL SPECIFIC RATES OF SOLVOLYSIS OF TERTIARY BUTYL NITRATE, $(k)_0$, $(k_1)_0$, AND $(k_2)_0$, TIME IN SECONDS

t, °C.	% Dioxane in solvent	Initial concn. $BuNO_3$	Added solutes concn., mole/l.		$(k)_0 \times 10^5$	% Olefin	$(k_1)_0 \times 10^5$	$(k_2)_0 \times 10^5$
25	95	0.11402			0.1429	44.91	0.0787	0.0642
25	85	.09543			3.335	15.35	2.821	.512
25	75	.15898			19.27	8.71	17.59	1.68
10	60	.12697	NaOH	0.1069	21.16	5.35	20.03	1.13
10	60	.12454			21.86	4.76	20.82	1.04
10	60	.12389	$NaClO_4$	.1124	25.77	4.50	24.61	1.16
0.3	60	.12992			5.167	4.24	4.948	.219
0.3	60	.12598	$NaClO_4$	.1127	6.168	4.05	5.918	.250

Discussion

General.—Like other *t*-butyl esters[10] the nitrate ester shows no acceleration of hydrolysis by hydroxyl ion except at high concentration of dioxane (see Table IV, hydroxide–perchlorate solute in 75% dioxane). In 60% dioxane a small retardation is produced by sodium hydroxide, the occasion for which will be discussed later. In all important respects the reaction behaves like the $(k_6)_0$ increases with decreasing concentration of either reactant, increasing by 57.0% in going from the largest ester and hydroxyl ion concentration to the lowest in each. At both temperatures $(k_5)_0$ shows an increase with decreasing ester concentration and a decrease with decreasing hydroxyl ion concentration. Since the ionic strength is maintained constant by the introduction of sodium perchlorate, the change in rate

(10) (a) Hughes, *J. Chem. Soc.*, 225 (1935); Cooper and Hughes, *ibid.*, 1183 (1937).

(11) Bateman, Cooper, Hughes and Ingold, *ibid.*, 925 (1940).

(12) McCleary and Hammett, THIS JOURNAL, **63**, 2254 (1941).

TABLE VI

INITIAL SPECIFIC RATES OF SOLVOLYSIS OF BENZYL NITRATE IN 60% DIOXANE, TIME IN SECONDS

Initial concn. $BzNO_3$	Added solutes concn., mole/l.		$(k')_0 \times 10^6$
	At 50°		
0.14971			1.484
.14913	KNO_3	0.1084	1.516
.14833	$NaClO_4$	.1083	1.672
.12078	$NaClO_4$	.1088	1.732
.10043	KNO_3	.1063	1.627
.09639			1.573
.09507			1.595
.09085	KNO_3	.1090	1.591
.09068	$NaClO_4$	.1091	1.869
.09050			1.579
.09038	$HClO_4$	.1103	1.835
.09038	$NaClO_4$	.1080	1.868
.06063	$NaClO_4$	.1096	1.884
	At 25°		
.15239			.06675
.13703	$NaClO_4$	.1108	.07861
.11079	$NaClO_4$	.1110	.07867
.09116			.07072
.06115	$NaClO_4$	.1119	.08503

Energies of Activation.—The Arrhenius energies of activation appear in Table IX. Those for *t*-butyl nitrate are in excellent agreement with those observed in the unimolecular reactions of alkyl halides[10b] which all lie within the range 22 ± 2 kcal. The difference between k_1 and k_2 is consistent with those observed for unimolecular solvolytic reactions of secondary and tertiary halides and for alkyl sulfonium ions where the increases in the proportion of olefin produced with rise of temperature correspond to activation energies which are larger by about 2–5 kcal. for the elimination than for the substitution.[13]

The energy of activation for the solvolytic reaction $(k_3)_0$ of benzyl nitrate is appreciably larger than that for benzyl chloride,[14] being 24,170 as compared to 20,600. The energy of activation for the hydroxyl ion displacement $(k_5)_0$ is even more strikingly higher than for the corresponding displacement reactions of benzyl chloride; 23,970 compared with 18,400 for the hydroxyl ion dis-

TABLE VII

INITIAL SPECIFIC RATES OF SOLVOLYSIS OF BENZYL NITRATE (k'), $(k_3)_0$ AND $(k_4)_0$ IN 60% DIOXANE, TIME IN SECONDS

Initial concn. $BzNO_3$	Added solutes concn., mole/l.		$(k')_0 \times 10^7$	% PhCHO	$(k_3)_0 \times 10^7$	$(k_4)_0 \times 10^7$
			At 25°			
0.15109	$NaClO_4$	0.1106	0.7289	7.2	0.6764	0.0525
.13001			.6478	8.6	.5921	.0557
.10402	$NaClO_4$	.1113	.7697	8.8	.7020	.0677
			At 50°			
.10530			15.71	6.25	14.73	.98
.07843	$NaClO_4$	.1094	18.55	7.4	17.18	1.37
.07996	H_2Q	.0498	16.65	None		
.07524	(Solv. aged $2^1/_2$ weeks)		15.80	13.5	13.67	2.13
.07115			16.48	7.2	15.29	1.19

TABLE VIII

INITIAL SPECIFIC RATES OF THE HYDROXYL ION REACTION $(k'')_0$, $(k_5)_0$ AND $(k_6)_0$ OF BENZYL NITRATE IN 60% DIOXANE, TIME IN SECONDS

Initial concn. $BzNO_3$	Initial concn. NaOH	Concn. $NaClO_4$	$(k''')_0 \times 10^4$	$(k'')_0 \times 10^4$	% PhCHO	$(k_5)_0 \times 10^4$	$(k_6)_0 \times 10^4$
			At 50°				
0.16321	0.05374	0.05409	3.675	3.403	42.5	1.855	1.548
.15721	.10836		3.755	3.620	33.6	2.365	1.255
.07962	.05435	.05470	5.093	4.798	39.0	2.834	1.964
.07499	.10961		4.693	4.546	34.2	2.952	1.594
			At 25°				
.14802	.05505	.05540	0.2983	0.2870	67.8	0.0858	0.2012
.14776	.11096		.3133	.3077	67.5	.0967	.2110
.07850	.05556	.05592	.3064	.2935	65.0	.0955	.1980
.07835	.11202		.3389	.3325	58.0	.1365	.1960
.07880	.11161	(aged)[a]	.4144	.4080	53.6	.1865	.2215
.07764	.11104	H_2Q = .0500	.5769	.5704	None		

[a] Solvent aged $2^1/_2$ weeks at 50°.

with hydroxyl ion must be due to the effect of replacing perchlorate ions by hydroxyl ions in the reaction medium.

(13) For a comprehensive review and references, see Hughes and Ingold, *Trans. Faraday Soc.*, 657 (1941).

(14) (a) Weber, *Rec. trav. chim.*, **53**, 869 (1934); (b) Bennet and Jones, *J. Chem. Soc.*, 1815 (1935).

TABLE IX

ENERGIES OF ACTIVATION FOR THE VARIOUS REACTIONS

[ESTER] = 0.100

Spec. rate constant	Medium	Temp. range	$E_{act.}$, cal.
k	75% Dioxane	0.3–25	22,800
k	60% Dioxane	0.3–10	22,870
k	60% Dioxane	10 –25	(22,010)[a]
k_1	60% Dioxane	0.3–10	22,810
k_2	60% Dioxane	0.3–10	24,730
k_3	60% Dioxane	25 –50	24,170
k_4	60% Dioxane	25 –50	21,570
k_5	60% Dioxane	25 –50	23,970
k_6	60% Dioxane	25 –50	14,920

[a] Less reliable because it involves the constant at 25° where the error is probably rather high.

TABLE X

PERCENTAGE CHANGE IN SPECIFIC SOLVOLYSIS RATE OF 0.1 *M* ESTER CAUSED BY ADDITION OF INDICATED SOLUTES AT 0.108 *M* CONCENTRATION

t, °C.	% Dioxane in solvent	Solute	% Change in spec. rate
		For $BuNO_3$	
0.3	60	$NaClO_4$	+19.24
10	60	$NaClO_4$	+16.48
10	60	NaOH	− 4.28
25	75	$NaClO_4$	+37.21
25	75	$HClO_4$	+36.62
25	75	KNO_3	+16.12
25	75	NaCl	+10.30
25	75	$C_7H_7SO_3Na$	+10.30
		For $BzNO_3$	
25	60	$NaClO_4$	+16.38
50	60	$NaClO_4$	+15.62
50	60	$HClO_4$	+15.51
50	60	KNO_3	+ 2.67

placement of benzyl chloride in 50% acetone[14a] and with 18,300 for the iodide ion displacement of benzyl chloride in acetone.[14b] The significance of these differences will be discussed under the mechanism of the solvolytic reaction.

Kinetics of the Elimination Reaction.—Table V gives the proportions of olefin formed in the solvolysis of tertiary butyl nitrate in various media at various temperatures. These correspond in every way with those observed for tertiary butyl halides in water–alcohol media.[13] In agreement with the *t*-butyl halides the ratio of elimination to the over-all reaction decreases as the ionizing power of the medium increases and increases with increasing temperature. The rate constant $(k_2)_0$ is unchanged by the basicity of the reagent (comparison of hydroxyl ion and perchlorate ion runs) and has a positive salt effect. The latter feature has not heretofore been reported for such reactions and is probably, although not certainly, beyond experimental error. As indicated in Table IX the increase in per cent. olefin with rising temperature leads to a difference in the energies of activation of the two competing solvolytic reactions of approximately two kilo-calories.

Mechanism of the Solvolytic Reaction.—The reaction of an alkyl nitrate with water may be (1) a displacement of nitrate ion by a water molecule; (2) a true solvolysis, *i. e.*, an incipient solvation of the anion leading to a rupture of the carbon–oxygen bond with more or less transient formation of a carbonium ion; (3) a rupture of the oxygen–nitrogen bond by a mechanism analogous to the hydrolysis of a carboxylic ester.

The great similarity of the solvolysis of *t*-butyl chloride and of *t*-butyl nitrate, notably the near identity of energy of activation and of the ratio of olefin to alcohol in the reaction product, strongly supports the conclusion of an identity of mechanism. This is, no doubt, the mechanism (2) above, the true solvolysis.

On the other hand, the marked difference in energies of activation of the reactions of benzyl chloride and benzyl nitrate suggests the idea of a materially different mechanism. There is much reason for expecting the reaction of the chloride to partake of both mechanisms (1) and (2), in particular the fact that a strong hydroxyl ion displacement is observed. Since the rates of reaction of nitrate and chloride are nearly the same the entropy of activation must be much greater in the nitrate case than in the chloride.

There is evidence that solvolytic reactions of halides which show marked hydroxyl ion displacement reactions and which may therefore be expected to react significantly by mechanism (1) are likely to show smaller entropies of activation than the reactions of halides which go by mechanism (2). Thus benzylidene chloride which shows no measurable hydroxyl ion reaction has an entropy of activation for the solvolytic reaction greater by 11.2 cal./dg. than that of benzyl chloride.[14a]

It is probably also significant that the entropies of activation of substituted benzyl halides may differ considerably: thus *p*-methylbenzyl chloride has an entropy of activation 6.8 cal./dg. greater than benzyl chloride while *p*-nitrobenzyl chloride has an entropy of activation 1.8 cal./dg. lower.[15]

Kinetics of *t*-Butyl Nitrate Solvolysis.—The large dependence of rate on solvent composition

(15) Oliver, *Rec. trav. chim.*, **56**, 247 (1937).

and the characteristic salt effects shown, clearly indicate that tertiary butyl nitrate reacts with water by a true solvolysis. The striking difference between the effects of sodium perchlorate or perchloric acid on one hand and of potassium nitrate, sodium chloride or sodium toluenesulfonate on the other parallels those observed in the hydrolysis of tertiary butyl halides, various benzhydryl halides[16] and benzyl chloride.[6] If the rate determining step is the ionization

$$R - X \longrightarrow R^+ + X^-$$

then the rate of reaction will be increased by the presence of electrolyte. This effect is observed in the case of perchlorate ion. The decrease from this rate produced by nitrate, chloride, azide or acetate ion has then been interpreted to mean that some of the carbonium ion was diverted to form either the original ester ("common ion" effect) or a more stable ester.

$$R^+ + X^- \longrightarrow RX$$
$$R^+ + OAc^- \longrightarrow ROAc$$

The marked reduction in rate by hydroxyl ion which we have observed cannot however be explained by any such diversion of the carbonium ion, because attack by hydroxyl ion produces alcohol and would not decrease the rate as measured by acid production. Such an effect is understandable only in terms of a decreased activity on the part of one of the reactants, either water or butyl nitrate. That the effect is through the water, *i. e.*, by way of a varying affinity of the different anions for water molecules, is suggested by the fact that the order of the various ions is approximately that of the Hofmeister series.[17]

In an effort to establish their effect on the activity of the water, the freezing points of 60% dioxane containing 0.108 *M* concentration of various solutes were measured in a standard Beckmann freezing point apparatus, the temperature indicated being that of disappearance of sharply defined crystals of dioxane. That the crystallizing phase was dioxane was shown in the case of solvent alone and for the hydroxyl solution by cooling 2–3° below the temperature of first crystals and removing the remaining liquid through a sintered-glass filter under suction. The crystals were melted and distilled free of traces of electrolyte, and the composition measured by refractive index. In both cases the liquid contained more than 80% dioxane. The temperatures in Table XI are average values of four determinations and are probably reliable to ±0.05, that for 60% solvent being consistent with data by Hovorka, Schaefer and Dreisbach, for that medium.[18]

TABLE XI

FREEZING TEMPERATURE DATA FOR 60% DIOXANE CONTAINING 0.108 *M* CONCENTRATIONS OF ELECTROLYTE

NaOH	−2.70	KNO_3	−3.92
NaAc	−3.08	Solvent	−4.65
NaCl	−3.35	$NaClO_4$	−4.80

For this three-component system at equilibrium the Gibbs–Duhem relationship must hold

$$N_1 d\mu_1 + N_2 d\mu_2 + N_3 d\mu_3 = 0$$

subscript 1 referring to water, 2 to dioxane and 3 to the electrolyte to be added, and for constant ratio N_1/N_2 we may write it in the form

$$N_1 \left(\frac{d\mu_1}{dN_3}\right)_{N_1/N_2} + N_2 \left(\frac{d\mu_2}{dN_3}\right)_{N_1/N_2} + N_3 \left(\frac{d\mu_3}{dN_3}\right)_{N_1/N_2} = 0$$

Since $(d\mu_3/dN_3)$ is positive both $(d\mu_1/dN_3)$ and $(d\mu_2/dN_3)$ might be negative, *i. e.*, both μ_1 and μ_2 might decrease with increasing electrolyte concentration. If, however, one bracketed term can be shown to be positive the other bracketed term must be sufficiently negative to maintain the condition that the sum of the three terms is zero. Since the freezing temperature of the solution with respect to dioxane is raised then the activity of the dioxane in the solution must also be raised, the elevation of the freezing point being a measure of the relative positive value of $(d\mu_2/dN_3)$. In comparing various electrolytes $(d\mu_3/dN_3)$ is approximately a constant and $(d\mu_1/dN_3)$ must vary inversely with $(d\mu_2/dN_3)$. Therefore when the added electrolyte tends to raise the activity of the dioxane component strongly it must act to lower the activity of the water to a corresponding extent.

If the decrease in rate in the presence of hydroxide must be interpreted in terms of such a decrease in the water activity, then the effect of chloride, acetate and nitrate on the freezing point strongly suggests an analogous explanation of their action on the rate of the solvolytic reaction. The data therefore weaken materially the argument of Ingold and Hughes and of Beste and Hammett that direct kinetic evidence exists for a carbonium ion intermediate in the solvolytic reaction.

(16) Bateman, Hughes and Ingold, *J. Chem. Soc.*, 960 (1940); Church, Hughes and Ingold, *ibid.*, p. 966; Church, Hughes, Ingold and Taher, *ibid.*, p. 971; Bateman, Church, Hughes, Ingold and Taher, *ibid.*, p. 979.

(17) Traube, *J. Phys. Chem.*, **14**, 452 (1910).

(18) Hovorka, Schaefer and Dreisbach, THIS JOURNAL, **58**, 2264 (1936).

Kinetics of the Oxidation–Reduction Reaction.—Table VII gives the proportion of benzaldehyde formed in the solvolysis of benzyl nitrate, and Table VIII gives the proportion formed in the hydroxyl ion reaction.

The two oxidation–reduction reactions which lead to benzaldehyde and nitrate appear to have the same order as the two hydrolytic ones, although the proportion of benzaldehyde does show some small dependence upon the concentration of hydroxyl ion. In view of the importance recently ascribed to a radical chain mechanism in the Cannizzaro reaction[19] the experiments using "aged" solvent containing large proportions of peroxides are of interest. In the first order reaction the total rate of reaction of benzyl nitrate was unchanged, but the proportion of benzaldehyde produced was approximately doubled. In the reaction with hydroxyl ion the total rate of reaction was materially increased, while the proportion of benzaldehyde decreased slightly if at all.

As was to be expected from the well-known behavior of nitroglycerine and nitrocellulose with alkaline reducing agents, hydroquinone completely suppressed the formation of benzaldehyde in alkaline medium. A similar suppression of aldehyde formation appeared in neutral and acid solutions also. In alkaline media hydroquinone materially increased the total rate of reaction of benzyl nitrate. This suggests some direct attack of hydroquinone or of its ions upon the benzyl nitrate. No such change in the total rate of reaction was observed in neutral or acid solutions.

At the present stage of our knowledge it would seem to be premature to offer any mechanism for the oxidation–reduction reaction.

(19) Weiss, *Trans. Faraday Soc.*, 782 (1941).

Summary

The reactions with water and with sodium hydroxide of *t*-butyl nitrate and of benzyl nitrate have been studied kinetically in various dioxane–water mixtures.

The reaction of *t*-butyl nitrate produces alcohol and olefin in proportions similar to those in which they are formed from *t*-butyl halides. Since, further, the energies of activation of nitrate and halide reactions are nearly identical, an identity of mechanism is strongly indicated. No appreciable reaction with hydroxyl ion or catalysis by acids has been observed.

Although perchlorate ion accelerates, hydroxyl ion retards and other anions have intermediate effects which parallel their effects upon the activity of water in the medium. This materially weakens the direct kinetic argument of Ingold and Hughes and of Beste and Hammett for a free carbonium ion intermediate in solvolytic reactions.

The solvolysis of benzyl nitrate to benzyl alcohol has a much higher energy and entropy of activation than the analogous reactions of benzyl chloride. This suggests that the reaction of the nitrate partakes more largely of a true solvolysis rather than a displacement of anion by water molecule than does that of the halide. There is a pronounced acceleration by hydroxyl ion but acids have no effect.

The conversion of benzyl nitrate to benzaldehyde and nitrite also shows both a kinetically first order reaction of benzyl nitrate and a second order reaction with hydroxyl ion. Both are completely suppressed by the addition of hydroquinone.

NEW YORK, N. Y. RECEIVED MAY 12, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Hydration of Isobutene in Dilute Nitric Acid

BY GLENNARD R. LUCAS AND LOUIS P. HAMMETT

While the rate of hydration of isobutene in dilute nitric acid at constant ionic strength is strictly first order with respect to isobutene and oxonium ion, the specific rate constant divided by oxonium ion concentration varies with ionic strength by a factor of 2.64 between ionic strengths of 0.1 and 2.[1] The effect is approximately linear so that the expression for the rate constant can be written in the form

$$k = k' [H_3O^+](1 + k''\mu)$$

and the effect is of unexpected magnitude according to the Brönsted theory of salt effects.[2] Since the ionic strength was varied by the addition of potassium nitrate it is interesting to consider whether the effect can be accounted for in terms of the formation of *t*-butyl nitrate as a transient intermediate. We have investigated this possibility in connection with a recent study of *t*-butyl nitrate hydrolysis in water–dioxane mixtures.[3]

The reaction of an alkyl chloride and mercuric nitrate has been thoroughly investigated and the lack of correspondence between effects on rate and product composition clearly indicates that the reaction occurs by way of a carbonium ion intermediate.[4] We have therefore examined the reaction between *t*-butyl chloride and mercuric nitrate in various dioxane–water mixtures. We have also investigated the effect of the partial substitution of dioxane for water on the rate of reaction of isobutene in dilute nitric acid solutions and established under what conditions *t*-butyl nitrate is found in the reaction product.

Experimental

Materials.—*t*-Butyl chloride (Eastman Kodak Co. best grade) was fractionated, the middle half being taken; b. p. 50.9°. C. P. mercuric nitrate was used directly. The isobutene was prepared by refluxing *t*-butyl alcohol (Eastman best grade) with crystallized oxalic acid[5] and passed through wash bottles containing water and stored over water. When used it was passed from the storage bottle through a long drying tube containing soda lime and calcium chloride. Reagent grade concentrated nitric acid was used in preparing the solutions containing nitric acid. The lithium nitrate was A. C. S. grade recrystallized from water and dried over phosphorus pentoxide.

Method.—The method of preparing solutions was that followed in the solvolytic studies of *t*-butyl nitrate.[3] The *t*-butyl chloride was sealed and weighed in tared thin glass bulbs blown from 6-mm. tubing. The procedure was to deliver the approximate amount of the cooled ester into the tared bulb through the 6-mm. neck which was 3–4 inches long; bulb and contents were cooled to dry-ice temperature and the neck sealed quickly in an oxygen flame, preserving the portion of the neck which had been sealed off to be weighed with the sealed bulb. In starting an experiment the reaction bottle containing all the solutes except the ester was placed in the thermostat and brought to temperature equilibrium. The bulb containing the ester was then broken beneath the surface and the initial time taken.

With *t*-butyl chloride Roberts' method of determination of the product ratio by determination of both chloride ion concentration and acidity[4] is unsatisfactory since the hydrolysis of *t*-butyl chloride is appreciable under the conditions of the chloride determination. It was found, however, that the primary reaction between the *t*-butyl chloride and mercuric nitrate producing *t*-butyl alcohol, *t*-butyl nitrate and isobutene is complete within a small fraction of the time required for the subsequent hydrolysis of the *t*-butyl nitrate formed in the reaction. Hence after the preliminary experiments no effort was made to determine the initial slopes, samples being taken at the frequencies previously found satisfactory in the hydrolysis of *t*-butyl nitrate. The reaction was stopped by running a sample into a cold solution of 50% alcohol and 50% dioxane, in which medium lithium chloride was sufficiently soluble to remove the excess mercuric ion, and the titration of acidity was carried out with standard sodium hydroxide using brom phenol blue indicator.

The experiments on the hydration of isobutene were of a semi-quantitative nature since we were interested in the order of magnitude of the rates of reaction in the various media. Into the proper dioxane–water mixture a known volume of dry isobutene gas was bubbled, the acid was added by pipet and the initial time was noted. The sampling was done by a crude modification of the method of Lucas and Ebertz.[1] The end of a pipet similar to the one they used was passed through a two-hole rubber stopper, the other hole containing a short piece of tubing attached to an air bulb. At the time of sampling this rubber stopper was quickly inserted in place of the ground glass stopper of the reaction flask so that the flask was never open for any appreciable time. Pumping the bulb forced the liquid into the pipet until it overflowed and the isobutene concentration was then determined as previously described.[3]

The determination of the amount of *t*-butyl nitrate produced in the hydration reaction offered some difficulty, because the errors in sampling and titration were of the order of the difference between the initial acid titer and that at the time of measurement. The method finally adopted consisted of running the sample into approximately 100 ml. of cold dioxane, adding the approximate amount of 0.1 *N* sodium hydroxide and completing the titration to a

(1) H. J. Lucas and Eberz, THIS JOURNAL, **56**, 460 (1934).
(2) Brönsted, *Z. physik. Chem.*, **102**, 169 (1922).
(3) G. R. Lucas and Hammett, THIS JOURNAL, **64**, 1928 (1942).
(4) Roberts and Hammett, *ibid.*, **59**, 1063 (1937).
(5) Hurd and Spence, *ibid.*, **51**, 2561 (1929).

TABLE I

PRODUCT COMPOSITION IN THE REACTION OF *t*-BUTYL CHLORIDE AND MERCURIC NITRATE IN DIOXANE–WATER MIXTURES

t, °C.	% Dioxane in solvent	Molar concentration of BuCl	$Hg(NO_3)_2$	HNO_3	$LiNO_3$	% Nitrate ester	% Olefin
0.3	60	0.0245	0.0255	0.0127		6.9	
0.3	60	.0228	.0255	.0126		7.0	
25	75	.0429	.0486	.0239		15.5	5.6
25	75	.0423	.0483	.0238	0.1070	25.6	5.4
25	75	.0249	.0256	.0125		15.4	
25	75	.0206	.0249	.0125	.0985	21.8	
25	85	.0240	.0250	.0126		21.6	
25	95	.0250	.0275	.0138		38.8	
25	95	.0248	.0274	.0138	.0977	58.5	

brom phenol blue end-point with 0.025 *N* sodium hydroxide. The flask was then allowed to warm up and to stand for twenty-four to thirty-six hours. During this period the *t*-butyl nitrate hydrolyzes and titration to a new end-point gives the amount of nitrate ester.

Rate Calculations.—The specific rate constant for the disappearance of isobutene was calculated from the first order equation $\ln a/(a - x) = kt$ where a is the initial concentration of the isobutene and $(a - x)$ is the concentration at time t, t in seconds.

The fraction of the mercuric nitrate–*t*-butyl chloride reaction product which is *t*-butyl nitrate was determined by a plot of $\ln (b - x)$ against time, where b is the initial concentration of *t*-butyl chloride and x is the number of moles reacted as determined by titration at time t. That this is actually the plot of the hydrolysis of the *t*-butyl nitrate formed in the reaction was established by comparing the slope of the curve with curves independently determined for *t*-butyl nitrate. The slopes agree within the experimental error. The intercept of the plot at zero time, converted to molar concentration, was used in calculating the per cent. nitrate ester produced. The percentage of olefin formed in the primary reaction between the *t*-butyl chloride and mercuric nitrate was estimated from determinations of the isobutene concentration at several different times early in the run, effort being made not to include any resulting from the hydrolysis of the *t*-butyl nitrate.

Results

Data for the *t*-butyl chloride–mercuric nitrate reaction are given in Table I. The rates of disappearance of isobutene are given in Table II, together with the amounts of *t*-butyl nitrate appearing in the reaction product.

Discussion

If we consider the hydration of olefins in dilute nitric acid under conditions where *t*-butyl nitrate

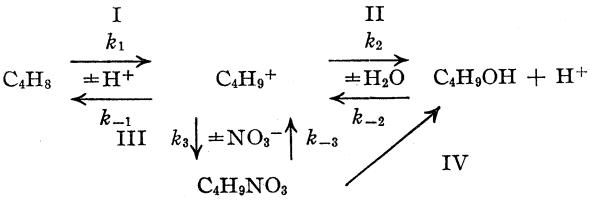
TABLE II

EFFECT OF DIOXANE ON THE RATE OF DISAPPEARANCE OF ISOBUTENE FROM 0.1 *M* HNO_3 AT 25° (TIME IN SECONDS)

Medium	$k \times 10^6$	% Nitrate ester found in product
Water	39	None
50% Dioxane	3.3	None
95% Dioxane	0.14	25–30[a]

[a] In 0.288 *N* HNO_3.

is formed, the simplest picture we could give would be



In order that the increase in rate of hydration of olefin upon the addition of nitrate ion be explained by the formation of the unstable intermediate, *t*-butyl nitrate, the following conditions must hold

1. Reaction I cannot be the rate determining step $-k_{-1} \gg k_2$.

2. To show first order kinetics in respect to isobutene an equilibrium concentration of $C_4H_9^+$ must be maintained $-k_{-1} \gg k_2$.

3. Step IV, another route between *t*-butyl nitrate and alcohol, must be postulated.

The rate of reaction in the absence of nitrate ion would then be the relatively slow addition of a water molecule; when nitrate ion is present an alternate path is possible. The linearity of the salt effect on the rate would simply require that k_2 be unaffected by the addition of nitrate ion. Hence

$$k_{H_3O^+} = k_{obs.}/[H_3O^+] = k_2 + k_3[NO_3^-]$$

from which $k_{H_3O^+}$ would be a linear function of the nitrate ion concentration.

Such a theory though plausible is in conflict

with certain experimental facts. The reaction of *t*-butyl chloride with mercuric nitrate, by analogy with the corresponding benzyl chloride system, must occur by way of a carbonium ion. If $k_{-1} \gg k_2$ then the ratio of olefin to alcohol should be very large. Actually in 75% dioxane the respective percentages of olefin, nitrate and alcohol are shown in Table I to be approximately 5:15:80 where the nitrate ion concentration is 0.014 and 5:25:70 where the nitrate ion concentration is 0.130.

Furthermore the effect of dioxane on the rate of disappearance of olefin seems to be inconsistent with any mechanism involving the combination of isobutene, oxonium ion and nitrate ion to give *t*-butyl nitrate since the rate of such a reaction should be affected by a change in the medium in the same way as is the equilibrium constant of the formation of acetic acid from its ions, which increases markedly with increasing dioxane content.[6]

The amount of *t*-butyl nitrate found in the hydration reaction in 95% dioxane appears to be of the order expected from the product ratio observed in the mercuric nitrate–*t*-butyl chloride reaction and the specific rate constant of hydrolysis of the *t*-butyl nitrate in that medium.[3] If the butyl nitrate did not hydrolyze, upward of 60% of the ester should be produced from the reaction of isobutene as it is in the mercuric nitrate–*t*-butyl chloride reaction. The hydrolysis constant (*i. e.*, the rate of disappearance of *t*-butyl nitrate at unit butyl nitrate concentration) must be at least seventy times as large as the rate at which the substance is formed from isobutene under the prevailing conditions the uncertainty arising from the unknown salt effect. Consequently the value of 25 to 30% nitrate ester observed is of the order expected.

Finally the hydrolysis of *t*-butyl nitrate by its resemblance to that of *t*-butyl chloride appears to be a true solvolytic reaction involving a carbonium ion intermediate[3] and step IV which necessarily by-passes this intermediate is questionable.

(6) Harned and Kazanjian, THIS JOURNAL, **58**, 1912 (1936).

Reaction III will therefore ordinarily be significant only under special conditions, *e. g.*, 95% dioxane medium for the hydration reaction, or very rapid formation of carbonium ion as in the *t*-butyl chloride–mercuric nitrate reaction. Hydration of isobutene in water as well as the reaction of mercuric nitrate with *t*-butyl chloride in water would not be expected to produce any nitrate ester because the ratio $k_2[H_2O]/k_3[NO_3^-]$ clearly increases rapidly with increasing water concentration.

It therefore seems unlikely that the effect of added nitrate ion is due to the formation of *t*-butyl nitrate. In terms of the Brönsted theory of salt effects

$$v = k_0 f_{H_3O^+} f_{C_4H_8}/f_{X^+}$$

the activity coefficient of the positively charged transition state complex decreases more rapidly than does the product of activity coefficients of the oxonium ion and isobutene. Like effects have been observed in the acid-catalyzed hydration reactions of various ethylene oxides,[7] the acid-catalyzed decomposition of diazoacetic ester[8] and the acid-catalyzed hydrolysis of various acetals,[9] and the effect seems to be general for such reactions.

Summary

The distribution of products in the reaction of mercuric nitrate with *t*-butyl chloride has been studied in various dioxane–water mixtures. Semi-quantitative results show that the rate of disappearance of isobutene in dilute nitric acid decreases rapidly with increasing proportion of dioxane.

The experimental facts indicate that *t*-butyl nitrate is not an intermediate in the hydration of isobutene in dilute nitric acid, and H. J. Lucas' conclusion that the pronounced acceleration produced by nitrate ion is a salt effect is therefore verified.

NEW YORK, N. Y. RECEIVED MAY 12, 1942

(7) Brönsted, Kilpatrick and Kilpatrick, *ibid.*, **51**, 420 (1929).

(8) Fraenkel, *Z. physik. Chem.*, **60**, 202 (1907).

(9) Brönsted and Wynne-Jones, *Trans. Faraday Soc.*, **25**, 59 (1929); Brönsted and Grove, THIS JOURNAL, **52**, 1394 (1930).

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

The Dipole Moments of Some Bile Acids

BY W. D. KUMLER AND I. F. HALVERSTADT[1]

The cyclopentanoperhydrophenanthrene nucleus or one of its modifications occurs in over eight types of physiologically active compounds including the bile acids, sex hormones, antirachitic vitamins, sterols, etc. A knowledge of the structure of this nucleus is of much importance both from a theoretical and practical standpoint.

At present the points of attachment of the rings are known but the evidence is conflicting in regard to whether some of the rings are linked *cis* or *trans* and very little, if anything, is known in regard to whether the individual rings are *cis* or *trans*.

A dipole moment study appeared to offer a new and rather fruitful method of attack on the problem. This nucleus is particularly suited to a dipole moment study for two reasons. First, it is saturated so that complicated resonance effects will not obscure the interpretation of the data. Second, the groups with appreciable dipoles are usually widely separated so steric or inductive effects will not interfere.

The bile acids were used to start the study because a number of these compounds were available and there is considerable evidence that the nuclei in the various bile acids studied have the same configuration. In this paper the dipole moments of ten bile acids have been measured and such factors as association, choleic acids and possible nonrotation of the molecules in the field are considered. In a later paper a detailed analysis of the moments of these compounds will be given in terms of their stereostructure.

Results

The symbols used in the equations and tables are the same as those given previously.[2] The equations used in calculating the moments are[2]

$$p_{2_0} = \frac{3\alpha v_1}{(\epsilon_1 + 2)^2} + (v_1 + \beta)\frac{(\epsilon_1 - 1)}{(\epsilon_1 + 2)}$$

$$P_{2_0} = p_{2_0} M_2$$

$$\mu = 0.0127\sqrt{(P_{2_0} - P_{E_2})T}$$

The P_{2_0} values are obtained by a method described previously[2] which is more accurate than the usual method. P_{E_2} values were calculated from the molar refractivities of the atoms present in the molecules.

TABLE I

MEASUREMENTS IN DIOXANE AT 25°

ω_2	v_{12}	ϵ_{12}	ω_2	v_{12}	ϵ_{12}
Lithocholic			Cholic		
0.004032	0.97361	2.2157	0.002182	0.97343	2.2177
.007756	.97343	2.2246	.005316	.97315	2.2324
.010121	.97321	2.2290	.007498	.97298	2.2424
.013622	.97300	2.2374	.014975	.97213	2.2779
Desoxycholic			3-Hydroxy-12-keto-cholanic		
.004653	.97339	2.2215	.003448	.97326	2.2327
.008239	.97301	2.2342	.005759	.97297	2.2470
.011673	.97264	2.2459	.007714	.97272	2.2576
.015707	.97227	2.2602	.008794	.97266	2.2655
Hyodesoxycholic			Dehydrodesoxycholic		
.004084	.97322	2.2264	.001978	.97342	2.2235
.006502	.97398	2.2343	.004666	.97320	2.2440
.008288	.97276	2.2396	.008451	.97268	2.2729
.010803	.97256	2.2486	.016242	.97182	2.3333
Apocholic			Reductodehydrocholic		
.002418	.97339	2.2161	.004449	.97303	2.2486
.004160	.97322	2.2214	.006828	.97263	2.2692
.008166	.97272	2.2334	.008716	.97234	2.2852
.015352	.97198	2.2555	.010111	.97217	2.2967
Dehydrolithocholic			Dehydrocholic		
.002806	.97348	2.2232	.003157	.97327	2.2448
.004882	.97334	2.2338	.006077	.97272	2.2744
.006346	.97324	2.2407	.015443	.97122	2.3695
.008862	.97309	2.2523			

Discussion

The bile acids are comparatively large molecules with molecular weights around 400, hence it is possible that they might not orient in the field at the frequency used, which was 680 kilocycles. There is no evidence, however, that such is the case. The moments obtained are of the magnitude expected for compounds having the groups present in these acids.

The bile acids are carboxylic acids and much evidence has accumulated which indicates that carboxylic acids are associated through hydrogen bonds to form dimers both in solvents such as hexane and in the vapor state. If such an association occurs in our solutions, it will make the interpretation extremely difficult. A good criterion for lack of association[2] is the linearity of the dielectric constant–concentration, ϵ_{12}–ω_2 curves, plus evidence that the extrapolated ϵ_1 value is approximately equal to ϵ_1 measured. We have plotted these curves for the ten acids in Fig. 1.

(1) Abraham Rosenberg Fellow in Pharmaceutical Chemistry 1941-1942.

(2) Halverstadt and Kumler, "A Critical Study of Dielectric Polarization Concentration Curves," in publication.

TABLE II

MEASUREMENTS IN DIOXANE AT 25°

Acid	Groups on nucleus	ϵ_1 measured	ϵ_1 extrapolated	v_1 extrapolated	α	$-\beta$	P_{20}	P_{E_2}	μ
Lithocholic	1 Hydroxyl (3)	2.2067	2.2068	0.97390	2.240	0.0660	237.3	107.3	2.50
Desoxycholic	2 Hydroxyl (3, 12)	2.2067	2.2053	.97385	3.493	.1015	324.7	108.8	3.22
Hyodesoxycholic	2 Hydroxyl (3, 6)	2.2105	2.2129	.97361	3.283	.0988	310.9	108.8	3.12
Apocholic	2 Hydroxyl (3, 12)	2.2098	2.2086	.97365	3.055	.1099	293.6	108.4	2.98
Dehydrolithocholic	1 Ketone (3)	2.2100	2.2101	.97365	4.794	.0627	393.9	105.8	3.72
Cholic	3 Hydroxyl (3, 7, 12)	2.2067	2.2075	.97369	4.682	.1030	417.7	110.4	3.84
3-Hydroxy-12-keto-cholanic	1 Hydroxyl (3) 1 Ketone (12)	2.2100	2.2119	.97365	6.032	.1164	484.2	107.3	4.26
Dehydrodesoxycholic	2 Ketone (3, 12)	2.2077	2.2081	.97367	7.707	.1145	589.4	105.8	4.82
Reductodehydrocholic	1 Hydroxyl (3) 2 Ketone (7, 12)	2.2111	2.2109	.97369	8.503	.1528	662.1	107.3	5.16
Dehydrocholic	3 Ketone (3, 7, 12)	2.2093	2.2127	.97377	10.15	.1654	766.2	105.8	5.63

The curves are all linear, showing that the bile acids are not associated in dioxane at concentrations less than weight fraction 0.017.

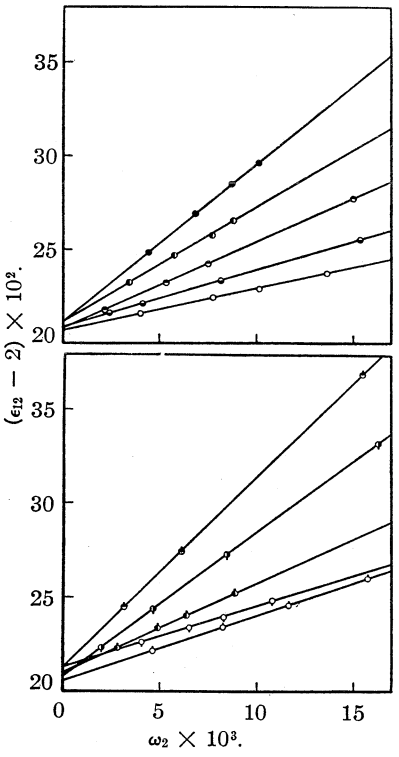


Fig. 1.—O, Lithocholic; ◒, apocholic; ◓, cholic; ◐, 3-hydroxy-12-keto-cholanic; ●, reductodehydrocholic.

Fig. 1a.—◑, Desoxycholic; ♀, hyodesoxycholic; ◑, dehydrolithocholic; ♀, dehydrodesoxycholic; ◒, dehydrocholic.

Another point of interest is whether this study gives any evidence of the presence of choleic acids in these solutions. Choleic acids are "molecular compounds" formed between desoxycholic acid and a wide variety of other types of compounds. A logical procedure would be to dissolve a choleic acid in some non-polar solvent and then determine the resulting dipole moment. Such a procedure does not seem feasible because the only solvent in which choleic acids appear to be soluble is dioxane, and dioxane itself forms a choleic acid. However, this permits some evidence to be obtained from the measurement of desoxycholic acid in dioxane, for if the choleic acid structure persists in the solution then the observed dipole moment of desoxycholic acid should be abnormal with respect to the other bile acids that do not form these molecular complexes. This would be the case if the complex either did or did not orient in the field. If the complex did not orient the apparent moment would be low, if it did orient the apparent moment would be expected to be different from that of a "free" molecule of desoxycholic acid.

An examination of the observed moments in Table II indicates that desoxycholic acid with two hydroxyl groups has a moment of 3.22 about midway between the moment 2.50 of lithocholic acid with one hydroxyl group and the moment of cholic acid 3.84 with three hydroxyl groups; thus the moment of desoxycholic acid is normal with respect to the moments of lithocholic and cholic acids.

The desoxycholic acid moment is also consistent with the moments of hyodesoxycholic and apocholic acids. Hyodesoxycholic acid is an isomer of desoxycholic acid with hydroxyl groups in the 3,6 positions instead of the 3,12 positions. One would thus expect not much difference in their moments and such is the case, hyodesoxycholic having a moment of 3.12 and desoxycholic a moment of 3.22. Apocholic acid differs from desoxycholic acid by having a double bond, which would be expected to alter the moment by only a small amount. The moment of apocholic, 2.98, is 0.24 less than that of desoxycholic acid. Since the moment of desoxy-

cholic acid which forms choleic acids with a large number of substances and the moment of apocholic which also shows this same property to a certain extent are normal with respect to the moment of cholic, lithocholic and hyodesoxycholic acids, which do not form choleic acids, we conclude that the dipole moment data give no evidence for the existence of the choleic acids in our solutions.

It is interesting to see what effect the introduction of an additional hydroxyl group and of an additional ketone group has on the moment. The difference between the moment of the compounds differing by one hydroxyl group and by one ketone group are as follows.

DIFFERENCE—ONE HYDROXYL	
Desoxycholic–Lithocholic	3.22 − 2.50 = 0.72
Hyodesoxycholic–Lithocholic	3.12 − 2.50 = 0.62
Cholic–Desoxycholic	3.84 − 3.22 = 0.62
Cholic–Hyodesoxycholic	3.84 − 3.12 = 0.72
3-Hydroxy-12-keto-cholanic–Dehydrolithocholic	4.26 − 3.72 = 0.54
Reductodehydrocholic–Dehydrodesoxycholic	5.16 − 4.82 = 0.34
DIFFERENCE—ONE KETONE	
3-Hydroxy-12-ketocholanic–Lithocholic	4.26 − 2.50 = 1.76
Dehydrodesoxycholic–Dehydrolithocholic	4.82 − 3.72 = 1.10
Reductodehydrocholic–3-Hydroxy-12-ketocholanic	5.16 − 4.26 = 0.90
Dehydrocholic–Dehydrodesoxycholic	5.63 − 4.82 = 0.81

The introduction of a hydroxyl group into desoxycholic or hyodesoxycholic acid has about the same effect as its introduction into lithocholic acid. In all the other cases, however, as a polar group (either hydroxyl or ketone) is introduced, its increment to the resultant dipole moment of the molecule decreases as the number of polar groups and moment of the compounds into which it is introduced become larger. This effect can be accounted for on the basis of the vector addition of the dipoles and does not demand the contribution of saturation effects.

Experimental

The measurements were carried out as described in the previous paper.[3]

(3) Kumler and Halverstadt, THIS JOURNAL, **63**, 2182 (1941).

Materials

The purification and constants of the dioxane were as described previously.[3]

Lithocholic Acid.—This sample was obtained from Dr. H. L. Mason of the Mayo Foundation; m. p. 187–188° $[\alpha]^{25}_{5461}$ +40.6°; equivalent weight by titration 378.

Desoxycholic Acid.—The Riedel–de Haen product was converted to the dioxane–choleic acid which was decomposed by boiling with water, then dried; m. p. 174–175°; equivalent weight 391.

Apocholic Acid.—The Riedel–de Haen product was crystallized from dioxane; m. p. 172–173°; equivalent weight 392.

Cholic Acid.—The Riedel–de Haen product was dried in a pistol over phosphorus pentoxide; m. p. 197–198°; equivalent weight 407.

Dehydrodesoxycholic Acid.—The Riedel–de Haen product was used without further purification; m. p. 185–186°; equivalent weight 387.

Dehydrocholic Acid.—The Riedel–de Haen product was used without further purification; m. p. 234–235°; equivalent weight 399.

Hyodesoxycholic Acid, Dehydrolithocholic Acid, Reductodehydrocholic Acid, and 3-Hydroxy-12-keto-cholanic Acid.—These four compounds were obtained from Dr. Willard M. Hoehn of the George A. Breon Co. The constants of the acids are:

Hyodesoxycholic acid; m. p. 192–194°
Dehydrolithocholic acid; m. p. 138–139°
Reductodehydrocholic acid, m. p. 186–187°
3-Hydroxy-12-keto-cholanic acid; m. p. 156–157°

Acknowledgment.—We wish to thank Dr. Willard M. Hoehn for supplying us with the four above mentioned bile acids, Dr. H. L. Mason for the lithocholic acid, and Dr. C. L. A. Schmidt for the samples of the Riedel–de Haen products.

Summary

The dipole moments of ten bile acids have been measured in dioxane. The values are lithocholic 2.50, desoxycholic 3.22, hyodesoxycholic 3.12, apocholic 2.98, dehydrolithocholic 3.72, cholic 3.84, 3-hydroxy-12-keto-cholanic 4.26, dehydrodesoxycholic 4.82, reductodehydrocholic 5.16, dehydrocholic 5.63.

These bile acids are not associated in dioxane in concentrations up to a weight fraction of 0.017. The ϵ_{12}–ω_2 curves are linear in this range.

The dipole moment evidence points to the nonexistence of choleic acids in our solutions. The dipole moment of desoxycholic acid is normal with respect to the moment of other bile acids that do not form choleic acids.

SAN FRANCISCO, CALIF. RECEIVED JANUARY 5, 1942

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

The Dipole Moment and Structure of Urea and Thiourea[1]

BY W. D. KUMLER AND GEORGE M. FOHLEN

The only work in the literature on the dipole moment of urea is that of Bergmann and Weizmann,[2] who obtained a value of 8.6 in dioxane. A redetermination of the moment of this very important compound seems desirable for several reasons. First, the previous value is based on only one measurement at very high dilution; second, the value seems extraordinarily large compared with the dipole moments of other amides and substituted ureas; third, a recent study by Halverstadt and Kumler[3] shows that measurements in very dilute solutions are apt to give results that are too high due to solvent polarization (water) error unless rigid precautions are taken to exclude moisture; fourth, the previous authors filtered the solutions, thus giving ample opportunity for absorption of water.

The measurement of the dipole moment of urea in a non-polar solvent is complicated by the insolubility of the compound in all non-polar solvents. The only available solvent in which it is appreciably soluble is dioxane and here its solubility is only about 35 mg. per 100 cc. The low solubility of urea makes any solvent polarization error of great importance in the resultant value for the dipole moment. Errors in the dielectric constant will have a larger effect on the moment than usual, due to the small difference between the dielectric constant of the solvent and the various solutions.

The dipole moment of thiourea has also been redetermined. The value[2] 7.6 in the literature appears likewise to be high.

Thiourea has a somewhat greater solubility in dioxane than urea but it still is necessary to measure the compound in comparatively dilute solutions.

Results

The results are given in Table I.

The symbols have the same significance as in the previous papers.[3] The moments have been calculated by a method described previously,[3]

TABLE I

MEASUREMENTS IN DIOXANE AT 25°

Urea

ω_2	ϵ_{12}
0.0001225	2.2175
.0001655	2.2196
.0001847	2.2201
.0002751	2.2243

Thiourea

ω_2	ϵ_{12}	v_{12}
0.0002715	2.2239	0.97362
.0005179	2.2334	.97355
.0006755	2.2403	.97350
.0008978	2.2488	.97342

	ϵ_1	v_1	α	$-\beta$	P_{2_0}	P_{E_2}	μ
Urea	2.2120	0.97371	44.44	0.3	456	16	4.56
Thiourea	2.2130	.97371	40.43	.322	521	24	4.89

employing the graphic modification, and using the equations

$$p_{2_0} = \frac{3v_1\alpha}{(\epsilon_1 + 2)^2} + (v_1 + \beta)\frac{(\epsilon_1 - 1)}{(\epsilon_1 + 2)}$$

$$P_{2_0} = p_{2_0}M_2$$

$$\mu = 0.0127\sqrt{(P_{2_0} - P_{E_2})T}$$

This method of calculating P_{2_0} is more accurate than the usual method and is particularly advantageous in dilute solutions where solvent polarization error may have a large effect on the moment.

In the case of urea the difference in density between the solutions and the pure solvent was within the experimental error, hence, the value of β could not be determined directly. We have taken a value of -0.3, which seems reasonable compared with the value of -0.322 for thiourea. In any event β does not have a very large effect on the moment. If β is taken as zero the value of the moment is raised by only 0.04.

The ϵ_{12}–ω_2 curves are linear in both cases showing that the molecules are not associated in these solutions.

Discussion

The values for the dipole moments of urea, 4.56, and thiourea, 4.89, are much smaller than the values in the literature 8.6 and 7.6, respectively. This is the most striking example we have found to date of the large amount of error that can be

(1) We are indebted to Professor John T. Edsall for suggesting this problem.

(2) Bergmann and Weizmann, *Trans. Faraday Soc.*, **34**, 783 (1938).

(3) Halverstadt and Kumler, "A Critical Study of Dielectric Polarization Concentration Curves," in publication.

introduced in dipole moment values by solvent polarization errors.

The new values are in general consistent with the dipole moment values of substituted ureas that appear in the literature. The substituted ureas are sufficiently soluble so that a solvent polarization error would not have an enormous effect on their moment. It is perhaps also significant that none of the solutions of these substituted ureas were filtered, thus they did not have the same opportunity to pick up water as did the solutions of urea and thiourea. In some cases when determinations have been made by different workers they check reasonably well. Thus values of 4.85[4] and 4.9[2] are given for diphenylthiourea and values of 4.8[4] and 5.1[5] for *sym*-dimethylurea.

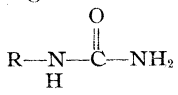
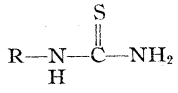
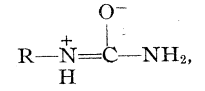
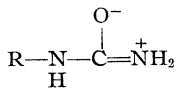
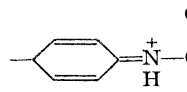
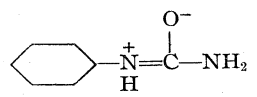
Let us examine the moment of urea and thiourea in the light of the published values for the substituted ureas which are listed in Table II.

TABLE II

Urea	4.56
Propylurea[5]	4.1
Phenylurea[2]	3.6
sym-Dimethylurea[4]	4.8
sym-Diethylurea[4]	4.9
sym-Diphenylurea[4]	4.6
unsym-Diphenylure [2]	2.7
N,N-Diethyl-N′-phenylurea[2]	3.2
sym-Dimethyl-diphenylurea[2]	3.6
Tetraethylurea[5]	3.3
Thiourea	4.89
Methylthiourea[2]	4.2
sym-Diethylthiourea[4]	4.9
sym-Diphenylthiourea[4]	4.85
Allyl-piperylthiourea[6]	4.61

Urea and thiourea have moments about 1 unit higher than those of the simple amides whose moments are in the range 3.7–3.9.[7] A calculation similar to that made previously with acetamide[7] where the contribution of the excited form was of the order of 6–15%, gives a contribution of 20–30% for the excited form in urea and thiourea. This is in qualitative agreement with the greater resonance energy[8] of these compounds and the fact that they have two equivalent forms with a separation of charge that can contribute to their structure.

Thiourea and the substituted thioureas have slightly higher moments (0.1–0.3) than the corresponding ureas. The introduction of an alkyl group into urea or thiourea lowers the moment by 0.5–0.7. The introduction of one phenyl group reduces the moment by 1.0. Two phenyl groups, if placed on the same nitrogen, reduces the moment by 1.9. In contrast with these reductions in moments is the fact that when two alkyl or two phenyl groups are placed symmetrically in the molecule the moment remains virtually the same. Thus urea, *sym*-dimethylurea, *sym*-diethylurea and *sym*-diphenylurea have moments differing by 0.3, while thiourea, *sym*-diethylthiourea and *sym*-diphenylthiourea have moments that differ by only 0.05.

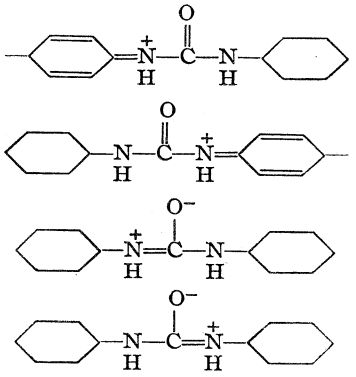
These moments can be interpreted on the basis of the number and contribution of the resonating forms.[8] Thus in compounds of the type  or  the two forms with a separation of charge,  ,  etc., do not have the same energy and consequently do not contribute much to the structure, hence the moments of these compounds are less than those of the unsubstituted molecules. If R is a phenyl group the resonance between the phenyl group and the group,  etc., will further decrease the contribution of the form  due to cross conjugation. Furthermore, this resonance between the ring and the  group introduces forms with a separation of charge which can oppose the resultant moment in the molecule and hence reduce the moment. When two phenyl groups are substituted on the same nitrogen these combined effects are sufficient to bring the moment down to 2.7 which is one unit less than the moment of simple amides.

When two like groups are substituted on different nitrogen atoms so the molecules are symmetrical the forms with a separation of charge are again equivalent and these forms, as in the case of the unsubstituted compounds, make a comparatively larger contribution to the structure.

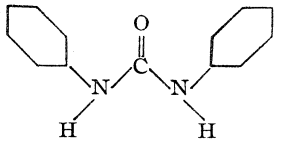
(4) Hunter and Partington, *J. Chem. Soc.*, 87 (1933).
(5) Devoto and Di Nola, *Gazz. chim. ital.*, **63**, 495 (1933).
(6) Kremann and Fruhwirth, *Monatsh.*, **69**, 319 (1936).
(7) Kumler and Porter, THIS JOURNAL, **56**, 2549 (1934).
(8) Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, New York, 1939.

Hence, the moments of the symmetrical disubstituted compounds are approximately the same as those of the parent compounds, urea and thiourea.

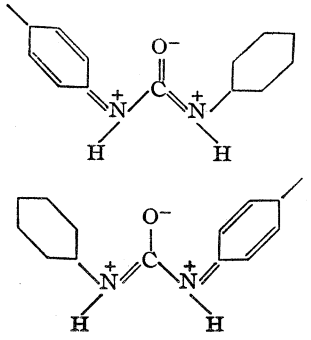
The cases of *sym*-diphenylurea and *sym*-diphenylthiourea are very interesting. It might be thought that these compounds would have lower moments than the parent compounds due to the cross conjugation between the main resonance and the ring resonance plus the possible opposition of the moment from the main resonance and the ring resonance. However, for all four forms to contribute, the molecule must be co-planar. A



study of the Fisher–Hirschfelder models reveals that the only way the molecule can get in a co-planar form is for the molecule to be arranged with the phenyl groups on the same side as the oxygen thus



in which case the moment from the ring— —N— H resonance would be in a direction to augment the moment from the main resonance. Furthermore with a phenyl group on both nitrogens a new powerful resonance is possible between the following forms.



Here the ring resonance now supports the urea resonance in the other part of the molecule due to the conjugation, and the negative charge can oscillate from one phenyl group to the other while both nitrogens remain positively and the oxygen negatively charged. The contribution of these equivalent forms with separation of charges will raise the moment. Two symmetrically placed phenyl groups thus introduce factors which lower the moment and others which raise it and the factors balance one another so the moments of *sym*-diphenylurea and *sym*-diphenylthiourea are about the same as the moments of the parent compounds.

Although tetraethylurea and *sym*-dimethyldiphenylurea are both symmetrical molecules, and therefore might be expected to have moments of about 4.6 these values are considerably less, 3.3 and 3.6, respectively. It is likely that steric hindrance in these tetrasubstituted compounds prevents their atoms from getting in a suitable position for the forms with a separation of charge to make an appreciable contribution. Examination of the models supports this view.

The new dipole moment values throw some light on the old controversy in regard to whether urea and thiourea are zwitterions. The use of the term "zwitterion" applied to these compounds was first taken to mean the structure $H_3\overset{+}{N}-\underset{\displaystyle O^-}{\underset{|}{C}}=NH$. This structure has two things in common with a typical zwitterion, it has a separation of charge, and a shift of a proton is necessary to form it from the normal form. This structure, however, is very untenable and has been discarded in favor of the structure $H_2\overset{+}{N}=\underset{\displaystyle O^-}{\underset{|}{C}}-NH_2$ which also has a separation of charge but a shift of a proton is not necessary for its formation. The term "zwitterion" was carried over to this structure although it is a resonance hybrid and not a typical zwitterion. When we use the term "zwitterion" in the rest of this discussion we refer to a molecule with a complete separation of charge regardless of how it comes about. The dipole moments indicate very definitely that in dioxane these compounds are not chiefly in the zwitterion forms. The evidence for and against[9] the zwitterion structure has been summarized in "Sidgwick's Organic Chemistry of Nitrogen." One argument is that since amino

(9) Taylor and Baker, "Sidgwick's Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 1937, p. 280.

acids are zwitterions and have high melting points, the high melting points of urea and thiourea suggest they are also zwitterions. The high melting points of urea and thiourea, however, can be accounted for on the basis of the number and strength of the hydrogen bonds that are formed between molecules in the solids. In fact, it is likely that with amino acids themselves the hydrogen bonds formed between molecules may be more responsible for the high melting points than is the zwitterion structure. The compound oxamide has a higher melting or decomposition point, 420°, than any of the amino acids and oxamide is most certainly not a typical zwitterion. However, each molecule in the solid has the possibility of being attached to the surrounding molecules by eight hydrogen bonds.

Another argument is that the short carbon–nitrogen distance of 1.37 Å. suggests a zwitterion structure. Pauling[8] has pointed out that this value for the carbon–nitrogen distance amounts to about 20% double bond character, hence the normal form makes a greater contribution to the structure than do the forms with a separation of charge.

Evidence considered most convincing for the zwitterion structure of urea and thiourea is the fact that these compounds and the aliphatic aminoacids raise the dielectric constant of water (have a positive dielectric increment) while most amides and other nitrogen compounds lower it. However amides in which a major portion of the molecule consists of the amide group such as formamide, malonamide and malamide have positive dielectric increments.[9a,10] The dipole moment of formamide[11] 3.68 is quite normal with respect to the moment of the other amides 3.7–3.9 and the moment value gives no evidence of formamide being a zwitterion.

Whether a compound raises or lowers the dielectric constant of water depends essentially on the number and size of the dipoles per unit volume compared with water. Or stated a bit differently it depends on whether the value of $\mu\bar{\mu}/v$ for the compound is greater or less than its value for water where μ is the dipole moment of a single molecule in the liquid, $\bar{\mu}$ a related dipole moment[12] and v the molal volume. The value of this function for water is about 0.7 taking Kirkwood's value for $\mu\bar{\mu}$ as 3.55 μ_0^2 where μ_0 is 1.88 the dipole moment of water in the vapor. The value of μ_0^2/v for water is about 0.2. Using 44.3 cc.[13] for the apparent molal volume of urea and our value for the moment, the value of μ^2/v for urea is about 0.48 considerably higher than the value of μ_0^2/v for water. The larger value of $\mu\bar{\mu}$ compared with μ_0^2 for water arises mainly from the hydrogen bonds that are formed between the water molecules in the liquid,[12] four such bonds being possible for each water molecule. An analogous effect would take place between urea and water with six possible hydrogen bonds for each urea molecule. Furthermore it is likely that some of these bonds are stronger than those in water due to the greater plus charge on the nitrogen resulting from the resonance.[14,15] The net effect would be to make the value of $\mu\bar{\mu}/v$ for urea considerably larger than the corresponding value for water. Consequently these factors alone are sufficient to account for the positive dielectric increment of urea in water without making the assumption that the molecule is a zwitterion.

Evidence of a chemical nature pointing to structures of the type $HN{=}C(H,S){-}NH_2$ can be accounted for just as well on a basis of a 20–30% contribution of forms $H_2\overset{+}{N}{=}C(S^-){-}NH_2$, $H_2\overset{+}{N}{-}C(S^-){=}\overset{+}{N}H_2$.

Convincing evidence against the zwitterion structure for urea is that of Cohn, McMeekin, Edsall and Blanchard,[13] who found that the ratio of the solubility of urea in alcohol to its solubility in water is much higher for urea than for a typical amino-acid zwitterion. This points rather strongly to urea not being a zwitterion in alcohol. Our dipole moment data are definite evidence that urea and thiourea are not zwitterions in dioxane. The evidence in the solid state and in water solution does not demand the existence of urea as a zwitterion, but the facts can adequately be accounted for on the basis of factors such as the number and strength of dipoles per unit volume, hydrogen bonds, etc.

A consideration of all the available evidence thus leads to the conclusion that urea and thiourea are resonance hybrids with 20–30% contribution of the forms with a separation of charge and that this structure adequately accounts for their behavior whether in the solid state or in dioxane,

(9a) Ref. 9; p. 144.
(10) Wyman, *Chem. Rev.*, **19**, 213 (1936).
(11) Kumler, THIS JOURNAL, **57**, 600 (1935).
(12) Kirkwood, *J. Chem. Phys.*, **7**, 911 (1939).
(13) Cohn, McMeekin, Edsall and Blanchard, *J. Biol. Chem.*, **100**, Proc. XXVIII (1933).
(14) Kumler, THIS JOURNAL, **57**, 604 (1935).
(15) Lu, Hughes and Giguère, *ibid.*, **63**, 1507 (1941).

alcohol or water solutions. Their structure is essentially the same as that of the simple amides except for a higher contribution of the forms with a separation of charge.

Experimental

The measurements were carried out as was described in a previous paper.[16]

Materials

Dioxane.—The purification and constants of dioxane were as described previously.[16]

Urea.—A C. P. grade of urea was recrystallized twice from methyl alcohol, heated with pure dioxane to remove any alcohol; m. p. 132.6°.

Thiourea.—Eastman Kodak Co. best grade thiourea was recrystallized from methyl alcohol, heated with pure dioxane. The product gave no test for thiocyanate.

Summary

The dipole moments of urea 4.56 and thiourea 4.89 have been measured in dioxane at 25°. Plots of the dielectric constants against weight fractions were linear, showing the molecules were not associated in these solutions.

The dipole moment values indicate that urea and thiourea are resonance hybrids with a 20–30% contribution from the forms with a separation of charge.

The magnitude of our values for these compounds together with those for substituted ureas appearing in the literature are correlated from the standpoint of resonance. Urea and thiourea have nearly the same moments as the corresponding symmetrical disubstituted compounds. All of these compounds have two equivalent forms with a separation of charge. The moments of the monosubstituted compounds in which the two forms with a separation of charge are not equivalent are smaller, and those of the unsymmetrical disubstituted compounds still less. The low moments of the symmetrical tetrasubstituted compounds are attributed to steric hindrance.

The evidence of the existence of urea and thiourea as zwitterions is examined and it is shown that all the evidence can be adequately accounted for by the resonance hybrid structure whether urea is in the solid state or in dioxane, alcohol, or water solutions.

The structure of urea and thiourea is not essentially different from that of the simple amides except for a somewhat larger contribution of the forms with a separation of charge.

(16) Kumler and Halverstadt, THIS JOURNAL, **63**, 2182 (1941).

SAN FRANCISCO, CALIFORNIA RECEIVED JANUARY 19, 1942

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

The Dissociation Constant, Dipole Moment and Structure of α-Nitrotetronic Acid

BY W. D. KUMLER

α-Nitrotetronic acid was originally assigned the isonitro form.[1] The structure of this compound is reconsidered here in the light of present day viewpoints. The dissociation constant and dipole moment have been measured and the results interpreted.

Results

TABLE I

MEASUREMENTS IN WATER AT 25°

M	% Neutralized	pH	pKa	Average pKa
0.00875	40	2.40	1.63	
.00752	50	2.55	1.70	1.68
.00710	60	2.67	1.70	

MEASUREMENTS IN DIOXANE AT 25°

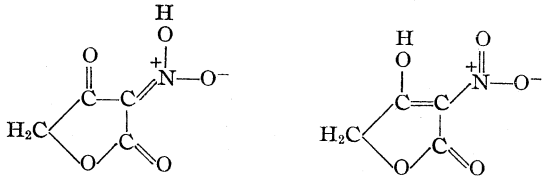
ω_2	ϵ_{12}	ν_{12}
0.0005308	2.2275	0.97349
.0008488	2.2380	.97328
.0012674	2.2507	.97315
.0015091	2.2593	.97306

ϵ_1	ν_1	α	$-\beta$	P_{20}	$P_{E_{20}}$	μ
2.2100	0.97364	32.50	0.386	802	27	6.10

(1) Wolff and Lüttringhaus, *Ann.*, **312**, 133 (1900).

Discussion

The possibilities for the structure are the isonitro and the enol.



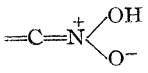
The structure of analogous compounds suggests that the enol is by far the more stable structure. Thus tetronic acid and α-halogen substituted tetronic acids are largely in the enol form[2] while no stable isonitro compound of any kind has been isolated. The isonitro compounds that have been obtained[3] change into the nitro form on standing. These facts in themselves suggest that the enol form is the more probable.

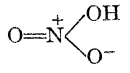
The structure of an isonitro compound is ana-

(2) Kumler, THIS JOURNAL, **60**, 857, 859 (1938).

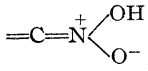
(3) Hantzsch and Schultze, *Ber.*, **29**, 699, 2253 (1896).

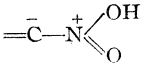
logous to that of nitric acid, which is of course a strong acid.





The fact that the two forms with a separation of charge are not equivalent





as they are in the case of nitric acid would cause the isonitro compound to be somewhat weaker than nitric acid. However, the compound would be much stronger than nitrous acid $Ka = 4 \times 10^{-4}$ and would probably have a Ka greater than 10^{-2}. The observed Ka of 2.1×10^{-2} therefore, does not exclude the isonitro structure.

Some of the factors likely to affect the dissociation constant of the enol form of α-nitrotetronic acid are illustrated by the ratios in Table II.

TABLE II

$$\frac{Ka\ \alpha\text{-Nitrotetronic acid}}{Ka\ \alpha\text{-Chlorotetronic acid}} = \frac{21 \times 10^{-3}}{7.4 \times 10^{-3}} = 2.8$$

$$\frac{Ka\ o\text{-Nitrophenol}}{Ka\ o\text{-Chlorophenol}} = \frac{6.8 \times 10^{-8}}{7.97 \times 10^{-10}} = 86$$

$$\frac{Ka\ p\text{-Nitrophenol}}{Ka\ p\text{-Chlorophenol}} = \frac{7.0 \times 10^{-8}}{1.46 \times 10^{-10}} = 478$$

$$\frac{Ka\ o\text{-Nitrobenzoic acid}}{Ka\ o\text{-Chlorobenzoic acid}} = \frac{6.71 \times 10^{-3}}{1.14 \times 10^{-3}} = 5.9$$

$$\frac{Ka\ p\text{-Nitrobenzoic acid}}{Ka\ p\text{-Chlorobenzoic acid}} = \frac{3.76 \times 10^{-4}}{1.05 \times 10^{-4}} = 3.7$$

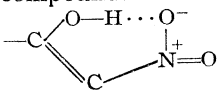
The fact that the ratios for the phenols are considerably greater than those for the benzoic acids is due to two effects. Acid strengthening groups have a greater relative effect on weak acids than on strong ones and with the phenols the nitro group is in a position to exert its rather large acid strengthening resonance effect. The nitro group cannot do this in the benzoic acids and here the major factor is the inductive effect, which is greater the nearer the groups are to the dissociating hydrogen. The ratio for the *ortho* benzoic acids is thus greater than for the *para* acids.

If a hydrogen bond is formed by the dissociating hydrogen it would weaken the acid because the hydrogen would be held by an additional force. As Branch and Yabroff pointed out,[4] this factor is reponsible for the anomalously small second dissociation constant of salicylic acid. In the *ortho* chloro and nitro benzoic acids, however, if any hydrogen bonds are present they are quite weak and do not have a major effect on the acid strength. It is known that only weak hydrogen bonds are formed to chlorine atoms and in the case of the ortho nitro compound apparently unfavorable angles and distances cause the bond to be weak. If a strong hydrogen bond were present in this compound, the ratio for the ortho acids would be much smaller.

The acid weakening effect of a hydrogen bond formed by a dissociating hydrogen is shown very strikingly by the ratios for the phenols. Thus while the ratio Ka *o*-nitrophenol/Ka *o*-chlorophenol would be expected to be about twice that of the para compounds, or about 900, it is actually 86 or about one-tenth the expected value. The strong hydrogen bond in *o*-nitrophenol thus reduces the dissociation constant of the compound by a factor of more than ten.

Tetronic acids are of about the same strength as the ortho benzoic acids, so a comparison of the Ka's of the two series will not be invalidated by a great difference in acid strength. In α-nitrotetronic acid, however, the nitro group, as in the case of the ortho and para nitrophenols, is in a position to increase the acid strength due to resonance. As a result one would expect the ratio of the Ka's for the nitro and chloro compounds to be greater for the tetronic acids than for the ortho nitro benzoic acids. The fact that it is considerably less is evidence that a strong hydrogen bond is present in α-nitrotetronic acid.

In α-nitrotetronic acid the same possibilities are present for hydrogen bond formation that are present in *o*-nitrophenol and nitroacetophenone. The last two compounds are known to contain strong hydrogen bonds so by analogy one would expect such a bond in the first compound. In all these compounds the structure



is present.

The fact that α-nitrotetronic acid does not give a color with ferric chloride is evidence that a strong hydrogen bond is present in the molecule. Ordinary enols and isonitro compounds give colors with ferric chloride. Thus the α-halogen tetronic acids and the isonitro form of *p*-bromophenylnitromethane[5] show this reaction but compounds with strong hydrogen bonds like *o*-nitrophenol do not.

(4) Branch and Yabroff, THIS JOURNAL, **56**, 2568 (1934).

(5) Sidgwick, "Organic Chemistry of Nitrogen," Oxford University Press, London, 1937, p. 232.

When the moment of 6.10 for α-nitrotetronic acid is compared with that of tetronic acid 4.80, and that of α-chlorotetronic acid 5.83, it is apparent that there is a factor present in the nitro compound that is not present in the other two. The carbon–chlorine moment is about 1.5–1.8. The moment of α-chlorotetronic acid is 1.03 units higher than that of tetronic acid which seems reasonable in that the carbon–chlorine moment most probably is not directly in line with the resultant moment of the rest of the molecule. The large moment of the nitro group, 3–4, is directed along the carbon–nitrogen bond in the same direction in the nitro compound as the carbon–chlorine moment is directed in the corresponding chloro compound. This means that the moment of the nitro compound should be 1.5–2 units greater than that of the chloro compound. Actually it is only 0.27 unit greater which suggests some factor being present in the nitro compound which changes the direction and(or) magnitude of the moment of the nitro group. The formation of a hydrogen bond to one of the oxygens of the nitro group would have such an effect. Thus the dipole moment as well as the dissociation constant is consistent with the presence of a hydrogen bond in the enol form.

Experimental

The *p*H values of the solutions were measured with a glass electrode in connection with the *p*H meter of Goyan, Barnes and Hind.[6]

The dielectric constant measurements were carried out as described previously,[7] as was the purification of the dioxane.

The α-nitrotetronic acid had an equivalent weight of 145.5 and a melting point of 183–184° with decomposition.

The moment also was calculated by a method described previously[8] using the equations

$$p_{2_0} = \frac{3\alpha v_1}{(\epsilon_1 + 2)^2} + (v_1 + \beta)\frac{(\epsilon_1 - 1)}{(\epsilon_1 + 2)}$$

$$P_{2_0} = p_{2_0} M_2$$

$$\mu = 0.0127\sqrt{(P_{2_0} - P_{E2_0})T}$$

The dielectric constants were linear with the weight fractions indicating no association effects in the solutions.

Summary

α-Nitrotetronic acid has a *pKa* of 1.68 and a dipole moment of 6.10. From considerations of general stability the enol form is more probable than the isonitro structure. Both the dissociation constant and the dipole moment are consistent with the presence of a strong hydrogen bond in the enol form.

(6) Goyan, Barnes and Hind, *Ind. Eng. Chem., Anal. Ed.*, **12**, 485 (1940).

(7) Kumler and Halverstadt, THIS JOURNAL, **63**, 2182 (1941).

(8) Halverstadt and Kumler, "A Critical Study of Dielectric Polarization Curves," in publication.

SAN FRANCISCO, CALIFORNIA RECEIVED MARCH 23, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE WASHINGTON SQUARE COLLEGE OF NEW YORK UNIVERSITY]

The Absorption Spectra and the X-Ray Examination of the Isomeric Glucononitriles[1]

BY PHILIPPOS E. PAPADAKIS

Two forms of gluconononitriles are known[1a,2,3] melting at 120.5 and 145°, and obtained by crystallization from absolute alcohol and glacial acetic acid, respectively.[3] Aqueous solutions of the two forms have initially practically the same specific rotation, but whereas that of the high melting form, to be now referred to as the A form, remains unchanged with time, that of the low melting B form shows a complex time-dependence. The present report describes investigations on the X-ray diffraction and absorption spectra of the two modifications, in an attempt to discover the reason for this contrast in behavior. Three samples of the B form,[3] checked as to melting point and microcombustion analysis, served as material.

X-Ray Examination.—Specimens of the two forms A and B were subjected to X-ray powder analysis using focusing cameras of the Bohlin type as modified by Phragmen. Possible atmospheric action was prevented by enclosing the samples in sheaths of regenerated cellulose which themselves gave no diffraction pattern. Twenty-seven lines were observed between θ values of 15 and 45° on the photograms of both specimens, corresponding in the two cases in position and intensity. These experiments within their limits of resolution did not help much in answering the problem.

(1) Original manuscript received August 15, 1940.

(1a) Zemplén, *Ber.*, **60**, 171 (1927).

(2) Wohl and Wollenberg, *Ann.*, **500**, 281 (1932).

(3) Papadakis and Cohen, THIS JOURNAL, **60**, 765 (1938).

Ultraviolet Absorption Spectra.—The absorption spectra of aqueous solutions of the A and B forms were examined by means of a small Hilger quartz spectrograph and a continuous hydrogen source. The molar extinctions were evaluated, with a precision of some 3 or 4% in the value of ϵ, by the method of Stücklen,[4] with the use of potassium nitrate as standard. Microdensitometer tracings were made of the plates by means of the Moll microdensitometer, and wave lengths were measured on these tracings.[5]

The B form in aqueous solution showed an absorption band with a maximum at 2780 Å. and log $\epsilon_{max.}$ of 0.9, besides a region of short wave absorption extending into the Schumann region. The band at 2780 Å. was present at full intensity in spectra taken as soon as possible after addition of the solid to water and persisted on standing for ten months. The characteristic band of the B form gradually disappeared on crystallization from pure acetic acid, which favors the A form, and returned on recrystallization from alcohol. The A form had no band near 2780 Å. Its spectrum was like that of β-hydroxypropionitrile and the substance was assumed to have a straight chain structure. The absorption spectra of boiled aqueous solutions of the A form showed considerable change, with a shift of the beginning of the further ultraviolet absorption toward the longer wave lengths. No such change was observed with unboiled solutions.

Although all specimens of the B form showed a band in the neighborhood of 2780 Å., irrespective of the time elapsed since the preparation of the solution, there were, nevertheless, changes in the details of the band with time. Approximately 0.113 *M* solutions of the B form were examined at various thicknesses and with an exposure of ten seconds. The plot of log ϵ molar against λ (Fig. 1) shows the curves 1, 2, 3 and 4 as a function of time. Four preparations gave similar curves. The characteristic band broadened with time, especially on the short wave side, and the beginning of the further ultraviolet band shifted first to longer wave lengths and then reverted to shorter. The absorption maxima[6] of the characteristic band in curves 1, 2, 3 and 4 as measured are 2780, 2775, 2770, 2750 and the absorption minima 2510, 2535, 2525 and 2530, respectively.

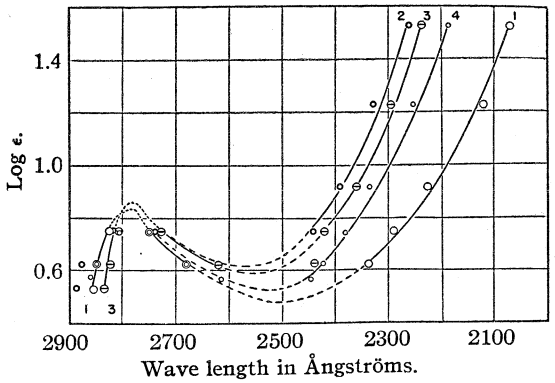


Fig. 1.—Time from mixing glucononitrile and water. Spectra photographed for Curve 1, first one-half hour; Curve 2, after twenty-five hours; Curve 3 after seventy-three hours; and Curve 4 after 672 hours.

Curves 1 and 2 of Fig. 2 are for a more dilute solution, 0.056 *M* in a cell 3.5 cm. long, photographed, respectively, one and 233 minutes from the time of mixing with water. These solutions showed evidence of discrete band structure, with bands at about 2730, 2678, (2608) (2530) for curve 1 and 2723, 2662, 2608 and 2530 Å. for curve 2, which became more distinct with time. Other preparations in similar conditions showed a hint of these bands, but not so distinctly as in the plate for which the curves of Fig. 2 were obtained. These bands caused the apparent maximum of the general band to shift toward the shorter wave lengths.

Scission of Hydrogen Cyanide from Gluconononitrile.—In explanation of the change in rotation of aqueous solutions of gluconononitrile with time, Dr. M. L. Wolfrom of the Ohio State University has suggested the possibility of the formation of *d*-arabinose, which has a negative rotation, by the loss of hydrogen cyanide. Pure nitrogen was bubbled for four and one-half hours through 10 cc. of an aqueous solution containing 0.4 g. of the gluconononitrile and the gas evolved was passed through silver nitrate solution. A precipitate shown to be silver cyanide was collected and found to weigh 0.028715 g. The corresponding amount of *d*-arabinose was calculated to be 0.03216 g. This amount, dissolved in 10 ml. of water and examined in a 1-dm. tube, would have contributed rotations of −0.17, −0.57 and −0.34°, respectively, if present in the α,β or mutarotated form.[7]

(4) Stücklen, *J. Opt. Soc. Am.*, **29**, 37 (1939).

(5) The apparent extinction coefficients in Fig. 1 were computed on the assumption that the absorbing material was a pure substance at the stoichiometric concentration of gluconononitrile.

(6) The absorption maxima and minima were determined from microphotometer tracings of respective spectra of the plates representing solutions of smaller depth. The extinction due to the band in these spectra was not complete and the microphotometric tracings afforded well-defined maxima and minima.

(7) The calculations were based upon the values for the specific rotations found by Hudson and Yanowski, THIS JOURNAL, **39**, 1013 (1917).

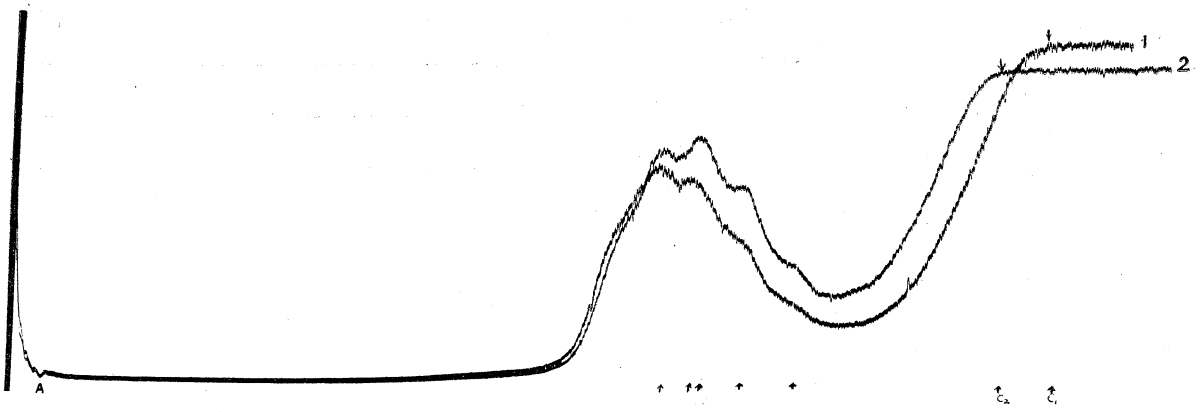
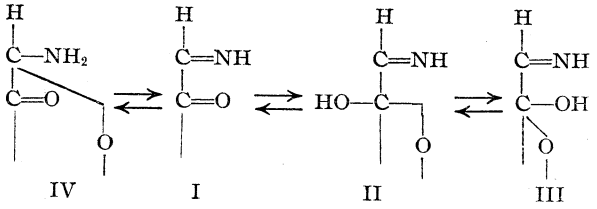


Fig. 2.—Microphotometric curves 1 and 2: A = H_B = 4861·327 Å.; C_1 and C_2 are beginnings of continuous absorption respectively.

Since the calculated drop in the rotation of the 4% solution of glucononitrile was approximately 1.40° (l = 1), the scission of hydrogen cyanide, even when favored by the passage of nitrogen, was not sufficient to account for all the change.

Discussion

The foregoing work showed that the essential difference between the absorption spectra of aqueous solutions of the A and B forms of glucononitrile is that the former has the type of spectrum to be expected of a hydroxy nitrile while the latter has a characteristic band at about 2780 Å., which may be due to some group not present in the A form. Hydrolysis products of the nitrile, as ammonium gluconate, gluconamide, glucono-γ or δ lactone or gluconic acid are not responsible for the characteristic band, since these substances,[8a] as has been verified in the course of this work, have no band near 2780 Å. Arabinose (see previous paragraph) is also without characteristic absorption in this region.[9] It seems necessary to seek for some chromophoric group which might result from internal changes in the glucononitrile molecule as the origin of the 2780 Å. band. Aliphatic aldehydes or ketones are known to have a band in this region, regarded as characteristic of aldehydic or ketonic carbonyl. The practical identity in the spectra of benzophenone and benzophenonimine[10] suggests that the C=NH group absorbs like carbonyl, and the iminolactone forms of imino-gluco-ascorbic[11] and imino-galacto-ascorbic acid have a strong band with a maximum at 2750 Å. A 1-imino-glucosone structure previously suggested[3] (formula I), on mutarotation might give II and III, while mutarotation involving the imino group might give the ketone derivative IV. Compound I by analogy



to glucosone[8b,12] may show selective absorption at a wave length somewhat higher than 2780 Å. Compounds II, III and IV may absorb at or near 2780 Å., by analogy with the behavior of aldehydes and ketones, and their interconversion might cause both the optical rotational changes and the changes in the characteristic band. The changes with time of the long wave side of the far ultraviolet band may be due to such interconversion products. Although the formation of hydrolysis products[8,9] could not account for the absorption band at 2780 Å., the possibility of slow hydrolysis may have an effect on the changes observed in the short wave spectrum. Analysis of aged sirups of form B evaporated at room temperature and dried at 80° and *in vacuo* showed that loss of nitrogen had occurred which could not be explained by assuming a loss of hydrogen cyanide. The changes observed in the short wave spectrum curves 1, 2, 3, and 4, Fig. 1, are compatible with the relative position of the spectrophotometric curves from glucononitrile, gluconyl-*d*-lactone, gluconamide and ammonium gluconate. In addition, the shift of the beginning

(8) Bednarczyk and Marchlewski, *Bull. intern. acad. polon. sci., Classe sci. math. nat.* (a) 1937A, 140 in English; (b) 1938A, 524.

(9) Kweicinski and Marchlewski, *Bull. soc. chim.*, **45**, 591–611 (1929).

(10) Meisenheimer and Dorner, *Ann.*, **502**, 164 (1933).

(11) Haworth, Hirst, Jones and Smith, *J. Chem. Soc.*, 1192 (1934).

(12) Guillaume and Lardy, *Compt. rend.*, **176**, 1548 (1923).

of the further ultraviolet absorption of boiled aqueous solutions of form A may suggest hydrolysis. On account of the inconclusive evidence concerning the question of the slow hydrolysis of the B form, it is not possible at present to associate the spectral observations with the details of the chemical changes and the problem requires further investigation.

Finally a suggestion may be made on the origin of the different melting points of the two forms. Glucononitrile may resonate between the structures $RC:::N:$ and $RC^+: \ddot{N}:^-$ as the alkyl cyanides are supposed to do.[13] The rather ionic character of the CN group might then lead to the formation of hydrogen bonds between the highly electro-negative hydroxyl oxygen and the nitrogen atoms. According to Thompson's infrared investigations[14] intermolecular bonding is more prominent in liquid hydroxy nitriles. As the presence of intermolecular hydrogen bridges is associated with higher melting points than their absence,[13] it seems plausible to associate the high melting point of the A form with the presence of intermolecular hydrogen bonds, while in the B form the bonds are either weaker or of the intramolecular type. More direct information on this question might be gained from a study of the infrared spectra of appropriate glucononitrile derivatives in which all but one hydroxyl group is blocked.

The author wishes to express his thanks to Dr. Wm. F. Ehret for the X-ray work, to Dr. Wm. West for the use of the spectrograph, to Dr. Raymond L. Garman and Dr. Marcel E. Droz for the microphotometer curves, and to Mr. D. Rigakos for the micro-analyses.

(13) Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, pp. 183–84, 270–272, 300–314.

(14) Thompson, THIS JOURNAL, **61**, 1396 (1939).

Summary

The two forms of glucononitrile, A and B, melting at 145 and 120.5°, respectively, shown by earlier work to differ in their optical activity, exhibited, within the accuracy of the measurements, the same X-ray powder diffraction spectra, but different ultraviolet absorption spectra. Aqueous solutions of the B form displayed an absorption band at 2780 Å. and an extinction coefficient given by $\log \epsilon_{molar} = 0.9$, approximately. The (ultraviolet) spectrum also underwent complex changes with time. The A form gave a spectrum resembling that of β-hydroxypropionitrile and showing no absorption maximum at λ 2780 Å. Several cyclic compounds containing carbonyl or imino groups, derivable from the nitrile, are regarded as causing the band at 2780 Å. Interconversion of these compounds may be responsible for the changes with time in the details of the characteristic band, and for the changes in optical rotation as well as for other spectral changes in the short wave ultraviolet. A gradual hydrolysis of the B form would not account for some facts and degradation by loss of hydrogen cyanide was shown to be inconsiderable. Consideration was given to the possibility that the two crystalline forms A and B differed in the nature of the hydrogen bonding.

NEW YORK, N. Y. RECEIVED JUNE 4, 1942

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 877]

Hydration of Unsaturated Compounds. XI. Acrolein and Acrylic Acid[1]

BY D. PRESSMAN AND H. J. LUCAS

Kinetics.—The hydration of acrolein[2] is shown by Eq. 1. That of acrylic acid[3] is similar.

$$H_2C{=}CHCHO + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} HOCH_2{-}CH_2CHO \quad (1)$$

At a given hydronium ion concentration in dilute aqueous solution, the hydration is first order with respect to the unsaturated compound and the dehydration is first order with respect to the hydrated compound, as shown by the straight line character of the plots of $\log_{10} \epsilon/(\epsilon - x)$ against t (Fig. 1), which is the case of two first order reac-

(1) Previous communication, X, THIS JOURNAL, **64**, 1122 (1942).

(2) J. U. Nef has shown that acrolein undergoes hydration in hot aqueous solution to form hydracrolein, *Ann.*, **335**, 219 (1904). Hydration of acrolein in aqueous sulfuric acid can explain the results of Lobry de Bruyn, who isolated a colorless syrup, probably hydracrolein, from a dilute aqueous sulfuric acid solution of acrolein, *Rec. trav. chim.*, **4**, 232 (1885).

(3) Acrylic acid undergoes hydration in aqueous sodium hydroxide, E. Lennemann, *Ber.*, **8**, 1095 (1875); E. Erlenmeyer, *Ann.*, **191**, 281 (1878). Hydracrylic acid undergoes dehydration in 50% sulfuric acid, W. Moldenhauer, *ibid.*, **131**, 335 (1864); J. Wislicenus, *ibid.*, **166**, 23 (1873).

tions coming to an equilibrium, according to the integrated Eq. 2

$$\log_{10} \epsilon/(\epsilon - x) = t(k_1 + k_{-1})/2.303 \qquad (2)$$

Here x is the fraction of the original unsaturated compound hydrated at time, t, ϵ is the fraction hydrated at equilibrium and k_1 and k_{-1} are the specific first order rate constants of hydration and dehydration, respectively, at a given hydronium ion concentration.

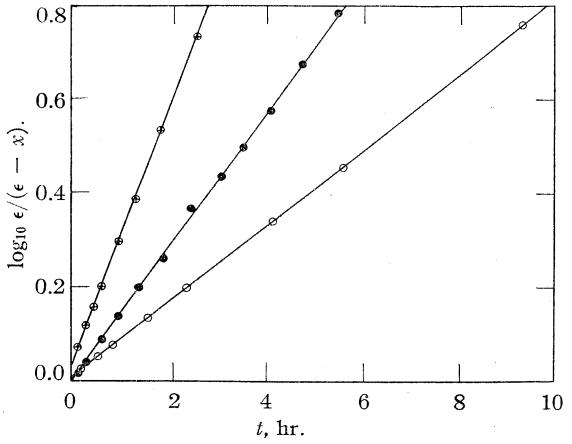


Fig. 1.—Hydration of acrolein and acrylic acid, dehydration of hydracrylic acid:

	Starting compound	Temp., °C.	(H_3O^+), N	μ, N
○	Acrolein	29.20	0.493	0.493
◉	Acrylic acid	119.8	1.01	2.00
⊕	Hydracrylic acid	119.8	1.92	2.00

The individual values of k_1 and k_{-1} were calculated from the values of $(k_1 + k_{-1})/2.303$, the slope of the curves of the type of those of Fig. 1, and the equilibrium constant, Eq. 3.

$$K = k_1/k_{-1} = \epsilon/(1 - \epsilon) \qquad (3)$$

All of the values of ϵ are experimental except the one for acrylic acid at 119.8°, which is calculated from the values at 110.6 and 134.8 by the use of the Arrhenius equation. In Table I are listed the values of k_1, k_{-1}, ϵ and K for acrolein and acrylic acid.

The reversibility of the hydration–dehydration system was demonstrated in each case by lowering the temperature after the system had already reached equilibrium and then returning the system to the original temperature after equilibrium had been established at the lower temperature. The system returned to the original equilibrium. In each case the extent of hydration was greater at the lower temperature, thus showing that the equilibrium could be approached from both sides and demonstrating the exothermic character of the hydration reaction.

The reversibility in the case of acrylic acid was confirmed by observing the rate of dehydration of hydracrylic acid at 119.8°. The values thus obtained for k_1, k_{-1}, ϵ and K agree well with values from the hydration experiments. The two systems are remarkable in the stability of the equilibrium. Evidently the β-hydroxy compound is the only reaction product in these two cases.

The effect of replacing sodium ion by hydronium ion is evident from the slight decrease in the values of $k_1/(H_3O^+)$ and $k_{-1}/(H_3O^+)$, (Table I), and of the equilibrium constants K. Undoubtedly these effects are due primarily to the presence of oxonium complexes, as was demonstrated previously in the case of the mesityl oxide-diacetone alcohol system.[1] The decreases in $k_1/(H_3O^+)$ and $k_{-1}/(H_3O^+)$ probably are due to the fact that each oxonium complex is less reactive than the uncomplexed compound. The decreases in the equilibrium constants probably are due to the fact that each hydrated compound is a weaker base than the respective unsaturated compound. The roles of the oxonium complexes were not investigated further.

Thermochemistry.—The heats of activation of the hydration and dehydration reactions were calculated by means of the Arrhenius equation. The heats of activation in the temperature range 19.98 to 29.70° are: for the hydration of acrolein, 18.0 kcal. in 0.249 N perchloric acid and 17.5 kcal. in 0.493 N acid; for the dehydration of hydracrolein, 24.0 kcal. in 0.249 N acid and 24.5 kcal. in 0.493 N acid. The heats of activation, 110.6 to 119.8°, are: for the hydration of acrylic acid, 20.4 kcal. in 1.01 N acid and 20.2 kcal. in 2.00 N acid; for the dehydration of hydracrylic acid, 27.0 kcal. in 1.01 N acid and 26.8 kcal. in 2.00 N acid.

It is probable that the heat of activation of the complexed form approximates that of the uncomplexed form, since the heat of activation is essentially constant even though the hydrogen ion concentration changes.

Values of ΔH for the hydration reactions were obtained from plots of log K against $1/T$. For the hydration of acrolein in 0.249 N acid three points fell on a straight line, giving for ΔH the value of −5.8 kcal. and at 0.493 N acid two points gave −5.8 kcal., while the third point, at 19.98°, was inconsistent. For the hydration of acrylic acid in 1.01 N and 2.00 N acid, ΔH is −6.5 and −6.7 kcal., respectively.

TABLE I

KINETIC DATA

Temp., °C., ±0.03	(H_3O^+), N	Unsatd. compd., initial M	ϵ	K	$k_1 + k_{-1}$	k_1, hrs.$^{-1}$	k_{-1}, hrs.$^{-1}$	$k_1/(H_3O^+)$	$k_{-1}/(H_3O^+)$
Acrolein–Hydracrolein at Ionic Strength 0.493 N									
19.98	0.249	0.0337	0.9234	12.08	0.0366	0.0338	0.00281	0.136	0.0113
19.98	.493	.0342	.9236	12.00	.0693	.0640	.00530	.130	.01075
29.70	.249	.0350	.896	8.62	.1015	.091	.01054	.365	.0424
29.70	.493	.0350	.892	8.26	.1885	.168	.0204	.341	.0414
39.93	.249	.0329	.865	6.41					
39.93	.493	.0234	.861	6.20					
Acrylic Acid–Hydracrylic Acid at Ionic Strength 2.00 N									
±0.2									
110.6	1.01	0.0375	0.9195	11.40	0.177	0.163	0.0143	0.161	0.0142
110.6	2.00	.0502	.9184	11.23	.341	.313	.0279	.157	.0140
119.8	1.01	.0375	(.903)[a]	(9.37)[a]	.338	.305	.0327	.302	.0325
119.8	2.00	.0502	(.902)[a]	(9.17)[a]	.643	.580	.0633	.290	.0317
134.7	1.01	.0375	.873	6.88					
134.7	2.00	.0502	.870	6.69					
119.8[b]	1.92	.084[b]	.905	9.5	.622	.564	.059	.288	.0306

[a] Calculated by interpolation. [b] Reaction started with hydracrylic acid.

The replacement of hydronium ion by sodium ion appears to have no effect on the heat of hydration. This would be expected if the uncomplexed and complexed forms of the unsaturated compound have identical heats of hydration, as was noted in the case of mesityl oxide.[1]

The Hydration of Acrolein in Water.—Nef[2] observed that hydracrolein was formed when a 25% solution of acrolein was heated in a sealed tube at 100°, and that the yield decreased, due to polymerization, if the heating was continued longer than seventy hours. Recently Rodebush[4] and co-workers have measured the absorption spectra of aged aqueous acrolein solution, and have found that they are quite similar to the absorption spectrum of aqueous aldol. They claim that the material responsible for the characteristic absorption is a polycondensation product similar in nature to the hydrated pentamer which Gilbert and Donleavy[5] consider to be the product resulting from the polycondensation of acrolein in dilute aqueous alkaline solutions and to which they assign the structure

$$HOCH_2CH\text{—}\left[\text{—}CH_2CH\text{—}\right]_3\text{—}CH_2CH_2CHO$$
$$\qquad\quad |\qquad\qquad\quad |$$
$$\qquad CHO\qquad\quad CHO$$

The arguments advanced by Rodebush, *et al.*, in substantiation of their claim are: (1) similarity in absorption spectra of aqueous aldol and aged acrolein solutions; (2) structural resemblance between aldol and the pentamer of Gilbert and Donleavy, in that both are β-hydroxyaldehydes; (3) absence of absorption due to a conjugated double bond, as would be the case if acrolein underwent the aldol condensation, which it is not known to do anyway. They completely overlook the possibility of a simple hydration of acrolein to hydracrolein, which explains in a highly satisfactory manner the effects they observed. On this account it became desirable to investigate the hydration of acrolein in water, in the absence of a catalyst.

Experiment showed that 0.03 M aqueous acrolein solution after heating at about 100° gave, at successive intervals, the following fractions of unchanged acrolein: 0.6 hr., 0.88; 1.3 hr., 0.715; 3.3 hr., 0.433; 7.5 hr., 0.395; 23 hr., 0.391. The equilibrium value 0.39 is close to 0.411 and 0.416, the values obtained when aliquots of a solution 0.02 M in acrolein and 0.5 N in perchloric acid were heated in boiling water for five and thirteen minutes, respectively, before quenching.[6] It appears from these results that in water at 100° the acrolein comes to a fairly stable equilibrium with hydracrolein, which is known to be formed in this solution.[2]

At 29.70 and 19.98° it was possible to follow the reaction more closely than at 100°. From the nature of the curves obtained by plotting x and $\log x$ against t, Fig. 2, it is evident that the reaction is essentially first order with respect to acrolein. The nature of the curves seems to indicate

(4) A. M. Buswell, E. C. Dunlop, W. H. Rodebush and J. B. Swartz, THIS JOURNAL, **62**, 328 (1940).

(5) E. Gilbert and J. Donleavy, *ibid.*, **60**, 1737 (1938).

(6) Even after two and one-half hours of heating, the value is 0.392, showing the stability of the system.

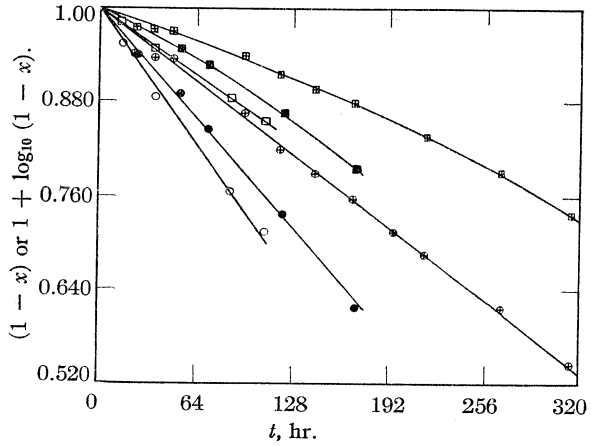


Fig. 2.—Hydration of acrolein in pure water, plot against time of $(1 - x)$ and $1 + \log_{10}(1 - x)$:

Temp., °C.	Initial concn., M	Plot of $(1 - x)$	Plot of $1 + \log_{10}(1 - x)$
30	0.0340	○	□
20	0.0338	⊕	⊞
20	0.0316	●	■

that the rate constant increases as the reaction proceeds. This is due to cumulative evaporation losses into the free space above the solution. As this space becomes larger the percentage loss by evaporation increases, thus giving the effect of a continually accelerating reaction. This effect was not observed in the acid-catalyzed studies because the loss due to evaporation was negligible in comparison to decrease of acrolein through hydration.

Non-reproducibility of the hydration data in water points to an extreme sensitivity to catalysis as, for example, slight daily variations in the *p*H of the water. In any event, the rate of hydration in water is negligible, when compared to the rate in acid solution.

Experimental

Acrolein.—Eastman Kodak Co. acrolein was distilled immediately before use. Determination of unsaturation by bromine absorption showed 1:000 double bond per mole. The analysis was carried out with an acetic acid solution, since acrolein is miscible with this solvent. Thus it is possible to make up a solution quantitatively by weight.

Acrylic Acid.—This was prepared by the action of metallic zinc upon a refluxing aqueous solution of α,β-dibromopropionic acid.[7] The fraction of acrylic acid which distilled at 138–140° and melted at 8° was purified by freezing about half way and decanting the liquid. After four such treatments the acid melted at 10.3°. When debromination was carried out without external heating, the boiling point of the acrylic acid was 140.0–0.3°, and the melting point of the distilled acid was 11.0°. This higher melting point when debromination is carried out at the lower temperature is due to the fact that there is less propionic acid present. The presence of propionic acid is indicated by the fact that whereas the neutralization equivalent as determined by titration with standard base was low by 2% (probably due to evaporation losses) bromine absorption was low by 5%.

Calcium Hydracrylate.—Hydracrylic acid was prepared by Mr. Frank Dickey from ethylene cyanohydrin.[8] After purification by ether extraction from the aqueous solution, it was shaken with a paste of calcium hydroxide and water. The resulting liquid was made neutral to phenolphthalein with carbon dioxide. Following removal of insoluble material by filtration, the solution of calcium hydracrylate was concentrated to a viscous mass in a vacuum desiccator. This was dried at 75° in an Abderhalden dryer. The resulting white deliquescent powder gave negative tests for chloride and sulfate ions with silver and barium nitrate solutions, respectively. *Anal.* Calcd. for $C_6H_{10}O_6Ca$: Ca, 18.4. Found: Ca (by ashing), 18.98, 19.02.

Analysis.—Acrolein was determined by the bromine absorption technique described previously in connection with crotonic acid.[9] Bromine was absorbed as rapidly as it was liberated from the bromate–bromide mixture. There was no interference from any hydracrolein present.

Acrylic acid reacted so slowly that after ten minutes, with 150% excess of bromide, only 90% of the theoretical amount of bromine was absorbed. On the addition of aqueous mercuric sulfate (so that the ratio of the concentration of mercuric ion[10] to the final concentration of bromide ion was about 1.3), absorption of bromine was quantitative after two minutes, with 50% excess bromine. Substitution was negligible. Actually this was only 4% in twenty-five minutes, even when the excess of bromine was 400%. Hydracrylic acid did not interfere. Substitution here was comparable to that in the dibromo acid.

Procedure.—For runs at 100° or above, the organic material was added to the acid or water, aliquots were sealed in ampoules and then placed in the thermostat at the required temperature. Ampoules were removed from time to time, quenched in cold water and analyzed. For runs at 40° or lower, acrolein was added to water or aqueous acid solution in a flask at the proper temperature. Immediately after thorough mixing an aliquot was analyzed. Other aliquots were removed at various intervals of time.

Correction was made for the change in hydrogen ion concentration when calcium hydracrylate was added.

No correction was made for the change in volume when the organic material was dissolved in the aqueous solution, usually about 1 ml. per liter, since any error is so small (about 0.1%) that it can be neglected. No account was taken of the change in concentration with temperature since the equilibria and, hence, the heats of hydration are not affected.

Summary

The equilibria in aqueous perchloric acid solutions in the systems, acrolein–hydracrolein, and acrylic acid–hydracrylic acid, have been studied.

(7) Biilman, *J. prakt. Chem.*, [2] **61**, 491 (1900).

(8) "Organic Syntheses," Coll. Vol. I, J. Wiley and Sons, Inc., New York, N. Y., 1932, p. 314.

(9) D. Pressman and H. J. Lucas, THIS JOURNAL, **61**, 2271 (1939).

(10) H. J. Lucas and D. Pressman, *Ind. Eng. Chem., Anal. Ed.*, **10**, 140 (1938).

The rates of hydration and dehydration are first order with respect to hydronium ion and to the organic compound involved.

In each case the drop in the values of the specific reaction rate constants of hydration and dehydration when hydronium ion replaces sodium ion is ascribed to the formation of an oxonium complex which is less reactive than the uncomplexed compound.

In each case the decrease in the value of the equilibrium constant with the above change is ascribed to the fact that the unsaturated compound probably is a stronger base than the corresponding hydrated compound.

Acrolein hydrates at 100° in pure water and in 0.5 *N* perchloric acid to the same extent.

The values for ΔH of hydration are: -5.8 kcal. in the case of acrolein, and -6.6 kcal. in the case of acrylic acid.

PASADENA, CALIF. RECEIVED APRIL 6, 1942

[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Reactions Relating to Carbohydrates and Polysaccharides. LXV. An Improved Technique for the Fractionation of Partially Methylated Glucosides[1]

BY IRVING LEVI, W. LINCOLN HAWKINS AND HAROLD HIBBERT

The quantitative separation of mixtures of partially methylated glucosides obtained on hydrolysis of methylated polysaccharides has been attempted by three general methods.[2,3,4] Several of the techniques described during recent years have been complicated, requiring large amounts of the methylated polysaccharide, and no procedure has been reported by which a complete quantitative separation of mixtures of tetra-, tri- and dimethylmethyl glucosides can be effected.

A description is now given of an improved procedure based on the fractionation principles and technique described by Podbielniak.[5] Several control fractionations carried out with mixtures of synthetic 2,3,4,6-tetramethyl-, 2,3,4-trimethyl- and 2,3-dimethylmethyl glucosides yielded excellent separations of the glucosides with a total recovery of 95–97%. The fractionation results on a typical mixture of these glucosides are shown in Table I. With this apparatus the 2,3,4-trimethylmethyl glucosides could be readily fractionated into the pure solid β and the liquid α isomer. In no case was there any appreciable decomposition.

In a recent investigation[6] on the structure of dextran, the present procedure gave very satisfactory results; an excellent separation was obtained using only three to four grams of the mixed glucosides. Intermediate fractions were very small and there was *practically no non-volatile residue* (not more than 1% and in some cases not detectable). The application of this fractionation technique is thus of particular significance in the field of structural carbohydrate chemistry, especially where the amount of material is limited and more than one distillation undesirable.

TABLE I

FRACTIONATION OF SYNTHETIC MIXTURES OF METHYL GLUCOSIDES

Fraction	Fraction, g.	OCH_3, %	"Tetra," g.	"Tri," g.	"Di," g.
1	0.746	60.5	0.746		
2	.151	59.6	.113	0.038	
3	.387	52.5		.387	
4	.665	52.3		.665	
5	.257	52.4		.257	
6	.300	50.8		.249	0.051
7	.451	42.1			.451
Total wt.	2.957		.859	1.596	.502
Starting wt.			.872	1.660	.516

The theoretical methoxyl values for tetra-, tri- and dimethylmethyl glucosides are 62.0, 52.6 and 41.9%, respectively. The amounts of each present in the small intermediate fractions (2 and 6) were calculated on this basis.

The fractionating column used is shown in Fig. 1. It is packed with a gold-plated wire (20 gage) spiral with $1/8$" pitch. The vacuum-jacket, column head and delivery tube of the small condenser were wound with a heating element (nichrome ribbon) and the small condenser adapted for the passage of cold water or steam, depending on the nature of the distillate.

(1) Original manuscript received August 13, 1941.

(2) Haworth and Machemer, *J. Chem. Soc.*, 2270 (1932); Haworth and Percival, *ibid.*, 2277 (1932).

(3) Macdonald, THIS JOURNAL, **57**, 771 (1935).

(4) Hess and Neumann, *Ber.*, **70B**, 710 (1937).

(5) Podbielniak, *Ind. Eng. Chem., Anal. Ed.*, **3**, 177 (1931); **5**, 119 (1933).

(6) Levi, Hawkins and Hibbert, THIS JOURNAL, **64**, 1959 (1942).

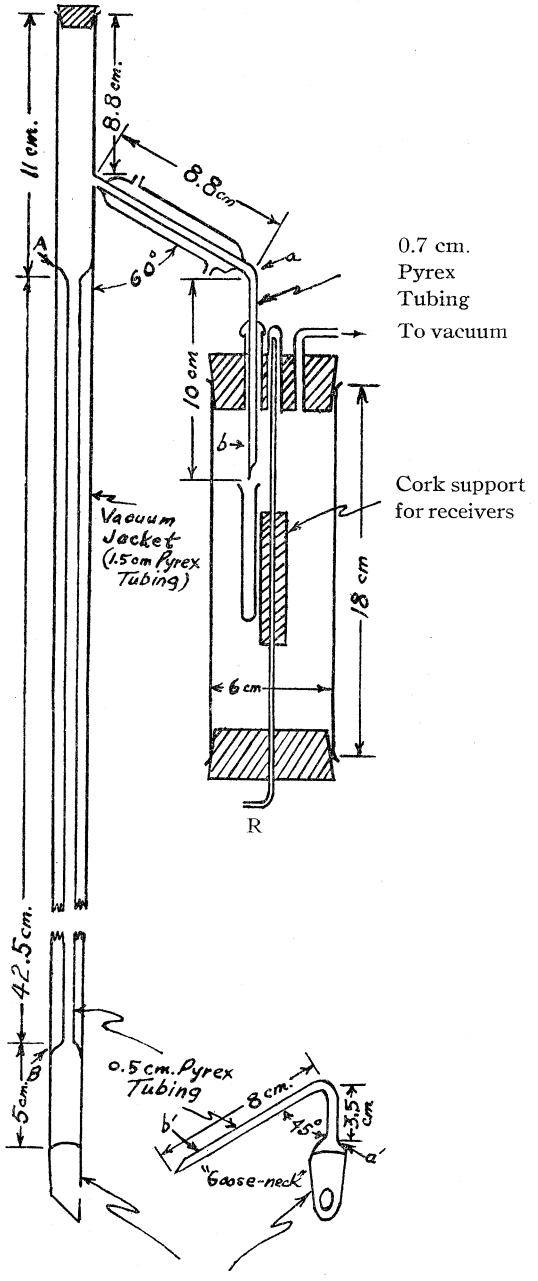


Fig. 1. No. 12/18 Pyrex ground bevelled to 45° angle and with hole in bottom as shown.

Fractionation Technique

The glucoside mixture is placed in a pear-shaped flask (25-cc. capacity) loosely packed with glass wool to maintain smooth boiling, and fitted to the bottom of the fractionating column by means of a ground-glass joint. After evacuation of the system to a constant pressure (regulated by a "bleeder" stopcock), the bath temperature is slowly increased until the maximum height of the reflux level is attained (about one-third up the column). Heat is then applied very gradually to the column (but not to the condenser top), while the bath temperature is kept constant, until the liquid refluxes to within 2.5 cm. of the top of the column. These conditions are then maintained for several hours to establish equilibrium, the gold-plated wire becoming, meanwhile, completely wet with the liquid.

The column temperature is raised slightly (3–4°) and the tetramethylmethyl glucoside collected at the rate of 150 to 200 mg. per hour, cold water being passed through the condenser during this operation. Due to the slow rate at which the column is operated at reduced pressure, the true boiling points cannot be determined, but the thermometer installed in the column head, with its bulb opposite the condenser side arm, gives the approximate values. The approximate column temperatures are read on a thermometer placed within the column air-jacket.

After a certain number of hours (dependent on the amount of tetramethylmethyl glucoside in the mixture) of constant distillation under these conditions, a dry spot on the previously completely wet gold-plated spiral wire becomes clearly visible, usually at about one-fifth the distance from the base, and during the next one to two hours the column dries completely with the exception of several cm. at the bottom. The receiver is now changed by turning the glass rod (R), the vacuum being maintained constant. The first fraction is pure tetramethylmethyl glucoside.

The bath temperature is slowly increased and also that of the column, until the spiral wire is again wet, and equilibrium conditions maintained for four hours. The column temperature is raised a further 2–3°, thus assuring the same uniform rate of distillation. The first four or five drops of distillate suffice to remove any residual "tetra" and are retained as an intermediate fraction of "tetra" and "tri." The third fraction is pure trimethylmethyl glucoside. It was necessary at this point to insert the condenser tip (a-b, Fig. 1) into the heating system, and to pass steam instead of cold water through the condenser to prevent solidification of the β-isomer of 2,3,4-trimethylmethyl glucoside.

After complete distillation of the trimethylmethyl glucoside, the column again becomes "dry," only the lowest 5 cm. being wet with dimethylmethyl glucoside. The column is now allowed to cool to room temperature and the vacuum released.

The pear-shaped distilling cup is removed and the column and condenser washed by distilling through them a small amount of chloroform. The chloroform distillate and washings from the column are combined and taken to dryness, this residue constituting the fraction intermediate between tri- and dimethylmethyl glucosides.

The dimethylmethyl glucoside should not be removed through the column because of its high boiling point but is distilled out of the flask through a short "goose-neck" (Fig. 1). This has a glass joint ground to fit the distilling flask and is wound with nichrome ribbon. This heating element is inserted in series with the heating unit of the column, thus permitting temperature control. The temperature of the "goose-neck" is kept at 100° during the distillation and the pressure reduced to 0.010 mm.

The authors are indebted to Dr. L. M. Cooke for designing the column described.

Summary

An improved apparatus is described and pro-

cedure outlined for the separation of small quantities of partially methylated glucosides whereby an almost quantitative recovery (95–97%) can be effected.

The glucosides can be separated in a high degree of purity and with accompaniment of only very small intermediate fractions.

The amount of non-volatile residue formed was never more than one per cent.

MONTREAL, CANADA RECEIVED MAY 12, 1942

[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Reactions Relating to Carbohydrates and Polysaccharides. LXVI. Structure of the Dextran Synthesized by the Action of *Leuconostoc Mesenteroides* on Sucrose[1]

BY IRVING LEVI, W. LINCOLN HAWKINS AND HAROLD HIBBERT

In a previous communication[2] an investigation of the structure of dextran synthesized by the action of *L. mesenteroides* on sucrose was described. Hydrolysis of the trimethyl dextran by the action of methanolic hydrogen chloride yielded dimethyl, trimethyl and tetramethyl methyl glucosides in the approximate ratio of 1:3:1. The products of hydrolysis were identified as 2,3-dimethyl methyl glucoside, 2,3,4-trimethyl methyl glucoside and 2,3,4,6-tetramethyl methyl glucoside. Based on these results a branched chain structure for the dextran was proposed.

These results were subsequently criticized by Brauns[3] on the following grounds: (a) the dextran was incompletely methylated; (b) the ratio of tetra- to tri- to dimethyl methyl glucosides of 1:3:1 was not conclusive because of the inefficient fractional distillation employed; and (c) the large percentage (18.4%) of material lost during fractionation. A re-investigation of this dextran was therefore made in order definitely to establish its structure.

Discussion of Results

Most complex polysaccharides such as mannan,[4,5] glycogen,[6,7,8] and araban[9] contain intricately branched chains, every branching position of which yields a dimethyl methyl glycoside in the case of hexosans and a monomethyl methyl glycoside in the case of pentosans. In methylation studies of such polysaccharides a final methoxyl value of one or two per cent. lower than the theoretical can render the results worthless with respect to the extent of branching and so preclude an accurate structural assignment. The great importance of complete methylation of polysaccharide products prior to structural determination by hydrolysis cannot be over-stressed and has been all too frequently neglected[10,11] with the result that conclusions drawn have only a restricted value.

Throughout this investigation every precaution was taken to obtain yields of material as nearly quantitative as possible in order that the results obtained could be based on a very high percentage of the starting material and therefore be of true significance. With dextran and its derivatives this involved reducing experimental manipulations and transfers to a minimum since these compounds are very difficult to handle because of their physical properties.

Dimethyl sulfate and alkali yielded a partially methylated dextran (40–41% OCH_3) which was further methylated to the theoretical value of 45.6% OCH_3 (calcd. for $C_6H_7O_2(OCH_3)_3$) in 71.4% over-all yield by a modified Muskat technique.[12] Hydrolysis of the completely methylated dextran was carried out with methanol–hydrogen chloride, in sealed glass bombs, heated to 140–142° for sixty to sixty-five hours in a tilting electric oven. The resulting glucosidic mixture, obtained in 95% yield, was fractionated by the new technique described in the preceding communication[13] using the modified Podbielniak column,[14] and an excellent separation of the glucosides effected with an over-all recovery of 97%. Of the 5% lost during

(1) Original manuscript received August 13, 1941.
(2) Fowler, Buckland, Brauns and Hibbert, *Can. J. Research*, **B15**, 486 (1937).
(3) Brauns, *ibid.*, **B16**, 73 (1938).
(4) Haworth, Hirst and Isherwood, *J. Chem. Soc.*, 784 (1937).
(5) Haworth, Hirst, Isherwood and Jones, *ibid.*, 1878 (1939).
(6) Bell, *Biochem. J.*, **30**, 1612, 2144 (1936).
(7) Bell, *ibid.*, **31**, 1683 (1937).
(8) Haworth and Isherwood, *J. Chem. Soc.*, 577 (1937).
(9) Hirst and Jones, *ibid.*, 496 (1938).
(10) Freudenberg, *Ber.*, **69**, 2043 (1936).
(11) Haworth, Raistrick and Stacey, *Biochem. J.*, **29**, 612 (1935).
(12) Muskat, THIS JOURNAL, **56**, 693, 2448 (1934).
(13) Levi, Hawkins and Hibbert, *ibid.*, **64**, 1957 (1942).
(14) Podbielniak, *Ind. Eng. Chem., Anal. Ed.*, **3**, 177 (1931); *ibid.*, **5**, 119 (1933).

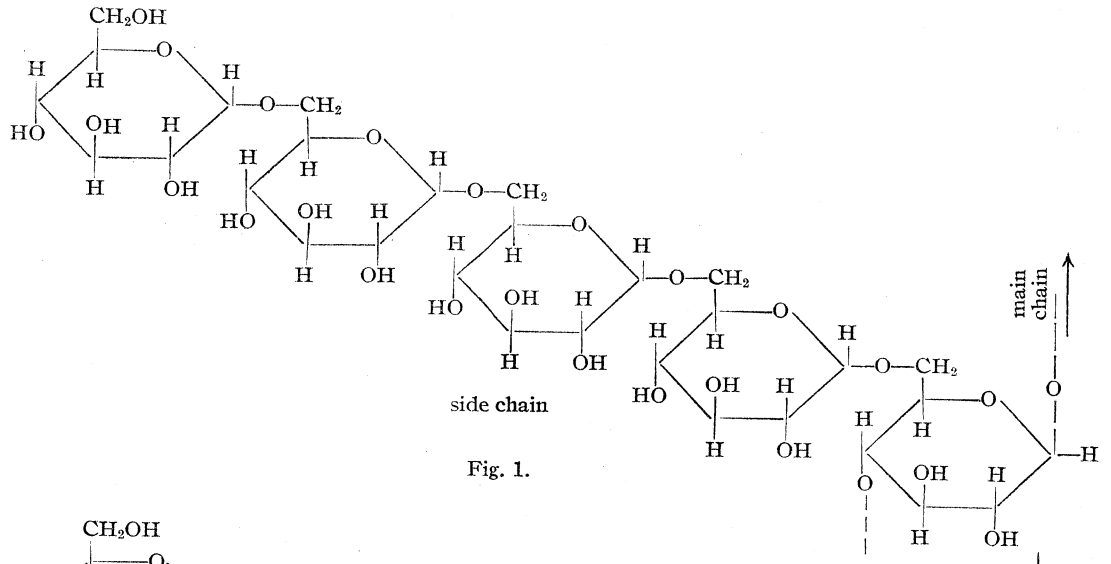


Fig. 1.

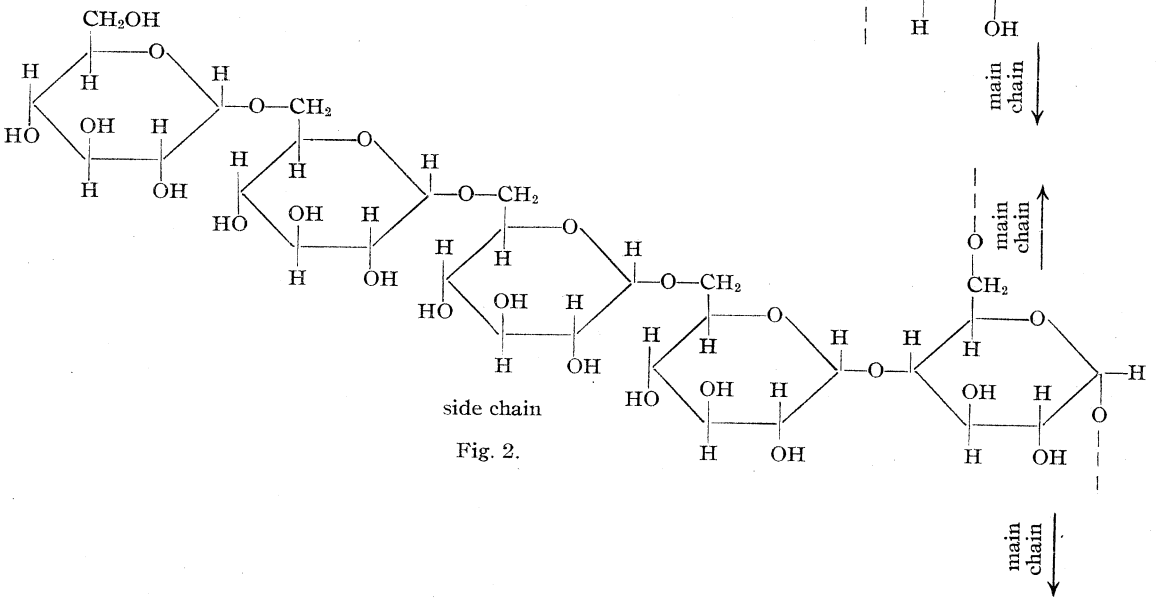


Fig. 2.

hydrolysis, 4% could be accounted for as methyl levulinate. It was shown by control experiments that the three partially methylated monosaccharides obtained from the hydrolysis of methylated dextran were all decomposed in this manner and to the same extent (1.5%) so that this side reaction does not affect the final ratio. By this procedure the ratio of tetra- to tri- to dimethyl methyl glucoside was established as exactly 1:3:1, thus verifying the earlier results of Hibbert and co-workers.[2]

The tetramethyl methyl glucoside and trimethyl methyl glucoside were identified as 2,3,4,6-tetramethyl methyl glucoside and 2,3,4-trimethyl methyl glucoside, respectively.

The dimethyl methyl glucoside was identified as the 2,3-derivative by oxidation of the dimethyl glucose to the corresponding dimethyl gluconic acid (84% yield) by the method of Hudson and Isbell.[15]

The dimethyl gluconic acid was characterized as the crystalline 2,3-dimethyl gluconophenylhydrazide (81% yield).

Based on the above evidence, two tentative formulas for dextran (Figs. 1 and 2), differing only in the position of attachment of the side chain, are suggested. These, however, do not exhaust all the possibilities and it is conceivable that the side chain may consist of three, two or even one unit with a corresponding lengthening of the primary chains.

Three of the linkages between the building units are of the 1,6 type while the remaining two are

(15) Hudson and Isbell, THIS JOURNAL, **51**, 2225 (1929).

either 1,4 or 1,6. No decision can be reached at present as to whether the linkages are α or β.

Experimental

Methylation of Dextran.—Thirty grams of dextran was suspended in 300 cc. of water, made alkaline by the addition of 25 cc. of 30% sodium hydroxide and methylated by the Haworth method in an atmosphere of nitrogen, using ten successive portions of 100 cc. of sodium hydroxide and 40 cc. of dimethyl sulfate. The alkali and the dimethyl sulfate were added to the reaction mixture concurrently. The complete reaction was carried out at room temperature.

The sodium sulfate formed during the methylation was removed by dialysis through a cellophane membrane. Three such methylations were carried out; yield, 34.0 g.; OCH_3, 40.5%.

Further methylations were effected using an original modification of Muskat's method.[12] The apparatus consisted of a cylindrical Pyrex container (7.5 × 22.5 cm.) with a side arm for the passage of ammonia. A condenser and mercury-sealed stirrer were attached to the flask by ground glass joints.

Thirty-four grams of dextran (OCH_3, 40.5%) was suspended in anhydrous anisole (340 cc.) in the reaction flask and 40 cc. of anisole distilled off under reduced pressure (20 mm.) to remove the last traces of water. The remaining dextran–anisole suspension (300 cc.) was stirred overnight. The anisole was then frozen by means of a chloroform–solid carbon dioxide-bath, and metallic sodium (0.9 g.) added to dry the ammonia (200 cc.), which was condensed on the solid anisole (time three to four hours). Metallic sodium (4 g.) was added, the anisole allowed to melt, and the mixture stirred for three to four hours. The ammonia was allowed to evaporate spontaneously. Twenty cc. of anisole was distilled off under vacuum and in an atmosphere of nitrogen, to remove the last traces of ammonia, methyl iodide (100 g.) added and the mixture refluxed overnight at 60° on the water-bath. Additions of both sodium and methyl iodide were made through the side-arm by temporarily removing the condenser.

The methyl iodide was removed by distillation under reduced pressure through a distilling head which fitted the reaction flask (ground glass joints throughout). Twenty cc. of anisole was added and then removed by vacuum distillation in order to expel traces of moisture.

This procedure was repeated twice more without removing the product from the flask (trial experiments had shown that the inorganic impurities did not interfere with the methylation).

After the third methylation there was considerable inorganic material present which was removed at this stage as follows. The reaction mixture was taken to dryness (20 mm.) in an atmosphere of nitrogen, water (300 cc.) added, the mixture heated, with occasional stirring, to the boiling point and kept at this temperature for ten minutes. The dextran was removed by centrifuging the cooled solution, then dried in the vacuum oven overnight at 55–60°. The well-dried, partially-methylated dextran dissolved readily in cold chloroform (10 cc. of chloroform per gram of methylated dextran) and any appreciable residue was removed by centrifuging the chloroform solution, followed by filtration. One to two volumes of 30–50° petroleum ether was added until an appreciable turbidity was apparent. This initial slight precipitate contained much of the residual ash. The clear filtrate was precipitated into 30–50° petroleum ether (total volume twenty times that of chloroform used), and the resulting precipitate washed twice with fresh 30–50° petroleum ether and dried [55° (20 mm.)] for thirty hours; yield, 29.8 g.; OCH_3: 1st Muskat methylation 41.5%; 2nd, 42.3%; 3rd, 44.0%. (The methoxyl values were obtained by removing and purifying a small representative sample.) The dextran was then methylated three more times as above and purified in the same manner; yield, 27.6 g.; OCH_3: 4th Muskat methylation 44.9%; 5th, 45.3%; 6th, 45.6%. Calcd. for: $C_6H_7O_2(OCH_3)_3$: C, 52.94; H, 7.84; OCH_3, 45.6. Found: C, 52.70; H, 7.92; OCH_3, 45.6.

Hydrolysis of Methylated Dextran.—Fully methylated dextran (7.100 g.) was hydrolyzed in three separate portions of 3.060, 1.520 and 2.520 g., respectively.

In a typical hydrolysis 3.060 g. of methylated dextran was suspended in anhydrous methanol (60 cc.) containing 2% hydrogen chloride, sealed in a glass bomb-tube and heated at 140–142° in a tilting electric oven for 60–65 hours. After this time the dextran had dissolved completely and the solution changed from a pale yellow to a clear reddish brown color.

The bomb was cooled to 0°, opened, and the excess hydrogen chloride gas allowed to escape while the solution attained room temperature. The open end of the bomb was fitted, during this period, with a Kjeldahl trap as a precaution in case of a too vigorous effervescence.

The solution was transferred to a centrifuge cup and neutralized (litmus) with silver carbonate, the insoluble silver salts removed by centrifugence and filtration and washed with three portions (15 cc. each) of anhydrous methanol, the washings being added to the original filtrate. At this point the methanolic solutions from the three separate hydrolyses were combined and the solvent removed under reduced pressure [20 mm. (50°)].

The resulting sirup was dissolved in 142 cc. of water so that a 10-cc. aliquot contained the glucosides originating from 0.5 g. of methylated dextran. To 10 cc. of this solution was added 50 cc. of 2,4-dinitrophenylhydrazine (containing 0.2 g. of reagent). After twenty minutes the precipitate (A) was filtered, dried under suction and finally in a vacuum desiccator; yield, 0.030 g. representing 4.2% decomposition of the dextran; recrystallized from methanol; melting point, 138–139°. A mixed melting point with an authentic sample of 2,4-dinitrophenylhydrazone of methyl levulinate showed no depression.

To the filtrate (B) an additional 50 cc. of reagent was added and the solution allowed to stand at room temperature for two and one-half hours. No further precipitate formed.

Removal of Methyl Levulinate.—To the remainder of the aqueous solution containing the glucosides from 6.6 g. of methylated dextran was added a barium hydroxide solution (20 cc.), saturated at 92–93°, and the mixture kept at 60–62° on the water-bath for two hours. It was then taken to dryness [20 mm. (50–60°)], and the residue extracted by hand shaking with the following successive portions of hot chloroform: 100, 50, 50, 50, 50, 25, 25, 25 cc.

TABLE I

FRACTIONATION OF GLUCOSIDIC MIXTURE OBTAINED FROM HYDROLYSIS OF FULLY-METHYLATED DEXTRAN

Fraction	Physical state	Fraction, g.	OCH_3, %	"Tetra," g.	"Tri," g.	"Di" g.
1	Colorless sirup	1.204	61.0	1.204		
2	Colorless sirup and white crystals	0.207	57.8	0.113	0.094	
3	White crystals (pure 2,3,4-trimethyl methyl glucoside)	0.605	52.8		0.605	
4	White crystals and colorless sirup (α and β mixture)	2.811	52.4		2.811	
5	Colorless sirup	0.397	46.5		0.172	0.225
6	Light yellow sirup	1.013	42.0			1.013
Total				1.317	3.682	1.238
Ratio				1.01	3.00	1.07

The theoretical methoxyl values for tetra-, tri-, and dimethyl methyl glucosides are 62.0, 52.6, and 41.9%, respectively. The amounts of each present in the small intermediate fractions (2 and 5, Table I) were calculated on this basis.

The combined extracts were evaporated at 40° and 20 mm. pressure, and the residue distilled under high vacuum (0.005 mm.) to give a clear sirup; yield, 7.245 g. (95%). Calcd. for $C_6H_8O_2(OCH_3)_4$: OCH_3, 52.6%; found, OCH_3, 52.3%.

Fractionation of the Glucosides.—The glucosidic mixture (6.43 g.) was fractionated using the same conditions and technique as described in the preceding paper.[13] The results of the fractionation, methoxyl analyses and allocation of the two intermediate fractions among the glucosides are summarized in Table I.

Identification of the Glucosides

(a) **Tetramethyl Methyl Glucoside.**—A portion (0.70 g.) of Fraction 1 was hydrolyzed with 15 cc. of 5% sulfuric acid at 100° for eighteen hours, after which time the rotation was constant.

The acid solution was neutralized to litmus with solid barium carbonate, filtered, and the filtrate taken to dryness [55° (20 mm.)], in an atmosphere of nitrogen. The residue was extracted with four 25-cc. portions of hot anhydrous acetone, the combined acetone solutions filtered, and the solvent removed at 20° leaving a pale yellow sirup, to which 10 cc. of anhydrous ether was added. On standing a precipitate of fine white needles was obtained as the ether evaporated; weight 0.50 g. (75% of theoretical). The product was recrystallized from low-boiling (30–50°) petroleum ether containing 5% diethyl ether; m. p. 90–91°. A mixed melting point with an authentic sample of 2,3,4,6-tetramethyl glucose showed no depression.

(b) **Trimethyl Methyl Glucoside.**—A portion (0.58 g.) of Fraction 3 was recrystallized from low boiling (30–50°) petroleum ether containing 5% diethyl ether. A mass of fine white needles was obtained (0.42 g.), m. p. 93–94°, which showed no mixed melting point depression with an authentic sample of 2,3,4-trimethyl-β-methyl glucoside.

(c) **Dimethyl Methyl Glucoside.**—A portion (0.60 g.) of Fraction 6 was hydrolyzed to the corresponding dimethyl glucose (0.538 g.) using the procedure outlined above for the hydrolysis of the tetramethyl methyl glucoside. Calcd. for $C_6H_{10}O_4(OCH_3)_2$: OCH_3, 29.9. Found: OCH_3, 30.2.

The dimethylglucose (0.538 g.) was oxidized to the corresponding dimethylgluconic acid by use of the method of Hudson and Isbell;[15] weight of dimethylgluconic acid, 0.487 g. (84%).

The dimethylgluconic acid (0.487 g.) was characterized as the crystalline 2,3-dimethylgluconophenylhydrazide.[16] The weight of recrystallized product (from ethanol) was 0.556 g. (81.4%), (of fine white needles); m. p. 166.5–167.5° (uncor.); mixed melting point with authentic 2,3-dimethylgluconophenylhydrazide showed no depression. Calcd. for $C_{14}H_{22}O_6N_2$: C, 53.5; H, 7.0; N, 8.9; OCH_3, 19.7. Found: C, 53.5; H, 7.1; N, 9.0; OCH_3, 19.5.

Summary

1. The complete methylation of the dextran, synthesized by *Leuconostoc mesenteroides*, has been accomplished in an over-all yield of 71.4%.

2. Hydrolysis of trimethyl dextran and fractionation of the resulting glucoside mixture, employing quantitative technique, have established the ratio of tetra- to tri- to dimethyl methyl glucoside as 1:3:1.

3. The three glucosides have been identified, and based on these results a tentative formula for the structure of dextran has been proposed.

MONTREAL, CANADA RECEIVED MAY 12, 1942

(16) Evans, Levi, Hawkins and Hibbert, *Can. J. Research*, forthcoming publication.

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

The Preparation and Properties of Certain Polyethoxyethanes and their Bromo Derivatives

BY S. M. MCELVAIN AND PHILIP M. WALTERS

The original object of most of the work that is described in this paper was the preparation of triethoxyethylene (ethoxyketene diethylacetal) in order that its properties might be recorded with those of the other ketene acetals recently reported[1] from this Laboratory. To date, however, all attempts to prepare this particular ketene acetal have been consistently unsuccessful, but the preparation and properties of the various ethoxyethanes and their bromo derivatives that have been used in these attempts seem to be of sufficient interest to record.

The unsymmetrical diethoxyethane, acetal (I), in the presence of pyridine is brominated readily (at 10–15°) and in fair yields (25–30%) to the mono- and dibromo derivatives II and III.[2] The unsymmetrical triethoxyethane, ethyl orthoacetate (IV), brominates in good yields (55–75%) in the presence of pyridine, but at slightly higher temperatures (10–35°) to the bromo derivatives V and VI, thus

Py = pyridine

$$CH_3CH(OEt)_2 \xrightarrow[\text{at } 10°]{Br_2 + Py} BrCH_2CH(OEt)_2 \xrightarrow[\text{at } 15°]{Br_2 + Py} Br_2CHCH(OEt)_2$$

I II III

$$CH_3C(OEt)_3 \xrightarrow[\text{at } 10°]{Br_2 + Py} BrCH_2C(OEt)_3 \xrightarrow[\text{at } 35°]{Br_2 + Py} Br_2CHC(OEt)_3$$

IV V VI

However, the corresponding symmetrically substituted compounds, ethylene glycoldiethyl ether and ethoxyacetal, $EtOCH_2CH(OEt)_2$, not only require a decidedly higher reaction temperature (65°) to cause one equivalent of bromine and pyridine to react with each of them, but yield a variety of cleavage products instead of monobromo derivatives. In all of the above mentioned brominations higher reaction temperatures are required if pyridine is not used, and under these conditions the bromination is not smooth but is accompanied by cleavage of ethoxyl groups by the hydrogen bromide produced in the reaction.

The differences in the behavior of the bromo compounds II, III, V and VI toward sodium or potassium alkoxides are interesting. As previously reported[3] bromoacetal (II) yields mainly ethoxyacetal when treated with an alcoholic solution of sodium ethoxide, but with potassium *t*-butoxide in *t*-butyl alcohol it is converted into ketene acetal.[4] Dibromoacetal (III) reacts readily with one equivalent of potassium ethoxide but is very resistant to further action of this reagent. It was first thought[5] that the product of the reaction of one equivalent of potassium ethoxide with III was bromoethoxyacetal, $EtOCHBrCH(OEt)_2$, together with a small amount of bromoketene acetal (VII), which added a molecule of alcohol to give the orthobromoester (V) that was always isolated as one of the reaction products. With potassium *t*-butoxide in *t*-butyl alcohol the dibromoacetal (III) was smoothly transformed with the loss of hydrogen bromide, into VII.

$$III \xrightarrow{-HBr} BrCH{=}C(OEt)_2 \xrightarrow{EtOH} V$$

VII

It is now found that the earlier observation was in error and that the reaction of III with potassium ethoxide in ethyl alcohol solution does not yield any detectable quantities of the bromoethoxyacetal by direct replacement of a bromine by ethoxy but instead gives bromoketene acetal (VII) by the elimination of hydrogen bromide from III. Indeed, if the reaction mixture is worked up within a few hours after the reaction is finished, yields of VII as high as those obtained in *t*-butyl alcohol may be isolated. As previously reported[5] ethyl orthobromoacetate (V) is always present as a reaction product; in fact, it is the only product if the reaction mixture is allowed to stand too long before working up. It appears from these results that bromoketene acetal reacts sufficiently slowly with alkaline alcohol to allow

(1) McElvain and Walters, THIS JOURNAL, **64**, 1059 (1942).

(2) This method of preparation, however, is not as satisfactory for II as is the bromination of vinyl acetate [Filachione, *ibid.*, **61**, 1705 (1939)] nor for III as is the bromination of II in the presence of calcium carbonate [Beyerstedt and McElvain, *ibid.*, **59**, 2267 (1937)].

(3) Beyerstedt and McElvain, *ibid.*, **58**, 529 (1936).

(4) Johnson, Barnes and McElvain, *ibid.*, **62**, 968 (1940).

(5) Beyerstedt and McElvain, *ibid.*, **59**, 2266 (1937).

it to be formed in and isolated from this medium.[6] This behavior is in a marked contrast to the instantaneous reaction of this ketene acetal with alcohol, containing a trace of acid, to produce the ortho-ester V.

Since it was not possible to obtain the bromoethoxyacetal $EtOCHBrCH(OEt)_2$ from III due to the ease with which this latter compound lost hydrogen bromide, the preparation of ethyl orthobromoethoxyacetate, $EtOCHBrC(OEt)_3$, from the orthodibromoester (VI) was undertaken. If this bromoethoxyorthoester were available it should be readily convertible into the desired triethoxyethylene by the action of sodium.[7] Although the dibromo-orthoester (VI) cannot lose hydrogen bromide it failed to give the expected bromoethoxyorthoester when treated with one equivalent of potassium ethoxide in alcohol solution. Instead the monobromo-orthoester (V) was the reaction product. This latter orthoester was found to react similarly with alcoholic potassium ethoxide with the formation of ethyl orthoacetate, thus

$$VI \xrightarrow[EtOH]{KOEt} V \xrightarrow[EtOH]{KOEt} CH_3C(OEt)_3$$

The positive character of the bromine in the orthoesters V and VI is striking. It is well known[8] that an increase in the number of negative (electron attracting) groups on a carbon carrying a halogen increases the tendency of that halogen to be replaced, through hydrolytic cleavage, by hydrogen (instead of hydroxyl) as, for example, in the hydrolysis of carbon tetrabromide to bromoform and bromomalonic ester to malonic ester. In the cases of the orthoesters, V and VI, however, it is seen that the effect of the three ethoxy groups is sufficiently great to render positive in its reaction a bromine one carbon removed from the carbon carrying the ethoxy groups.

The failure of the dibromo-orthoester VI to yield the bromoethoxyorthoester led to the attempt to prepare this latter compound by the bromination of ethyl orthoethoxyacetate (VIII). This latter ester was obtained through the following sequence of reactions

$$ClCH_2COOH \longrightarrow EtOCH_2COOH \longrightarrow EtOCH_2COOEt \longrightarrow EtOCH_2CONH_2$$
$$EtOCH_2CN \longrightarrow EtOCH_2C(OEt)=NH\cdot HCl \longrightarrow EtOCH_2C(OEt)_3$$
VIII

The orthoester VIII shows a resistance to bromination similar to that of ethylene glycol diethyl ether and ethoxyacetal mentioned above. It did react with bromine in the presence of pyridine at 80° to yield pyridine hydrobromide, but the ester was transformed in the process into a tar from which nothing could be distilled.

Experimental

Ethyl Orthobromoacetate.—This bromo-orthoester was prepared by the bromination of ethyl orthoacetate in pyridine employing the method of Beyerstedt and McElvain.[9]

Ethyl Orthodibromoacetate.—To a stirred mixture of 162 g. (1 mole) of ethyl orthoacetate and 158 g. (2 moles) of pyridine was added dropwise 320 g. (2 moles) of bromine over a period of two hours. The reaction mixture was cooled to about 30° until one-half of the bromine had been added, whereupon the temperature was allowed to rise to 60–70° for the remainder of the bromine addition. The reaction mixture was stirred for an additional two hours. The brominated ester then was separated from the precipitated pyridine hydrobromide and this salt thoroughly washed with anhydrous ether. These washings were combined with the dibromoester and distilled. The yield of ethyl orthodibromoacetate was 170 g. (53%); b. p. 102–104° (8 mm.); $n^{25}D$ 1.4691; d^{25}_{25} 1.5272.

This compound has been previously isolated and identified as a by-product of the monobromination of ethyl orthoacetate.[9]

Bromination of Acetal in Pyridine.—Diethyl acetal was brominated in pyridine by the above method at a somewhat lower temperature (10–15°) to monobromoacetal (23%) and dibromoacetal (29%).

Bromination of Ethoxyacetal and Ethylene Glycol Diethylether.—Bromination of ethoxyacetal[10] in pyridine at 65° failed to give the expected monobromination product, bromoethoxyacetal, but resulted in a variety of cleavage products. The only clean-cut fraction obtained on fractionation was a 15% yield of a material boiling at 79° (12 mm.); $n^{25}D$ 1.4175. This material gave a positive Fehling test and yielded a sodium bisulfite addition product, reactions which the original ethoxyacetal failed to show. These two tests and the ethoxyl analysis would indicate this fraction to be diethoxyacetaldehyde.

Anal. Calcd. for $C_6H_{12}O_3$: C_2H_5O, 68.1. Found: C_2H_5O, 68.3.

This compound has been reported previously by Fischer

(6) Dichloroacetal shows a similar behavior with alcoholic potassium ethoxide and yields 60% of the theoretical amount of chloroketene acetal even after the reaction mixture is allowed to stand overnight before it is worked up. In this connection it is interesting to note that Pinner (*Ber.*, **5**, 151 (1872)) reported the preparation of the symmetrical tetraethoxyethane, glyoxaltetraethylacetal, from the reaction of sodium ethoxide with dichloroacetal. He reported no yields or analyses, but did remark that he could not obtain a completely chlorine-free product. In the light of the present work it would seem that Pinner did not have the glyoxal-acetal but ethyl orthochloroacetate (from the addition of alcohol to chloroketene acetal) probably mixed with ethyl orthoacetate (from the reaction of sodium ethoxide with the orthochloroester).

(7) Walters and McElvain, This Journal, **62**, 1482 (1940).

(8) *Cf.* Schmidt, *et al.*, *Ber.*, **59**, 1876 (1926).

(9) Beyerstedt and McElvain, This Journal, **59**, 1274 (1937).

(10) Späth, *Monatsh.*, **36**, 4 (1915).

and Baer[11] who prepared it by the lead tetraacetate oxidation of glyceraldehyde acetal. However, they reported a considerably lower boiling point for their product than was obtained in the present work.

Bromination of ethoxyacetal in the absence of a solvent at 80° yielded a number of cleavage products. From one mole of acetal, there was obtained 0.48 mole of ethyl bromide, b. p. 38–40°; 0.97 mole of water, b. p. 98–100°; 0.75 mole of ethyl alcohol, b. p. 76–80°; and 0.275 mole of dibromoacetal, b. p. 95–97° (12 mm.); $n^{25}D$ 1.4788; C_2H_5O, 32.6% (calcd. 32.6%).

Bromination of ethylene glycol diethylether in pyridine at 65° and bromination in the absence of a solvent at a somewhat higher temperature (80°), resulted in a variety of cleavage products instead of monobromo derivatives.

The Reaction of Alcoholic Potassium Ethoxide with Ethyl Orthobromoacetate and with Ethyl Orthodibromoacetate.—To a stirred solution of 30 g. (0.77 atom) of potassium in 400 ml. of absolute alcohol was added 80 g. (0.25 mole) of ethyl orthodibromoacetate and the resulting mixture gently refluxed for thirty-six hours. The excess alcohol then was removed carefully by atmospheric distillation, and the orthoesters separated from the precipitated potassium bromide by extracting the residue several times with anhydrous ether. The ether extracts were combined and distilled. Twenty-one grams (52%) of ethyl orthoacetate, b. p. 68–70° (50 mm.), and 25 g. (42%) of ethyl orthobromoacetate, b. p. 78–80° (10 mm.), were obtained.

In a similar experiment employing equimolar quantities of potassium ethoxide and dibromo ester, there was obtained 30 g. (50%) of ethyl orthobromoacetate and 12 g. (15%) of unchanged ethyl orthodibromoacetate. Repetition of this experiment with ethyl orthobromoacetate as the starting material gave ethyl orthoacetate as the reaction product.

Reaction of Dibromo- and Dichloroacetal with Alcoholic Potassium Ethoxide.—To a stirred mixture of 138 g. (0.5 mole) of dibromoacetal and 100 ml. of absolute alcohol in a 1-liter three-necked flask, fitted with a dropping funnel and reflux condenser was added slowly a solution of 20 g. (0.5 atom) of potassium in 300 ml. of absolute alcohol. The flask was heated on a steam-bath during the addition and for two hours after the last of the alcoholic alkali had been added. The condenser then was set for downward distillation and 300 ml. of alcohol removed from the reaction mixture, after which the precipitated potassium bromide was filtered off. The filtered salt was washed thoroughly with anhydrous ether and the washings combined with the filtrate, and distilled. The yield of bromoketene acetal was 61 g. (62.5%); b. p. 72–3° (11 mm.); $n^{25}D$ 1.4610; d^{25}_4 1.319; C_2H_5O, 45.7% (calcd. 46.1%).

In a similar experiment employing dichloroacetal instead of dibromoacetal there was obtained 45 g. (60%) of chloroketene acetal, b. p. 57–58° (10 mm.); $n^{25}D$ 1.4378; d^{25}_4 1.052; C_2H_5O, 59.4% (calcd. 59.8%).

In each of the above preparations the product should be worked up as rapidly as possible to ensure the optimum yields of the respective ketene acetals.

(11) Fischer and Baer, *Helv. Chim. Acta*, **18**, 514 (1935).

Ethoxyacetonitrile.—Ethoxyacetamide, b. p. 225–230°, m. p. 82–83°, was obtained in 85% yields by the action of aqueous ammonia on ethyl ethoxyacetate.[12] A mixture of 103 g. of this amide and 142 g. of phosphorus pentoxide in a 1-l. distilling flask was heated in an oil-bath at 150–180° as long as the ethoxyacetonitrile distilled over. The crude distillate was redistilled from 5 g. of fresh phosphorus pentoxide. The yield of nitrile boiling at 133–134°, $n^{25}D$ 1.3888,[13] amounted to 51 g. (60%).

Ethyl Orthoethoxyacetate.—This orthoester was prepared by the method of McElvain and Nelson.[14] The iminoester hydrochloride precipitated in 88% yield when the procedure described for the preparation of the hydrochloride from chloroacetonitrile was followed. A 47% yield of the orthoester was obtained when 1 mole of the hydrochloride was alcoholysed in a refluxing mixture of 290 ml. of absolute alcohol and 340 ml. of absolute ether over a period of three hours. Ethyl orthoethoxyacetate boils at 69–70° (10 mm.) or 180–181° (740 mm.); $n^{25}D$ 1.4055; d^{25}_{25} 0.921.

Anal. Calcd. for $C_{10}H_{22}O_4$: C, 58.2; H, 10.8; C_2H_5O, 87.4. Found: C, 58.4; H, 10.7; C_2H_5O, 86.5.

Bromination of Ethyl Orthoethoxyacetate.—To a stirred mixture of 20.6 g. (0.1 mole) of ethyl orthoethoxyacetate and 7.7 g. (0.098 mole) of pyridine was added dropwise 16.0 g. (0.1 mole) of bromine over a period of thirty minutes. The reaction mixture was heated at a temperature of 80° during the bromine addition with no apparent reaction occurring until the bromine addition was practically completed. Then a vigorous reaction occurred which had to be controlled by the application of a cold water-bath. After the initial reaction had subsided, the reaction flask was heated for an additional hour at 80°. The precipitated pyridine hydrobromide (88%) was removed by filtration and thoroughly extracted with anhydrous ether. These washings were combined with the filtrate and distilled.

From none of the several brominations carried out could any bromination product be isolated and identified. The products obtained were mainly low-boiling liquids and a non-distillable, carbonaceous residue.

Summary

The behavior of acetal, ethyl orthoacetate, ethylene glycol diethyl ether, ethoxyacetal, and ethyl orthoethoxyacetate toward bromination is compared.

Dibromoacetal is shown to give only bromoketene acetal with alcoholic potassium ethoxide, and not bromoethoxyacetal as was reported previously. Both ethyl orthobromoacetate and ethyl orthodibromoacetate have their bromine replaced by hydrogen instead of ethoxyl with this reagent.

MADISON, WISCONSIN RECEIVED APRIL 27, 1942

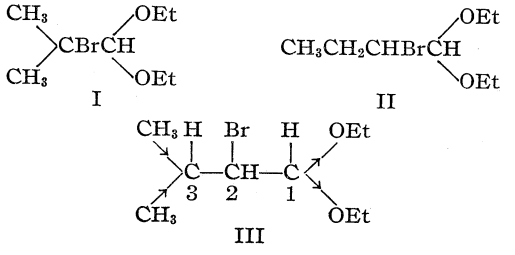
(12) "Organic Syntheses," **13**, 42 (1933).
(13) *Cf.* Henry, *Ber.*, **6**, 260 (1873).
(14) McElvain and Nelson, THIS JOURNAL, **64**, 1825 (1942).

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

Ketene Acetals. X. The Elimination of Hydrogen Bromide from the Acetals of α-Bromoaldehydes. Isopropyl- and *n*-Propylketene Diethylacetal

By S. M. McElvain, Robert L. Clarke[1] and Giffin D. Jones

The preparation of ketene diethylacetal by the elimination of a molecule of halogen acid from the iodo- or bromo-acetal[2] raised the question as to the applicability of this reaction to the α-bromo-acetals of the higher homologs of acetaldehyde. From a purely statistical consideration, such an acetal as α-bromoisobutyraldehyde acetal (I) with six β-hydrogens would seem much more likely to lose hydrogen bromide between the α- and one of the β-carbon atoms and yield the acetal of the unsaturated aldehyde. Similarly, the acetal of α-bromo-*n*-butyraldehyde (II) contains two β-hydrogens to compete with the single hydrogen of the acetal carbon atom. In the case of the acetal of α-bromoisovaleraldehyde (III), however, the single hydrogen in the β-position would indicate an even statistical chance that some of the ketene acetal as well as the unsaturated acetal would be formed. A consideration of the electronic nature of the groups of III would seem to lead more surely to the prediction that the ketene acetal rather than the unsaturated aldehyde acetal would be produced by the elimination of hydrogen bromide. If the mechanism of the elimination reaction involves, as is generally believed, first the removal of a proton[3] from the molecule by the base, followed by the emission of the bromide ion, then the inductive effects of the groups attached to carbons 1 and 3 of III should make the hydrogen on carbon 1 much more labile and consequently more likely to be removed with the bromine than the hydrogen on carbon 3.



I II

III

As a matter of fact, each of the bromo-acetals, I, II and III is converted by both sodium ethoxide in alcohol and potassium *t*-butoxide in *t*-butyl alcohol into the corresponding unsaturated acetals. There is no indication that a ketene acetal is produced in any of these reactions. An explanation of these results led to a consideration of (a) the validity of the proton-removal mechanism of the elimination reaction, (b) the possibility that the ketene acetal really was initially formed from III and then rearranged under the reaction conditions into the acetal of the α,β-unsaturated aldehyde.

Relative to the mechanism of the elimination reaction, Hughes, Ingold, Masterman and McNulty[4] in a recent paper have pointed out that there are two mechanisms by which hydrogen bromide may be eliminated from such a compound as III. The first of these involves the emission (or ionization) of the bromide ion from the molecule as the rate controlling step which is then followed by the rapid loss of a proton. Such a mechanism requires that the elimination be a first order reaction. The other alternative is the generally accepted proton-removal mechanism which postulates that the rate controlling step is the removal of a proton by the base followed by the rapid emission of the bromide ion. This mechanism requires that the reaction be second order. A third possibility that might be considered involves the intermediate formation of a β-alkoxy acetal with the subsequent loss of an alcohol molecule to form the unsaturated aldehyde acetal. It would be predicted that the *t*-butoxide ion should, due to steric effects, react more slowly than the ethoxide ion to form this intermediate were this the correct mechanism. This mechanism also requires that the reaction be second order unless the loss of the alcohol molecule be the controlling step.

In the hope of gaining some information as to which of these mechanisms is followed in the process of elimination of hydrogen bromide from III, three series of reaction rate determinations between this bromo-acetal and 0.75 *N* and 2.0 *N* sodium ethoxide in absolute alcohol and 0.75 *N* potassium *t*-butoxide in *t*-butyl alcohol were

(1) Wisconsin Alumni Foundation Research Scholar and Research Assistant, 1940–1942.

(2) (a) Beyerstedt and McElvain, This Journal, **58**, 529 (1936); (b) Johnson, Barnes and McElvain, *ibid.*, **62**, 968 (1940).

(3) Hauser, This Journal, **62**, 933 (1940); Drake and McElvain, *ibid.*, **56**, 697 (1934).

(4) Hughes, Ingold, Masterman and McNulty, *J. Chem. Soc.*, 899 (1940).

carried out. Plots of the reciprocal of the concentration against time are shown in Fig. 1. It is seen that these curves approximate the straight lines characteristic of a second order reaction in each case. It may also be seen from these plots that potassium *t*-butoxide causes a more rapid elimination of hydrogen bromide from III than does sodium ethoxide, a fact which eliminates the third possible reaction mechanism mentioned above. These facts lead to the rather contradictory conclusions that the elimination of hydrogen bromide from III follows the proton-removal mechanism and that the least labile proton is removed, unless it be that the proton of carbon 1 of III is really removed and the resulting ketene acetal, by a prototropic change, rearranges into the acetal of the unsaturated aldehyde which actually was isolated from the reaction.

In order to test this latter possibility it was necessary to prepare the ketene acetal in question. Both the isopropyl- and *n*-propylketene diethylacetals (V, R is isopropyl and *n*-propyl) were prepared by the action of sodium on the corresponding α-bromo-orthoesters,[5] thus

$$\underset{\text{IV}}{RCHBrC(OEt)_3} + Na \longrightarrow \underset{\text{V}}{RCH{=}C(OEt)_2} + NaOEt + NaBr$$

Both of these ketene acetals add water readily to give the corresponding esters and show no tendency to rearrange into the unsaturated acetals when refluxed in a *t*-butyl alcohol solution of potassium *t*-butoxide. In these respects their behavior is similar to that of methylketene diethyl acetal.[5,6]

It is seen from the results outlined above that the hydrogen on carbon 3 rather than the one on carbon 1 of α-bromoisovaleraldehyde acetal (III) is the more active and that electronic factors other than simple inductive effects are operative in the basic elimination of hydrogen bromide from this acetal. In this connection it might be noted that a halogen on a carbon carrying an ethoxyl group, *i. e.*, an α-chloro-ether, is very reactive, presumably on account of an electromeric polarization, $EtO\overset{\curvearrowright}{-}\underset{|}{\overset{|}{C}}\overset{\curvearrowright}{-}Cl$, that facilitates the removal of the chloride ion. If the ethoxy group is thus able to facilitate the removal of an anion from a carbon to which it is attached, it would seem reasonable to believe that it would impede the separation of a positive proton. That is to say, the failure of the acetal (III) to lose hydrogen bromide between carbons 1 and 2 is another case of the more potent electromeric (E) effect of an alkoxy group overshadowing an inductive (I) effect of opposite direction.[7] It must be admitted, however, that an illustration of the electromeric hindrance of the ethoxy groups of III to the loss of a proton from carbon 1 is difficult to imagine without some increase in this carbon's octet of electrons.

(5) Walters and McElvain, THIS JOURNAL, **62**, 1482 (1940).
(6) Rothstein, *J. Chem. Soc.*, 1558 (1940).

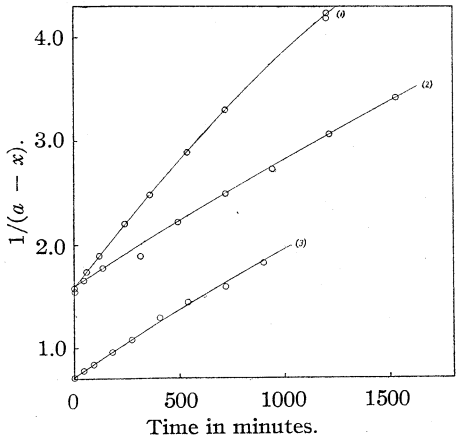


Fig. 1.—(1) 0.760 *N* KOBu (*t*); (2) 0.771 *N* NaOEt; (3) 2.040 *N* NaOEt.

The authors wish to acknowledge their indebtedness to Professor Farrington Daniels for suggestions relative to the kinetic studies reported in this paper.

Experimental

Acetals.—The diethyl acetals of isobutyraldehyde, *n*-butyraldehyde and isovaleraldehyde were prepared by the Tschitschibabin reaction from ethyl orthoformate and the appropriate Grignard reagent according to the procedure for the preparation of the acetal of hexaldehyde.[8] The following modifications were found to give considerable improvements in yield. After the addition of the ethyl orthoformate and a refluxing period of sixteen hours, crushed ice was added to decompose the excess of Grignard reagent. The ether layer was decanted and washed with water. The aqueous layer was covered with ether, cooled and treated slowly and with stirring with a 10% solution of acetic acid that contained 80% of the acetic acid required for the neutralization of the basic magnesium bromide produced in the reaction. Since all of the solids did not dissolve, the supernatant liquids were decanted, the ether layer separated, washed with water and a 10% sodium carbonate solution. The aqueous layer was extracted twice with ether and, after washing, the ether layers were combined, dried over potassium carbonate and fraction-

(7) *Cf.* the dissociation constants of benzoic acid with those of the *m*- and *p*-methoxybenzoic acids, Watson, "Modern Theories of Organic Chemistry," Oxford Press, New York, N. Y., 1937, p. 36.
(8) "Organic Syntheses," **16**, 41 (1936).

ated. Using these modifications of procedure and two-mole quantities of reactants isobutyraldehyde diethylacetal, b. p. 133–136°, *n*-butyraldehyde diethylacetal, b. p. 143–144°, and isovaleraldehyde diethylacetal, b. p. 156–158°, were obtained in yields of 83, 80 and 90% of the theoretical, respectively.

α-Bromo-acetals.—The three acetals mentioned above were brominated by the procedure of Hartung and Adkins.[9] The yields of α-bromoisobutyraldehyde diethylacetal, b. p. 63–64° (7 mm.), α-bromo-*n*-butyraldehyde diethylacetal, b. p. 82–84° (12 mm.), and α-bromoisovaleraldehyde diethylacetal, b. p. 87–88° (14 mm.), were 36, 20 and 40% of the theoretical, respectively.

Since the α-bromoisovaleraldehyde acetal was to be used for kinetic studies it was further purified, particularly since it was found that the product obtained from the bromination reaction gave low ethoxyl values as well as about 8% immediate reaction with an alcoholic solution of sodium ethoxide. In an attempt to hydrolyze the bromo-acetal to the corresponding bromo-aldehyde, it was accidentally discovered that the unchanged bromo-acetal recovered from the incomplete hydrolysis showed the correct ethoxyl content and gave a quite low (2%) zero-time reaction with sodium ethoxide. Apparently the lower boiling bromo-aldehyde had carried with it, as an azeotropic mixture, the unknown contaminants of the bromo-acetal leaving the unhydrolyzed acetal quite pure. Since as high a purity as possible for the acetal was desired, the following rather wasteful purification procedure was adopted: a mixture of 25 g. of the bromo-acetal from the bromination reaction and 7 ml. of dilute (1:10) sulfuric acid was heated on a steam-bath with occasional shaking for ten minutes. Then 10 ml. of ether was added, the layers separated and the ether layer washed with 7 ml. of a 10% potassium carbonate solution. After drying over anhydrous potassium carbonate, the ether layer was fractionated. After removal of the ether and the lower boiling fractions, 12 g. of α-bromoisovaleraldehyde diethyl acetal, b. p. 55–56° (3 mm.), or 92–93° (14 mm.); $n^{25}D$ 1.4438; d^{25}_4 1.163 was obtained.

Anal. Calcd. for $C_9H_{19}O_2Br$: C_2H_5O, 37.7; Br, 33.5. Found: C_2H_5O, 37.5; Br, 33.2.

α-Bromoisovaleraldehyde diethylacetal has been prepared by Fischer, Ertel and Löwenberg,[10] who reported it to have the following properties: b. p. 88–89° (13 mm.); $n^{20}D$ 1.4489; d^{20}_4 1.177.

Preparation of Isobutenal-, *n*-Butenal- and Isopentenal-diethylacetal.—Each of these unsaturated acetals was obtained when the corresponding bromo-acetal was heated with an equivalent amount of 1.4 *N* potassium *t*-butoxide in *t*-butyl alcohol solution in the manner described[2b] for the preparation of ketene acetal from bromo-acetal. When the reactions were carried out in 0.2-mole quantities the yields of the isobutenal acetal,[11] b. p. 136–137°, *n*-butenal acetal,[12] b. p. 48–49° (21 mm.), and isopentenal acetal,[9,10] b. p. 59–60° (16 mm.), were 64, 41 and 62% of the theoretical, respectively.

(9) Hartung and Adkins, This Journal, **49**, 2520 (1927).
(10) Fischer, Ertel and Löwenberg, *Ber.*, **64**, 30 (1931).
(11) Kinney and Adams, This Journal, **59**, 897 (1937).
(12) Wohl and Frank, *Ber.*, **35**, 1904 (1902); Düvel, *Ann.*, **410**, 69 (1915).

None of these unsaturated acetals showed the warming characteristic of a ketene acetal when treated with water containing a trace of hydrochloric acid. The isobutenal acetal yielded a resinous solid when hydrolyzed, but the *n*-butenal acetal and isopentenal acetal gave the corresponding unsaturated aldehydes which were identified as the known semicarbazones.

Rate of Reaction of α-Bromoisovaleraldehyde Diethyl Acetal with Alkali Alkoxides.—The determination of the reaction rates between the bromoacetal and sodium ethoxide was attempted at 55°, but the rate was so low (11% reaction in thirteen hours) at this temperature that 80° was used as the reaction temperature. Determinations were made with 0.771 *N* and with 2.040 *N* sodium ethoxide in absolute ethyl alcohol and 0.760 *N* potassium *t*-butoxide in *t*-butyl alcohol.

The alkali solutions were prepared by dissolving the metal in the alcohol and titrating the resulting solutions against standard hydrochloric acid solution.

For each rate determination a series of 10 reaction tubes 7 cm. in length and 1.5 cm. in diameter and constricted at the open end for sealing, was prepared from Pyrex test-tubes. Approximately a 0.5-g. sample of the bromo-acetal was accurately weighed into each of these reaction tubes. Then the volume of the alcoholic alkali solution containing alkoxide equivalent to the bromo-acetal in each tube was rapidly calculated and added to the reaction tube from a buret. Each tube was sealed and immersed in an ice-bath immediately after the addition of the alkali.

At zero time all of the tubes except nos. 1 and 10 (in order of filling) were placed in a constant temperature bath at 80 ± 2°. Tubes 1 and 10 were then opened in bottles containing 50 ml. of water and 25 ml. of ether. After thorough mixing 1.5 ml. of concentrated nitric acid was added to the mixture, and the bromide ion determined by adding an excess of standard silver nitrate solution and back titrating with potassium thiocyanate. The apparent per cent. reaction at zero time thus obtained was subtracted from the per cent. reaction at each subsequent time interval. The concentration of the reactants at zero time was calculated by multiplying the original concentration in moles per liter after mixing by the per cent. reaction at zero time and subtracting this value from the original concentration.

Plots against time of $1/(a - x)$, in which a represents the original concentration of the reactants in moles per liter and x represents the moles reacted in time t, are shown in Fig. 1.

Isovaleronitrile.—In a distilling flask of such size that the reactants occupied not more than 0.4 of the volume of the flask were placed 190 g. (1.88 moles) of isovaleramide[13] (which had been dried at 110°) and 230 g. (1.62 moles) of phosphorus pentoxide. The two solids were mixed very thoroughly by shaking and the flask was connected to a condenser for distillation. The solid mixture was heated slowly in an oil-bath to 90° and allowed to stand at this temperature overnight. The bath temperature was then raised to 130° and held there for two hours. The product was then distilled under reduced pressure (200 mm.). The resulting distillate was redistilled from 5 g. of phosphorus pentoxide. A yield of 125 g. (80% of the theoretical) of the isovaleronitrile, b. p. 127–129°,[14] was obtained.

(13) Mailhe, *Bull. soc. chim.*, **37**, 1394 (1925).
(14) *Cf.* Timmermans and Delacourt, *J. chim. phys.*, **31**, 85 (1934).

Ethyl Ortho-α-bromoisovalerate.—This ester was prepared from ethyl orthoisovalerate[15] by the following procedure. A mixture of 33 g. (0.162 mole) of ethyl orthoisovalerate and 13 g. (0.164 mole) of pyridine was introduced into a three neck flask fitted with a stirrer, condenser and dropping funnel. To this mixture was added 26 g. (0.162 mole) of bromine over a period of one hour, after which time the mixture was stirred overnight. Approximately 50 ml. of dry ether was then added and, after mixing and allowing the precipitate to settle, the ether solution was decanted. The solid remaining in the flask was washed by decantation with three 30-ml. portions of dry ether and the combined washings washed once with 25 ml. of 10% potassium carbonate. The ether solution was dried over anhydrous potassium carbonate and after the ether was removed, the product was distilled under reduced pressure. It boiled at 63–64° (1.3 mm.); $n^{25}D$ 1.4408; d^{25}_4 1.150. The yield amounted to 31 g. (67% of the theoretical). Although this ester possessed a very constant boiling point it showed an unexpectedly high bromine content and low ethoxyl values. The carbon and hydrogen analyses were fairly good.

Anal. Calcd. for $C_{11}H_{23}O_3Br$: C_2H_5O, 47.7; Br, 28.2; C, 46.65; H, 8.19. Found: C_2H_5O, 45.9; Br, 32.0; C, 46.33; H, 7.86.

Ethyl Ortho-α-bromovalerate.—This compound was prepared from ethyl orthovalerate[15] by the procedure described above for the preparation of ethyl ortho-α-bromoisovalerate. The yield amounted to 80% of the theoretical and the product boiled at 69–70° (2 mm.); $n^{25}D$ 1.4390.

Anal. Calcd. for $C_{11}H_{23}O_3Br$: C_2H_5O, 47.7. Found: C_2H_5O, 47.4.

Isopropylketene Diethylacetal.—This ketene acetal was prepared from ethyl ortho-α-bromoisovalerate and sodium by the procedure of Walters and McElvain.[5] It boiled at 96–97° (100 mm.) or 156–157° (745 mm.); $n^{25}D$ 1.4158; d^{25}_4 0.8385. The yield from 25.4 g. of the bromo-orthoester was 9.4 g. (65%).

Anal. Calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.46; C_2H_5O, 56.96. Found: C, 68.33; H, 11.64; C_2H_5O, 54.59.

A 1.7-g. sample of isopropylketene diethylacetal was treated with the theoretical amount of water containing a trace of hydrochloric acid. The reaction mixture underwent almost spontaneous reaction, the temperature rose rapidly to 60–65° and the ketene acetal was converted quantitatively into ethyl isovalerate. The reaction mixture was dried over anhydrous potassium carbonate and distilled under atmospheric pressure. The ethyl isovalerate thus obtained boiled at 134°; $n^{25}D$ 1.3947; sap. equiv., 128 (calcd. 130); m. p. of the toluidide of the acid, 107°.

n-Propylketene Diethylacetal.—This ketene acetal was prepared as was the isopropylketene diethylacetal. The yield of product boiling at 107–108° (100 mm.) or 167–168° (737 mm.); $n^{25}D$ 1.4204; d^{25}_4 0.850, amounted to 71% of the theoretical.

Anal. Calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.46; C_2H_5O, 56.96. Found: C, 67.89; H, 11.37; C_2H_5O, 54.58.

A 1.8-g. sample of *n*-propylketene diethylacetal was treated with the theoretical amount of water and converted quantitatively to ethyl valerate. This reaction was strongly exothermic as was the case with the isopropylketene diethylacetal. The ester so obtained boiled at 144°; $n^{25}D$ 1.3991; sap. equiv., 133 (calcd. 130); m. p. of the toluidide of the acid, 69.5°.

Each of the above described ketene acetals was recovered unchanged when it was refluxed in a 1.4 *N* solution of potassium *t*-butoxide in *t*-butyl alcohol for three hours.

Summary

The acetals of α-bromoisobutyraldehyde, α-bromo-*n*-butyraldehyde and α-bromoisovaleraldehyde are converted by potassium *t*-butoxide in *t*-butyl alcohol into the corresponding unsaturated acetals rather than into the ketene acetals.

The reactions between α-bromoisovaleraldehyde diethylacetal and both sodium ethoxide and potassium *t*-butoxide are shown to be second order and the implications of this fact are discussed.

Isopropylketene diethylacetal and *n*-propylketene diethylacetal have been prepared from the corresponding α-bromo-orthoesters and show no tendency to rearrange into unsaturated aldehyde acetals.

MADISON, WISCONSIN RECEIVED APRIL 27, 1942

(15) McElvain and Nelson, THIS JOURNAL, **64**, 1825 (1942).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Reduction of Iodate and Bromate at the Dropping Mercury Electrode in Neutral and Basic Media and the Effects of Salts upon the Current–Voltage Curves

BY E. F. ORLEMANN[1,2] AND I. M. KOLTHOFF

Rylich[3] found that the decomposition potentials of iodate and bromate ions observed in neutral or alkaline medium at the dropping mercury electrode are affected by the kind and concentration of indifferent salts in the solution. The decomposition potential becomes more positive with increasing valence of the cation and with increasing concentration of the salt. Rylich's data were not sufficiently extensive to allow a satisfactory interpretation of his results. In the present study we have made a systematic investigation of the effect of salts on the current–voltage (c. v.) curves of iodate and bromate in neutral or alkaline media, and an attempt has been made to devise a mechanism for the electroreduction of these ions which accounts for the experimental results. In a previous paper[4] the c. v. curves of iodate and bromate in buffered solutions at *p*H values smaller than 8 have been reported.

Experimental

The manual apparatus was used as described in previous papers,[4] and all the experiments were performed in a thermostat at 25.00 ± 0.05°. The potentials were measured against the saturated calomel electrode (S. C. E.) at 25°. Two different capillaries of marine barometer tubing with the following characteristics were used: Capillary 2, pressure = 90 cm. of mercury; m = 1.93 mg. sec.$^{-1}$ at −0.6 v.; t = 3.60 sec. at −0.6 v.; $m^{2/3}t^{1/6}$ = 1.92 at −0.6 v.; −capillary 3, pressure = 80 cm. of mercury; m = 1.80 mg. sec.$^{-1}$ at −0.6 v.; t = 3.52 sec. at −0.6 v.; $m^{2/3}t^{1/6}$ = 1.79 at 0.6 v. Changes of $m^{2/3}t^{1/6}$ with the potential of the dropping electrode were calculated with the aid of a table given in a previous communication.[5] Current–voltage curves shown in the figures have been plotted without making correction for the residual current. The plots have been made using an exaggerated potential axis in order to avoid crowding of the waves and to bring out small differences in the effect of the salt concentration. Values of the current used in the analysis of the waves and of the diffusion current reported in the tables have been properly corrected for the residual current of the particular medium used.

Effect of Alkali Salts and of Tetramethylammonium Bromide on the c. v. Curves of Iodate.—Salts were found to affect the relation between current and potential, the half wave potential, the value of K in the relation $i_d = Kc$, in which i_d is the diffusion current at a given potential and c the concentration of iodate. In addition, the change of the diffusion current with increasing negative potential was affected by the salt concentration. All the essential data are collected in a concise way in Table I. In all cases—with the exception of tetramethylammonium bromide—the equation of the wave was found to be given by the expression

$$\pi = \pi_{1/2} + a \log (i_d - i)/i \qquad (1)$$

in which π is the potential and i the current at any potential on the wave. The value of a was obtained from the slope of the linear relation between log $(i_d - i)/i$ and the potential. Examples of the linear relations found are given in Fig. 1. In this figure the plots obtained in 3.60, 0.91 and 0.09 M lithium chloride are shown. Values of a in the different salt solutions are listed in Table I.

In all cases—with the exception of tetramethylammonium bromide—the half wave potential (see equation 1) was found to be independent of the iodate concentration in a given salt solution. Values of $\pi_{1/2}$ are reported in Table I. The apparent diffusion current and the value of the potential at which it was obtained are listed in the column i_d at π. From the diffusion current and the concentration of iodate, also found in the table, the quantity $K_{ob} = i_d/c$ was obtained. The calculated value $K_{calcd.}$ was obtained from the Ilkovic equation

$$K_{calcd.} = i_d/c = 605nD^{1/2}m^{2/3}t^{1/6} \qquad (2)$$

in which n is taken equal to six and $D = 1.09 \times 10^{-5}$ cm.^{2} sec.$^{-1}$ at 25°.

The effect of the salt concentration on the change of the diffusion current with increasing

(1) From a thesis submitted by Edwin F. Orlemann to the Graduate School of the University of Minnesota in partial fulfillment of the requirements of the degree of Doctor of Philosophy, 1941.

(2) DuPont Fellow in Chemistry 1940–41. Present address: Department of Chemistry, University of California, Berkeley, California.

(3) A. Rylich, *Coll. Czechoslov. Chem. Commun.*, **7**, 288 (1935).

(4) E. F. Orlemann and I. M. Kolthoff, THIS JOURNAL, **64**, 1044 (1942).

(5) *Ibid.*, **63**, 2083 (1941).

TABLE I

EFFECT OF SALTS ON C. V. CURVES OF IODATE

Salt	Salt concn., M	$KIO_3 \times 10^3$ M	$\pi_{1/2}$ vs. S. C. E.	a in m. v. in eq. (1)	i_d obs. $\times 10^6$ amp. at −1.45 v.	i_d change with π	$K_{obs.}/K_{calcd.}$	$K_{cor.}/K_{calcd.}$	$D_{IO_3} \times 10^5$ cm.^{2} sec.$^{-1}$
KCl	4.0	0.500	−1.150	85	17.10	Abn.	1.50	1.00	1.09
KCl	1.0	.500	−1.180	75	14.20	Abn.	1.25	1.00	1.09
KCl	0.5	.500	−1.195	75	12.20	Abn.	1.07		
KCl	.2	.500	−1.235		11.40	Norm.	1.00		1.09
KCl	.05	.500	−1.280	85	11.40	Norm.	1.00		1.09
KNO_3	.2	.500	−1.230		11.30	Norm.	0.99		1.07
KNO_3	.2	.100	−1.230		2.25	Norm.	.99		1.07
KNO_3	.2	1.00	−1.230		22.5	Norm.	.99		1.07
CsCl	1.20	1.00	−1.155		20.7	Abn.	1.01		
CsCl	0.60	1.00	−1.170		20.5	Abn.	1.00		1.09
CsCl	.30	1.00	−1.190	70	20.8	Abn.	1.01		1.11
CsCl	.15	1.00	−1.220	65	20.4	Norm.	1.00		1.09
CsCl	.075	1.00	−1.240	65	20.3	Norm.	0.99		1.07
NaCl	3.60	0.91	−1.085	60	18.90	Abn.	1.02	0.73	0.58
NaCl	0.91	.91	−1.155	60	19.70	Abn.	1.05	.91	.90
NaCl	.09	.91	−1.270	65	18.80	Norm.	1.00		1.09
NaCl	.09	.375	−1.265		7.73	Norm.	1.00		1.09
LiCl	3.60	.91	−1.040	60	16.30	Abn.	0.875	.62	0.42
LiCl	1.80	.91	−1.090		18.15	Abn.	.970	.80	.70
LiCl	0.91	.91	−1.130	55	18.30	Abn.	.980	.86	.82
LiCl	.45	.91	−1.160		18.40	Norm.	.985	.975	1.03
LiCl	.09	.91	−1.215	60	18.65	Norm.	1.00	1.00	1.09
$N(CH_3)_4Br$	1.80	.91	−1.280	80[X]	16.50	Norm.	0.88	0.88	0.85
$N(CH_3)_4Br$	0.90	.91	−1.270	70[X]	17.90	Norm.	.96	.96	1.00
$N(CH_3)_4Br$	.45	.91	−1.270	65[X]	18.60	Norm.	1.00	1.00	1.09
$N(CH_3)_4Br$	.09	.91	−1.300	65[X]	18.50	Norm.	1.00	1.00	1.09

[X] In tetramethylammonium bromide the equation of the wave is: $\pi = \text{Const.} - a \log (i_d - i)/i^2$.

negative potential is shown qualitatively in the column "i_d change with π." According to the Ilkovic equation the ratio $i_d/m^{2/3}t^{1/6}$ in a given solution should be constant and independent of the potential. When this relation was found to hold the notation "Norm." is used in the column "i_d change with π." At high salt concentrations the ratio $i_d/m^{2/3}t^{1/6}$ was found to decrease markedly with increasing negative potential. In such cases the notation "abn." is used in the table. As a demonstration of the normal and abnormal effects we give in Fig. 2 the c. v. curves obtained in different concentrations of potassium chloride.

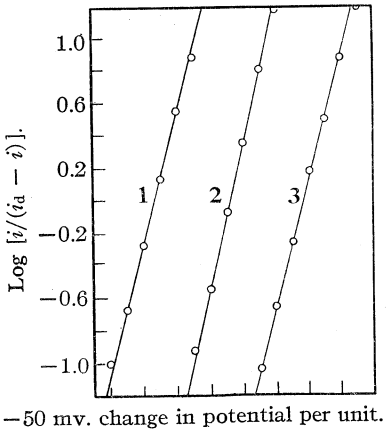


Fig. 1.—Analysis of the waves of iodate in lithium chloride solutions: Curves 1, 2 and 3 correspond to 3.6, 0.91 and 0.090 M lithium chloride, respectively.

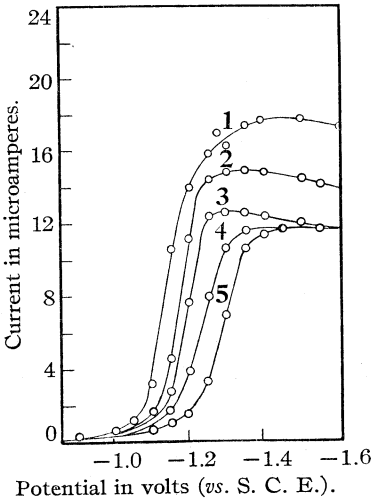


Fig. 2.—Current–voltage curves of 5×10^{-4} M potassium iodate in potassium chloride solutions of the following concentrations, using capillary 2: Curve 1, 4.0 M; curve 2, 1.0 M; curve 3, 0.5 M; curve 4, 0.2 M; curve 5, 0.05 M.

The cause of the abnormal change was found to be the occurrence of a "water current" at high salt concentrations. In a previous paper[6] the conditions have been described under which such a "water current" occurs at high salt concentrations. In the present study it happens that this water wave overlaps with the iodate wave. Hence, the diffusion current observed is not the true diffusion current of iodate, but the sum of the latter and the water wave. That this interpretation is correct is demonstrated by the following figures. It has been shown[6] that gelatin eliminates the water wave. Working with a 0.500×10^{-3} M iodate solution in 4 M potassium chloride, we found a diffusion current of 14.6 microamp., which was reduced to 10 microamp. in the presence of 0.01% of gelatin. Similarly, in 4 M lithium chloride we measured a diffusion current of 9.7 microamp. which was reduced to 7.2 microamp. in the presence of 0.01% of gelatin.

From the data given in the paper on the water wave[6] it was possible to calculate the magnitude of the water wave in the various salt solutions at a given potential. For the sake of brevity we will omit the various values and refer to the thesis of the junior author.[1] Only the final result is given in Table I in the column $K_{cor.}/K_{calcd.}$, in which $K_{cor.}$ is the experimental value of $K_{obs.}$ corrected for the water current. From the value of $K_{cor.}$ the diffusion coefficient of the iodate ion D_{IO_3} in the particular salt solution was calculated with the aid of equation (2), and is reported in Table I.

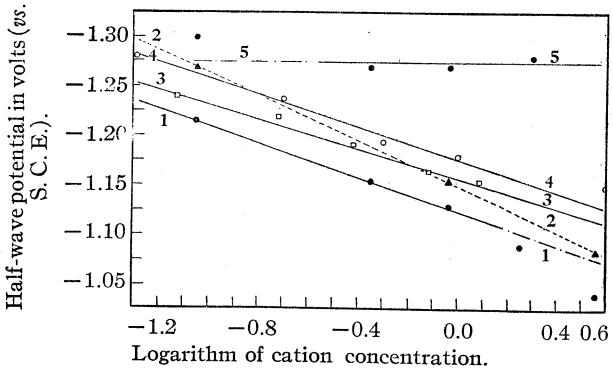


Fig. 3.—The relation between the half-wave potential of iodate and the concentration of cations in neutral or basic solutions at 25°: Curve 1, lithium ion; curve 2 sodium ion; curve 3, cesium ion; curve 4, potassium ion; curve 5, tetramethylammonium ion.

From the results reported in Table I the following conclusions are drawn: The observed and the corrected diffusion currents are proportional to the iodate concentration in a given salt solution. When the salt concentration is smaller than 0.2 M the water current is negligibly small. Under such circumstances $i_d/m^{2/3}t^{1/6}$ becomes constant and independent of the potential or the "i_d change with π" becomes normal, while the calculated value of D_{IO_3} (equation 2) agrees exactly with the value of 1.09×10^{-5} cm.^{2} sec.$^{-1}$ calculated from the mobility of the iodate ion at infinite dilution. It is of interest to notice that the diffusion coefficient of the iodate ion is not affected by the potassium chloride concentration. Even in 4 M potassium chloride it was found equal to the value at infinite dilution. On the other hand, the diffusion coefficient decreases markedly with increasing concentration of the other salts, the effect being LiCl > NaCl > Me_4NBr.

The relation between the half wave potential and the concentration of various univalent cations is shown in Fig. 3. Evidently, there is an approximately linear relation between the half wave potential and the logarithm of the concentration of the cation in the solution. The half wave potentials are necessarily somewhat uncertain as their measurement involves a liquid junction potential which cannot be corrected for in a satisfactory way. From Fig. 3 and the data in Table I the equations of the iodate waves and the characteristics of the waves were found. The corresponding data are summarized in Table II.

Effect of Divalent Cations on the c. v. Curves of Iodate.—The effects of barium and calcium chloride have been studied and the results are summarized in Table III. When the salt concentration is equal to or smaller than 0.1 M, the normal value of the diffusion coefficient of the iodate ion is found. The latter decreases rapidly when the barium or calcium chloride concentration becomes greater than 0.1 M. The equations and characteristics of the waves obtained upon graphical analysis are found in Table II. Again, there is a linear relation between the half wave potential and the logarithm of the barium or calcium concentration. We have tried to study the effect of trivalent cations on the iodate waves, but it was difficult to find ions which allowed an unambiguous interpretation of the c. v. curves. Salts of most trivalent cations are hydrolyzed and cause an acid reaction in the solution. In such cases the c. v. curves correspond to the "acid mechanism" of the iodate reduction[4] or the re-

(6) THIS JOURNAL., 64, 833 (1942).

TABLE II

CHARACTERISTICS AND EQUATION OF IODATE WAVES IN UNIVALENT AND DIVALENT CATION SOLUTIONS (25°)

Salt	$\pi_{1/2}$ in 1 M salt	$\Delta\pi_{1/2}/\Delta \log M$, m. v.	Empirical equation of wave
LiCl	−1.125	85	$\pi = -1.125 + 0.08 \log [Li^+] + 0.06 \log (i_d - i)/i$
NaCl	−1.150	115	$\pi = -1.150 + 0.12 \log [Na^+] + 0.06 \log (i_d - i)/i$
KCl	−1.175	80	$\pi = -1.175 + 0.08 \log [K^+] + 0.08 \log (i_d - i)/i$
CsCl	−1.160	75	$\pi = -1.160 + 0.07 \log [Cs^+] + 0.06 \log (i_d - i)/i$
$(CH_3)_4NBr$	−1.275	0	$\pi = -1.275 + 0.07 \log (i_d - i)/i^2$ (i in μ amp.)
$CaCl_2$	−0.940	50	$\pi = -0.94 + 0.051 \log [Ca^{++}] + 0.06 \log (i_d - i)/i$
$BaCl_2$	−0.980	60	$\pi = -0.98 + 0.061 \log [Ba^{++}] + 0.06 \log (i_d - i)/i$

TABLE III

EFFECTS OF BARIUM AND CALCIUM CHLORIDE ON C. V. CURVES OF IODATE. CAPILLARY 3 WAS USED

Salt	Concn., M	$\pi_{1/2}$ vs. S. C. E.	a in m. v. in eq. (1)	i_d change with π	$K_{obs.}/K_{calcd.}$ at −1.4 v.	$K_{cor.}/K_{calcd.}$ at −1.4 v.	$D_{IO_3} \times 10^{-5}$ cm.^{2} sec.$^{-1}$
$BaCl_2$[a]	1.50	−0.970	60	Abn.	0.90	0.72	0.56
$BaCl_2$	0.75	− .990	60	Abn.	.955	.92	.93
$BaCl_2$	.37	−1.010	60	Abn.	.940	.93	.95
$BaCl_2$	.187	−1.025	60	..	.920	..	..
$BaCl_2$	.05	...	..	Norm.	.990	.99	1.07
$CaCl_2$[b]	5	(−0.800)	..	Abn.	.346	..	..
$CaCl_2$	1	− .940	65	Abn.	1.04	.87	0.83
$CaCl_2$	0.5	− .960	60	Abn.	1.02	.95	.99
$CaCl_2$	.2	− .980	60	Abn.	1.03	..	..
$CaCl_2$	.1	− .990	60	Norm.	1.01	1.01	1.11
$CaCl_2$	.05	−1.005	60	Norm.	1.01	1.01	1.11

[a] The iodate concentration in the barium chloride solutions was 0.91×10^{-3} M. The diffusion current was measured at −1.4 v. [b] The iodate concentration was 1.00×10^{-3} M.

duction takes place according to both the acid and neutral mechanism. Lanthanum salts of strong acids are practically unhydrolyzed. However, in this case a complication arises due to a film formation of lanthanum hydroxide on the mercury drop during the reduction and to the slight solubility of lanthanum iodate. Lanthanum salts shift the half wave potential markedly to more positive potentials. Examples of the striking lanthanum effect upon iodate waves in unbuffered solutions are shown in Fig. 4.

The solutions were 0.1 M in potassium chloride and 5×10^{-4} M in iodate. In the presence of 0.1 to 0.01 M lanthanum chloride identical and steep waves were obtained (curves 1 and 2) with a half wave potential of −0.38 v. An equally steep wave was obtained in 0.001 M lanthanum salt (curve 3), but the half wave potential was shifted to −0.49 v. In 0.0001 M lanthanum solution (curve 4) the wave started at −0.6 v. and became poorly defined, probably as a result of precipitation of most of the lanthanum as hydroxide during the reduction of iodate. That the film of lanthanum hydroxide has some effect upon the shape and location of the wave is evident from a comparison of curves 2 and 5. Both solutions were identical in composition except that the solution corresponding to curve 5 contained 0.01% of gelatin. The "decomposition potential" of the iodate

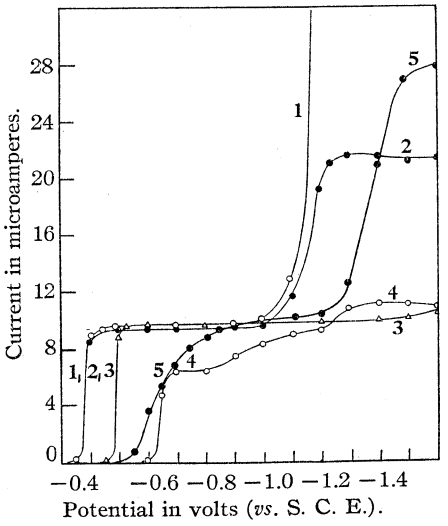


Fig. 4.—Current–voltage curves (using capillary 3) of 5×10^{-4} M potassium iodate, 0.1 M potassium chloride solutions (unbuffered) in the presence of lanthanum chloride: The concentrations of lanthanum chloride are, curve 1, 0.1 M; curve 2, 0.01 M; curve 3, 0.001 M; curve 4, 0.0001 M; curve 5, 0.01 M lanthanum chloride with 0.01% gelatin present.

was shifted from −0.4 to −0.6 v. by the addition of gelatin. The drops of mercury falling in the diffusion current region in the absence of gelatin did not coalesce readily, presumably as a consequence of the presence of a film of lanthanum hydroxide, whereas they did coalesce in buffered iodate solutions containing lanthanum. In addition in buffered solutions (pH 7) of lanthanum the iodate wave is found at a potential of the order of −0.8 instead of −0.4 v., indicating that the iodate reduction is catalyzed by the precipitation of lanthanum at the electrode.

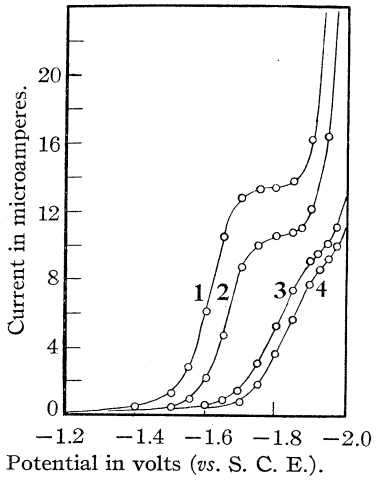


Fig. 5.—Current–voltage curves (using capillary 2) of 4 × 10^{-4} M potassium bromate in potassium chloride solutions of the following concentrations: Curve 1, 4.0 M; curve 2, 1.0 M; curve 3, 0.10 M; curve 4, 0.05 M.

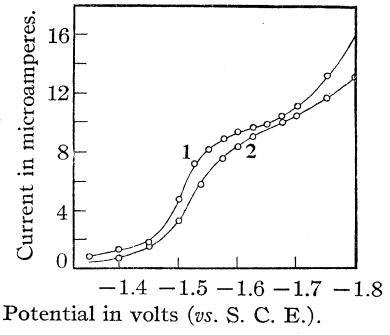


Fig. 6.—Current–voltage curves (using capillary 2) of 4 × 10^{-4} M potassium bromate in barium chloride solutions of the following concentrations: Curve 1, 0.165 M; curve 2, 0.05 M.

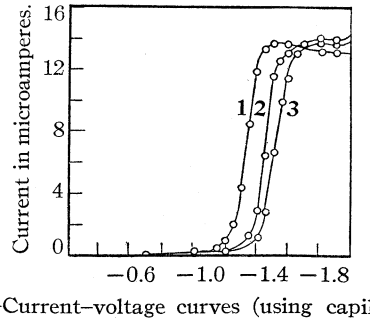


Fig. 7.—Current–voltage curves (using capillary 3) of 6 × 10^{-4} M potassium bromate in calcium chloride solutions of the following concentrations: Curve 1, 2.0 M; curve 2, 0.4 M; curve 3, 0.1 M.

Effect of Salts on the c. v. Curves of Bromate.—Bromate is reduced at a much more negative potential than is iodate. Consequently, it is hardly possible to find well-defined diffusion currents in dilute solutions of alkali or barium salts, as the reduction of the alkali or barium ion sets in before the diffusion current is attained. In concentrated solutions of alkali salts, well-defined diffusion currents are found. Their values, however, are affected by the water current. For analytical purposes, therefore, it is not to be recommended to use concentrated solutions of alkali or barium salts as supporting electrolytes. Current–voltage curves obtained in solutions of potassium, barium and calcium chlorides are shown in Figs. 5, 6, and 7.

From Fig. 7 it is seen that, from the analytical viewpoint, dilute solutions of calcium chloride (0.025 to 0.2 M) are most suitable as supporting medium for the polarographic determination of bromate. Calculating from the mobility of the bromate ion at infinite dilution a coefficient of diffusion of 1.44 × 10^{-5} cm.^{2} sec.$^{-1}$ at 25°, it was found that the values of i_d calculated with the aid of the Ilkovic equation (equation 2) agreed within 1 to 2% with the experimental data. The diffusion current was found proportional to the bromate concentration. For the sake of brevity we omit a complete account of all experimental data[1] and summarize the most important characteristics of the waves in Table IV.

TABLE IV

CHARACTERISTICS OF BROMATE WAVES IN SOME SALT SOLUTIONS

Salt	$\pi_{1/2}$ in 0.1 M salt	$\Delta\pi_{1/2}/\Delta$ log cation in m. v.	Value of a in eq. (1) in m. v.
KCl	−1.780	115	60
$CaCl_2$	−1.510	(150)	(90)
$BaCl_2$	−1.555	(70)	100

Lanthanum chloride shifted the bromate waves to much more positive potentials. This is shown in Fig. 8. The solutions were 0.1 M in potassium chloride and 6 × 10^{-4} M in bromate. In the presence of 0.1 to 0.001 M lanthanum chloride identical and steep waves were obtained (curves 1, 2 and 3) at a potential of −0.82 v. The wave

in 0.0001 M lanthanum solution (curve 4) was irregular probably as a result of exhaustion of lanthanum around the drop by precipitation as hydroxide. The solutions corresponding to curves 2 and 5 were identical (0.01 M lanthanum), except that the solution of curve 5 contained 0.01% of gelatin. The gelatin shifted the wave from −0.82 to −1.1 v.

Discussion

The linear relation between the half-wave potential and the logarithm of the concentration of cations noted in Fig. 3 and Tables II and IV shows that cations play a very definite part in the potential determining step involved in the reduction of iodate and bromate ions. A mechanism which accounts for this regular shift in half-wave potential with a change in concentration of cations has been developed by extending the ideas described in connection with the reduction of iodate and bromate ions in acid media.[4] Considering only iodate, for convenience, the general mechanism proposed may be represented by the scheme

$$yM + IO_3^- = M_yIO_3^{z+} \quad \text{(fast)} \qquad (3)$$

(in which M is the cation, y an integer, and z an integer depending upon y and the valence of M)

$$M_yIO_3^{z+} + e = M_yIO_3^{(z-1)+} \quad \text{(slow)} \qquad (4)$$

$$M_yIO_3^{(z-1)+} + 5e + 3H_2O = yM + I^- + 6OH^- \quad \text{(fast)} \qquad (5)$$

(this process probably occurs in several steps).

The above mechanism is identical with that proposed in connection with the studies in acid media if the cation M is taken as an hydrogen ion and the substance $M_yIO_3^{z+}$ is iodic acid. In the discussion of the acid mechanism for the iodate and bromate reductions it was shown that if both iodate ions and a species such as $M_yIO_3^{z+}$ coexist in a solution, it is easier to transfer an electron from the electrode into the species which has the lowest vacant electron level. If we make the reasonable assumption that the vacant electron level in $M_yIO_3^{z+}$ is lower than it is in an iodate ion, then there will be a reduction of the former substance instead of a direct reduction of iodate ions. The reason for assuming that the slow step in the reduction is the transfer of one electron from the electrode to the iodate is discussed in the thesis of the junior author.

A quantitative formulation of the above mechanism readily can be made using the method of derivation given in the previous communication.[4]

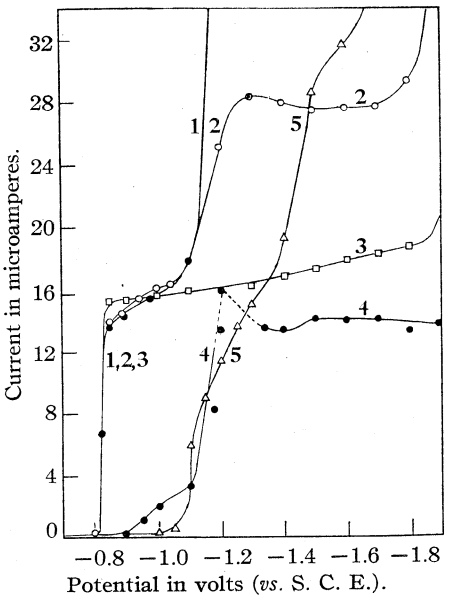


Fig. 8.—Current–voltage curves (using capillary 3) of 6×10^{-4} M potassium bromate, 0.1 M potassium chloride solutions (unbuffered) in the presence of lanthanum chloride. The lanthanum chloride concentrations are: Curve 1, 0.1 M; curve 2, 0.01 M; curve 3, 0.001 M; curve 4, 0.0001 M; and curve 5, 0.01 M lanthanum chloride with 0.01% gelatin present.

The equation for the c. v. curves found in this way is

$$\pi = \pi_{1/2} + \frac{RT}{\alpha F} \ln \frac{(i_d - i)}{i} \qquad (6)$$

$$\pi_{1/2} = \text{const.} + \frac{RT}{2\alpha F} \ln \frac{t}{D} + \frac{RT}{\alpha F} \ln \frac{f_M^y f_{IO_3^-}}{f_{M_yIO_3^{z+}}} + \frac{yRT}{\alpha F} \ln [M] \qquad (7)$$

In the above equations, α is the fraction of the total potential difference between the electrode and the bulk of the solution which acts in the reduction, t is the drop time, D is the diffusion coefficient of iodate ions, and f is the activity coefficient of the species indicated by the subscript used. The true definition of α is given in the previous communication,[4] where it is shown that if the reduction occurs at a negatively charged surface the value of α would be expected to lie close to one. There was a variation of less than 5% in the drop time over the range of salt concentrations used in the experiments described. The diffusion coefficient of iodate ions varies with the salt concentration as shown by Table I. In the most extreme case shown in Table I, that of lithium chloride, the diffusion coefficient decreased approximately by a factor of two when the concentration of lithium chloride was increased from 0.1 to 4 M. In the concentration range from 0.1

to 4 M it is difficult to find reliable data on the activity coefficients of the species involved and this factor will be neglected. To some extent the decrease in the diffusion coefficient tends to offset the decrease in activity coefficients in equation (7). The experiments reported were carried out at 25° and with the above considerations in mind equations (6) and (7) may be applied to the experimental data in the following approximate form:

$$\pi = \pi_{1/2} + \frac{0.060}{\alpha} \log \frac{(i_d - i)}{i} \quad (8)$$

$$\pi_{1/2} \cong \text{const.} + \frac{0.06y}{\alpha} \log [M] \quad (9)$$

From the experimentally determined slopes of the linear log $(i_d - i)/i$ *versus* potential plots values of α were found with the aid of equation (8). Using the values of α determined in this way and the experimentally observed slopes of the linear relation between half-wave potential and the logarithm of the concentration of cations values of y were obtained with the aid of equation (9). Values of α and y determined in this way are shown in Table V. Since the reductions occur

TABLE V

VALUES OF α AND y IN EQUATION (7) IN THE IODATE REDUCTION

Salt	$\Delta\pi_{1/2}/\Delta \log (i_d - i)/i$ mv.	α	$\Delta\pi_{1/2}/\Delta \log M$, mv.	y	Species reduced
LiCl	60	1	85	1.8[a]	$Li_2IO_3^+$
NaCl	60	1	115	2	$Na_2IO_3^+$
KCl	60 (to 80[b])	1	80	1	KIO_3
CsCl	65	1	75	1	$CsIO_3$
$BaCl_2$	60	1	60	1	$BaIO_3^+$
$CaCl_2$	60	1	50	1 (0.85)	$CaIO_3^+$

[a,b] See text.

at a negatively charged mercury surface (see Fig. 3) the expected value of α is approximately one. With the exception of tetramethylammonium bromide this prediction is borne out. In the presence of tetramethylammonium salt the potential is not a linear function of log $(i_d - i)/i$ but was found to be a linear function of log $(i_d - i)/i^2$. We have not been able to find any reasonable explanations for this relation. In Table V values of 0.75 and 1 are listed for α in potassium chloride solutions. When the solution around the drop was suitably observed with a microscope during electrolysis in potassium chloride solution it was found that there was a stirring of the solution until the diffusion current was reached in those cases where the apparent value of α was 0.75. Addition of 2×10^{-3} per cent. tropeoline 00 to these solutions completely eliminated this stirring and under these conditions the observed value of α was 1. In view of the approximate nature of equation (9) the values of y in Table V would be expected to deviate from unity. Taking this fact into consideration the values of y in Table V are reasonably close to an integral with the exception of those in lithium chloride solutions. In this case a better approximation of y was found by plotting the quantity

$$\pi_{1/2} + 0.03 \log D - 0.06 \log \frac{f_{Li^+} f_{IO_3^-}}{f_{Li_2IO_3^+}}$$

(see equation (7)) against the logarithm of the lithium chloride concentration. Values of the diffusion coefficient of iodate at the concentrations of lithium chloride used were found in Table I. It was assumed that $f^2_{Li} f_{IO_3^-}/f_{Li_2IO_3^+}$ was equal to the mean activity coefficient of lithium chloride. The plot was found to be linear and the observed slope of 110 millivolts leads to a value of 1.8 for y which is reasonably close to an integral value of 2. To account for the observed values of y it is necessary to assume that the species being reduced in each case are those listed in the last column in Table V. The species $BaIO_3^+$, $CaIO_3^+$, KIO_3 and $CsIO_3$ listed in Table V appear reasonable but those listed with lithium and sodium do not.

The shift in half-wave potential with a change in drop time predicted by equation (7) was checked. At a drop time of 2.05 sec. the half-wave potential in 0.05 M potassium chloride was −1.256 v. and became −1.250 v. at a drop time of 4.10 sec. in the same solution. Therefore, the observed shift in half-wave potential with the above increase in drop time was 0.006 v. The shift calculated from equation (9) is 0.009 v., in reasonable agreement with the observed value.

The bromate reduction has been treated in the same manner as described above for the reduction of iodate and the results found are presented in Table VI. Qualitatively, the results in Table VI are in agreement with the mechanism proposed

TABLE VI

VALUES OF α AND OF y IN EQUATION (7) IN THE BROMATE REDUCTION

Salt	$\Delta\pi_{1/2}/\Delta \log (i_d - i)/i$ mv.	α	$\Delta\pi_{1/2}/\Delta \log M$, mv.	y	Species reduced
KCl	60	1	115	2	$K_2BrO_3^+$
$CaCl_2$	80–100	0.75–0.6	(150)		$(CaBrO_3^+)$
$BaCl_2$	100	0.6	(70)	0.7	$BaBrO_3^+$
$LaCl_3$[a]	100–140	0.6–0.4	90	0.6–0.9	$LaBrO_3^{++}$

[a] Buffered solution.

but quantitatively they are not. The conclusion that there is a reduction of $K_2BrO_3^+$ is not reasonable although the other species indicated by the data in Table VI are acceptable. We are unable to give a reasonable quantitative explanation for these results on the basis of our present knowledge of the mechanism of electrolysis phenomena in general. In view of the qualitative and partial quantitative success of the proposed mechanism it seems reasonable to conclude that the mechanism is essentially correct but must be modified in some way to include secondary effects of cations, such as their effect on the detailed structure of the double layer.

Some experiments were done in 50% acetone solution to see whether the expected increase in association of the ions in this medium would result in a change in the species which were apparently reduced. The relations observed between the half-wave potentials and the salt concentration in these cases are shown in Fig. 9. It is evident from Fig. 9 that the relation between these quantities is quite complex, but it is interesting to note that the half-wave potential is shifted with a change in concentration of tetramethylammonium bromide in this medium whereas it was practically unaffected by the concentration of tetramethylammonium bromide in aqueous medium. No attempt was made to extend these data or attempt an interpretation since too little is known about the behavior of concentrated salt solutions in 50% acetone.

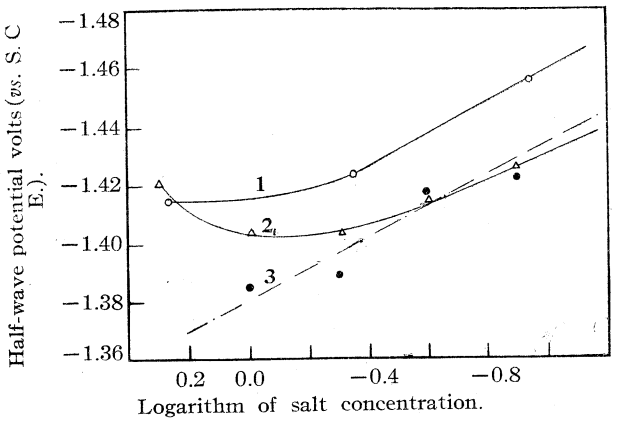


Fig. 9.—The half-wave potential of iodate as a function of the concentration of salt in 50% acetone solution. Curves 1, 2 and 3 correspond to solutions of tetramethylammonium bromide, potassium bromide and sodium chloride, respectively.

Summary

1. In the reduction of iodate and bromate at the dropping mercury electrode in neutral or alkaline media, the following relation exists between the potential on the one hand and $(i_d - i)/i$ and the concentration of the indifferent cation M on the other

$$\pi = \pi_{1/2} + a \log(i_d - i)/i + b \log M$$

The relation does not hold in solutions of tetramethylammonium bromide. Values of a and b in the iodate reduction have been determined in solutions of varying concentrations of potassium, sodium, lithium, cesium, calcium and barium.

2. There is a linear relation between the shift of the half-wave potential and the concentration of the different cation in the solution (with the exception of tetramethylammonium ion).

3. The half wave potential is slightly dependent upon the drop time.

4. A mechanism has been proposed for the reduction of iodate and bromate in salt solutions. It has been postulated that in the case of iodate the following species are reduced: KIO_3, $CsIO_3$, $Na_2IO_3^+$, $Li_2IO_3^+$, $BaIO_3^+$, $CaIO_3^+$.

MINNEAPOLIS, MINNESOTA RECEIVED MAY 20, 1942

NOTES

Identification of Alcohols and Alkyl Hydrogen Sulfates with S-Benzylthiuronium Chloride

By Robert K. Bair and C. M. Suter

The sodium salts of many acids including sulfonic acids[1] react with S-benzylthiuronium chloride to form derivatives which are of value in the identification of the original materials. The reagent is produced in nearly quantitative yield by the action of benzyl chloride with thiourea.[1,2] It has now been found that most alcohols are easily identified by this same reagent through first converting them to the corresponding alkyl hydrogen sulfates by warming in dioxane solution with chlorosulfonic acid. The benzylthiuronium salts of

$$ROH + ClSO_3H \longrightarrow ROSO_3H + HCl$$

$$ROSO_3H + C_6H_5CH_2SC(NH_2)_2Cl \longrightarrow ROSO_3(NH_2)_2CSCH_2C_6H_5 + HCl$$

methyl and ethyl hydrogen sulfate are too soluble in water to be isolated readily and the *n*-octyl compound showed an anomalous melting point behavior although the analysis was satisfactory. Ethylene glycol was identified as the bis-(hydrogen sulfate) but the behavior of other glycols was not studied.

Table I

S-Benzylthiuronium Derivatives

Alcohol	M. p., °C. (cor.)	Nitrogen,[a] % Calcd.	Found
n-Propyl	111.5–112.5	9.15	9.16
i-Propyl	142–143	9.15	9.07
n-Butyl	100–101	8.75	8.83
s-Butyl	117–119	8.75	8.73
i-Butyl	136–137	8.75	8.91
n-Amyl	85–86[e]	8.38	8.25
n-Hexyl	85–86[e]	8.04	7.87
n-Heptyl	77–79	7.74	7.33
n-Octyl	42–70	7.45	7.91
n-Decyl	73–75[e]	6.93	6.88
Lauryl[b]	74–76	6.48	6.55
Myristyl[b]	87–88	6.08	6.02
Cyclohexyl[c,d]	163–164	8.10	8.05
Bornyl[c]	174–175	7.01	7.12
Menthyl[c]	149–150	6.98	6.97
Ethylene glycol	180–181	10.10	10.39

[a] Nitrogen analyses by Dr. T. S. Ma, University of Chicago.

[b] Chlorosulfonic acid added to solid alcohols dissolved in dioxane.

[c] Thiuronium derivatives made from alkyl hydrogen sulfates.

[d] We are indebted to Dr. Sydney Archer for purifying samples of the last four compounds.

[e] Mixed melting points were taken: *n*-amyl and *n*-hexyl, 77–82°; *n*-heptyl and *n*-decyl, 53–71°.

Obviously this method of identification is applicable to sodium alkyl sulfates as such and this is of considerable interest because of the varied commercial uses of these compounds. However, the difference in melting point for the decyl and lauryl compounds is small.

Procedure.—About 5 drops of the alcohol is added to a mixture of 4 drops of chlorosulfonic acid and 5 drops of dioxane. If hydrogen chloride is not immediately evolved, the resulting mixture is warmed with shaking and allowed to stand for five or ten minutes. Then after the addition of 1 ml. of water, 1 ml. of a saturated aqueous solution (or 15% alcohol solution) of S-benzylthiuronium chloride is added. If crystals do not form in a few minutes the solution is chilled in an ice-bath. The derivatives of the lower molecular weight alcohols (to *n*-hexyl inclusive) can be recrystallized from 10% ethyl alcohol, and derivatives of higher alcohols from 50% alcohol. In preparing samples for analyses the quantities used in this procedure were multiplied by five.

The corresponding *p*-chlorobenzylthiuronium derivatives were also made from about eight alcohols; however, several of these were waxy, difficult to filter and to obtain in a pure state. Also five of them melted between 80 and 90°. No derivatives of methanol and ethanol were obtained by using either the *p*-chloro-S-benzyl- or S-benzylthiuronium chloride.

Chemical Laboratory
Northwestern University
Evanston, Illinois

Received May 22, 1942

(1) Chambers and Watt, *J. Org. Chem.*, **6**, 376 (1941).

(2) Donleavy, This Journal, **58**, 1004 (1936).

The Dehydration of 1,5-Hexadiene-3-ol to 1,3,5-Hexatriene and 1,3-Cyclohexadiene[1]

By Lewis W. Butz

That the dehydration of 1,5-hexadiene-3-ol under the conditions recently described[2] yields about 70% of 1,3,5-hexatriene was demonstrated by conversion of part of the products to 1-vinylanthraquinone. At the same time it appeared that 1,3-cyclohexadiene was formed in about 30% yield, since reaction of the hydrocarbon products with 1,4-naphthoquinone gave a 1,4-ethano adduct. The alternative explanation would be that hexatriene is converted to cyclohexadiene when

(1) Not subject to copyright.

(2) L. Butz, E. Butz and Gaddis, *J. Org. Chem.*, **5**, 178 (1940).

heated with naphthoquinone at 50°, a result hardly to be expected.

In contact with maleic anhydride at 30°, the hydrocarbon products gave a crystalline compound which was different from the adduct obtained by Farmer and Warren[3] from hexatriene and maleic anhydride at 100°. Since Farmer and Warren considered their compound to be an ethylidenetetrahydrophthalic anhydride, it appeared likely that the new isomer was the vinyltetrahydrophthalic anhydride, the normal adduct, and this view was expressed publicly.[4]

This has now been shown not to be the case. The substance, m. p. 147°, does not depress the m. p. of the ethanotetrahydrophthalic anhydride prepared[5] from cyclohexadiene and maleic anhydride. This is further evidence that the hydrocarbon obtained by the dehydration of the hexadienol contained cyclohexadiene. While the possibility of a direct hexatriene → cyclohexadiene transformation is still not excluded, it must be supposed that it occurs, if at all, during the dehydration of the hexadienol rather than during the reaction with naphthoquinone or maleic anhydride at 50 or 30°. However, it appears that the hexatriene prepared by this method is not always contaminated with so much cyclohexadiene, and the formation of the latter must depend on small variations in procedure, because the hydrocarbon has been found[6] not to yield, upon reaction with 5-acetoxy-1,4-toluquinone, any of the adducts obtained from cyclohexadiene and this quinone.

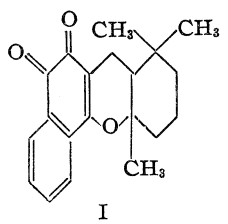
(3) Farmer and Warren, *J. Chem. Soc.*, 897 (1929).
(4) *J. Wash. Acad. Sci.*, **29**, 548 (1939).
(5) I. G. Farbenindustrie A.-G., *Chem. Zentr.*, **100**, II, 2502 (1929).
(6) E. Butz and L. Butz, *J. Org. Chem.*, **7**, 199 (1942).

BUREAU OF ANIMAL INDUSTRY
U. S. DEPARTMENT OF AGRICULTURE
BELTSVILLE, MARYLAND RECEIVED JUNE 13, 1942

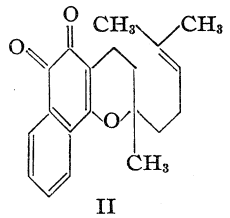
The Condensation of β-Cyclogeraniol with Leucoisonaphthazarin

BY MARSHALL D. GATES AND FERNANDA MISANI

In a recent paper Fieser and Gates[1] described the preparation of β-geranolapachone, a member of the β-lapachone series, by cyclization of 2-hydroxy-3-geranyl-1,4-naphthoquinone with concentrated sulfuric acid. The high melting point of this compound (234°) suggests that further cyclization of the side chain may have taken place to give structure I rather than the supposed structure II.

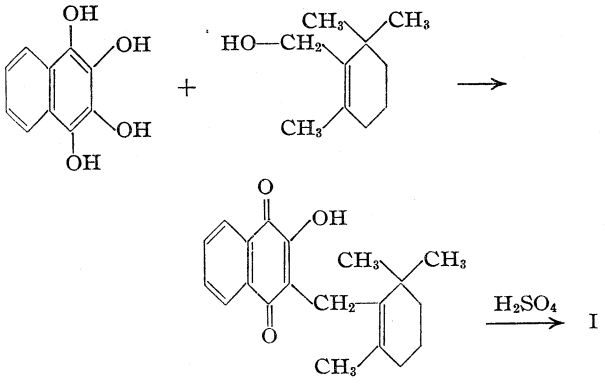


I



II

A choice between these two structures was readily made by synthesizing structure I by application of the general scheme employed by Fieser and Gates.[1]



The β-cyclogeraniol employed (m. p. 44°) was prepared by Meerwein–Ponndorf reduction of β-cyclocitral according to Kuhn and Hoffer.[2] Condensation with leucoisonaphthazarin gave the desired 2-hydroxy-3-(β-cyclogeranyl)-1,4-naphthoquinone in rather poor yield, but in easily isolated form. On cyclization with sulfuric acid, β-cyclogeranolapachone (I) was obtained. It proved to be identical with β-geranolapachone prepared according to Fieser and Gates, and their β-geranolapachone must therefore be regarded as β-cyclogeranolapachone (I).

The conditions used in the condensation of allylic alcohols with hydroxyhydroquinones in these syntheses are not sufficiently acidic (oxalic acid) to bring about cyclization of the geranyl group during the condensation. This is shown by the non-identity of the products obtained by the condensation of geraniol and β-cyclogeraniol with leucoisonaphthazarin.

Experimental Part[3]

Isonaphthazarin.—The following procedure represents an improvement over that reported by Fieser and Gates.[1] A solution of 8.9 g. of 2-hydroxy-1,4-naphthoquinone

(1) Fieser and Gates, THIS JOURNAL, **63**, 2948 (1941).
(2) Kuhn and Hoffer, *Ber.*, **67**, 357 (1934).
(3) All melting points are corrected.

(purified through the methoxy compound) in 500 cc. of water containing 4.3 g. of sodium bicarbonate was treated with 20 cc. of 30% hydrogen peroxide (superoxol). The solution rapidly darkened and, after standing for thirty-four hours, a crop of dull red large leaves had separated, 3.2 g. (43% based on 2-hydroxy-1,4-naphthoquinone utilized). One crystallization from dioxane gave pure isonaphthazarin. Acidification of the aqueous filtrate yielded 2.1 g. of orange precipitate which consisted of unchanged 2-hydroxy-1,4-naphthoquinone plus a small amount of isonaphthazarin. On several occasions, use of less pure 2-hydroxy-1,4-naphthoquinone as starting material led to much lower yields.

2-Hydroxy-3-(β-cyclogeranyl)-1,4-naphthoquinone.—Isonaphthazarin (2.0 g.) was reduced as described by Fieser and Gates[1] and the leuco compound heated in the dark under nitrogen for forty-eight hours at 65–70° with 1.0 g. of β-cyclogeraniol[2] (m. p. 44°),, 0.6 g. of anhydrous oxalic acid and 20 cc. of dioxane. The processing of the reaction mixture included the following steps: extraction of the unchanged leucoisonaphthazarin with aqueous hydrosulfite, reduction with concentrated aqueous hydrosulfite, and extraction from ether–petroleum ether with Claisen's alkali. The crude phenolic portion thus obtained was chromatographed after air oxidation on freshly ignited magnesium sulfate. On development with petroleum ether, a weakly adsorbed bright yellow band readily passed into the filtrate. Similar filtrates from systematic readsorptions of the column eluate were combined and on concentration to dryness under reduced pressure afforded 99 mg. of solid residue which after three crystallizations from ether–petroleum ether gave 36 mg. of golden yellow rectangular plates, m. p. 135–135.5°. It is quite soluble in the ordinary organic solvents, fairly soluble in warm petroleum ether, much less soluble cold, and dissolves in dilute alcoholic alkali to give the beautiful scarlet characteristic of alkali salts of 2-hydroxy-1,4-naphthoquinones. It dissolves in concentrated sulfuric acid to give a deep orange-red solution. Two further crystallizations to obtain a sample for analysis did not alter the melting point.

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.38; H, 7.15. Found: C, 77.50; H, 7.23.

β-Cyclogeranolapachone (I).—A solution of 11 mg. of 2-hydroxy-3-(β-cyclogeranyl)-1,4-naphthoquinone in ice-cold concentrated sulfuric acid (0.3 cc.) was allowed to stand several minutes, then diluted with ice water. The precipitated dark orange-brown material was taken into ether, washed with water, bicarbonate and brine, and concentrated to dryness. The residue was taken into benzene–hexane and chromatographed on freshly ignited magnesium sulfate. Development with 50% benzene–hexane left a broad salmon-pink band in the middle of the column which was sectioned out and eluted with ether. After evaporation of the ether, the solid residue was crystallized twice from pure acetone to give 3.5 mg. of orange-red prismatic blades, m. p. 232–233.3°. A mixed melting point with β-geranolapachone prepared according to Fieser and Gates[1] showed no depression.

DEPARTMENT OF CHEMISTRY
BRYN MAWR COLLEGE
BRYN MAWR, PENNSYLVANIA

RECEIVED MAY 29, 1942

Riboflavin Estimation in Fruits and Vegetables

BY G. MACKINNEY AND J. M. SUGIHARA

As part of a collaborative project,[1] it was recently necessary to make a series of chemical determinations of thiamin and riboflavin in certain fruits and vegetables, and the Conner–Straub procedure[2] was followed. Unfortunately, at the beginning, Supersorb,[3] the specific adsorbent for riboflavin was unavailable. An empirical method was, therefore, evolved, and we hoped, later, to correlate results into the series by concurrent assays on additional samples on arrival of the adsorbent. This comparison may now be made and, subject to certain provisos, we believe the modification accurately reflects differences in riboflavin content within a series. With respect to absolute values, it is in accord with microbiological assay by means of *Lactobacillus casei.* It has, further, certain advantages: increased light stability, no adsorbent is needed and the riboflavin in the aqueous buffer exhibits approximately twice the fluorescence found in pyridine–acetic solution, with consequent decrease in the percentage reading error.

The Conner–Straub procedure is followed in detail in extraction and preparation of the sample, except that, in the case of fruits, 10 ml. of pectinol (1 g. in 25 ml.) is added per 50-ml. of sample, in addition to the clarase. The whole is then incubated at 45° for two hours. The pectinol is absolutely necessary for prunes, apricots, dates, etc., to produce a satisfactory solution. A 10–20 ml. aliquot is then heated to boiling with 5 ml. of 2% acetic, as in (1), made to volume, 50 ml., with buffer, and a 15-ml. aliquot treated for a minimum of three minutes with 1 ml. of potassium permanganate, and decolorized with 3 ml. of 3% hydrogen peroxide. The solution is then filtered and compared with buffered standards at *p*H 6.0 in a Coleman fluorophotometer. The B_2 filter for the exciting light (Hg arc) cuts out completely above 4900 Å. and for the fluorescent light, below 5100 Å. The cut-out is sharp, and, for the latter filter, the transmission rises from zero at 5100 to over 90% at 5400 Å. Quinine sulfate and thiochrome have no effect on the galvanometer with these filters, at least in the concentrations used. In the majority of plant extracts treated as above, there appear to be no other water-soluble fluorescent compounds in sufficient quantities to interfere, though trouble might be anticipated in those botanical families where anthraquinone glucosides occur. However, since we do not know the behavior of these compounds on Decalso or Supersorb, similar difficulties might arise with either method.

(1) With the Department of Home Economics.

(2) Conner and Straub, *Ind. Eng. Chem., Anal. Ed.*, **13**, 385 (1941).

(3) Supersorb, Florisil or Floridin is a Fuller's Earth; Decalso, a synthetic zeolite, obtainable through supply houses, Clarase (Takamine Laboratories, N. Y.) and Pectinol (Röhm and Haas, Philadelphia) are commercial enzyme preparations.

TABLE I

RIBOFLAVIN ESTIMATES IN FRUITS AND VEGETABLES[a] IN MICROGRAMS PER GRAM

Material	Aqueous buffer, no adsorption	20 hours later	Pyridine–acetic adsorbed	20 hours later	Microbiological[b]	Thiamin, μg./g.
Asparagus, fresh	1.15	1.00	1.13	0.45		2.19
Asparagus, blanched	1.25		1.18			2.60
Broccoli, fresh	...		0.79			0.77
Broccoli, dehydrated	6.28		4.30			3.71
Broccoli, dehydrated	8.66		7.16			3.97
Broccoli, dehydrated	13.0		13.4		12.6	7.25
Peas, fresh	0.86	0.65	0.67	.22	1.5	1.16
Peas, fresh	.80		.72			0.91
Peas, cooked	.83	0.63	.78	.33		1.00
Peas, dehydrated	4.01		5.73		5.5	4.38
Peas, dehydrated	3.36		4.78			4.16
Spinach, dehydrated	23.4		18.6		23.7	10.2
Rice bran, concd.	7.74	6.85	5.44	2.71		141.0
Apricots, dried, sulfured	1.94	1.94	1.63	0.51		0.21
Prunes, dried	1.59	1.64	1.27	.20		1.24
Dates, Deglet Noors	1.14		0.30			0.53
Dates, Deglet Noors	0.73	0.77	0.40	.05		0.52
Grass, dehydrated	8.23	7.80	11.5	4.78		5.28

[a] It should be understood that the estimates on the materials assayed are valid only for these samples, purchased for the most part on the local market, without consideration of variety, maturity or possible abnormal local conditions caused by climate, Jan.–March, 1942. [b] We thank Miss M. B. Smith of the Department of Home Economics for these values.

Riboflavin estimates are given, Table I, in column 2 by the above procedure, and in column 4 after passage over Decalso and Supersorb, where the Conner–Straub procedure for both B_1 and B_2 is followed. The same samples measured twenty hours later, columns 3 and 5, after standing in the laboratory away from direct lighting, clearly show the higher light stability of our extract. We are greatly indebted to Professor Agnes Fay Morgan for permission to include, in column 6, certain microbiological assays on the same samples with *Lactobacillus casei*. They indicate very satisfactory agreement with the chemical method over the range 1 to 20 μg. per gram of sample. We include thiamin values in column 7. The rice bran concentrate, a trade product, is of interest because the thiamin value is approximately 10% higher than the minimum stated on the label, the riboflavin roughly 8 or 35% lower, depending upon whether we take the value of column 2 or 4. The thiamin content of the sulfured apricot is low, as might have been predicted.

With two reproducible exceptions, grass and peas *after* dehydration, our simpler procedure yields consistently higher results. In the case of the dehydrated peas there is definitely interference, possibly from a compound which forms a discrete yellow zone on the Supersorb, not found in the fresh peas, removed with the riboflavin by the eluting solvent. The values listed in Table I for a given vegetable are from different samples, variously treated. In general, at levels of 20 μg. per g., the results are reproducible within 5–10%, and 5–20% at 1.0 μg. per g.

The effect of diffuse light on the standards is shown in Table II. The concentration used at zero time is approximately 0.1 μg. per ml.

Our simpler procedure is certainly worth consideration where the adsorbent is unavailable, because comparative variations are reflected with accuracy in the figures. It is necessary to be more cautious in considering absolute values. Discussing specifically the vitamin A potency of foods, Booth[4] suggests that physiological responses should be expressed in International Units, and that only chemical results should be based on the gram and the liter. We may also note that it does not follow *a priori* that either of the above procedures has been absolutely (as distinct from comparatively) calibrated against *Lactobacillus* or any other bio-assay. In other words, the true chemical concentration may not represent the real biological potency. This may be illustrated in the case of carrots and spinach, where the former may have 2 to 4 times the carotene content, but where there is still doubt concerning the relative biological potencies, in terms of vitamin A bio-assay.

TABLE II

EFFECT OF LIGHT ON PERCENTAGE RETENTION OF RIBOFLAVIN IN STANDARDS

Time in hours	0	3	6	24
Pyridine–acetic	100	81.1	64.9	32.4
Buffer, *p*H 6.0	100	91.5	88.1	76.3

DIVISION OF FRUIT PRODUCTS
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIF.

RECEIVED MAY 4, 1942

(4) Booth, *Food Manuf.*, **17**, 60 (1942).

The Dipole Moments of Cyclohexanol and Cyclohexanone in Dioxane

BY I. F. HALVERSTADT[1] AND W. D. KUMLER

In the course of an investigation on the structure of the bile acids it was desirable to know the dipole moments of cyclohexanol and cyclohexanone in dioxane. These compounds have been measured in benzene by Williams,[2] the moments being cyclohexanol, 1.9, and cyclohexanone 2.9.[3]

$$P_{2_0} = p_{2_0} M_2$$

$$\mu = 0.0127 \sqrt{(P_{2_0} - P_{E_2})T}$$

P_{E_2} values were calculated from the molar refractivities of the electron groups present in the molecules.

The ϵ_{12}–ω_2 curves were linear for both compounds and the extrapolated value of ϵ_1 was approximately equal to the observed value, indicating that the compounds are not associated in these solutions.

TABLE I

MEASUREMENTS IN DIOXANE AT 25°

Cyclohexanol			Cyclohexanone		
ω_2	v_{12}	ϵ_{12}	ω_2	v_{12}	ϵ_{12}
0.002696	0.97424	2.2237	0.002580	0.97422	2.2395
.005279	.97447	2.2337	.004785	.97448	2.2631
.007566	.97476	2.2432	.008013	.97472	2.2972
.010630	.97508	2.2554	.009462	.97491	2.3128
.012633	.97524	2.2639	.011496	.97512	2.3342
.014741	.97549	2.2723	.014441	.97546	2.3657

	ϵ_1 measured	ϵ_1 extrapolated	v_1 extrapolated	α	β	P_{2_0}	P_{E_2}	μ
Cyclohexanol	2.2123	2.2126	0.97395	4.05	0.104	97.8	29.2	1.82
Cyclohexanone	2.2128	2.2121	0.97395	10.63	0.102	202.2	27.7	2.90

The symbols in the equations and tables are the same as those given previously.[4] The equations used in calculating the moments are[4]

$$p_{2_0} = \frac{3\alpha v_1}{(\epsilon_1 + 2)^2} + (v_1 + \beta)\frac{(\epsilon_1 - 1)}{(\epsilon_1 + 2)}$$

Eastman Kodak Co. practical cyclohexanol was dried over "Drierite" and twice fractionally distilled through a Widmer column, b. p. 160.9–161.3° cor. at 759 mm.

Eastman Kodak Co. practical cyclohexanone was twice fractionally distilled through a Widmer column, b. p. 157.0–157.5° cor. at 759 mm.

COLLEGE OF PHARMACY,
UNIVERSITY OF CALIFORNIA
SAN FRANCISCO, CALIFORNIA

RECEIVED MAY 5, 1942

(1) Abraham Rosenberg Fellow in Pharmaceutical Chemistry 1941–1942.

(2) Williams, THIS JOURNAL, **52**, 1831 (1930).

(3) Through a typographical error, the moment of cyclohexanone is listed in William's article as 2.8.

(4) Halverstadt and Kumler, "A Critical Study of Dielectric Polarization Concentration Curves," in publication.

NEW BOOKS

The Tools of the Chemist. Their Ancestry and American Evolution. By ERNEST CHILD. Reinhold Publishing Corporation, New York, N. Y., 1940. 220 pp. Price, $3.50.

"Tools of the Chemist," by Ernest Child is an historical account of the development of laboratory apparatus and ware with special emphasis on American enterprise. The book is divided into three parts. Part I, "People and Events in American Chemistry," is entirely historical and biographical and reviews the accomplishments of the pioneers of our science in this country. This part of the book is particularly valuable to the student of the history of chemistry and makes interesting and fascinating reading.

The major portion of the book, Part II, describes the "Ancestry and Development of American Chemical Laboratory Apparatus." In turn, the following appliances, ware and other materials are taken up: balances, glass, porcelain and silica ware, filter paper, heating apparatus, metal laboratory ware, platinum, alundum, rubber ware and optical apparatus. The section on balances is by far the best presented and is given in greatest detail, the illustrations being particularly well chosen to show the earlier forms. One is forcibly reminded throughout the reading of this section of the important and vital role the American chemist has had in developing and perfecting our modern chemical tools. More illustrations of present types of apparatus would have added interest to the book.

The book closes with a short historical account of the leading supply houses and distributors of laboratory apparatus.

The book is profusely and attractively illustrated with over one hundred illustrations. It is an admirable and valuable addition to our growing libraries on historical chemistry. Every chemist will delight and profit in perusing it.

CARL J. ENGELDER

Fluorescent Chemicals and their Applications. By JACK DE MENT, Research Chemist, The Mineralogist Laboratories; Associate Editor, the Mineralogist Magazine. With a Special Chapter on Ultraviolet Radiation Sources by H. C. Dake, Editor, the Mineralogist Magazine. Chemical Publishing Company, Inc., 232 King Street, Brooklyn, N. Y., 1942. xiii + 240 pp. Illustrated. 14 × 22 cm. Price, $4.25.

During the last few years, fluorescence phenomena have been arousing scientific scrutiny because of the remarkable results obtained from them in fluorescent lighting and in cathode ray tubes. Such successful application has stimulated attempts to develop still other commercial uses. The author of the present book has evidently been diligent in conversing with many who are engaged in these developments, and he records some novel applications, though not all, which are quite up to the minute. Furthermore, he has examined a large number of chemical compounds and listed the color of their fluorescence.

It is in these two respects that interest in the book lies. Its discussion of the theory is inadequate to the needs of the scientist, and there is not to be found the critical viewpoint that characterizes some older books on the subject.

The information given on the fluorescence of chemical compounds is no doubt helpful in chemical analysis as a guide, but the real value of fluorescence in this field can best be determined by the individual chemist for those specific cases with which he is confronted. The colors involved are generally subtle and, particularly at low intensities, are influenced by the low visible transmission of the ultraviolet lamp filter employed. Consequently, the chemist must ultimately depend on judgments formed from his own observations.

While it is true that the book contains some information that may be interesting or helpful to the chemist, yet it is necessary to point out some serious deficiencies. Its style gives evidence of haste and carelessness in composition. The treatment is superficial and too often pseudo-scientific. Its discussions, which are sometimes poorly balanced, indicate a lack of comprehension and understanding of present scientific viewpoints. The price for such a small book seems inexcusably high.

G. R. FONDA

The Polarographic Method of Analysis. By OTTO H. MÜLLER, Department of Anatomy, Cornell University Medical College, New York City. Journal of Chemical Education, Easton, Pennsylvania, 1941. vi + 114 pp. 30 figs. 13 × 20.5 cm. Price, $1.00.

Dr. Müller's stated intention in writing this little monograph on polarographic analysis has been "to present a simple account of polarography in a form which can be used by teachers and students in courses of physical chemistry as well as in advanced courses of analytical chemistry." The tone of the book is thus that of an elementary text, and the discussion is limited mainly to fundamental principles with only cursory mention of practical applications.

The book comprises five chapters, the first of which is well described by its title, "Review of Electro-Analytical Methods." The second chapter, entitled "Apparatus," is devoted practically entirely to the description of simple home-made equipment that should be very useful for instructional purposes. The third chapter, "Fundamentals of Quantitative Analysis," contains a discussion of the factors that govern the limiting current. The analysis of polarographic waves and the significance of the half-wave potential are treated in the fourth chapter under the title, "Fundamentals of Qualitative Analysis." The last chapter contains a good résumé of the types of analyses to which the polarographic method can be applied, and a discussion of various points that must be considered in practical work.

The following misstatements and errors have been noticed. Opposite sign conventions are given on p. 21 and p. 39 for cathodic and anodic currents. The discussion on p. 52 of the relation between diffusion current and diffusion coefficient, and the comparison of observed and theoretical diffusion current ratios, lacks conviction because no mention is made of the source of the diffusion coefficient data. It is unfortunate in this connection that the author did not make use of recent data in the literature that demonstrate conclusively the validity of the Ilkovic equation. In the statement at the top of p. 55 the author implies that the use of a "capillary constant" P/m is less laborious than the use of m itself for characterizing and checking the behavior of a capillary, which is misleading. On p. 74, and again on p. 81, it is stated incorrectly that the cathodic and anodic half-wave potentials of a reversible oxidation–reduction system will only be identical if the diffusion coefficients of the reduced and oxidized forms are identical. Actually the cathodic and anodic half-wave potentials will be identical regardless of any difference in the diffusion coefficients. In stating on p. 79 that the theory regarding the shift of the half-wave potential of a metal ion by complex formation "has not yet been subjected to critical tests" the author has apparently overlooked recent work in this field.

On p. 84 the author discusses anodic waves that involve the oxidation of the mercury itself under the general heading "Irreversible Reactions," and he states that "The curves are not the usual S-shape and the half-wave potentials are not independent of concentration." It is thus implied that such reactions are always irreversible, whereas certain waves of this type have actually been shown to correspond to reversible reactions. On p. 98 it is stated incorrectly that a polarogram of a mixture of thallous and cadmium salts in a potassium cyanide supporting electrolyte would only show the cadmium wave. Actually such a polarogram does show a wave and diffusion current for the thallium preceding the cadmium wave, but the position of the thallium wave corresponds to the potential at which cyanide ion depolarizes the dropping electrode rather than the true reduction potential of the thallous ion. In the discussion on p. 111 of amperometric titrations in which the current changes sign, it is stated incorrectly that the end-

point is indicated by zero current. Actually the end-point is reached when the current has become equal to the residual current of the medium.

The author's style is clear and easy to follow and the arrangement of topics is good. An outstanding feature of the book is the inclusion at numerous points throughout the text of directions for well-chosen experiments that illustrate important theoretical points. This feature, combined with a laudable emphasis on simplicity of apparatus, should make this little monograph quite useful as an elementary text of the subject.

JAMES J. LINGANE

Organic Reagents in Inorganic Analysis. By PAUL VON STEIN, Director of Analytical Developments, Cadmium Residue and Pigment Department, Harshaw Chemical Company, Elyria, Ohio. Chemical Publishing Co., Inc., Brooklyn, N. Y., 1942. viii+ 242 pp. 22 × 14.5 cm. Price, $4.50.

In this book forty-seven elements and radicals are arranged in alphabetical order, and brief abstracts of the more pertinent methods of detection, using organic reagents, are given. Each abstract is accompanied by an average of only one or two references to the literature.

Although a majority of the more useful of the methods given can be found in brief form in the larger reference books of qualitative analysis and in Lange's "Handbook of Chemistry," such a compilation as the one under consideration should be useful to the analytical chemist. Unfortunately, the book is so replete with errors of omission and commission that its value is considerably lowered. Certainly in a book that the author states is intended to be "a complete reference work of organic compounds which yield indicative reactions with inorganic materials," the omission of dimethylglyoxime as a precipitant for nickel is surprising, to say the least. The scantiness of the bibliography is also disappointing.

Typographical errors begin at the second line of the text and continue with alarming frequency throughout the book, including the appendix and index. On page 56, where the author sees fit to take time out to show us how to oxidize chromic ions to chromate, he makes two glaring grammatical errors in as many sentences.

The reviewer questions the implication that dimethylglyoxime precipitates so many metals from acid solution that its use as a precipitant for palladium is of little importance. But he is completely baffled to learn that the test for gold with dimethylaminobenzylidene rhodamine is specific only in the absence of *gold*, mercury and palladium. A great many other errors could be listed if space permitted. The above merely serve as examples.

Most of the material in the appendix is either repetitious or could well be incorporated in the text. The index is incomplete.

Altogether, the impression the book gives is that it was too hastily compiled and even more hastily printed.

STEPHEN G. SIMPSON

BOOKS RECEIVED

June 10, 1942–July 10, 1942

F. E. BROWN. "A Short Course in Qualitative Analysis." Revised Edition. D. Appleton-Century Company, Inc., 35 West 32nd Street, New York, N. Y. 367 pp. $2.60.

WILLIAM S. DUTTON. "Du Pont—One Hundred and Forty Years." Charles Scribner's Sons, New York, N. Y. 396 pp. $3.00.

L. A. GOLDBLATT, Editor. "Collateral Readings in Inorganic Chemistry." Second Series. D. Appleton-Century Company, Inc., 35 West 32nd Street, New York, N. Y. 198 pp. $1.40.

FRANK THOMSON GUCKER, JR., AND WILLIAM BUELL MELDRUM. "Physical Chemistry." American Book Company, 88 Lexington Avenue, New York, N. Y. 683 pp. $4.00.

MORRIS B. JACOBS. "War Gases." Interscience Publishers, Inc., 215 Fourth Avenue, New York, N. Y. 180 pp. $3.00.

VLADIMIR A. KALICHEVSKY AND BERT ALLEN STAGNER. "Chemical Refining of Petroleum." Revised edition. (American Chemical Society Monograph Series.) Reinhold Publishing Corporation, 330 West 42nd Street, New York, N. Y. 550 pp. $7.50.

JAMES MURRAY LUCK, Editor. "Annual Review of Biochemistry." Vol. XI. Annual Reviews, Inc., Stanford University P. O., California. 736 pp. $5.00.

JOSEPH J. MATTIELLO, Editor. "The Microscopic Identification of Azo Dyes and Organic Pigments" (Reprint of Chapter 3 of Protective and Decorative Coatings, Vol. II, published by John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y.). Harmon Color and Chemical Co., Inc., Haledon, New Jersey. 163 pp.

H. J. S. SAND. "Electrochemistry and Electrochemical Analysis." Vol. III. "Electrical Methods Applied to Titration, Moisture Determination and *p*H Measurement." Chemical Publishing Company, 234 King Street, Brooklyn, New York. 118 pp. $2.25.

RUDOLF SCHOENHEIMER. "The Dynamic State of Body Constituents." Harvard University Monograph in Medicine and Public Health, No. 3. Harvard University Press, Cambridge, Mass. 78 pp. $1.75.

H. B. WATSON. "Modern Theories of Organic Chemistry." Second Edition. Oxford University Press, 114 Fifth Avenue, New York, N. Y. 267 pp. $5.00.

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

VOLUME 64 SEPTEMBER 11, 1942 NUMBER 9

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

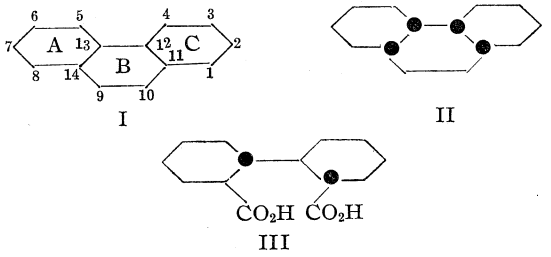
The Stereochemistry of Catalytic Hydrogenation. I. The Stereochemistry of the Hydrogenation of Aromatic Rings

BY R. P. LINSTEAD, W. E. DOERING, SELBY B. DAVIS, PHILIP LEVINE AND RICHARD R. WHETSTONE

This paper and the six that follow it give an account of the main results which have been obtained from a stereochemical study of the catalytic hydrogenation of a number of aromatic compounds. We have examined derivatives of phenanthrene substituted in the central ring and the hydro-diphenic acids which can be obtained from them by oxidation. The key substances in the elucidation of the configuration were the perhydrodiphenic acids. The six possible isomeric forms of these have been prepared and oriented. The information so obtained has been used to orientate the hydrogenation products of the phenanthrene derivatives.

The experimental results and the determination of configuration are given in Parts II to VII. The present paper summarizes the data, and analyzes their bearing on the phenomena of catalytic hydrogenation.

The system of nomenclature for these compounds is the following.[1] When phenanthrene is completely hydrogenated, four (potential) asymmetric carbon atoms appear. These are numbered 11, 12, 13 and 14 in formula I. The configurations of the ring fusions AB and BC are designated *cis* or *trans* in the usual manner, according to whether the pair of hydrogen atoms on C_{13} and C_{14} (or C_{11} and C_{12}) are on the same side of the molecule. The configuration of the backbone (the C_{12}–C_{13} bond) is designated *syn* if the two hydrogens on C_{12} and C_{13} are on the same side of the molecule and *anti* if they are on opposite sides. The positions of the hydrogen atoms are represented in the formulas by black dots, a dot indicating that a hydrogen atom is above the molecule. A dot is always placed on C_{13}. On this convention, formula II represents *cis-syn-cis* (*c. s. c.*) perhydrophenanthrene. The related perhydrodiphenic acids are similarly named and represented, the molecule being written in the coiled state with the carboxyl groups together. Formula III thus represents *trans-anti-trans* (*t. a. t.*) perhydrodiphenic acid.



I II III

The catalytic hydrogenations were carried out over Adams platinum oxide in acetic acid unless otherwise stated. The following compounds were hydrogenated to the corresponding perhydro products: diphenic acid[2] (in alcohol as well as in acetic acid), diphenic ester,[2] diphenic anhydride,[2] *cis*-hexahydrodiphenic acid,[3] *trans*-hexahydrodiphenic acid,[3] 9-phenanthrol,[4] *cis-as*-octahydro-9-

(1) Linstead, *Chemistry and Industry*, **56**, 510 (1937); Linstead and Walpole, *J. Chem. Soc.*, 842 (1939).

(2) Linstead and Doering, THIS JOURNAL, **64**, 1991, 2003 (1942).

(3) Linstead and Davis, *ibid.*, **64**, 2006 (1942).

(4) Linstead, Whetstone and Levine, *ibid.*, **64**, 2014 (1942).

phenanthrol[4] (in alcohol as well), *cis*-9-keto-octahydrophenanthrene[4] (in alcohol), and 9,10-phenanthrenequinone.[5]

There is a remarkable regularity in these results. *All the hydrogenations studied have given largely cis- and syn-material.* The only compound which gives a main per-hydrogenation product containing a *trans*-linkage is the *trans*-hexahydrodiphenic acid which already contains such a linkage. The results refer to the *main* stereoisomer formed, which constitutes 75% or more of the total perhydro product. Diphenic acid both in alcohol and in acetic acid gives a small amount of the *cis-syn-trans* and *cis-anti-cis* perhydro acids. Diphenic ester gives some *anti*-material. The remaining compounds mentioned probably yield small quantities of stereoisomers containing different skeletal configurations, but these have not as yet been isolated in the pure state.

The regularity in these experiments invites a theoretical analysis. We propose three hypotheses to account for the results: (1) that when one or more aromatic rings are hydrogenated during a single period of adsorption, the hydrogen atoms add to one side of the molecule; (2) that the orientation of the adsorption of the aromatic molecule on the catalyst is affected by hindrance between the catalyst and the substrate ("catalyst hindrance"); (3) that the derivatives of diphenic acid which have been studied are hydrogenated in the coiled phase. These will now be considered in turn.

(1) **One-Sided Addition.**—Willstätter in 1908[6] made the basic discovery that aromatic compounds could be hydrogenated at room temperatures over a platinum catalyst. It was some years before it was observed, mainly owing to the work of Skita[7] and von Auwers,[8] that, when two or more nuclear substituents were present, the products obtained by the use of platinum were isomeric but not identical with those obtained by Sabatier hydrogenations of the same compounds over nickel at high temperatures. As is well known, it was generally accepted that the products were geometrical isomers of the von Baeyer type, the compounds prepared over platinum being *cis*, and those by the Sabatier method being *trans*. Moreover, Skita,[7] in particular, noted that in hydrogenations over platinum a *cis*-orientation was favored in acid media, a *trans*-orientation in neutral or basic media.

Most of the configurations of the hydrogenation products in the early work were assigned on the basis of von Auwers' generalization that, of a pair of stereoisomers of this type, the *cis*-compound has the higher density and refractive index but the lower molecular refractivity. This rule has been of considerable service, although the differences in the physical constants become slight among the more complicated molecules. For our present purpose, however, we wish to emphasize those results in which the configurations have been determined by absolute methods, depending (ultimately) on optical resolution. A number of examples of this kind are collected in Table I, which is not exhaustive. The evidence for the configuration of the product is outlined at the foot of the table, and is, in all cases, conclusive. The substances all owe their isomerism to the presence of carboxyl groups, fatty acid residues or fused rings. Compounds in which one (or more) of the orientating groups is a hydroxyl, amino or similar group have deliberately been excluded, because of the danger of stereochemical inversions in these cases.

TABLE I

CATALYTIC HYDROGENATIONS OVER PLATINUM IN ACETIC ACID

	Substance	Catalyst	Configuration of product	References
1	(*o*-) Phthalic acid	Willstätter Pt	*cis*	9
2	Phthalic anhydride	Willstätter Pt	*cis*	9
3	Phthalimide	Willstätter Pt	*cis*	9
4	Isophthalic acid	Willstätter Pt Adams Pt	mainly *cis*	9, 10
5	Terephthalic acid	Willstätter Pt Adams Pt	*cis* + *trans*	9, 10
6	Benzene-1-acetic-2β-propionic acid	Willstätter Pt	*cis*	11
7	β-Naphthol	Skita Pt	*cis*	11
8	*ar*-β-Tetralol	Willstätter Pt Skita Pt	*cis*	11
9	*ac*-β-Tetralol	Willstätter Pt Skita Pt	*cis*	11
10	*ac*-α-Tetralol	Willstätter Pt	*cis*	11, 12
11	*ar*-α-Tetralol	Willstätter Pt	*cis*	11, 12
12	5-Hydroxy-hydrindene	Adams Pt	*cis*	13

The configuration of the products is proved by the following evidence: nos. 1–3: From the resolution of *trans*-hexahydrophthalic acid (Werner

(5) Linstead and Levine, THIS JOURNAL, **64**, 2022 (1942).

(6) Willstätter and Mayer, *Ber.*, **41**, 1479 (1908).

(7) Skita, *ibid.*, **53**, 1792 (1920); Skita and Schneck, *ibid.*, **55**, 144 (1922); Skita, *ibid.*, **56**, 1014 (1923); Skita, Hauber and Schönfelder, *Ann.*, **431**, 1 (1923).

(8) v. Auwers, *Ann.*, **420**, 84 (1920).

(9) Willstätter and Jacquet, *Ber.*, **51**, 767 (1918).

(10) Kuhn and Wassermann, *Helv. Chim. Acta*, **11**, 61 (1928).

(11) Hückel, *Ann.*, **441**, 1 (1925).

(12) Hückel, Danneel, Gross and Naab, *ibid.*, **502**, 99 (1933).

(13) Cook and Linstead, *J. Chem. Soc.*, 946 (1934).

and Conrad[14]). No. 4: From the resolution of *trans*-hexahydro-isophthalic acid (Böeseken and Peek[15]). No. 5: From the work of Mills and Keats.[16] Nos. 6–11: From the resolution of *trans*-cyclohexane-1,2-diacetic acid (Hückel and collaborators[17]; Barrett and Linstead[18]). No. 12: From the resolution of *trans*-cyclopentane-1,2-diacetic acid (Barrett and Linstead[18]).

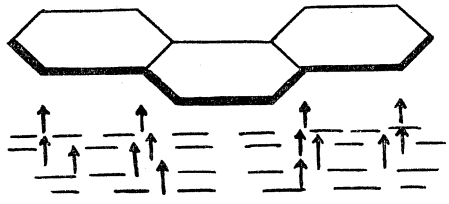
Of the twelve compounds given in Table I, all except terephthalic acid hydrogenate nearly exclusively *cis*- under these experimental conditions. It would be possible to bolster up the case by including a great deal of confirmatory evidence from hydrogenations in which the configuration of the product was known with a high degree of probability but not with certainty. However, the clear-cut evidence obtained from our studies and that presented in Table I is sufficient to demonstrate that aromatic compounds hydrogenate predominantly *cis*-, under the stated conditions. The new work summarized above is the most rigorous test of this generalization, because four asymmetric centers instead of two are involved. The generalization is restricted to the mildest type of catalytic hydrogenation, namely, that which occurs over platinum at room temperature, and in the solvent, acetic acid, which gives the most rapid addition.

This preferential addition can be explained by an application of the ideas of Farkas and Farkas.[19] They have shown that the catalytic hydrogenation of benzene and the exchange of hydrogen and deuterium proceed by different mechanisms. The hydrogenation involves the simultaneous addition of pairs of hydrogen atoms, whereas the exchange involves a radical or atomic reaction. Farkas and Farkas[20] have shown that these views can satisfactorily explain the preferential formation of *cis*-ethylenes in the half-hydrogenation of acetylenes over catalysts. It has been shown, notably by Bourguel,[21] that such hydrogenations yield initially *cis*-compounds but that *trans*-compounds may be formed if the hydrogenations are protracted.

In applying these conceptions to the aromatic series, we shall assume that the hydrogenation of a compound containing one aromatic ring proceeds to completion during one period of adsorption of the molecule on the catalyst surface. This assumption simplifies the argument and is in harmony with the experimental fact that benzene derivatives, except phenols, normally hydrogenate without yielding intermediates (see, for example, Vavon[22]). This is further connected with the fact that the hydrogenations of cyclohexene and the cyclohexadienes are exothermic.

There is an increasing body of evidence that the adsorption of an organic molecule on a catalyst, and hence the ease of hydrogenation, is affected by stereochemical considerations. The recent work of Beeck, Smith and Wheeler[23] has shown the importance of the orientation of the metallic atoms in the lattice of the catalyst on its activity. It is possible that the catalytic hydrogenation of large aromatic molecules, which are planar and comparatively rigid, will be determined largely by the ability of the molecule to find an area in the catalyst which has sufficient size, suitable spacing of the metallic atoms, and sufficient flatness.

We suggest that the stages in the hydrogenation which determine that the product shall have a *cis*-configuration are: (1) the adsorption of the aromatic molecule upon a suitable part of the catalyst; and (2) the addition of the hydrogen to the molecule from the underside so that all the atoms appear on the same side of the asymmetric carbon atoms. This is illustrated diagrammatically below for the case of a phenanthrene nucleus. The arrows represent the approach of the hydrogen atoms from the catalyst.

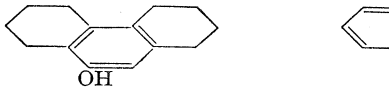


In the case of polynuclear compounds, there is little doubt that this is an oversimplification. These substances may give rise to incompletely hydrogenated compounds which are comparatively stable, of the type of tetralin. In several of the hydrogenations studied in the present work such intermediate hydrogenation products were isolated from the reaction products; for example,

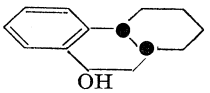
(14) Werner and Conrad, *Ber.*, **32**, 3046 (1899).
(15) Böeseken and Peek, *Rec. trav. chim.*, **44**, 841 (1925).
(16) Mills and Keats, *J. Chem. Soc.*, 1373 (1935); compare Malachowski and Jankiewiczówna, *Ber.*, **67**, 1783 (1934).
(17) Hückel, *et al.*, *Ann.*, **451**, 132 (1926); **518**, 155 (1935).
(18) Barrett and Linstead, *J. Chem. Soc.*, 1069 (1935).
(19) Farkas and Farkas, *Trans. Faraday Soc.*, **33**, 827 (1937).
(20) Farkas and Farkas, *ibid.*, **33**, 837 (1937).
(21) Bourguel, *Bull. soc. chim.* [4], **51**, 253 (1932); *Compt. rend.*, **182**, 224 (1926).
(22) Vavon, *Bull. soc. chim.*, [4] **41**, 1253 (1927).
(23) Beeck, Smith and Wheeler, *Proc. Roy. Soc.* (London), **A177**, 62 (1940).

diphenic acid yields some *cis*-hexahydrodiphenic acid and 9-phenanthrol gives the *sym*-octahydro derivative. There is no doubt, therefore, that desorption of the organic molecule from the catalyst can occur at an intermediate state of hydrogenation, and it is reasonable to suppose that some of the perhydrogenated material is formed as a result of two (or even more) separate periods of adsorption.

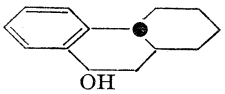
Consider the final stage of the hydrogenation of the *sym*-octahydrophenanthrol (IV). Simple one-sided addition of hydrogen to the remaining benzene ring would determine the configuration of all four asymmetric carbon atoms, and a *cis-syn-cis* product would be expected. The isomeric *as*-octahydro compounds (V and VI), however, do not present such a simple case. We should expect



IV



V



VI

the final hydrogenation to go *cis*- to both the *cis*-alcohol (V) and the *trans*-alcohol (VI), but the principle of one-sided addition does not enable us to predict the backbone configuration of the perhydro product. It appears equally possible for V to give a *cis-syn-cis* or a *cis-anti-cis* perhydro alcohol. The same is true of the diphenic acids, where the stable intermediate is a hexahydro acid with an unsymmetrical arrangement of hydrogen atoms. It is only possible to account for completely *cis*- and *syn*-perhydrogenation of a phenanthrene or diphenic acid derivative on the basis of the principle of one-sided addition by making the following subsidiary postulates: (1) no desorption of the molecule occurs at an intermediate stage, or (2) the intermediate which is hydrogenated in the stage which determines the configuration has double bonds at all the potential asymmetric carbon atoms. These are highly arbitrary and improbable assumptions, and a more reasonable suggestion is that a second determining factor, that of catalyst hindrance, comes into play. This is discussed later.

It has already been stated that Skita observed many cases in which *cis*-hydrogenation occurs in an acid, and *trans*- in a neutral or basic medium. It is true that the configurations of his products were often not conclusively proved, but there is no doubt of the variability of the orientation of addition to the compounds which he studied. We have so far confined ourselves to one main set of hydrogenation conditions and have little experimental evidence to offer in this connection. A few comments may, however, be made. (1) In most of our experiments either the solvent or the molecule undergoing hydrogenation was an acid. However, *cis-as*-octahydro-9-phenanthrol and the corresponding ketone both hydrogenate *cis*- and *syn*- in a neutral (alcoholic) medium, and in the case of the phenanthrol the orientation was shown by direct comparison to be the same as that obtained in acetic acid solution. This is contrary to Skita's generalization. (2) Many of the examples studied by Skita involved the hydrogenation of phenols and aromatic amines. We think this evidence of doubtful value in relation to the stereochemistry of hydrogenation of the aromatic ring because of the possibility of the formation of hydroaromatic ketones (as has often been demonstrated experimentally) or of ketimines. These substances are capable of stereochemical inversion by enolization or an analogous process, so that the final orientation, for example, of the hydroxyl group to the methyl in a perhydrocresol, has no necessary bearing on the course of the hydrogenation of the aromatic ring.[23a] (3) In spite of these reservations there are a number of examples in which the acidity of the medium appears to affect the orientation of aromatic hydrogenation, and in which the orienting groups are alkyls or other groups incapable of inversion. Under suitable experimental conditions *trans*-hydrogenation can occur. It appears probable that in these reactions (and, indeed, in other cases of *trans*-hydrogenation) the mechanism of hydrogenation is different from the molecular addition involved in *cis*-hydrogenation. Atoms of hydrogen and organic radicals may well be involved, as in the exchange reactions studied by Farkas and Farkas.[19] The intervention of radicals is indeed strongly indicated in some of the hydrogenations of aromatic bases studied by Skita which readily yield compounds of the dicyclohexylamine type.[24]

Particular reference may be made to Skita's studies[25] of the hydrogenation of the xylenols and

(23a) With the hydrogenation of hydroaromatic ketones, which has been thoroughly studied by Vavon, Skita, Hückel and others, we are not concerned in this paper.

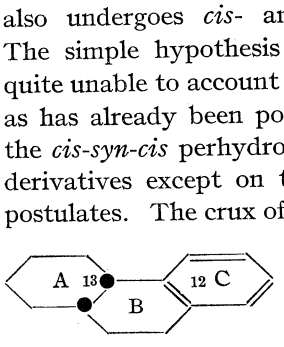
(24) Skita and Berendt, *Ber.*, **52**, 1519 (1919).

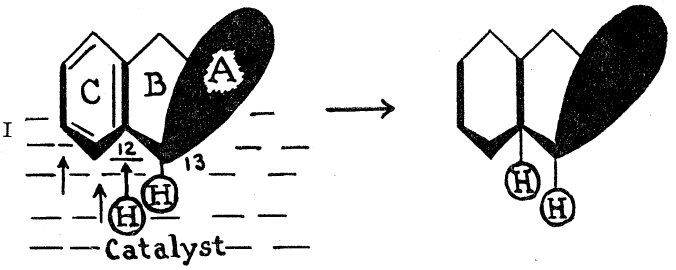
(25) Skita, *Angew. Chem.*, **34**, 230 (1921); *Ber.*, **56**, 2234 (1923).

xylidines, especially of *vic-m*-xylenol (2,6-dimethylphenol). In this case good evidence was obtained that the methyl groups in the product were oriented *trans* to each other whether the hydrogenation was carried out in a neutral or an acid medium. This not only conflicts with the run of Skita's own observations but also is opposed to the evidence summarized above and in Table I. We propose to undertake a further study of the hydrogenation of the xylenols when conditions permit. In the meantime it would seem that this is an example of the abnormal (atomic) mechanism already mentioned.

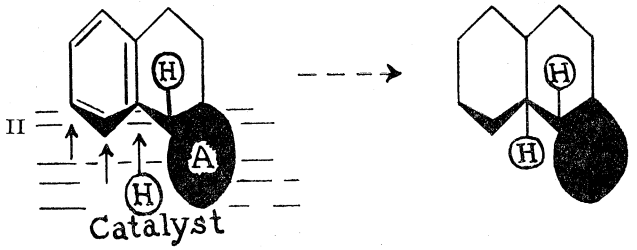
The abnormal mechanism is much more evident in hydrogenation over nickel, and may be presumed to account for the formation of predominantly *trans*-products in Sabatier hydrogenations. In the somewhat milder hydrogenations over Raney nickel the orientations are irregular, and it appears certain that both mechanisms may function. Thus we find that phenanthraquinone hydrogenates *cis-syn-cis* over platinum at 25° and almost exclusively *cis-syn-cis* over nickel at 160°. A very small amount of a *cis-syn-trans* glycol is formed under the latter conditions. On the other hand, diphenic ester can yield considerable quantities of *anti*-perhydro material over nickel,[26] under very similar conditions, but here the results of a number of recent experiments show considerable variations and *syn*-perhydro ester has frequently been almost the sole product.

(2) **Catalyst Hindrance.**—As was pointed out above *cis-as*-octahydro-9-phenanthrol (V), the corresponding ketone and the related *cis*-hexahydrodiphenic acid all yield *cis-syn-cis* perhydro-products. *Trans*-hexahydrodiphenic acid also undergoes *cis*- and *syn*-perhydrogenation. The simple hypothesis of one-sided addition is quite unable to account for these results, and also, as has already been pointed out, cannot explain the *cis-syn-cis* perhydrogenation of phenanthrene derivatives except on the basis of two unlikely postulates. The crux of the problem is this: Why should the position of the hydrogen on C_{13} determine the position taken up by that which enters on C_{12}? No explanation based on a disproportionation or a migration of the hydrogens already in position can be accepted, because the integrity of the configuration already established is preserved. In our view the determining factor is one of *catalyst hindrance, i. e.*, a steric hindrance between the catalyst and the substrate. This is illustrated for the case of a *cis-as*-octahydrophenanthrene derivative in the diagrams given below:





Preferred adsorption; Ring A clear of catalyst; *syn*-hydrogenation occurs.



Hindrance between catalyst and ring A; adsorption inhibited; little or no *anti*-hydrogenation.

It may be taken that it is the aromatic part of the molecule which anchors it to the catalyst. Two arrangements are then possible, in which ring A is either inclined away from or toward the catalyst. In diagram I the A ring is away from the catalyst and the hydrogen atom on C_{13} toward it. The hydrogens adding to the molecule from the underside will therefore come from the same side as the hydrogen on C_{13}. The hydrogen atom which attaches itself to C_{12} and determines the backbone configuration thus takes up a *syn* arrangement with respect to C_{13}. In diagram II, the opposite state of affairs holds; ring A will be on the same side as the catalyst and any hydrogen which becomes attached to C_{12} (by the normal mechanism) will take up the *anti*-configuration. It appears reasonable to suppose that the adsorption corresponding to I will be greatly preferred to that represented by II and therefore that *syn*-hydrogenation will preponderate. This is what is found experimentally.

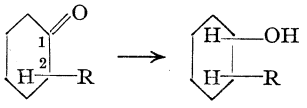
The same argument can be applied to the diphenic acid derivatives, providing these sub-

(26) Vocke, *Ann.*, **508**, 1 (1934); Linstead and Walpole, *J. Chem. Soc.*, 850 (1939).

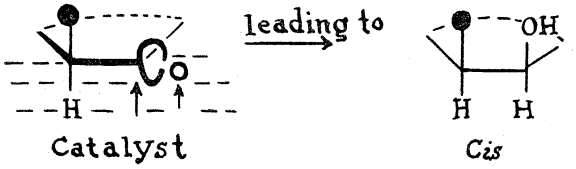
stances are considered as reacting in a coiled or "pseudo-tricyclic" state. This question is dealt with in the next section.

To the best of our knowledge, the proposal that there can be a steric hindrance between a metallic catalyst and its substrate is novel. There appears to be no other reasonable way of accounting for the regular occurrence of *syn*-hydrogenation over platinum. There is a philosophical connection with Bergmann's explanation[27] of the selective action of proteolytic enzymes (peptidases) on polypeptides made from natural and unnatural amino acids, respectively.

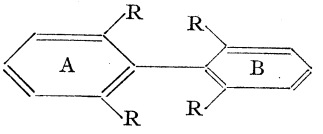
It seems probable that catalyst hindrance is a determining factor in many other reactions. Vavon has proposed[28] that the production of a *cis*-alcohol in the catalytic hydrogenation of substituted hydroaromatic ketones, particularly those of the ortho series, is due to a steric hindrance between the substituent group R and the entering hydrogen. This, he suggests, makes the hydrogen



attack the carbonyl double bond from the side removed from the group R, so that the hydroxyl group which is formed takes up the *cis*-position with respect to this. We agree with Vavon that steric hindrance of the group R is the operative factor but regard it as acting at an earlier stage, namely, that of adsorption. The adsorption can most readily occur with the group R inclined away from the catalyst so that the entering hydrogen on C_1 takes up the *cis*-position with respect to that on C_2. The preferred reaction is illustrated below:

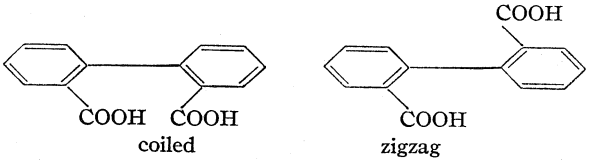


Catalyst hindrance can also account in a simple way for a remarkable discovery made by Adkins and his co-workers in 1933.[29] They studied the hydrogenation of various substituted diphenyls in which the rotation about the internuclear bond was restricted so that optical activity of the well-known type was possible. It was found to be quite *impossible to hydrogenate* these compounds over Raney nickel even under remarkably drastic conditions, in contrast to the comparatively easy hydrogenation of diphenyl derivatives in which free rotation was possible. We suggest that this reluctance to react originates with the fact that these restricted molecules cannot lie in one plane.



Hence if one ring lies flat on the catalyst, the other will interfere with it. Adsorption, and hence hydrogenation, is therefore inhibited. It appears that the forces which would be involved in the complete adsorption of the molecule on the catalyst are too weak to overcome the repulsion between the substituent groups R. Adkins commented upon his results in the following words: "It is possible that the same factors which prevent the rotation of the rings . . . in resolvable derivatives of diphenyl, also prevent the reaction (adsorption) of the benzenoid ring by the catalyst, and so inhibit the first step in the catalytic hydrogenation of the former." Our proposal in this connection is therefore an extension of Adkins' suggestion.

(3) **Coiling.**—A remarkable feature of the new results is that diphenic acid and its ester hydrogenate in the same stereochemical manner as do its anhydride and the phenanthrene derivatives to which it is related. The hexahydro acids also simulate their tricyclic counterparts. It is to be presumed that diphenic acid can exist in all the possible phases intermediate between the two extremes shown.



On the basis of the hypotheses already advanced, the coiled form would yield a *cis-syn-cis* perhydroproduct and the zigzag form one with a *cis-anti-cis* configuration. We indeed anticipated that diphenic acid would yield a stereochemically different perhydro product from its anhydride, but this was found not to be true. Unfortunately, we have so far been unable to bring about catalytic hydrogenation of the diphenate anion in water

(27) Bergmann, *Harvey Lectures*, **31**, 37 (1935–36); Bergmann and Zervas, *Z. physiol. Chem.*, **224**, 11 (1934).

(28) Vavon, *Bull. soc. chim.*, (4) **39**, 668 (1926).

(29) Waldeland, Zartman and Adkins, THIS JOURNAL, **55**, 4234 (1933).

over platinum. The anion would be expected to exist preferentially in the zigzag form and to yield *anti*-material on hydrogenation.

As it is unlikely that the agreement of the results is purely due to coincidence, it appears that the "open-chain" derivatives of diphenic acid (the acid itself, its ester and its two hexahydrides) *all hydrogenate in the coiled or pseudo-tricyclic phase.* This would mean that this phase is the one which is most readily adsorbed on the catalyst. We can see no particular reason for this preference. Hydrogen bonding between the carboxyl groups could be invoked for the acid but not for its ester.

The hypotheses which are advanced in this paper are tentative and require additional experimental investigation from many points of view. This we hope to provide in due course. One aspect which has not yet been mentioned will have to be considered before these hypotheses could be applied generally. The present work has been almost completely confined to the ortho-substituted compounds. (This is to some extent inevitable in the study of polycyclic aromatic structures). It may be found that the behavior of compounds in which the orienting groups are further apart may be much less regular than those studied in the present work. There are several indications in the literature that this may be true, for example, the considerable degree of *trans*-hydrogenation of terephthalic acid, as mentioned in Table I.

Summary

The stereochemistry of the hydrogenation of a number of derivatives of diphenic acid and of phenanthrene over a platinum catalyst is discussed. The nine compounds studied all hydrogenate *cis* and *syn*.

The results are explained on the basis of three hypotheses.

1. When one or more aromatic rings are hydrogenated during a single period of adsorption, the hydrogen atoms add to one side of the molecule.

2. The orientation of the adsorption of the aromatic molecule on the catalyst is affected by hindrance between the catalyst and the substrate.

3. The open-chain derivatives of diphenic acid are hydrogenated in the coiled phase.

Earlier work is discussed in the light of these views, and certain applications to related fields are indicated.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 30, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Stereochemistry of Catalytic Hydrogenation. II. The Preparation of the Six Inactive Perhydrodiphenic[1] Acids

BY R. P. LINSTEAD AND W. E. DOERING

Earlier work by Linstead and A. L. Walpole[2] on the hydrogenation of diphenic acid had revealed the following facts: (1) Catalytic hydrogenation of the free acid in acetic acid solution over platinum gave a perhydro acid of m. p. 273°. (2) Similar hydrogenation of dimethyl diphenate gave a solid perhydro ester, m. p. 73°, which on alkaline hydrolysis gave a perhydro acid of m. p. 220°. (3) Hydrogenation of dimethyl diphenate over Raney nickel by Adkins' procedure gave a mixture of the ester of m. p. 73° and a liquid ester which on alkaline hydrolysis gave a third perhydro acid of m. p. 244°. Other early work on the perhydro acids is reviewed later in the present paper.

We have now made a fuller study of the hydrogenation of diphenic acid and its derivatives over platinum, and of the stereochemical inversion of the products. This has led to the isolation of eleven distinct optically inactive hydrodiphenic acids. Six of these are dodecahydro- (perhydro-) derivatives; three are decahydro-, containing one double bond; and the remaining two are hexahydro-, and contain one intact benzene ring. This paper is concerned only with the perhydro acids.

As pointed out by Linstead and Walpole,[2] perhydrodiphenic acid can exist in six inactive modifications, four of which are resolvable. All the possible forms have therefore been obtained. Experiments on their resolution are described in the following paper.

(1) The common 2,2′-diphenic acid is referred to as diphenic acid for the sake of brevity throughout these papers. Its hydrogenated derivatives are correspondingly named without prefix.

(2) Linstead and Walpole, *J. Chem. Soc.*, 850 (1939).

The *syn*-Series

When diphenic acid is exhaustively hydrogenated in acetic acid solution over Adams catalyst, one main product and three by-products are obtained. The main product is a perhydro-acid, $C_{12}H_{20}(CO_2H)_2$, m. p. 289°. This is easily isolated and purified owing to its low solubility. Accompanying this, in low amounts, are two isomeric perhydro-acids melting at 198 and 200°, respectively. Usually also there is a certain amount of a hexahydro-acid $C_{12}H_{14}(CO_2H)_2$ of m. p. 242°, which occurs even when the uptake of hydrogen appears to have ceased completely. The proportions of the products appear to vary slightly with variations in the experimental procedure and in the catalyst, but the acid of m. p. 289° always constitutes the bulk of the product.

The acid of m. p. 289° is a slightly purer form of the material of m. p. 273° already reported by Linstead and Walpole[2] and by Hückel.[3] The m. p. varies with the rate of heating, and this fact may contribute to the lower m. p.'s previously recorded.

The same compound (accompanied by the same impurities) is formed when the hydrogenation of the acid is carried out in acetic acid containing 2% of hydrochloric acid. The hydrogenation also takes the same course in alcohol but in this case the reaction is much slower. When diphenic anhydride is hydrogenated over platinum and the product hydrolyzed, the perhydro acid of m. p. 289° is also obtained. Sodium diphenate resisted catalytic hydrogenation in aqueous solution. Dimethyl diphenate, however, was exhaustively hydrogenated over platinum without difficulty, and, in agreement with Linstead and Walpole,[2] the main product was a perhydro ester, m. p. 73°. It is proved below that this is the dimethyl ester of the 289° acid and that its alkaline hydrolysis is anomalous. There is, therefore, a general tendency for the diphenic acid system to be hydrogenated over platinum to the perhydro form corresponding with the acid of m. p. 289°.

Because of the complicated inversions which can occur in the chemistry of the 289° acid and its derivatives, it was necessary to establish conclusively its relationship with its anhydride and esters. This was done as follows.

The perhydrodiphenic acid of m. p. 289° on treatment with acetic anhydride yielded a mixed anhydride, $CH_3COOOCC_{12}H_{20}COOOCCH_3$, which on sublimation gave the simple perhydrodiphenic anhydride, $C_{12}H_{20}(CO)_2O$, m. p. 146–147°. From this the parent acid could be regenerated. These results confirm those already reported.[2] Treatment of the anhydride with sodium methoxide yielded a monomethyl ester, m. p. 129°. When either the 289° acid or its monomethyl ester was treated with diazomethane, there was obtained a dimethyl ester of m. p. 73–74°. This was identical with the perhydro ester prepared by the direct hydrogenation of dimethyl diphenate. Fischer-Speier esterification of the 289° acid or of the 129° acid ester also yielded the 73° dimethyl ester, but the reaction was slow. The best preparative method for the esterification of the acid is to boil it for several days with methanol containing 2% of fuming sulfuric acid. Treatment of the anhydride with methanol and a trace of oleum gave a mixture of the 129° acid ester and the 73° dimethyl ester. When the 289° acid was treated with one equivalent of diazomethane, the main reaction was the formation of the dimethyl ester, an approximately equivalent amount of the acid remaining unchanged. A small amount (10%) of the 129° acid ester was also formed. It therefore appears that the acid ester reacts more readily with diazomethane than does the dicarboxylic acid. Acid hydrolysis of the 73° ester yielded a mixture of the 289° acid and the 129° acid ester. Acid hydrolysis of the 129° acid ester gave the 289° acid.

It was shown by Linstead and Walpole[2] that hydrolysis of the 73° dimethyl ester with alcoholic potash yielded an acid of m. p. 220°, identical with that formed by heating the 289° (273°) acid with hydrochloric acid at 200°. In the present work, this result was confirmed and the perhydro-acid produced was found to melt, in the pure state, at 223°. This hydrolysis involved an inversion of configuration at one or both of the carboxyl groups. It has frequently been observed[4] that esters, in which the carbalkoxyl group is directly attached to a cyclic carbon atom which carried a hydrogen, can be inverted in configuration by treatment with sodium alkoxide. (This inversion normally proceeds in the direction *cis*→*trans;* however, it is the existence rather than the direction of the inversion which we wish to stress at the moment.) We therefore attempted to invert the 73° ester without hydrolysis by

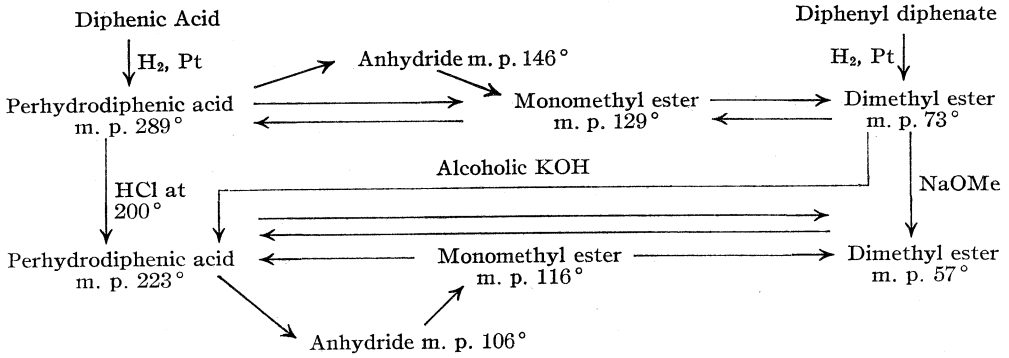
(3) Hückel, note in Vocke's paper, *Ann.*, **508**, 1 (1934).

(4) Hückel and Goth, *Ber.*, **58**, 447 (1925); Cook and Linstead, *J. Chem. Soc.*, 946 (1934).

heating it with sodium methoxide. This was successful; the ester was converted almost completely into an isomeride of m. p. 57°. A small amount of another isomeride, m. p. about 10°, also was formed. This is discussed later.

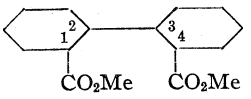
Acid hydrolysis of the 57° ester yielded the perhydrodiphenic acid of m. p. 223°. Esterification of the 223° acid with diazomethane yielded the ester, m. p. 57°. The acid was also characterized by conversion into the anhydride, m. p. 106° (in agreement with Linstead and Walpole[2]) and thence the monomethyl ester, m. p. 116°. Acid hydrolysis of the latter regenerated the 223° acid, while treatment with diazomethane formed the dimethyl ester, m. p. 57°.

The inter-relationships between the substances so far mentioned are summarized.



A curious anomaly in the literature should be mentioned at this point. Hückel[3] reported that his acid, m. p. 273°, on esterification with diazomethane gave an ester, m. p. *57°*. There can be little doubt that Hückel's acid was substantially our 289° acid. We have performed this esterification many times with diazomethane, as well as by the other methods already mentioned. Our product has always melted at 73° and we are convinced that this material is the authentic dimethyl ester. It would appear most probable that Hückel's note contains a misprint. This is supported by the fact that our 73° ester crystallizes in beautiful long needles, and this is the form described by Hückel for his "57°" ester. On the other hand, our 57° ester has never crystallized in this form. From the agreement of the m. p. with that of the invert ester, an alternative explanation for Hückel's result is that an inversion due to some contamination by alkali may have occurred in his work.

The question now arises, what is the nature of the inversion of configuration which occurs when the ester of m. p. 73° is converted into its isomeride of m. p. 57°? We are concerned only with the stereochemistry at carbons 1 and 4 (in the formula given below).



The configuration at C_2 and C_3—the "backbone configuration"[4a]—is fixed in the catalytic hydrogenation and will not be affected by the experimental conditions of our inversions. As regards C_1 and C_4, there are three possibilities. (1) Either these both have the same configuration in the 289° acid (and 73° ester) and both centers are inverted (*e. g., cis–cis-* → *trans–trans-*); or (2) both have the same initial configuration and only one center is inverted, because the *cis–trans* is the alkali-stable form, (*e. g., cis–cis* → *cis–trans*); or (3) they have different initial configurations and one center is inverted (*e. g., cis–trans-* → *trans–trans-*). It is proved below that the first of these possibilities is correct.

It was first shown by direct experiment that the 289° acid was stable to hot aqueous alkali. The inversion of the ester during treatment with alcoholic alkali therefore occurs in the unhydrolyzed ester, and cannot be brought about at the carbon atom carrying the ionized carboxyl. (This is of course due to the difference in the ease of enolization of the two groups.) The half-ester of the 289° acid therefore contains *one* group which is capable of effecting an inversion. If possibility (1) is correct, treatment with alkali should yield either a new acid (inversion + hydrolysis) or a new half-ester (inversion) according to the experimental conditions. If possibility (2) is correct, then either there will be no inversion

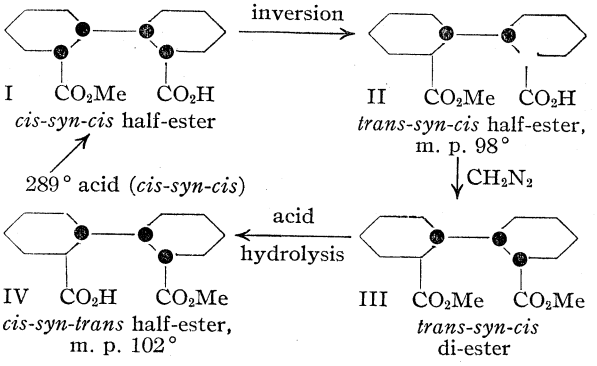
(4a) See Linstead and Walpole[2] and the preceding paper for a general outline of the stereochemistry.

or inversion to the 223° acid series will occur; the same is true of possibility (3).

The monomethyl ester of the 289° acid (m. p. 129°) was accordingly refluxed first with sodium methoxide, and the solution was then diluted somewhat with water and the heating continued. The product was a new perhydrodiphenic acid, m. p. 200°. (When the same acid ester was hydrolyzed with boiling aqueous alkali it gave the parent acid, m. p. 289°. The small amount of alcohol formed in this hydrolysis was clearly insufficient to effect any appreciable inversion.) When the 129° monomethyl ester was refluxed with sodium methoxide in the absence of water, it was converted into an isomeride of m. p. 98°. Acid hydrolysis of the new monomethyl ester yielded the new acid, m. p. 200°. Esterification of both the 98° monomethyl ester and the 200° acid with diazomethane yielded a dimethyl perhydrodiphenate, m. p. 14°. This material was identical with the by-product obtained in the inversion of the 73° dimethyl ester into the 57° isomeride.

An interesting observation which shows the ease of inversion in alkaline medium is the following. The anhydride of the 289° acid was boiled with some methanol which had been freshly distilled from baryta. It yielded mainly the corresponding monomethyl ester, m. p. 129°, but also, in 14% yield, the acid ester (m. p. 98°) of the half-invert acid. The partial inversion was traced to the presence of a small amount of barium methoxide in the methanol.

When the dimethyl ester (m. p. 14°) of the new acid was hydrolyzed for a comparatively short time with hydrochloric and acetic acids, it gave a mixture of the parent acid (m. p. 200°) and an acid ester. The latter melted at 102° and was not identical with that (m. p. 98°) described above; it depressed its m. p. and behaved differently on alkaline hydrolysis. It is clear therefore that this is the second acid ester which is theoretically possible for the half-invert acid, owing to the non-equivalence of the two carboxyl groups. The carbomethoxyl group preferentially hydrolyzed by acid is that on the *inverted* side of the molecule. To make this clearer we shall anticipate the assignment of the configuration to the acids. The 200° acid has been conclusively proved to have the *cis-syn-trans* configuration (see Part III). To distinguish between its two acid esters we shall refer to the configuration *on the ester side* first. Thus, in the *trans-syn-cis* half-ester, the hydrogen atom on the carbon which carries the carbomethoxyl group is orientated *trans-* to that on the neighboring backbone carbon; whereas that on the carbon which carries the free carboxyl group is orientated *cis-* (II). The preparation and naming of the two acid esters is shown in the following scheme.



The *cis-syn-trans* acid with acetic anhydride yields a distinct anhydride, m. p. 104°, from which it can be regenerated. The anhydride is not inverted by prolonged boiling with acetic anhydride.

It was pointed out above that the *trans-syn-cis* half-ester (II) was prevented from inverting further because its configurationally unstable (*cis*) ring carried the carboxyl group which was unable to provide a path for the inversion under the experimental conditions used. This is not true of the second half-ester (IV), for this carries the carbomethoxyl group on the unstable ring. It was accordingly expected that this would invert on hydrolysis with alcoholic alkali and this was realized. The 102° half-ester yielded the fully inverted acid of m. p. 223°. This series of reactions makes it certain that the 200° acid is intermediate in configuration between its isomers of m. p. 289° and 223°. We can now answer the question raised at the beginning of this section explicitly by saying that the inversion of the 73° to the 57° ester is a *double inversion*. We are not concerned at the moment with the proof of the direction of this but it is shown in later papers that it is *cis* → *trans*.

The acids of m. p. 289, 200 and 223° form one of the "backbone" series (*syn-* and *anti-*). It is proved later that this is the *syn*-series of perhydrodiphenic acids.

The *anti*-Series

The acids of this group are less accessible than their *syn*-isomers. This is particularly true of the

two members which contain configurationally unstable (*cis*-) arrangements.

It has already been stated that the catalytic hydrogenation of diphenic acid yields, besides the 289° acid, minor quantities of other hydrogenation products. The separation of these was laborious and difficult. Little or no benefit was achieved by converting the acids into their esters and carefully fractionating these. Direct fractional crystallization was useless in the early stages except for the isolation of the 289° acid. The following technique was of considerable assistance. The mixed acids were dissolved in sodium carbonate and the solution acidified in stages at the boiling point with dilute hydrochloric acid. Successive small crops of acids were so obtained. The method depends upon differences in acidity as well as in solubility. By its use the perhydro acids separate first and incompletely hydrogenated acids, which are aromatic and hence stronger, come down later. It was also possible by this means to separate a resinous ψ-acidic material (probably a lactone) which was sometimes present.

As an example, when the product of the hydrogenation of diphenic acid over platinum in alcohol was fractionated in the above manner, a succession of fractions were obtained, of which the principal components were

Crops 1–4:	Perhydro acid, m. p. 289° (*cis-syn-cis*)
Crop 5:	Perhydro acids, m. p. 289° and m. p. 198° (*cis-anti-cis*)
Crop 6:	Perhydro acid, m. p. 198°
Crop 7:	Perhydro acids, m. p. 198° and m. p. 200° (*cis-syn-trans*)
Crop 8:	Perhydro acid, m. p. 200°, and hexahydro acid, m. p. 242° (*cis*)
Crops 9–10:	Mainly diphenic acid

The various fractions could subsequently be further purified by direct crystallization. This enabled an estimate to be made of the relative amounts of the various products. In the above mixture these were approximately

Perhydro acids:	*cis-syn-cis*, 53%; *cis-anti-cis*, 10%; *cis-syn-trans*, 7%
Hexahydro acid:	10%
Diphenic acid:	20%

The method was found superior to that used by Vocke[5] for the separation of perhydro and hexahydro diphenic acids, which involves the use of barium salts.

In material exhaustively hydrogenated over platinum in acetic acid solution, the amount of unchanged or incompletely reduced acid was much lower. The proportion of *cis-syn-cis* material expressed as a percentage of the total perhydro acids was about the same, 70–80%, and the by-products were the same, namely, the *cis-anti-cis* acid, m. p. 198°, and the *cis-syn-trans* acid m. p. 200°. The isolation of these products is described in detail in the experimental section. The two acids were quite distinct and gave different series of derivatives. The *cis-syn-trans* (200°) acid was identical with that obtained by the half-inversion of the *cis-syn-cis* (289°) acid as described above. The final purification of the new acid (m. p. 198°) was conveniently achieved through the anhydride (m. p. 100°). The acid yielded crystalline di- and mono-methyl esters, melting at 44 and 99°, respectively. Acid hydrolysis of both these esters regenerated the parent acid.

It seemed reasonable to suppose that the new acid would have two configurationally unstable centers and would therefore be capable of half-inversion and of double inversion, as in the case of the 289° acid and its derivatives. The methods used in the *syn*-series were therefore applied to the new *anti*-acid. The monomethyl ester on hydrolysis with alcoholic potash yielded a new acid, m. p. 206°, which gave a distinct anhydride, m. p. 93°. The dimethyl ester (m. p. 44°) on similar hydrolysis gave the known acid m. p. 244° of Vocke[5] and of Walpole and Linstead.[2] This is now found to melt at 246–248° and to yield a dimethyl ester, m. p. 86°. The fact that this acid has previously been obtained by the hydrolysis of perhydro esters with alcoholic alkali is understandable. It represents the final alkali-stable form of all the *anti*-material originally present in the ester.

The above results make it clear that the *anti*-series consists of the three acids of m. p. 198, 206 and 248°, and that the acid of m. p. 206° is intermediate in configuration between the other two.

The melting points (in round numbers) of the six inactive perhydrodiphenic acids and of their derivatives are summarized in the table. Un-

Acid, probable (or certain) configuration	Melting points, °C.			
		Anhydride	Mono-methyl ester(s)	Di-methyl ester
cis-syn-cis	289	147	126	73
cis-syn-trans	200 (and 174)	104	98 and 102	14
trans-syn-trans	223	106	117	57
cis-anti-cis	198	100 (and 96)	99	44
cis-anti-trans	206	93	..	..
trans-anti-trans	247	242	..	86

(5) Vocke, *Ann.*, **508**, 1 (1934).

stable dimorphous modifications are given in parentheses.

There is no doubt that these six isomers are distinct individuals. The three acids with very similar melting points (200°, 198°, 206°) depress each others' melting points, and have distinctive crystalline forms. Their derivatives are also different. All the six inactive forms, which are theoretically possible, have therefore been made and interrelated.

There were on record in the literature, however, two other substances to which the perhydrodiphenic acid structure has been assigned. These are the acid of m. p. 213°, described by Vocke,[5] and that of m. p. 203°, prepared by Linstead and Walpole.[2] After the present work had been completed, Marvel and White[6] described what appeared to be a further isomer, m. p. 174–175°. It became necessary, therefore, to consider the nature of these compounds.

Vocke Acid, m. p. 213°.—This acid was obtained by Vocke[5] by alkaline hydrolysis of the product of the hydrogenation of dimethyl diphenate over nickel. It was separated from the *trans-anti-trans* (247°) acid, which was Vocke's main perhydro-product, by a tedious fractional crystallization. We have never obtained a substance with these properties. It seems most probable that Vocke's acid was an impure form of our *trans-syn-trans* acid (m. p. 223°). This would tally with the method of preparation, for all the *syn*-material would be expected to assume the *trans-trans* configuration during the alkaline hydrolysis. Moreover, there is no doubt that *syn*-material is formed in hydrogenations over nickel, because the solid *cis-syn-cis*-dimethyl ester can be isolated in quantity from the unhydrolyzed reaction product.[2] The m. p. of Vocke's anhydride (80°) does not agree with ours (106°) but his compound was not analyzed and it is possible that it was a mixed anhydride with acetic acid, similar to that which Linstead and Walpole isolated from the *cis-syn-cis* acid.[2] The other discrepancy lies in the ease of ketonization. Linstead and Walpole[2] were able to form a pyroketone from the 223° acid, whereas Vocke observed that his acid and anhydride sublimed practically undecomposed. An alternative possibility is that Vocke's 213° acid may have contained one double bond, *i. e.*, it may have been a decahydrodiphenic acid. We have isolated a decahydrodiphenic acid of m. p. 212° as a by-product in certain hydrogenations. Vocke's analytical figures, however, correspond with a perhydro product.

Linstead and Walpole Acid, m. p. 203°.—This differs from the six isomerides described above. The position with regard to it is more complicated. It was prepared[2] by the nitric acid oxidation of a ketone, m. p. 51°, itself obtained[7] by the hydrogenation of two unsaturated ketones of m. p. 39 and 94°. These two unsaturated ketones were first prepared by Marvel and co-workers[8] by cyclization of di-Δ^1-cyclohexenylacetylene with formic acid, and were considered by them to have a hydrophenanthrene structure. Linstead and Walpole[7] reduced the two unsaturated ketones to hydrocarbons which were dehydrogenated to phenanthrene. Moreover, treatment of the saturated ketone with methylmagnesium iodide followed by dehydrogenation yielded 9-methylphenanthrene.[7] This provided definite evidence in support of Marvel's proposed skeletal structure. Further supporting evidence by the same method of attack has been reported by Marvel, Pearson and White.[9] It appeared to follow that the saturated ketone was 9-keto-perhydrophenanthrene and the acid obtained from it by oxidation was a perhydrodiphenic acid.

Marvel[8] was originally led to assign the hydrophenanthrene structure to his ketones from the behavior of a hydrocarbon obtained from one of them. This yielded on selenium dehydrogenation a product very similar in properties to what was at the time believed to be *trans-as*-octahydrophenanthrene. Levitz, Perlman and Bogert[10] have conclusively proved that this substance is a spirane. They therefore suggested that Marvel's ketones are also spiranes, a possibility earlier rejected by Marvel.[11]

The evidence summarized above on the structure of Marvel's ketones is inconclusive. However, now that six distinct perhydrodiphenic acids have been prepared and interrelated, there are only two possibilities for the 203° acid. Either it has a different skeletal structure, or the perhydrodiphenic acid series contains more isomeric forms than are demanded by classical

(6) Marvel and White, THIS JOURNAL, **62**, 2739 (1940).

(7) Linstead and Walpole, *J. Chem. Soc.*, 842 (1939).

(8) Marvel and co-workers, THIS JOURNAL, **58**, 972 (1936); **59**, 2666 (1937).

(9) Marvel, Pearson and White, *ibid.*, **62**, 2741 (1940).

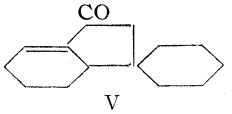
(10) Levitz, Perlman and Bogert, *J. Org. Chem.*, **6**, 105 (1941).

(11) Marvel, Mozingo and Kirkpatrick, THIS JOURNAL, **61**, 2003 (1939); *cf.* Marvel and Walton, *J. Org. Chem.*, **7**, 88 (1942).

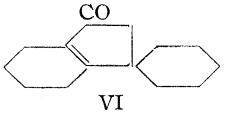
stereochemical theory. In the latter connection, the least unreasonable suggestion would be that there was a restriction of free rotation about the inter-nuclear bond, as in the case of various substituted diphenic acids. Many arguments could be raised against this possibility. It will be sufficient to quote the following direct experimental evidence. We find that *all* the authentic perhydrodiphenic acids yield pyroketones, whereas the 203° acid does not. It is inconceivable that the delicate isomerism due to restricted rotation could survive the high temperatures (300°) involved in this reaction.

It is, therefore, concluded that the 203° acid cannot be a perhydrodiphenic acid. Hence the 51° ketone is not a perhydrophenanthrene derivative and the unsaturated ketones of Marvel cannot have a phenanthrene skeleton.

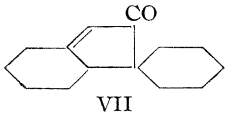
We, therefore, accept as probable the spirane skeleton proposed by Levitz, Perlmán and Bogert,[10] which is most easily reconciled with the dehydrogenation results. The following further suggestions as to the structure are made. It was shown by Linstead and Walpole[7] that both the unsaturated ketones have $\alpha\beta$-double bonds and give the same pair of saturated ketones on hydrogenation. The carbonyl group is now placed in the five-membered ring because of the consistent formation of 9-alkyl phenanthrenes after Grignard reaction and dehydrogenation, as noted above.[7,9] Moreover, this offers a simple explanation for the fact that the 203° acid forms an anhydride but no pyroketone.[2] The three possible structures for the two unsaturated ketones which came up for consideration are (V), (VI) and (VII)



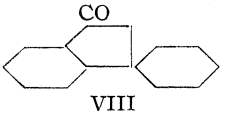
V



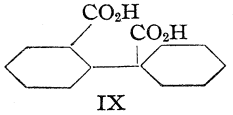
VI



VII



VIII



IX

The structure corresponding to (VII) in the hydrophenanthrene series was eliminated by a stereochemical argument (Linstead and Walpole[7]), which is not valid in the spirane series. However, (VII) can be ruled out because it cannot possibly give the same ketones on hydrogenation as either (V) or (VI). Structures (V) and (VI), therefore, are the most acceptable for the two unsaturated ketones. Woodward[12] has given spectrographic evidence which indicates that (VI) is to be preferred for the ketone of m. p. 94°, and (V) for the more common isomeride, m. p. 39°. Essentially the same spectrochemical deduction has independently been drawn by Evans and Gillam[13] from Woodward's generalization. They placed the bonds in the equivalent positions in ketodecahydrophenanthrene molecules.

The two saturated ketones of Linstead and Walpole now become the *cis-* and *trans*-forms of (VIII). It is probable that the more stable modification (m. p. 51°) is the *cis*-form, judging from the relative stabilities of the α-hydrindanones. The acid of m. p. 203°, must have structure (IX) if the spirane skeleton is correct. It is therefore dicyclohexyl-1,2′-dicarboxylic acid.

Marvel and White Acid, m. p. 174°.—A sample of this material was kindly sent us by Professor Marvel. It was found to be essentially a dimorphic modification of the *cis-syn-trans* acid (m. p. 200°). When crystallized from dilute acetic acid it separated in the high melting form and was then identical with our material. Moreover, the melt of the 174° form soon solidified and then remelted at 198–200°.

Before the present work was completed, two "perhydrodiphenic acids" were known which apparently broke the Blanc rule regarding the pyrolysis of adipic acids. These were the 203 and 213° acids, which have been discussed above. It is now plain that the 203° acid is not a perhydrodiphenic acid at all, and the validity of the work on the 213° acid is doubtful. We propose to reserve further discussion on this general topic until our investigation of the pyrolysis of the new perhydrodiphenic acids is complete.

The optical resolution of the perhydrodiphenic acids is described in Part III, and the evidence for the assignment of configuration is given in Parts III and V. The bearing of the new result on the stereochemistry of perhydrophenanthrene derivatives is discussed in Parts VI and VII.

(12) Woodward, THIS JOURNAL, **64**, 76 (1942); *cf. ibid.*, **63**, 1123 (1941).

(13) Evans and Gillam, *J. Chem. Soc.*, 818 (1941).

Experimental[14]

Intermediates

The following procedures, based on those of Oyster and Adkins[15] and Linstead and Walpole,[2] respectively, were found satisfactory for the routine preparation of pure diphenic acid from crude phenanthrene.

Potassium dichromate (300 g.) was dissolved in a mixture of 500 cc. of concentrated sulfuric acid and 1500 cc. of water contained in a 4-l. beaker. Without cooling, 100 g. of crude phenanthrene was added with vigorous stirring. This operation requires caution as much heat is evolved. After the reaction had quieted, a further 300 g. of potassium dichromate was added. The mixture was allowed to stand for one hour, and was then diluted with water (2 l.) and allowed to cool. The granular product was filtered off, washed thoroughly with water and dried; yield of crude phenanthraquinone, 89 to 94 g. (76–80%), m. p. 190–194°.

The quinone was oxidized in 100-g. lots in a 2-l. flask, fitted with stirrer and condenser, by means of a mixture of 120 cc. of 30% (100 vol.) hydrogen peroxide, 900 g. of 3% hydrogen peroxide and 300 cc. of glacial acetic acid. The mixture was boiled *very gently* for three hours. The product was filtered hot (steam funnel) from a little unreacted anthraquinone, and allowed to crystallize overnight in the ice-box. The crude diphenic acid was filtered off and dried (45 to 48.5 g.). To obtain material capable of being readily hydrogenated, the following procedure was used: 12 g. of the crude acid was dissolved in 1.5 l. of boiling water, the solution filtered and boiled for one-half hour with 2 g. of Norit. The solution was then filtered and the treatment repeated twice, using thirty minutes of boiling with 2 g. and 1 g. of Norit, respectively. The final filtrate deposited on cooling 6–7 g. of glistening plates of diphenic acid, m. p. 232–233°. The over-all yield from the crude phenanthrene varied between 18 and 21%.

The acid (25 g.) was esterified by five days of refluxing with 250 cc. of absolute methanol (freshly distilled from magnesium methoxide) containing 14 g. of dry hydrogen chloride. The product was separated by means of sodium carbonate into neutral and acid fractions. The neutral product was crystallized once from methanol which yielded 25.4 g. (91%) of pure dimethyl diphenate, m. p. 73–74°. Acidification of the sodium carbonate extract yielded a small quantity of *the monomethyl ester* of diphenic acid, which does not appear to have been described previously. It crystallizes from dilute alcohol in delicate plates, m. p. 110–111°.

Anal. (material dried at 80° *in vacuo*). Calcd. for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72. Found: C, 70.45, 70.34; H, 4.80, 4.64.

syn-Series

289° Acid (*cis-syn-cis*[16]).—All the hydrogenations described in this paper were carried out in a Parr apparatus using an initial gage pressure of hydrogen of about 60 lb./sq. in. The glacial acetic acid was refluxed over, and then distilled from potassium permanganate. The Adams catalyst was prepared following Bruce.[17]

A solution of 20 g. of diphenic acid in 250 cc. of acetic acid was shaken under hydrogen with 1 g. of catalyst. Most hydrogenations went to completion in from one to four days without the addition of more catalyst. Occasionally a further gram of platinum oxide had to be added to complete the reduction. The bulk of the perhydro-acid separated from the solution during the reaction.

The catalyst and precipitate were filtered off from the product on a sintered-glass funnel and washed with 100 cc. of glacial acetic acid. The investigation of the filtrate (A) is described later. The solid acid was extracted from the catalyst by means of 5% aqueous alkali and was precipitated by dilute hydrochloric acid. The crude product weighed 11.2–12.7 g. (56–63%) and melted at 282–284°. Recrystallization from 500 cc. of glacial acetic acid yielded the pure *cis-syn-cis*-perhydrodiphenic acid, m. p. 287–289°.

The m. p. of this acid varies with the rate of heating owing to the formation of anhydride and to stereochemical inversion. For these reasons, also, very sharp values cannot be obtained. The above constant was obtained by immersing the capillary at 280° and raising the temperature 1° every six seconds. A mixture with a sample of the acid of Linstead and Walpole[2] (recorded m. p. 273–274°) melted under the same conditions at 285–287°.

Anal. (material dried at 110° *in vacuo*). Calcd. for $C_{14}H_{22}O_4$: C, 66.13; H, 8.72. Found: C, 66.21, 66.43; H, 8.83, 8.88.

The hydrogenation in alcohol solution was much slower and required frequent addition of fresh catalyst. The main product was the 289° acid. The separation of the products is more conveniently considered later under the 198° (*cis-anti-cis*) acid. The *cis-syn-cis* acid can also be prepared by catalytic hydrogenation of *cis*-hexahydrodiphenic acid. This is described in Part IV.

Derivatives of the 289° Acid

Anhydride.—Following Linstead and Walpole,[2] the acid (6 g.) was refluxed for twenty hours with 100 cc. of acetic anhydride. The excess of reagent was removed *in vacuo* and the solid residue sublimed onto a cold "finger" at 130° and 2 mm. After three sublimations, the acetic anhydride had been practically all eliminated and 4.0 g. (72%) of a crude anhydride m. p. 137–142° remained. Crystallization of this (1.6 g.) from 100 cc. of ligroin (b. p. 60–90°) gave 1.15 g. of the pure anhydride, shining plates, m. p. 146–147°; 1.5 g. of unsublimable material, probably polymeric anhydride, was also obtained.

Dimethyl Ester.—(1) The acid (5 g.) was refluxed for four days with 100 cc. of absolute methanol and 2 cc. of fuming sulfuric acid, containing 15% SO_3. The alcohol was boiled off and the residue was stirred with 100 cc. of hot 10% sodium carbonate solution. On cooling the ester crystallized, and was filtered off (m. p. 67–72°, yield, 5.3 g., 95%). One crystallization from dilute methanol gave 4.7 g. (85%) of long needles of pure *cis-syn-cis* dimethyl perhydrodiphenate, m. p. 73–74°. This material was identical with that prepared by Linstead and Walpole[2] by hydrogenation of dimethyl diphenate. Acidification of the sodium carbonate solution gave 0.13 g. (2.5%) of the

(14) All melting points are corrected.

(15) Oyster and Adkins, THIS JOURNAL, **43**, 208 (1921).

(16) The configurations assigned are discussed more fully in the following papers. They have been added for convenience in reference.

(17) Bruce, THIS JOURNAL, **58**, 687 (1936).

monomethyl ester, m. p. 124–126°, which is described more fully below.

(2) The acid (5.08 g.) dissolved in 150 cc. of dioxane was added to an ethereal solution of diazomethane, prepared from 10.3 g. of nitroso-methyl urethan. After two days at room temperature the product was treated with acetic acid, the solvent removed and the residue crystallized from methanol, yield 89%, m. p. and mixed m. p. 73–74°.

Monomethyl Ester.—The anhydride, m. p. 147° (3.22 g.) was treated with a solution of sodium methoxide from 1.26 g. (4 moles) of sodium in 60 cc. of methanol. After three hours at room temperature, the solvent was removed, the residue taken up in water and the solution filtered and acidified. The crude half-ester which separated was dried and recrystallized from ligroin, b. p. 60–90° (*ca.* 250 cc.). This yielded 2.80 g., 76.5%, of the pure *monomethyl ester* of *cis-syn-cis*-perhydrodiphenic acid, small plates, m. p. 128.5–129.5°.

Anal. (material dried *in vacuo* at 110°). Calcd. for $C_{15}H_{24}O_4$: C, 67.14; H, 9.02. Found: C, 67.32, 67.12; H, 9.09, 9.08.

An alcoholic solution of 2.54 g. of the 289° acid was treated with one equivalent of diazomethane (from 2.11 cc. of nitrosomethyl urethan). The solution was immediately decolorized. It was extracted with 5% aqueous sodium hydroxide. The ethereal layer yielded 1.07 g. (38%) of the dimethyl ester, m. p. 72–74°. The alkaline extract was acidified and the crystalline precipitate so obtained was extracted with boiling ligroin (b. p. 60–90°). The residue (1.12 g., 44%) was the unchanged acid (m. p. 270–277°). The ligroin extract yielded the acid ester (0.28 g., 11%) which melted at 127–129° after one crystallization from ligroin.

When the monomethyl ester (150 mg., m. p. 129°) was treated with diazomethane in ether, it yielded the dimethyl ester (150 mg., m. p. and mixed m. p. 73°).

The anhydride, m. p. 147° (470 mg.), was refluxed for sixty-four hours with 20 cc. of methanol containing a drop of fuming sulfuric acid (15% SO_3), moisture being excluded. The methanol was removed and the residue extracted with boiling ligroin (b. p. 70–90°). Fractional crystallization of the ligroin solution yielded 160 mg. (30%) of the acid ester (less soluble) and 280 mg. (50%) of the dimethyl ester, identical with material already described.

Hydrolyses.—The dimethyl ester, m. p. 74° (500 mg.), was refluxed for twenty hours with 5 cc. of glacial acetic acid and 2 cc. of concentrated hydrochloric acid. The product was diluted with water and the precipitate so obtained was extracted with aqueous sodium carbonate. The insoluble portion (170 mg.) was the unchanged dimethyl ester. The carbonate solution was heated to the boiling point and treated with hydrochloric acid in drops until crystals began to appear. The acid ester (150 mg., m. p. 126–127.5°) then separated. Completion of the acidification yielded the slightly impure dicarboxylic acid, m. p. 270–272°, mixed m. p. 275–285° (140 mg.).

A similar acid hydrolysis of the monomethyl ester also yielded the *cis-syn-cis* acid (m. p. 282–285°, mixed m. p. 284–287°). The acid ester (10.3 mg.) was refluxed for fifty-two hours in a soft-glass apparatus with 2 cc. of 20% aqueous sodium hydroxide. The acidic product, crystallized from acetic acid, yielded 6.5 mg. (67%) of pure *cis-syn-cis* acid, m. p. and mixed m. p. 287–290°. No appreciable inversion had therefore occurred. On the other hand, hydrolyses of both the dimethyl and monomethyl esters with alcoholic potash led to inversions. These are described below under the headings of the appropriate acids.

200° Acid (*cis-syn-trans*)

The monomethyl ester of *cis-syn-cis*-perhydrodiphenic acid (1 g., m. p. 129°) was refluxed for seventeen hours with a solution of 2.0 g. of sodium in 20 cc. of absolute methanol. Water (2.5 cc.) was then added and the refluxing continued for a further fifty-seven hours. The solution was diluted, acidified and extracted with ether. Removal of the ether left a solid residue which was extracted with three 20-cc. portions of boiling benzene. The united extracts, on cooling, deposited a crust of *cis-syn-trans* acid. One crystallization from dilute alcohol gave 430 mg. (46%) of the pure *acid* in small needles, m. p. 198–200°. A second crop (420 mg.) of less pure acid was isolated from the benzene mother liquors. For analysis the acid was crystallized from acetic acid containing a trace of water, and was dried *in vacuo* at 110°, m. p. 199–200°.

Anal. Calcd. for $C_{14}H_{24}O_4$: C, 66.13; H, 8.72. Found: C, 66.26, 66.22; H, 8.79, 8.72. Equivalent (dibasic): Calcd., 127.2. Found, 124.6.

The isolation of the same acid as a by-product in the hydrogenation of diphenic acid is described below under the *cis-anti-cis* (198°) acid. The acid has also been prepared by catalytic hydrogenation of *trans*-hexahydrodiphenic acid (see Part IV).

A sample of the material of Marvel and White[6] was supplied by Dr. Marvel. It was a white powder, melting at 173–175° alone and at 198–200° in admixture with the *cis-syn-trans* acid, m. p. 199–200°. This material (3 mg.) was dissolved in 0.2 cc. of acetic acid and the solution was diluted to 0.5 cc. with water. The acid then separated in needles, m. p. 197–199°, identical with our *cis-syn-trans* acid. We have had occasional examples of the separation of this low-melting dimorphous modification. When this material has melted (at about 174°) it will resolidify and then melt at 198–200°.

Derivatives of the 200° Acid

***trans-syn-cis* Monomethyl Ester.**—The acid ester of the *cis-syn-cis* acid (m. p. 129°, 540 mg.) was treated with sodium methoxide made from 460 mg. of sodium and 20 cc. of freshly dried methanol. The solution was refluxed for sixteen hours in a soft-glass apparatus. Some of the methanol was removed and the product acidified, diluted and extracted with ether. Evaporation of the ether left an oil which was taken up in 5 cc. of ligroin (b. p. 70–90°) and the solution left to crystallize. A mixture of *trans-syn-cis* and unchanged *cis-syn-cis* half esters crystallized, the former in large prisms, the latter in small plates. They were separated partly manually, and partly by fractional crystallization.

Yield of crude *cis-syn-cis* half-ester: 230 mg., (44%), m. p. 118–125°

Yield of purified *cis-syn-cis* half-ester: 140 mg., m. p. 125–127.5°

Yield of crude *trans-syn-cis* half-ester: 180 mg., (33%), m. p. 90–93°

Yield of purified *trans-syn-cis* half-ester: 130 mg., m. p. 97–99°

For analysis, the *trans-syn-cis*-monomethyl perhydrodiphenate was dried *in vacuo* at 56°. Calcd. for $C_{15}H_{24}O_4$: C, 6.14; H, 9.02. Found: C, 67.37, 67.21; H, 9.14, 9.02.

The following experiment illustrates the ease of inversion of the *cis-syn-cis* configuration. The *cis-syn-cis* anhydride, m. p. 145° (5 g.) was refluxed for seventy hours with 200 cc. of methanol which had been freshly distilled from barium oxide. (Subsequent examination showed that this methanol contained a trace of barium methoxide.) Removal of the solvent gave a residue, which on one crystallization from dilute alcohol gave 2.87 g. of the *cis-syn-cis*-monomethyl ester (m. p. 127–129°). The mother liquors were freed from solvent and the residue crystallized from ligroin in the manner described above. In this way there was separated 220 mg. more of the *cis-syn-cis* half-ester and 810 mg. of the *trans-syn-cis* half-ester. The latter after two more crystallizations from dilute alcohol melted at 97–99°, alone, or in admixture with that described above.

Acid hydrolysis of the 98° half-ester (13.3 mg.) with hydrochloric and acetic acids (1:2) yielded the *cis-syn-trans* acid (6 mg.) identified by m. p. and mixed m. p.

Dimethyl Ester.—Esterification of the acid (360 mg., m. p. 196–198°) was carried out with an excess of diazomethane in the usual way. The neutral product, an oil, was dissolved in a little petroleum ether and left at −70° to crystallize. After two days, prismatic clumps of the dimethyl ester separated. These melted at 12.5–14.5° alone and below 5° in admixture with the dimethyl ester (m. p. 57°) of the *trans-syn-trans* acid (see below). The same material was formed by diazomethane esterification of the *trans-syn-cis*-monomethyl ester, yield 86%; m. p. 12.5–14.5°. This dimethyl ester was also obtained as a by-product in the inversion of the *cis-syn-cis* dimethyl ester (*q. v.*).

cis-syn-trans-**Monomethyl Ester.**—The dimethyl ester (250 mg., m. p. 12–14°) was refluxed for eleven hours with 2 cc. of concentrated hydrochloric acid and 3 cc. of glacial acetic acid. The product was evaporated to dryness and the acidic material extracted with hot 10% aqueous sodium carbonate solution. The extract was filtered through a layer of Norit, diluted to 30 cc. with water, and heated to boiling. The solution was then treated at the b. p. with 10% hydrochloric acid, 2 drops at a time. The solution was cooled after each addition and any precipitate was filtered off. The first material to separate in this way was a new acid ester (60 mg.) which melted at 100–102.5° alone and at 80–90° in admixture with the acid ester (*trans-syn-cis-*), m. p. 98°, described above. Three further crops separated on further acidification. These were united and separated into fractions soluble and insoluble in boiling hexane. The hexane-soluble fraction gave a further 80 mg. of the new acid ester. The hexane-insoluble fraction was essentially the *cis-syn-trans* acid. After two crystallizations from dilute acetic acid, 40 mg. was obtained which melted at 194–196° alone and at 195–198° in admixture with a pure sample.

The pure *cis-syn-trans*-**monomethyl ester** formed small prismatic crystals from ligroin, m. p. 101.5–102.5°. The analytical sample was dried at 80° *in vacuo*. Calcd. for $C_{15}H_{24}O_4$: C, 67.14; H, 9.02. Found: C, 67.30, 67.20; H, 9.20, 9.08.

The *cis-syn-trans* acid (300 mg., m. p. 196–198°) was refluxed for an hour with 3 cc. of acetic anhydride. The **anhydride,** obtained by removal of the reagent, crystallized from petroleum ether (b. p. 35–60°) in glistening prisms, m. p. 104–104.5°.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.44; H, 8.29.

An oily product, probably a polymeric anhydride, was also formed. Both the crystalline anhydride and the oil, when boiled with aqueous alkali, regenerated the parent acid, m. p. and mixed m. p. 198.5–199.5°.

The crystalline *cis-syn-trans* anhydride was refluxed for twenty-four hours with 30 parts of acetic anhydride. The reagent was removed, the product treated with alkali and the acid fractionally precipitated by careful addition of dilute hydrochloric acid. Only *cis-syn-trans* acid was isolated. The absence of *cis-syn-cis* and *trans-syn-trans* acid was confirmed by the fact that neither of these could be obtained by seeding the mother liquor with authentic samples. (Experiments by Mr. Selby Davis; analysis by Miss E. Werble.)

Marvel and White[6] had described an anhydride, m. p. 104°, made from their acid of m. p. 174°. This was undoubtedly identical with our anhydride, although we were unable to make a direct comparison as a sample provided by Dr. Marvel had already largely hydrated back to the acid.

223° Acid (*trans-syn-trans*)

(1) **Double inversion and hydrolysis of *cis-syn-cis* ester.**—*cis-syn-cis*-Dimethyl perhydrodiphenate, m. p. 73–74°, (1 g.) was refluxed for fifty hours with a solution of 7 g. of potassium hydroxide in 20 cc. of commercial methanol. The product was diluted, freed from neutral material with ether, acidified and again extracted with ether. The second extract was freed from solvent and the sticky residue dissolved in benzene. On standing, the solution deposited three successive crops (0.43 g., 48%) of almost pure *trans-syn-trans*-perhydrodiphenic acid, m. p. 221–223° (Linstead and Walpole,[2] give 220°).

Derivatives.—Esterification of this acid with an excess of diazomethane in the usual way gave, in practically quantitative yield, the **dimethyl ester.** This crystallized from light petroleum in small opaque rosets, m. p. 56–57.5°. For analysis the material was dried *in vacuo* at 25°.

Anal. Calcd. for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 68.28, 68.36; H, 9.26, 9.35.

Acid hydrolysis of this ester (300 mg.) was carried out in the usual way (2 cc. acetic acid, 1 cc. hydrochloric acid, nineteen hours of refluxing). The product was evaporated to dryness and the residue dissolved in aqueous sodium carbonate. The solution was boiled with charcoal, filtered and fractionally acidified at the boiling point by the method already described. The first product to separate was an oil from which no crystalline material was isolated. Further acidification yielded 3 crops of crystalline *trans-syn-trans* acid, a total of 190 mg. (70%) melting above 216°. One recrystallization of this gave the pure acid, m. p. and mixed m. p. 220–222°.

The anhydride, prepared by means of acetic anhydride, crystallized from ligroin (b. p. 70–90°) in flat rhombic prisms, m. p. 105–106.5°, in agreement with Linstead and Walpole.[2] The anhydride (250 mg.) was refluxed for nineteen hours with 5 cc. of pure methanol, moisture being excluded. The product was evaporated to dryness, the residual oil taken up in ligroin and the solution filtered through a layer of charcoal. Removal of the solvent left an oil, which was dissolved in 4 cc. of petroleum ether (b. p. 20–40°) and the solution allowed to crystallize at 4°. Two types of crystals were obtained, which were separated by hand. The rarer type (20 mg., 7%) melted at 105–107° and was identified as unchanged anhydride. The common type (200 mg., 70%) melted at 109–114° and after three crystallizations from ligroin, formed hard prisms, m. p. 115.5–117.5°, of the pure **monomethyl ester** of the *trans-syn-trans* acid. For analysis it was dried at 80° *in vacuo*.

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.14; H, 9.02. Found: C, 67.26, 67.17; H, 9.04, 9.14.

Acid hydrolysis of this material (10 mg.) gave in 84% yield the parent acid, m. p. and mixed m. p. 221–223°. The same result was obtained by alkaline hydrolysis but the reaction was more difficult and the purity low.

Esterification of the acid ester (13.4 mg.) with diazomethane yielded the dimethyl ester (11.6 mg., 82%). This crystallized from petroleum ether at −70° in white rosets, m. p. and mixed m. p. 55.5–57°.

(2) **Inversion without Hydrolysis of *cis-syn-cis* Ester.**—*cis-syn-cis*-Perhydrodiphenic dimethyl ester (m. p. 74°, 1 g.) was refluxed for one hour with a solution of 0.1 g. of sodium in 4 cc. of dry methanol. The product was diluted and extracted twice with ether. The united extracts were washed with water, dried and evaporated to dryness. The oily residue was dissolved in 8 cc. of petroleum ether and the solution allowed to crystallize at −70°. The first two crops weighed 480 mg. (m. p. 51–56°) and 110 mg. (m. p. 47–51°), respectively. Recrystallization yielded 400 mg. of pure *trans-syn-trans* dimethyl ester, m. p. and mixed m. p. 56–57.5°. The mother liquor from the second crop was cooled to −70° and seeded with the dimethyl ester (m. p. 14°) of the *cis-syn-trans* acid. The solution then deposited 70 mg. of this ester, separating in the characteristic clumps, m. p. 8–11°.

(3) **Half-inversion and Hydrolysis of *cis-syn-trans* Half-ester.**—A solution of 10.6 mg. of *cis-syn-trans*-monomethyl ester (m. p. 102°) and 400 mg. of potassium hydroxide in 2 cc. of methanol was refluxed in soft glass for four days. The product was acidified, filtered from inorganic matter and the solvent removed. The residue was dissolved in ether and the solution washed with water. Removal of the ether left a crystalline solid which was crystallized from dilute acetic acid (charcoal). After the separation of a little oil, the solution deposited 3.6 mg. (36%) of *trans-syn-trans* acid crystallizing in prismatic needles, m. p. and mixed m. p. 220–223°.

anti Series—198° Acid (*cis-anti-cis*)

By-products in the Hydrogenation of Diphenic Acid.—(a) Diphenic acid (5 g.) was catalytically hydrogenated in absolute alcohol (200 cc.) at 60 lb. pressure. In all, 7.6 g. of Adams catalyst, added in 7 portions, was required. The precipitated acid was dissolved by heating and the catalyst was then filtered off. The first four crops which separated on concentrating the solution were the *cis-syn-cis* acid, m. p. 289° (see later), and no further crystalline material separated. The mother liquor on concentration gave a glass, which was dissolved in aqueous sodium carbonate and treated with charcoal. The filtrate was treated at the boiling point with 10% hydrochloric acid in drops until a faint permanent cloudiness could be seen. It was then left for fourteen days and the fifth crop of crystals was removed. The process of "fractional acidification" was then continued and five further crops were obtained. It was necessary to allow the solution to stand for several days after each acidification. The amounts, melting points and main components of the various fractions are summarized.

Crop	Wt., mg.	M. p., °C.	Main components
1	500	282–286	*c.s.c.* perhydro
2	850	274–284	*c.s.c.* perhydro
3	450	258–278	*c.s.c.* perhydro
4	400	250–270	*c.s.c.* perhydro
5	320	200–240	*c.s.c.* and *c.a.c.* perhydro
6	160	180–185	*c.a.c.* perhydro
7	240	90–130	*c.a.c.* and *c.s.t.* perhydro
8	600	165–205	*c.s.t.* perhydro and *cis*-hexahydro
9	320	185–222	Diphenic acid
10	520	188–210	Diphenic acid

The total recovery of acid was 4.36 g. or 87%, by weight. Fraction 5 was separated by benzene into a soluble and insoluble portion. The insoluble portion (100 mg.), together with fractions 1–4, on crystallization from acetic acid yielded 1.35 g. of pure *cis-syn-cis*-perhydro acid, m. p. 287–289° (26%). The benzene-soluble portion of fraction 5, together with fraction 6 and a small sample, obtained from fraction 7 by crystallization, were fractionally crystallized from dilute acetic acid. Eventually there was isolated a new perhydrodiphenic acid of m. p. 196–198° (120 mg., 2.3%). The mode of crystallization was characteristic. On rapid separation from dilute acetic acid the acid came out in fine feathery needles. After three weeks of standing in contact with the mother liquor these changed into a stable dimorphic form, which was also obtained by slow crystallization. The stable variety formed small clear prismatic parallelepipeds, m. p. 197–198.5°. A mixture with the *cis-syn-trans* acid m. p. 200°, melted at 162–182°. The analytical sample was dried at 110° *in vacuo*.

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.13; H, 8.72. Found: C, 66.21, 66.36; H, 8.74, 9.03.

The derivatives of this acid and another method of preparation are described later.

Fractional crystallizations of the remainder of fraction 7 and of fraction 8, yielded 110 mg. (2.1%) of *cis-syn-trans*-perhydrodiphenic acid, m. p. 197–199°, which was identified by a mixed melting point determination.

Fraction 8 gave as its main component 400 mg. (7.8%) of an acid, m. p. 241–242° (bath initially at 235°). Analysis showed that this was a **hexahydrodiphenic acid.** It was identical with material prepared by Mr. Selby Davis and described more fully in a later paper (Part IV), and is

presumably identical with Vocke's hexahydro acid of the same m. p.[5] The analytical sample was crystallized from acetic acid and dried *in vacuo* at 110°.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.72; H, 6.50. Found: C, 67.43, 67.68; H, 6.63, 6.65.

Fractions 9 and 10 yielded mainly impure starting material, melting at 222–227° alone and at 223–230° in admixture with diphenic acid (m. p. 232–233°). Even after a tedious series of crystallizations we were unable to separate the impurity which was obviously contaminating this.

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.24; H, 4.50.

(b) For preparative purposes the new (198°) acid was more easily obtained from the by-product of the catalytic hydrogenation of diphenic acid in acetic acid. Thus, 20 g. of diphenic acid was hydrogenated in the manner described under the *cis-syn-cis* acid; this substance (12 g.) was filtered off and the mother liquor was evaporated *in vacuo*. The colorless glass so obtained was dissolved in 15 cc. of acetic acid, and the sirup was allowed to crystallize. The first crop separated spontaneously, weighed 420 mg. and was essentially the perhydro acid of m. p. 289°. The mother liquor was then seeded twice with the 200° acid (*cis-syn-trans*) and two crops mainly composed of this acid were removed. These weighed 800 and 230 mg., and melted at 200–218° and 187–199°, respectively. The mother liquor was concentrated to 10 cc., seeded with the desired 198° acid (*cis-anti-cis*) and allowed to stand. A hard crust (3.25 g.) separated. An arduous series of fractional crystallizations from acetic acid yielded the acid in a state of moderate purity (prisms, m. p. about 190°), but it was found that final purification was best effected through the anhydride. In a typical experiment, 150 mg. of acid of m. p. 187–192° was refluxed with 2 cc. of acetic anhydride for thirty minutes. The excess of reagent was blown off in a stream of dry air and the residue crystallized from 2 cc. of ligroin (b. p. 60–90°), which yielded 57.3 mg. of the *cis-anti-cis* anhydride, m. p. 94.5–96°. Boiling 10% aqueous alkali regenerated the acid from this, m. p. 195–197°. In this manner a total quantity of 1.01 g. of the acid was prepared (4.8%).

Derivatives.—The pure acid, m. p. 198° (200.6 mg.), was refluxed for four hours with 3 cc. of acetic anhydride and the anhydride isolated and purified as described above, yield 156.1 mg., 83%. The **anhydride** is dimorphous; it separates in light needles, m. p. 95–96° and in prismatic needles, m. p. 99–100°. The melt of the lower melting form solidifies and the solid then remelts at 99–100°.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.52. Found: C, 71.19; H, 8.77.

When boiled with methanol for forty-eight hours, the anhydride yielded the **monomethyl ester** in 87% yield. This first crystallized when its solution in petroleum ether was scratched and subsequently separated in heavy prisms, m. p. 97.5–99°. The analytical sample was dried *in vacuo* at 56°.

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.14; H, 9.02. Found: C, 66.89; H, 9.09.

When the 198° acid (200 mg.) was esterified in the usual manner with diazomethane it gave an oil which soon crystallized. The pure **dimethyl ester** (94% yield) separated from dilute alcohol in prismatic plates, m. p. 43–44.5°. The same dimethyl ester was obtained by treating the monomethyl ester with diazomethane (m. p. and mixed m. p. 42–44°).

Anal. Calcd. for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 68.13; H, 9.30.

Hydrolysis both of the monomethyl ester, m. p. 98° and of the dimethyl ester, m. p. 44°, with hydrochloric and acetic acids, in the manner already described for isomeric compounds, yielded the parent *cis-anti-cis* acid, m. p. and mixed m. p. 196–198°.

206° Acid (*cis-anti-trans*)

This was prepared by a similar method to that used for the *cis-trans* acid of the *syn*-series, namely, by the half-inversion and hydrolysis of the acid-ester of the *cis-cis*-acid. 25.0 mg. of the monomethyl ester of *cis-anti-cis* perhydrodiphenate (m. p. 99°) was refluxed for 150 hours with 500 mg. of potassium hydroxide dissolved in 2.5 cc. of methanol. The product was acidified and evaporated to dryness. The residue was diluted with water and extracted with ether. Removal of the ether left a solid which was crystallized from dilute acetic acid, yield 14.2 mg., 60%, irregular prisms, m. p. 200–204°. Two recrystallizations from acetic acid gave 7.3 mg. of prisms, m. p. 205.5–206.5°. The *cis-anti-trans* **acid** was also obtained in the form of needles. For analysis it was dried *in vacuo* at 110°.

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.13; H, 8.72. Found: C, 66.28, 66.26; H, 8.87, 8.94.

The **anhydride** was prepared in the usual way, by refluxing the acid (80 mg.) for two and one-half hours with 2 cc. of acetic anhydride. It separated from ligroin in heavy prisms, m. p. 91.5–93° (yield, 53.7 mg.). A mixture with the *cis-anti-cis* anhydride (m. p. 99–100°) melted between 70 and 87°. For analysis it was dried *in vacuo* at 56°.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.52. Found: C, 71.16; H, 8.53.

The anhydride dissolved slowly in boiling 10% aqueous sodium hydroxide. Acidification of the solution regenerated the *cis-anti-trans* acid, m. p. and mixed m. p. 205.5–206.5°.

Acid, m. p. 247° (*trans-anti-trans*)

The racemic form of this acid has been described by Linstead and Walpole[2] and by Vocke.[5] It had been prepared by alkaline hydrolysis of a perhydro-ester obtained by hydrogenation of diphenic ester over Raney nickel, and also by the oxidation of a 9-keto-perhydrophenanthrene.[2] It has now been observed that the pure acid melts at 246–248° after a preliminary sintering at 237°. The following preparative method involves a double inversion and hydrolysis.

Dimethyl *cis-anti-cis*-perhydrodiphenate (50 mg., m. p. 42–44°) was refluxed for four days with a solution of 400 mg. of potassium hydroxide in 2 cc. of commercial methanol. The product was partly neutralized and evaporated to dryness. The solid was then shaken with dilute hydrochloric acid and ether. The ether layer was separated, washed, dried and evaporated to dryness. The residue was crystallized from dilute acetic acid. The first crop

was a partially inverted acid (24.6 mg., m. p. 192–234°). The mother liquor yielded 11.3 mg. of beautiful prismatic needles. This acid melted at 237–240° alone and in admixture with the authentic *trans-anti-trans* acid softened at 237° and finally melted at 246–248°.

The *dimethyl ester* of the *trans-anti-trans* acid was prepared by means of diazomethane in the usual way in 89% yield. It formed prisms, m. p. 84.5–86°.

Anal. Calcd. for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 67.85; H, 9.19.

Summary

All the six optically inactive forms of perhydrodiphenic acid, which are theoretically possible, have been prepared.

One of these, m. p. 289°, is the main product of the catalytic hydrogenation of diphenic acid over platinum, and its derivatives are similarly formed from the corresponding derivatives of diphenic acid. The monomethyl ester of the 289° acid is capable of half-inversion to an isomeric acid of m. p. 200°, or its derivatives. The dimethyl ester of the 289° acid is capable of double inversion to an isomeric acid of m. p. 223°, or its derivatives. The acid of m. p. 200° has two monomethyl esters. One of these can be inverted and hydrolyzed to the 223° acid. These three acids form the *syn*-stereoisomeric series. The 200° acid is intermediate in configuration between the 289 and 223° acids.

The catalytic hydrogenation of diphenic acid gives as by-products the 200° acid and a fourth isomer of m. p. 198°. The 198° acid can be converted by half-inversion into the fifth isomer of m. p. 206°, and by double inversion into the sixth isomer of m. p. 247°. The 198, 206 and 247° acids thus represent the second (*anti*-) stereoisomeric series, the 206° acid being intermediate in configuration between the other two.

The formation of esters by diazomethane or by the Fischer–Speier procedure, the formation of anhydrides and the acid hydrolysis of esters proceed normally. The hydrolysis of esters with alcoholic alkali proceeds with inversion.

The results are correlated with previous investigations in the field. It is shown that the tricyclic ketones of Marvel cannot belong to the hydrophenanthrene series.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 30, 1942

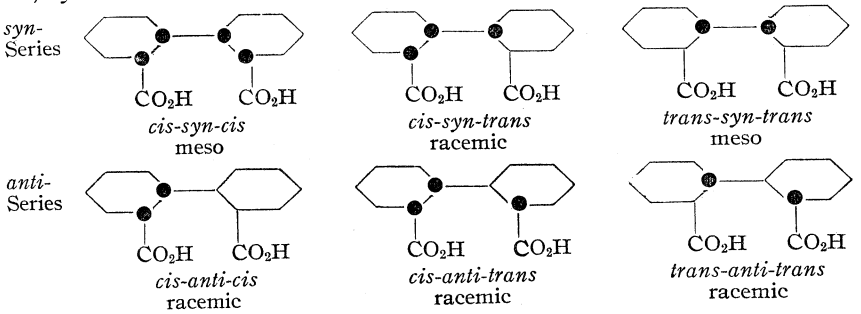
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Stereochemistry of Catalytic Hydrogenation. III. Optically Active Perhydrodiphenic Acids. A Proof of the Configuration of the Backbone

BY R. P. LINSTEAD AND W. E. DOERING

It has been shown in the preceding paper that the six perhydrodiphenic acids can be divided into two series of three members each. It has been found possible to interconvert the members within each series but not (as yet) to pass from one group to the other. These two series have the two possible backbone configurations, *syn*- and *anti*-. In order to assign the correct configuration to each of the six isomers, three questions must be answered: (1) Which series is *syn*- and which *anti*-? (2) In each series which member is the intermediate with the unlike (*cis-trans*) arrangement of the carboxyl groups? (3) In the terminal or symmetrical members of each series, which has the two *cis*- arrangements and which the two *trans*-? The first two of these questions are answered below. The third question is answered in Part V.

(1) **Backbone Configuration.**—As was pointed out by Linstead and Walpole,[1] of the six isomeric acids, four are capable of existence in optically active forms and two are internally compensated. This is shown below



The two symmetrical molecules are both in the *syn*-series. Two propositions therefore follow;

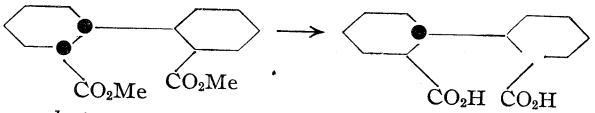
(1) Linstead and Walpole, *J. Chem. Soc.*, 850 (1939).

(1) That series which can be shown to contain *more than one* member capable of existing in optically active forms must have the *anti*-configuration of the backbone. (2) That series in which one (or more) member can be proved to have a meso configuration must be the *syn*-.

By both these tests it is proved below that the 289–200–223° acid series is *syn*-, and the 198–206–247° acid series is *anti*-.

The 247° (*trans-anti-trans*) acid was the first perhydrodiphenic acid to be resolved. The experimental work was carried out in 1939 by Dr. F. H. Slinger of the University of Sheffield, England. The resolution was effected by means of ephedrine. The *d*-acid[2] melted at 258° and had $[\alpha]_D$ +77.5°.

The 198° acid was resolved by means of cinchonidine into its enantiomorphs, which melted at 240° and had $[\alpha]_D$ ±44°. The *d*-enantiomorph was converted into the dimethyl ester by means of diazomethane. The ester had m. p. 27°, $[\alpha]_D$ +69°. When it was hydrolyzed by alcoholic potash it underwent a double inversion without racemization:



dextro-c.a.c. ester — *levo-t.a.t.* acid

The product was a levorotatory acid, m. p. 258°, $[\alpha]_D$ −79°. This was shown to be the enantiomorph corresponding to the *d*-acid obtained by the direct resolution of the 247° acid. A mixture of the two yielded the racemic *trans-anti-trans* acid, m. p. 247°.

This provides a refined confirmation of the corresponding experiment with the inactive materials, described in the previous paper.[3] The absence of racemization proves conclusively that the backbone carbon atoms are not involved in the reaction.

Attempts to resolve both the 289° and the 223° acids were fruitless. However, this does not prove the symmetry of their molecules, and to do this conclusively we made use of the principle used by Stoermer and Steinbeck[4] to prove the symmetry of the molecule of *cis*-hexahydrophthalic acid. According to this, an element of dissymmetry is first introduced by modifying one of the carboxyl groups, the compound is then resolved and the modifying group is removed by some mild reaction. If the resulting compound is inactive, then its molecule must be symmetrical.

The 289° acid was accordingly converted into its monomethyl ester. This was resolved by means of cinchonidine into two enantiomorphs of m. p. 134° and $[\alpha]_D$ ±10°. When the *l*-acid ester was hydrolyzed by acetic and hydrochloric acids it yielded the *inactive* parent acid, m. p. 289°. Even stronger evidence was provided by the fact that the *l*-acid ester on treatment with diazomethane yielded the *inactive* dimethyl ester, m. p. 73°, of the same acid. It will be recalled that the active form of the *cis-anti-cis* (198°) acid yielded the active ester on treatment with diazomethane. There is therefore nothing in the experimental conditions to cause racemization providing the molecule of the acid is unsymmetrical. These results prove that the 289° acid has a symmetrical structure. Hence the series to which it belongs has a *syn*-arrangement of the backbone.

We have also attempted to deduce the configuration of the backbone from a study of the formation of pyroketones from the acids. This work, which is still incomplete, will be the subject of a future communication.

(2) **Intermediate** (*cis-trans*) **Acids.**—In the preceding paper[3] it was shown by inversion experiments that the 200° acid was intermediate in configuration between the 289 and 223° acids. If this is so, it must be the *cis-syn-trans* acid, and be the only member of the *syn*-series capable of exhibiting optical activity. The following experiments confirm this view. The *l*-monomethyl ester of the 289° acid was inverted and hydrolyzed by treatment with sodium methoxide followed by the addition of a little water. This yielded a dextrorotatory acid, m. p. 173°, $[\alpha]_D$ +75°. A similar series of reactions performed with the *d*-monomethyl ester of the 289° acid gave the *levo*-enantiomorph, m. p. 173°, $[\alpha]_D$ −75°. A mixture of these acids gave the racemic acid of m. p. 200°, identical with that described in the preceding paper. This acid is thus conclusively proved to be *cis-syn-trans*-perhydrodiphenic acid. The existence of two acid esters[3] is in harmony with this conclusion.

We have not as yet had sufficient material to perform a similar partial asymmetric synthesis in the *anti*-series. As, however, the 206° acid has

(2) The prefixes *d*- and *l*- in this paper refer solely to the observed rotations and do not imply any relationships in configuration.

(3) Linstead and Doering, THIS JOURNAL, **64**, 1991 (1942).

(4) Stoermer and Steinbeck, *Ber.*, **65**, 413 (1932).

been shown to stand in precisely the same relation to the other *anti* acids as does the 200° acid in the *syn*-series, there can be no doubt that it has the *cis-anti-trans* configuration.

J. C. Speakman[5] has recently determined the first and second dissociation constants of two of the perhydrodiphenic acids (m. p.'s 222 and 247°), and has explored the possibility of estimating the inter-carboxyl distances from their ΔpK values, by the Bjerrum–Ingold method. This method has sometimes given significant results for cyclic dicarboxylic acids—a recent example is provided by Speakman's measurement of the *cis*- and *trans*-forms of tetralin 2,3-dicarboxylic acid.[5] However, each perhydrodiphenic acid has so many configurational possibilities that no safe deduction can be made from the results. It is nevertheless interesting that the 247° acid has a ΔpK of 1.1 and therefore behaves very like adipic acid, whereas the 222° acid has the high ΔpK of 1.7, which, from the usual calculation, would indicate that the mean intercarboxyl distance is unusually small.

The properties of the various forms of the acids are summarized in Table I.

TABLE I

OPTICALLY ISOMERIC PERHYDRODIPHENIC ACIDS

Configuration	dextro Form	levo Form	Inactive form, m. p., °C.
cis-syn-cis	Not possible		288–289 (meso)
cis-syn-trans	m. p. 170–174°, [α] +75°	m. p. 171–174°, [α] −75°	199–200 (rac.)
trans-syn-trans	Not possible		222–223 (meso)
cis-anti-cis	m. p. 238–240°, [α] +43°	m. p. 238–240°, [α] −45°	198–199 (rac.)
cis-anti-trans	Not yet prepared		206–207 (rac.)
trans-anti-trans	m. p. 257–259°, [α] +77.5°	m. p. 257–258.5°, [α] −79°	246–247 (rac.)

Experimental Part[6]

syn-Series

cis-syn-cis **Acid (289°).**—The cinchonidine, brucine, quinine, ephedrine and ψ-ephedrine salts were also crystalline but no resolution was observed. (Experiments by Dr. F. H. Slinger.)

The monomethyl ester,[7] m. p. 130° (3.80 g.), and 4.17 g. of cinchonidine were dissolved in 160 cc. of methanol and the solution diluted with 100 cc. of distilled water at the boiling point. On cooling the solution deposited long fine needles, which were filtered and washed with 50 cc. of 60% aqueous methanol. The dry salt weighed 3.55 g. (45% of the theoretical yield from both enantiomorphs) and melted at 186–188°. The acid ester was regenerated from it by means of 5% hydrochloric acid and crystallized from ligroin (b. p. 70–90°). The heavy prismatic needles so obtained weighed 1.35 g. (36%) and had m. p. 134° and $[\alpha]^{27}D$ −9.1°. This *levo* **acid ester** after one more crystallization from ligroin had m. p. 133.5–134.5°, $[\alpha]^{27}D$ −10.7 ± 0.3° (1% solution in alcohol containing 5% water). Subsequent recrystallization failed to change the specific rotation.

The aqueous alcoholic mother liquor from the original precipitate, containing 190 cc. of methanol and 120 cc. of water, was diluted at the b. p. with 70 cc. of water. The solution then deposited 2.64 g. (33%) of heavy needles, m. p. 172–174°. From this there was regenerated 1.34 g. of *d*-acid ester, m. p. 134°. The alcoholic mother liquor when boiled free from alcohol yielded a further 230 mg. of the *d*-acid ester and 270 mg. of the original racemate. The total *dextro* **acid ester** was crystallized to constant rotation from ligroin. It had m. p. 133.5–134.5°, $[\alpha]^{27}D$ +10.3 ± 0.3° (1% solution in 95% alcohol). The *d*-acid ester was dried at 80° *in vacuo* and analyzed.

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.14; H, 9.02. Found: C, 67.27, 67.21; H, 9.09, 9.03.

Esterification of the *levo*-monomethyl ester (160 mg.) with diazomethane in the usual manner gave 102 mg. of long prismatic needles of the meso dimethyl ester, m. p. and mixed m. p. 73–74°. A solution in alcohol showed no activity.

The *levo*-monomethyl ester (450 mg.) was boiled with 3 cc. of concentrated hydrochloric acid and 10 cc. of glacial acetic acid for twenty hours. The acid product was isolated by dilution and freed from starting material (160 mg.) by extraction with hot ligroin. The insoluble residue (220 mg.) on crystallization from 15 cc. of 95% alcohol yielded 170 mg. of inactive *cis-syn-cis* acid, m. p. 286–288.5°. The m. p. was not depressed by admixture with the authentic inactive acid and the solution showed no optical activity.

cis-syn-trans **Acid (200°).**—The *l*-acid ester of the *cis-syn-cis* acid (1.11 g., m. p. 134°, $[\alpha]^{27}D$ −10.5°) was refluxed with sodium methoxide from 2 g. of sodium and 20 cc. of absolute methanol. After forty-eight, seventy-two and ninety-six hours 1 cc. of water was added. After five days the solvent was evaporated, and the residue acidified and extracted with ether. Evaporation of the ether left an oil which solidified when boiled with 40 cc. of ligroin. Recrystallization of the powder (980 mg.) from acetic acid failed to remove a small amount of the *cis-syn-cis* acid which was present. The impure acid was accordingly extracted with several small quantities of boiling benzene. This removed the *cis-syn-trans* acid and left the *cis-syn-cis*. After several further crystallizations from dilute acetic acid and from alcohol the pure *dextro-cis-syn-trans* **acid** crystallized in needles, m. p. 170–174°, $[\alpha]^{29}D$ +75° (1% in alcohol).

A similar inversion and hydrolysis was carried out on the *dextro*-acid ester of the *cis-syn-cis* acid (780 mg.). The crude acid product weighed 760 mg. Extraction with hot benzene removed 530 mg. of *levo-cis-syn-trans* **acid** which was crystallized to constant rotation, m. p. 171–174°, $[\alpha]^{28}D$ −75° (1% in 95% alcohol).

trans-syn-trans **Acid (223°).**—The cinchonidine, quinine, ephedrine, ψ-ephedrine and strychnine salts could not be obtained crystalline. The brucine salt crystallized well from alcohol but showed no sign of resolution (experiment by Dr. Slinger).

(5) J. C. Speakman, *J. Chem. Soc.*, 490 (1941).

(6) All melting points are corrected.

(7) Linstead and Doering, THIS JOURNAL, **64**, 1991 (1942).

The half methyl ester of this acid should be capable of resolution but we have been unable as yet to find a suitable salt. The cinchonidine, cinchonine, ephedrine, brucine, quinine and strychnine salts could not be obtained crystalline (experiments by Miss E. J. Cook, Radcliffe College).

anti-Series

cis-anti-cis **Acid (198°).**—To a solution of 454.1 mg. of the acid and 1.051 g. of cinchonidine in 10 cc. of methanol there was added at the boiling point, 2.5 cc. of water. The solution deposited 1.03 g. of light needles, m. p. 194–200°, on cooling (A). The mother liquor was evaporated to dryness, the residue treated with acid and extracted with ether. The residue from the ether was crystallized from acetic acid. This yielded 100 mg. of the *dextro*-**acid** in heavy prisms, m. p. 235–239°. Recrystallization to constant rotation yielded material with m. p. 238.5–240.5°, $[\alpha]^{27}D$ +43 ± 1° (1% in 95% alcohol).

The salt (A) was recrystallized from 15 cc. of methanol and 2 cc. of water. This yielded 670 mg. of well-formed needles, m. p. 204.5–205.5°. Regeneration of the acid in the usual way gave the *levo*-**acid** which after two crystallizations from acetic acid formed prisms, m. p. 239–241° (132.8 mg.). This material was submitted to a second treatment with cinchonidine but its properties were unaltered (m. p. 238.5–240.5°). The specific rotation $[\alpha]^{26}D$ of a 1% solution in 95% alcohol was −45 ± 1°.

The *dextro-cis-anti-cis* **acid** was esterified in the usual manner with diazomethane, yield 75.1 mg. from 84.5 mg. The *d*-dimethyl ester crystallizes from light petroleum at −70° in large prisms, m. p. 26–28°. $[\alpha]^{25}D$ +69 ± 1° (1% in 95% alcohol).

trans-anti-trans **Acid (247°).**—The above *d*-dimethyl ester (140 mg.) of the *cis-anti-cis* acid was refluxed for 112 hours with 0.5 g. of potassium hydroxide in 2 cc. of methanol. A little water was added from time to time. The acidic product was isolated by means of ether in the usual way. After two crystallizations from dilute acetic acid, the *levo-trans-anti-trans* **acid** was isolated with m. p. 257–258.5°, $[\alpha]^{26}D$ −79.5 ± 5° (1% in 95% alcohol).

Resolution of the 247° Acid (Experiments by Dr. Slinger).—The acid (3.0 g.) and ephedrine (1.98 g.) were dissolved in 60 cc. of alcohol, 90 cc. of water was added and the mixture heated to effect solution. Slow cooling precipitated needles of a salt from which 950 mg. of a crude dextrorotatory acid was regenerated. This material was submitted to a second resolution with ephedrine. The product melted at 257.5–259° and had $[\alpha]^{20}D$ +77.5° (1% in alcohol). A further resolution failed to alter the m. p. or specific rotation.

An equal mixture of the *d*- and *l*-acids (4 mg. of each) was dissolved in dilute acetic acid. The solution deposited needles, m. p. 237–239°, of the *dl-trans-anti-trans* acid. After resolidifying, these melted at 245–247° and did not depress a sample of authentic *dl*-acid, m. p. 245–247°.

Summary

The perhydrodiphenic acid of m. p. 289° gives an acid methyl ester which can be resolved into *d*- and *l*-forms. Conversion of these into the acid or the dimethyl ester gives inactive material. The acid therefore has a symmetrical molecule and must belong to the *syn*-series.

The perhydrodiphenic acid of m. p. 198° (*cis-anti-cis*) can be resolved by means of cinchonidine. The dimethyl ester of the active ester on hydrolysis and double inversion with alcoholic alkali gives the *levo*-enantiomorph of the *trans-anti-trans* acid (m. p. 247°). The latter acid has been resolved to give the other enantiomorph. As two acids in this series can be resolved, it must be the *anti*-series.

The three acids of m. p.'s 289, 200 and 223°, therefore, constitute the *syn*-series and the acids of m. p.'s 198, 206 and 247°, the *anti*-series.

The acids of m. p.'s 200 and 206° are proved to be *cis-syn-trans* and *cis-anti-trans*, respectively.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 30, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Stereochemistry of Catalytic Hydrogenation. IV. Hexahydrodiphenic Acids

BY R. P. LINSTEAD AND SELBY B. DAVIS

Vocke[1] reported that the hydrogenation of diphenic ester over Raney nickel yielded a mixture of perhydro- and hexahydro-diphenic esters. From the hydrolysis product of this he isolated two hexahydrodiphenic acids of m. p. 242 and 220°. It was shown that the 242° acid could be converted into the 220° isomer, and the acids were assigned the structures of *cis*- and *trans*- modifications of the hexahydrodiphenic acid with one intact aromatic ring.

(1) Vocke, *Ann.*, **508**, 1 (1934).

We have investigated the partial hydrogenation of diphenic acid in acetic acid solution over a platinum catalyst. If hydrogenation is stopped arbitrarily at the half-way stage, there is obtained a mixture consisting substantially of *cis-syn-cis*-perhydrodiphenic acid, m. p. 289°,[2] a hexahydrodiphenic acid and unchanged diphenic acid. The hexahydro acid melts at 242° and has other properties which show its identity with Vocke's acid of similar m. p. The presence of an

(2) Linstead and Doering, THIS JOURNAL, **64**, 1991 (1942).

aromatic ring is shown by the absence of reactivity with potassium permanganate and by the formation of a mono-nitro derivative, m. p. 219°. The latter can be reduced to an amine which can be diazotized and coupled with β-naphthol.

The proportions of the three compounds in the hydrogenation product are approximately: *c.s.c.*-perhydro acid, 25%; hexahydro acid, 25%; unchanged diphenic acid, 40%. The indications are therefore that the half hydrogenated compound is hydrogenated rather more readily than the original diphenic acid. When the hexahydrodiphenic acid, m. p. 242°, is further hydrogenated over platinum it yields *cis-syn-cis*-perhydrodiphenic acid, m. p. 289°. The yield of the pure *cis-syn-cis* acid is 77% and no isomers have as yet been isolated. Both the first and the second stages of the hydrogenation of diphenic acid under these conditions thus follow a substantially homogeneous steric course.

It is shown in the next paper that the 242° acid has the *cis*-configuration.

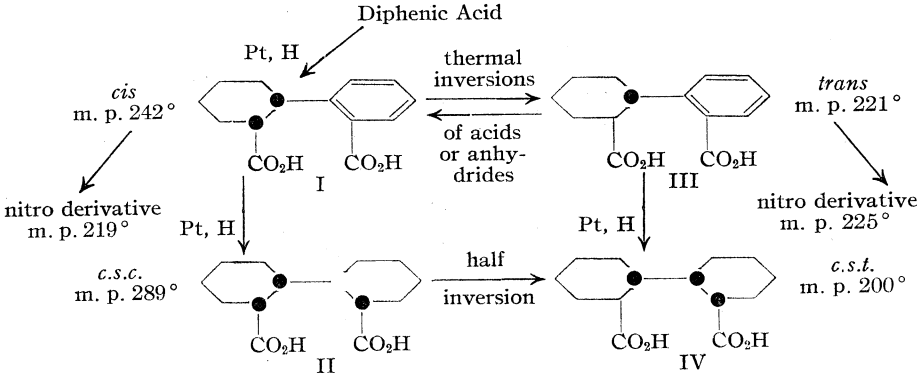
Treatment of the *cis*-hexahydro acid with acetic anhydride yielded a liquid anhydride from which the parent acid could be regenerated. If the *cis*-acid was kept at its melting point for an hour, it was converted into an isomeric acid which melts at 221°. The conversion is reversible with an equilibrium well on the side of the new acid. Catalytic hydrogenation of the new acid over platinum gave rise to *cis-syn-trans*-perhydrodiphenic acid (IV), m. p. 200°, identical with the material described in Part II.[2] The orientation of this perhydro acid has been completely proved.[3] The yield of the perhydro acid was at least 84% and a careful search failed to show the presence of any of the *cis-anti-trans*-isomer. A small amount of a decahydrodiphenic acid, m. p. 212°, was, however, isolated. It follows from these results that the new hexahydro acid, m. p. 221°, is the *trans*-isomer (III) of the 242° acid.

The presence of an intact aromatic ring in the *trans*-acid was shown by its nitration to a mono-nitro derivative, not identical with that obtained from the *cis*-isomer.

When the *cis*-hexahydro acid was inverted by heat and the crude *trans*-acid treated with acetic anhydride, there was formed the beautifully crystalline *trans*-anhydride, which on hydrolysis yielded the parent acid, m. p. 221°. There can be no doubt that our *trans*-acid is identical with Vocke's second hexahydro acid of m. p. 220° which he obtained by heating the 242° acid to about 300°.[1] He reported the anhydride as melting at 120°, whereas the m. p. of our material could not be raised above 116°. When the *trans*-anhydride was heated for some time, and the product hydrolyzed, a mixture of *cis*- and *trans*-hexahydro acids was obtained, which contained about 70% of the *trans*-isomer.

An important general result from this work is that in the further hydrogenation of our hexahydro acids over platinum at room temperature, the integrity of the configuration already established is preserved, and the further hydrogenation goes almost entirely *cis*- and *syn*-. This presents an instructive contrast to Vocke's observation on the perhydrogenation of the same acids over nickel at high temperatures. He observed the formation of two perhydro acids (*trans-anti-trans* and probably *trans-syn-trans*) from *each* of the hexahydro acids. Clearly, the use of nickel at high temperatures may lead to inversions of configuration.

The results are summarized in the scheme



Experimental[4]

cis-**Hexahydrodiphenic Acid.**—A solution of 10 g. of diphenic acid in 200 cc. of glacial acetic acid was hydrogenated in a Parr apparatus by means of 1 g. of Adams catalyst. After six and one-half hours, hydrogen equivalent to 3.0 moles had been taken up. The solution was then

(3) Linstead and Doering, THIS JOURNAL, **64**, 2003 (1942).

(4) All melting points corrected. Analyses by Miss Eleanor Werble.

filtered. Extraction of the catalyst and insoluble material with alkali and reprecipitation with hydrochloric acid yielded 1.24 g. of *cis-syn-cis*-perhydrodiphenic acid, m. p. 275–280°, identified by mixed m. p. The acetic acid filtrate was freed from solvent by vacuum evaporation and the solid residue dissolved in 100 cc. of 10% aqueous sodium carbonate. A second run on the same amount of material required eight and one-half hours for the absorption of 3.0 moles of hydrogen and yielded 1.48 g. of the *cis-syn-cis* acid, m. p. 278–286°. The filtrate was treated as above. The combined carbonate solution was then submitted to the process of fractional acidification with 10% hydrochloric acid which has been described in Part II.[2] The hydrochloric acid was added to the boiling solution to incipient cloudiness. No precipitate appeared on cooling. After this successive 10-cc. portions of 10% hydrochloric acid were added to the boiling solution, and the solution allowed to stand for twelve to twenty-four hours after each addition, with the following results:

Fraction	HCl added, cc.	Acid pptd., g.	M. p. (crude), °C.	Main component
1	10.0	2.08	204–262	*c.s.c.* perhydro
2	10.0	0.70	80–95	....
3	10.0	5.39	212–227	*cis*-hexahydro
4	10.0	3.30	199–214	Diphenic acid
5	10.0	3.98	211–216	Diphenic acid

The total amount of acid isolated at this stage, including the *cis-syn-cis* acid which separated from the solution originally, was 18.17 g. Evaporation of the final mother liquor gave no useful material.

Recrystallization of fraction 3 from acetic acid containing about 20% water at the boiling point, yielded 3.90 g. of practically pure *cis*-hexahydrodiphenic acid, m. p. 238–240°. Another crystallization gave the pure acid, m. p. 241–242° (bath preheated to 235°). The acid was identical with that obtained as a by-product in perhydrogenations (see Part II[2]). Fractions 4 and 5, after crystallization from acetic acid, yielded diphenic acid, m. p. and mixed m. p. 229–231°.

The subsequent preparations were done in a similar manner. In some cases the *cis*-hexahydro acid appeared in the second fraction. Completion of the precipitation of perhydro acid was marked by a drop in the *p*H of the solution from 8 to 5. In one run a very small amount of material identified as the *trans*-hexahydro acid was obtained after the diphenic acid had been precipitated. The average yield of crude material from 20 g. of diphenic acid was *cis-syn-cis*-perhydrodiphenic acid, 4.8 g.; *cis*-hexahydrodiphenic acid, 5.0 g.; recovered diphenic acid, 7.7 g.

***cis*-Anhydride.**—The *cis*-acid (400 mg.) was refluxed for five hours with 4 cc. of acetic anhydride. The anhydride failed to solidify on standing *in vacuo* at 3° or on attempted crystallization from hexane. The oily anhydride on boiling with dilute hydrochloric acid regenerated the *cis*-acid, m. p. and mixed m. p. 238–240°.

Mono-nitro Derivative.—The *cis*-acid (100 mg.) was stirred into a mixture of 1 cc. of concentrated sulfuric acid with 1 cc. of concentrated nitric acid. The solution was heated to 60°, allowed to stand for thirty minutes, and then poured into 10 cc. of ice and water to give 104 mg. of crude nitro compound, m. p. 184–190°. From 90 mg. there was obtained 56 mg. of irregular prisms, m. p. 201–202°, after two recrystallizations from acetone–benzene. Recrystallization from water, under such conditions that the substance separated as an oil and subsequently crystallized, gave identical material. By slow crystallization of a dilute aqueous solution the nitro compound is obtained in a stable higher melting form, needles, m. p. 218–219°. The mixed m. p. with the low-melting material was 218–219°.

Anal. Calcd. for $C_{14}H_{15}O_6N$: C, 57.34; H, 5.16. Found: C, 57.53; H, 5.02.

The high-melting form of the nitro derivative (5 mg.) was dissolved in 15 cc. of distilled water and shaken with hydrogen in the presence of 5 mg. of Adams catalyst. The theoretical amount of hydrogen for reduction to the amine was absorbed in fifteen minutes. Removal of the catalyst and solvent left the product as a clear, glassy film. On diazotization and coupling with alkaline β-naphthol in the usual manner, an immediate orange color was produced and a brown precipitate separated on standing.

Hydrogenation.—The *cis*-acid (2 g.) was hydrogenated in 200 cc. of acetic acid over 750 mg. of Adams catalyst. The theoretical quantity (3 moles) of hydrogen was taken up in thirty-five minutes and no further absorption was observed in another half hour. This is a remarkably quick hydrogenation of an aromatic ring. The reaction product was worked up in the usual manner. The precipitate yielded 1.32 g. (64%) of pure *cis-syn-cis*-perhydrodiphenic acid, m. p. 286–288°. Evaporation of the mother liquor yielded a solid residue, melting above 245°. Fractional crystallization of the latter yielded two successive crops of the *cis-syn-cis* acid and brought the total yield of this up to 77%. The small residue was not further examined.

***trans*-Hexahydrodiphenic Acid.**—The *cis*-acid (4 g.) was heated at 242 ± 3° for one hour. The residue set to a pale yellow glass. Crystallization from glacial acetic acid yielded 2.48 g. of nearly pure *trans*-acid, m. p. 215–218°. This substance was more easily purified through the anhydride. The *cis*-acid (1.5 g.) was heated as before and the residue was refluxed with 5 cc. of acetic anhydride for four hours. The reagent was removed and the sirup stirred with a few cc. of light petroleum in which it was practically insoluble. The solid *trans*-anhydride (1.2 g.) was so obtained. The yield corresponds with one of 87% of *trans*-acid in the thermal inversion. After three crystallizations from benzene the beautifully crystalline anhydride of the *trans*-acid was obtained, m. p. 115–116°. The m. p. could not be raised by further crystallization (compare Vocke[1]).

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.28; H, 6.19.

A small portion of the anhydride was converted into the corresponding acid by means of alkali. The *trans*-acid so obtained melted at 220–221.5° and failed to depress the m. p. (218–220°) of that isolated by crystallization. The mixed m. p. with the *cis*-isomer was 197–210°. This is a good method for the final purification of the *trans*-acid, for repeated crystallization of the acid, which had not been taken through the anhydride, failed to raise the m. p. above 220°.

Anal.[5] Calcd. for $C_{14}H_{16}O_4$: C, 67.72; H, 6.50. Found: C, 67.89; H, 6.65.

(5) Analysis by W. E. Doering.

Mono-nitro Derivative.—The *trans*-acid (96 mg.) was nitrated in the same manner as the *cis*- (*vide supra*) to obtain 116 mg. of the crude product, m. p. 212–217°. Two recrystallizations from acetone–benzene gave 65 mg. of irregular prisms, m. p. 218–219°. Further recrystallization from water, under such conditions that the substance separated as an oil and subsequently crystallized, gave material of similar appearance and m. p. Crystallization of 40 mg. from water, with slow cooling, gave 32 mg. of needles, m. p. 224–225°. The mixed m. p. with the low-melting material was 224–225°. The mixed m. p.'s of both forms with either form of the nitro derivative from the *cis*-acid showed depressions to about 185°.

Anal. Calcd. for $C_{14}H_{15}O_6N$: C, 57.34; H, 5.16. Found: C, 57.43; H, 5.12.

Hydrogenation.—The *trans*-acid (2 g.) in 200 cc. of acetic acid was hydrogenated over 550 mg. of Adams catalyst. The theoretical uptake of hydrogen (3 moles) occurred in one hundred minutes, after which there was no appreciable reaction. No precipitate separated. The catalyst was filtered and the solvent removed. The granular residue was crystallized from acetic acid, a seed of *cis-syn-trans*-perhydrodiphenic acid being introduced. The first crop, 1.60 g. (78%), melted at 190–194° alone, at 192–197° in admixture with *cis-syn-trans*-perhydrodiphenic acid (m. p. 198–200°) and at 192–196° after a further crystallization. As the m. p. of the *cis-syn-trans* acid is sensitive to traces of impurities, this material may be taken to be the nearly pure isomer. The mother liquor from this acid was submitted to an exhaustive fractional crystallization. It yielded three products: (a) more of the *cis-syn-trans* perhydro acid, bringing the total yield up to 84%; (b) about 10 mg. of an unsaturated acid, m. p. 210–211.5°, identical with material already isolated by Mr. Doering; (c) about 3 mg. of what was apparently another unsaturated acid. This formed soft needles of m. p. 261–264°, depressed the m. p. of the *cis-syn-cis* perhydro acid and readily reduced 0.5% potassium permanganate in aqueous sodium bicarbonate solution. (Under the same conditions the hexahydro- and perhydrodiphenic acids require from eight to twenty-four hours for a discharge of the color of one drop of 0.5% permanganate.) During this fractional crystallization, the solution was frequently seeded with *cis-anti-trans* perhydrodiphenic acid (m. p. 206°[2]), but none of this substance separated, and it can safely be concluded that it is either wholly or almost completely absent.

The pure *trans*-anhydride (150 mg.) was heated for one hour at 243 ± 3°. A little carbon dioxide was evolved, indicating the formation of some pyroketone. The acidic portion of the product was isolated by means of alkali and was crystallized from acetic acid. Seeding with the *cis*-hexahydro acid yielded three crops of this material (total, 20 mg.) and further seeding gave no more of it. The solution was accordingly seeded with the *trans*-hexahydro acid, which yielded five crops of *trans*-acid, totalling 45 mg. The acids were identified by m. p. and mixed m. p.

Summary

Half-hydrogenation of diphenic acid over platinum yields *cis*-hexahydrodiphenic acid. Thermal inversion of this acid yields the *trans*-isomer. Both the acids and their anhydrides yield mixtures rich in the *trans*-isomer when heated. The two acids yield distinct mono-nitro derivatives.

Further catalytic hydrogenation of the *cis*-hexahydro acid yields *cis-syn-cis*-perhydrodiphenic acid, and hydrogenation of the *trans*-hexahydro acid yields *cis-syn-trans*-perhydrodiphenic acid. The integrity of the configuration already established is therefore preserved, and further hydrogenation goes *cis*- and *syn*-.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 30, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Stereochemistry of Catalytic Hydrogenation. V. The Assignment of *cis*- and *trans*-Configurations

BY R. P. LINSTEAD, SELBY B. DAVIS AND RICHARD R. WHETSTONE

The stereochemical problem connected with the perhydrodiphenic acids which is left unsolved in the preceding papers is the allocation of *cis*- and *trans*-configurations to the terminal acids.[1] It has been shown that the 289 and 223° acids between them constitute the *cis-syn-cis* and *trans-syn-trans* acids, and the 198 and 247° acids share the *cis-anti-cis* and *trans-anti-trans*-configurations. There are many indications that the 289° and the 198° acids are the *cis*-members of the two series. The work described in the present paper proves this to be true.

The 289° perhydro acid has two similar arrangements of the carboxyl groups with respect to the backbone. It is made by the hydrogenation of the hexahydro acid of m. p. 242° by a method not involving an inversion.[2] Hence the configuration of the 242° acid is repeated twice in the 289° acid.

We therefore examined the configuration of

(1) Linstead and Doering, THIS JOURNAL, **64**, 2003 (1942).

(2) Linstead and Davis, *ibid.*, **64**, 2006 (1942).

this hexahydro acid by oxidizing away the aromatic ring and leaving a cyclohexane derivative of known configuration. Treatment of the acid with a mixture of concentrated and fuming nitric acids gave only nitration in the aromatic ring and permanganate oxidation also yielded no useful products. Ozonization, however, gave the desired information.

The acid was treated in acetic acid solution with ozonized oxygen and subsequently with hydrogen peroxide. The acidic product was separated by means of the fractional acidification technique which has already been described.[3] This effected a simple separation of the starting material and another acid which after one crystallization melted at 185–188° and was nearly pure *cis*-hexahydrophthalic acid (I). It was identified by direct comparison of the free acid with authentic material and by conversion into the known *cis*-dianilide, m. p. 238°.[4b] The *cis*-configuration of the latter was confirmed by the fact that it readily yielded the phenylimide (II) when boiled with acetic acid. The dianilide of *trans*-hexahydrophthalic acid, which was separately made for comparison, melted at 317–318° and failed to yield a phenylimide under the same conditions.

The *cis*-configuration of this form of hexahydrophthalic acid is known with certainty.[4] In the present work *cis*-hexahydrophthalic acid was formed in a yield of 44% by a mild series of operations in which there is no possibility of an inversion. Moreover, it must be borne in mind that the *cis*- is the *unstable* configuration and that any inversion would tend to yield a *trans*-product.

This evidence conclusively proves that the acid of m. p. 242° is *cis*-hexahydrodiphenic acid (III). Hence the acid of m. p. 289° is *cis-syn-cis*-perhydrodiphenic acid (IV) and the double invert acid, m. p. 223°, has the *trans-syn-trans*-configuration. It follows that among the diphenic acids, catalytic hydrogenation over platinum yields *cis*-products which can be inverted by chemical means into the *trans*-isomers. The usual rule-of-thumb generalizations are therefore correct in this series.

It is shown in the following paper[5] that the 289° acid is related to a 9-ketoperhydrophenanthrene of m. p. 44° (V). This ketone is easily inverted by the action of heat or bases into an isomer of m. p. 57°, which yields *cis-syn-trans*-perhydrodiphenic acid on oxidation. There is a complete analogy with Hückel's related experiments with dicyclic compounds and the rearrangement of the ketone corresponds precisely with the conversion of *cis*-α-decalone to its *trans*-isomer.

The chemical inversions of the *syn*-keto-hydrophenanthrenes and of the *syn*-hydrodiphenic acids accordingly fall into line with those of related substances of simpler structure. We may therefore make the corresponding deductions in the *anti*-series with confidence, thus: (1) Among the *anti* compounds the perhydro acid of m. p. 198° is the direct hydrogenation product and yields the isomer of m. p. 247° by double inversion. Hence these substances are *cis-anti-cis* (VIII) and *trans-anti-trans* (IX), respectively.

(2) The 247° acid has been prepared[6] by the oxidation of a 9-keto-perhydrophenanthrene of m. p. 49° which was stable to heat and alkali.[7] Hence the ketone will have a *trans*-fusion of the rings next to the keto group. Hence the 247° acid contains at least one *trans*-carboxyl; but as it is a terminal acid, it must have two such arrangements and be the *trans-anti-trans*-isomer. The 49° ketone must have the same configuration (X) and this is supported by the physical properties of the related perhydrophenanthrene.[7]

We have obtained independent evidence supporting these configurations from the following experiments. The 49° ketone is made by the catalytic hydrogenation of an olefinic ketone, m. p. 89°, originally prepared by Rapson and Robinson.[8] (The method of preparation of the unsaturated ketone itself supports a *trans*-configuration for its one-ring fusion.) We find that ozonization of the unsaturated ketone gives a δ-keto acid, $C_{13}H_{20}O_3$, isolated as a crystalline oxime. This is assigned the formula XII. Its formation shows the correctness of the Δ^{10}-9-keto-dodecahydrophenanthrene structure (XI) assigned to the unsaturated ketone by Rapson and Robinson. On acetylation and subsequent pyrolysis by the general method of Thiele[9] the keto acid was converted into an unsaturated lactone. This was not obtained as a homogeneous substance but contained some of the isomer (XIII) with the double bond adjacent to the backbone.

(3) Linstead and Doering, THIS JOURNAL, **64**, 1991 (1942).

(4) (a) Werner and Conrad, *Ber.*, **32**, 3046 (1899); (b) Stoermer and Steinbeck, *ibid.*, **65**, 413 (1932).

(5) Linstead, Whetstone and Levine, THIS JOURNAL, **64**, 2014 (1942).

(6) Linstead and Walpole, *J. Chem. Soc.*, 850 (1939).

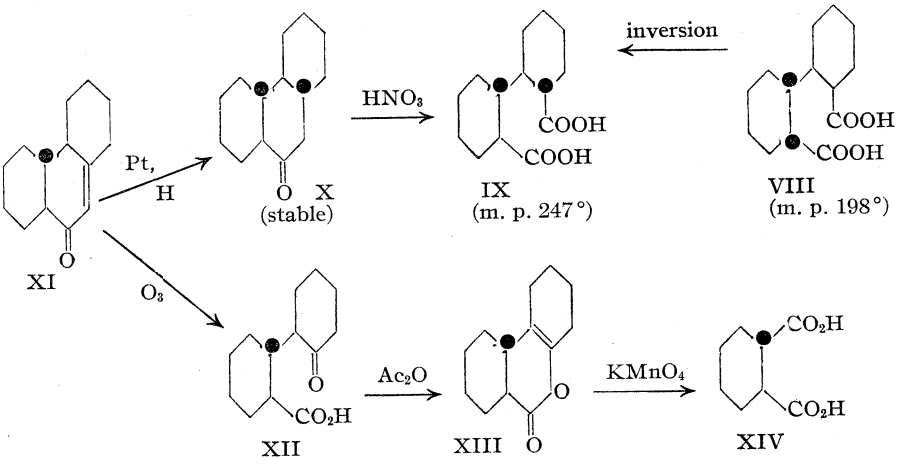
(7) Linstead and Walpole, *ibid.*, 842 (1939).

(8) Rapson and Robinson, *ibid.*, 1285 (1935).

(9) Thiele, Tischbein and Lossow, *Ann.*, **319**, 180 (1901).

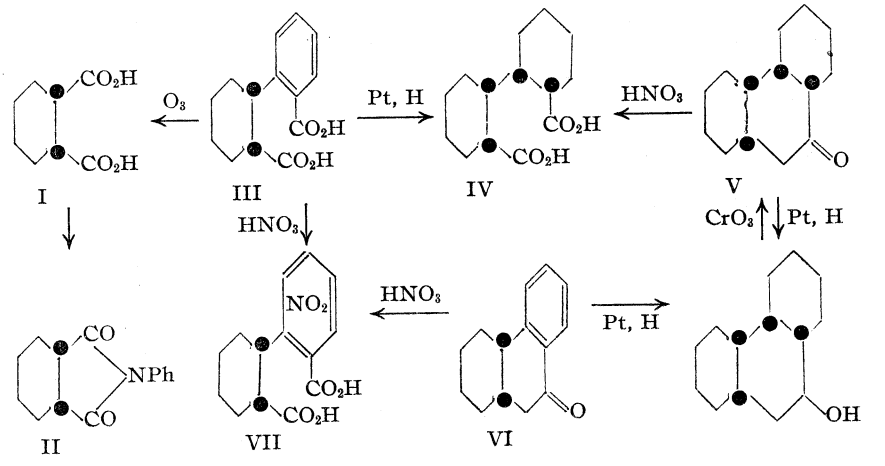
On oxidation with permanganate the lactone gave *trans*-hexahydrophthalic acid (XIV), in poor yield. Hence all the substances mentioned above have a *trans*-configuration. Some of the reactions used in this degradation were comparatively vigorous and the final product has the stable configuration. Hence, we do not regard this evidence as so unequivocal as that given above for the oxidation of *cis*-hexahydrodiphenic acid.

The most important configurational evidence in the *anti*-series is summarized in the following scheme



Finally, we have been able to establish two other stereochemical connections between the tricyclic compounds and the hydrodiphenic acids. It has already been pointed out that the 289 and 200° acids are related to the 44 and 57° perhydro ketones, respectively. In the next paper it is shown that the 44° ketone can be formed (through the corresponding perhydro alcohol) by the hydrogenation of a 9-keto-*as*-octahydrophenanthrene (VI). When the octahydro ketone was treated with nitric acid it yielded the mono-nitro derivative of *cis*-hexahydrodiphenic acid (VII). Hence it must have the *cis*-configuration. Its *trans*-isomer has been similarly oxidized and nitrated to the nitro- derivative of *trans*-hexahydrodiphenic acid. (A number of nitro-ketones are obtained as by-products in these oxidations. They are described in the experimental section.)

The stereochemical relationships between the tricyclic and dicyclic compounds are therefore firmly established by a number of independent links. The more important connections in the *syn*-series are indicated in the scheme



Experimental[10]

Ozonization of *cis*-Hexahydrodiphenic Acid.—The acid, m. p. 240–241°,[2] (1.00 g.) was dissolved in 20 cc. of warm glacial acetic acid and ozonized for four hours. The product was allowed to stand overnight with 50 cc. of 3% hydrogen peroxide and evaporated almost to dryness on the

(10) All melting points corrected. Analyses by Miss Eleanor Werble.

steam-bath in a current of air. The residue was then heated on the steam-bath for two hours with a further 25 cc. of 3% hydrogen peroxide and evaporated to dryness. The mainly crystalline residue was dissolved in 15 cc. of 10% aqueous sodium carbonate, a trace of insoluble material filtered off and the solution washed with ether. The alkaline solution was heated to boiling and concentrated hydrochloric acid added in drops to incipient crystallization. The subsequent fractional acidification by the method described in earlier papers[2,3] gave the following results

Fraction	Approx. vol. of concd. HCl, cc.	Weight, mg.	M. p., °C.	Identity
1	2.5	260	234–237	*cis*-Hexahydrodiphenic acid
2	0.5	240	237–239	
3	0.5	...	...	Trace of tar
4	0.5	9.1	174–181	*cis*-Hexahydrophthalic acid
5	1.0	82.2	177–184	
6	1.0	36.5	181–186	

A further 0.5 cc. of hydrochloric acid was added to the final mother liquor and the solution extracted with ether to give 0.11 g. of semi-crystalline residue.

Fractions 1 and 2 were identified as unchanged starting material by mixed m. p. Fractions 4, 5 and 6 in admixture with authentic *cis*-hexahydrophthalic acid (m. p. 191.5–192.5°) melted at about 185°. After one recrystallization from 80% acetic acid, nearly pure *cis*-hexahydrophthalic acid was obtained, m. p. 185–188°, mixed m. p. 186–189°. Recrystallization of the residue from the ether extract yielded 23 mg. of additional *cis*-hexahydrophthalic acid, m. p. 183–188°, mixed m. p. 185–189°.

The crystallized acid (53 mg.) was converted into the acid chloride by means of phosphorus pentachloride (130 mg.) in dry ether (3 cc.). After twenty minutes the solvent was removed and the residue evacuated at the water pump for half an hour. The residue was dissolved in 2 cc. of ether and treated with 120 mg. (2 mols) of aniline in 2 cc. of ether. The mixture was freed from solvent, the residue taken up in the minimum quantity of 95% alcohol (*ca.* 4 cc.), the solution filtered and allowed to cool. The dianilide of *cis*-hexahydrophthalic acid (43 mg.), so obtained, melted at 227–229° and after one crystallization from alcohol formed colorless needles, m. p. 237.5–238°.

Anal. Calcd. for $C_{20}H_{22}O_2N_2$: C, 74.50; H, 6.88. Found: C, 74.75; H, 6.70.

The dianilide was further identified by refluxing it for eighteen hours with 80% acetic acid which yielded the phenylimide (II), flat prisms from methanol, m. p. 131–132°. The m. p.'s of the dianilide and phenylimide prepared from authentic *cis*-hexahydrophthalic acid were the same and were not depressed by admixture with the above samples. For these substances Stoermer and Steinbeck[4b] give m. p.'s 234° (dianilide) and 132° (phenylimide).

Attempted oxidation of *cis*-hexahydrodiphenic acid with a mixture of fuming and concentrated nitric acids gave an acidic product, from which the only homogeneous substance which could be isolated was nitro-*cis*-hexahydrodiphenic acid, m. p. 219–220°. This was identical with the material described in Part IV.[2] Treatment of *cis*-hexahydrodiphenic acid with alkaline permanganate at 60–80°, left it largely unchanged and no useful products were isolated.

Oxidation of *trans*-Δ^{10}-9-Keto-dodecahydrophenanthrene (XI).—The unsaturated ketone was prepared from acetylcyclohexene by the method of Rapson and Robinson.[8] Preliminary experiments on the oxidation with nitric acid, permanganate, hypobromite and ozone indicated that the last-named reagent was the most suitable.

The ketone (8.9 g.) dissolved in 15 cc. of glacial acetic acid was treated with a current of ozonized oxygen for three hours. The product was refluxed for forty minutes with 45 cc. of water and 0.5 cc. of concentrated hydrochloric acid and then separated into neutral and acid fractions. The neutral fraction yielded 5.36 g. which was again ozonized and the product separated as before. The combined acid product from the two ozonizations was treated with 50 cc. of alcohol, 50 cc. of 10% aqueous sodium hydroxide and 4.6 g. of hydroxylamine hydrochloride. The mixture was refluxed for two hours, cooled, acidified with acetic acid and left overnight at 5°. An oxime separated, 3.07 g., m. p. 160–161°. Evaporation of the filtrate yielded material which separated as an oil and subsequently solidified in brown lumps, m. p. *ca.* 100–130°, 3.15 g. Crystallization of the first fraction from alcohol gave the pure **oxime** of ***trans*-2-keto-1,1'-dicyclohexyl-2'-carboxylic acid** (XII), m. p. 162–163°.

Anal. Calcd. for $C_{13}H_{21}O_3N$: C, 65.24; H, 8.85. Found: C, 65.64, 65.61; H, 8.92, 8.99.

When the oxime (3.07 g.) was refluxed with 10% hydrochloric acid (100 cc.) for two hours it regenerated the keto-acid as a pale yellow liquid which failed to solidify (yield: 2.45 g.). The keto-acid (1.31 g.) was refluxed for five hours with acetic anhydride (6 cc.), and the excess of reagent was then removed at about 65°, under reduced pressure. The residue was dissolved in ether, freed from acids by means of sodium bicarbonate solution, and isolated by removal of the ether, 1.12 g. of an orange oil being obtained. This lactone (partly XIII) was insoluble in aqueous sodium hydroxide in the cold but dissolved slowly on warming. Dissolved in acetone it decolorized alkaline permanganate. The equivalent was determined by warming the lactone for an hour with an excess of 0.1 *N* alkali and back-titration. *Anal.* Calcd. for $C_{13}H_{18}O_3$: equiv., 206.3. Found: equiv., 203.

The unsaturated lactone (1.1 g.) was suspended in a mixture of 100 cc. of acetone and 50 cc. of 5% sodium bicarbonate solution. To the solution, mechanically stirred at 0°, 100 cc. of 0.5% potassium permanganate solution was added during one-half hour, followed by 100 cc. of 1% permanganate solution during one hour and, finally, 60 cc. of 3% permanganate solution during one hour. Reduction of the permanganate was slow after the addition of the 1% solution. The mixture was finally allowed to come to room temperature and, after standing for two hours, was freed from manganese dioxide by filtration, and the filtrate and washings evaporated nearly to dryness. This residual solution was filtered, acidified with acetic acid and freed from carbon dioxide by boiling. A solution of barium acetate was then added which precipitated a mixture of barium salts, including that of *trans*-hexahydrophthalic acid. After various attempts by other methods

this acid was isolated as follows. The free acids were obtained as a glassy solid (1.02 g.) by treatment of the precipitate and filtrate with hydrochloric acid and extraction with ether. The glassy solid (0.70 g.) was dissolved in 10 ml. of boiling 10% sodium carbonate solution and the insoluble portion discarded. The solution was then fractionally acidified by the standard procedure. The early fractions were glassy solids, but the final fraction consisted of 9 mg. of a light brown, microcrystalline powder melting at 203–213° in the crude state and 216–223° after crystallization from water. The mixed m. p. of the crude material with authentic *trans*-hexahydrophthalic acid (m. p. 227–229°) was 212–217°, but the m. p. of *cis*-hexahydrophthalic acid was considerably depressed. The identity was confirmed by conversion to the anhydride with acetyl chloride, m. p. and mixed m. p. 142–144°. Extraction of the mother liquor from the fractional precipitation with ether gave a semi-crystalline residue from which 21 mg. of additional *trans*-hexahydrophthalic acid, m. p. 219–223°, was obtained by crystallization from aqueous acetic acid. This was treated with phosphorus pentachloride and aniline, as previously described for the preparation of the *cis*-compound, and the product crystallized from glacial acetic acid to give 10 mg. of the dianilide, colorless needles, m. p. (block preheated to 260°) 317–318°. The mixed m. p. with the dianilide of similar m. p. prepared from authentic *trans*-hexahydrophthalic acid showed no depression.

Anal. Calcd. for $C_{20}H_{22}O_2N_2$: C, 74.50; H, 6.88. Found: C, 74.27; H, 6.78.

It may be observed in passing that the m. p.'s of *trans*-hexahydrophthalic acid given in the literature are in the range 215–220° (see *e. g.*, reference 4). We find that by repeated crystallization from water it is possible to isolate the acid as prisms, m. p. 227–229°. The m. p. of the impure acid is considerably affected by the rate of heating, that of the pure acid less so. The above m. p. was obtained by introducing the acid into a bath at 200°. The pure acid of m. p. 227–229° yields the anhydride with the m. p. (142.5–144°) recorded in the literature.

Action of Nitric Acid on *cis*- and *trans*-9-Keto-*as*-octahydrophenanthrenes.—The two stereoisomeric 9-keto-*as*-octahydrophenanthrenes were prepared essentially by the methods of Cook and his co-workers[11] as described in the following paper.[5] The liquid ketone (*cis*-) (0.4 g.) was heated on the steam-bath for fifteen minutes with 5 cc. of concentrated nitric acid and 3 cc. of fuming nitric acid. The product was poured on ice and separated into neutral and acidic fractions by means of sodium carbonate solution. Acidification of the sodium carbonate solution yielded 20 mg. of *cis*-nitro-hexahydrodiphenic acid (VII) as a yellow solid, which was isolated by means of ether. It melted at 200–208° in the crude state, at 208–210° after one crystallization from acetone–benzene and at 217–219° in admixture with an authentic sample of the high-melting form (m. p. 218–219°) prepared as described in the preceding paper.[2] The neutral fraction from this reaction yielded 0.1 g. of a crystalline **trinitro-ketone,** which formed clear plates, m. p. 151.5–152° from hexane.

Anal. Calcd. for $C_{14}H_{13}N_3O_7$: C, 50.15; H, 3.91. Found: C, 50.57; H, 4.18.

This substance agrees in m. p. but not in analysis with the mononitro ketone reported by Cook, *et al.*[11] When the *cis*-octahydro ketone (500 mg.) was heated for thirty minutes on the steam-bath with 1 cc. of concentrated and 1 cc. of fuming nitric acid in 10 cc. of acetic acid, it gave 300 mg. of a neutral solid. After recrystallization from acetic acid and then from benzene–hexane, this formed colorless plates, m. p. 95–96.5°, and analysis showed it to be a **dinitro-ketone.** Its m. p. was depressed by admixture with the nitro-ketone of m. p. 152°.

Anal. Calcd. for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86. Found: C, 57.87; H, 4.55.

Further treatment of the dinitro-ketone with nitric acid on the steam-bath yielded the trinitro-ketone of m. p. 152°.

The dinitro-ketone very probably contains the nitro-groups ortho- and para- to the backbone. The introduction of a third nitro-group is abnormal and it is probable that it corresponds with an attack on the alicyclic portion of the molecule.

Oxidation of *cis*-9-keto-*as*-octahydrophenanthrene with hot chromic acid in acetic acid, or with alkaline permanganate, gave no useful products.

trans-9-Keto-*as*-octahydrophenanthrene (350 mg., m. p. 95°) was heated for fifteen minutes with 4 cc. of concentrated and 4 cc. of fuming nitric acid. The product was separated as before. Crystallization of the acid fraction from acetic acid yielded *trans*-nitro-hexahydrodiphenic acid (100 mg.). This melted crude at 211–221° and from dilute acetic acid gave thin yellowish plates, m. p. 224–225° alone or in admixture with the authentic *trans*-nitro acid. The neutral fraction from this reaction (100 mg.) crystallized in bold needles from acetic acid, m. p. 182–184°, and in thin plates from hexane, m. p. 182.5–183.5°. Analysis showed it to be a **trinitro-ketone.** It was not identical with either of the nitro-ketones derived from the *cis*-ketone.

Anal. Calcd. for $C_{14}H_{13}N_3O_7$: C, 50.15; H, 3.91. Found: C, 50.30; H, 3.67.

Summary

Ozonization of the hexahydrodiphenic acid of m. p. 242° yields *cis*-hexahydrophthalic acid. Ozonization of *trans*-Δ^{10}-9-keto-dodecahydrophenanthrene yields a keto-acid which can be converted into an unsaturated lactone. The latter on oxidation with permanganate gives *trans*-hexahydrophthalic acid.

Taken in conjunction with work described in the preceding papers, these facts establish the *cis*-configurations for the following substances: hexahydrodiphenic acid, m. p. 242°; perhydrodiphenic acids, m. p. 289° (*syn*) and 198° (*anti*); and the *trans*-configurations for the following: hexahydrodiphenic acid, m. p. 221°; perhydrodiphenic acids, m. p. 223° (*syn*) and 247° (*anti*).

Two additional stereochemical links between the hydrodiphenic acids and the hydrophenanthrenes have been established by the conversion

(11) Cook, Hewett and Lawrence, *J. Chem. Soc.*, 71 (1936); Cook, Hewett and Robinson, *ibid.*, 168 (1939).

of the *cis*- and *trans*-forms of 9-keto-*as*-octahydrophenanthrene into the corresponding nitro-hexahydrodiphenic acids.

The stereochemical implications of these results are discussed and it is shown that they are in agreement with other, less exact, evidence.

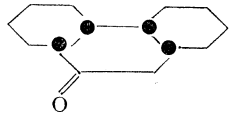
CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 30, 1942

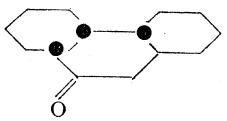
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

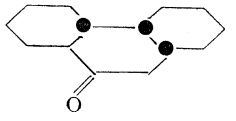
The Stereochemistry of Catalytic Hydrogenation. VI. The Hydrogenation of 9-Phenanthrol and Related Substances and the Identification of Three of the Possible Stereoisomeric Forms of the Perhydrophenanthrene Ring

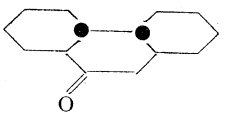
BY R. P. LINSTEAD, RICHARD R. WHETSTONE AND PHILIP LEVINE

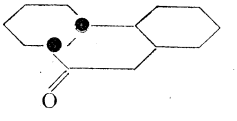
Perhydrophenanthrene can theoretically exist in six (inactive) stereoisomeric modifications.[1] Corresponding to each of four of these hydrocarbons (the *cis-syn-cis*, *trans-syn-trans*, *cis-anti-cis* and *trans-anti-trans* forms), there will be one ketone with the carbonyl group at C_9. Corresponding to each of the other two hydrocarbons (the *cis-syn-trans* and *cis-anti-trans* forms), there will be a pair of C_9 ketones, the additional forms being possible because the carbonyl can lie next to either a *cis*- or a *trans*-junction. All the ketones, and all the hydrocarbons except the *cis-syn-cis* and *trans-syn-trans* isomers, are capable of existence in enantiomorphic forms. Furthermore, each ketone can give rise to a pair of epimeric alcohols, so that eight inactive ketones and sixteen inactive alcohols become possible. The possibilities for the ketones are shown.

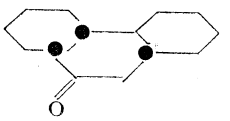

I. *c.s.c.*

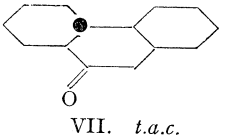

II. *c.s.t.*

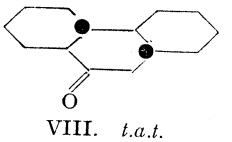

III. *t.s.c.*


IV. *t.s.t.*


V. *c.a.c.*


VI. *c.a.t.*

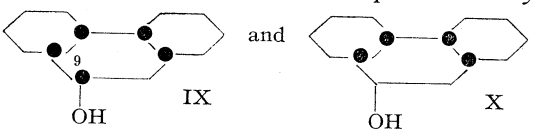

VII. *t.a.c.*


VIII. *t.a.t.*

(1) Linstead and Walpole, *J. Chem. Soc.*, 842 (1939).

This is parallel to the half esters of the perhydrodiphenic acids[2] and we use a similar convention for the nomenclature of the *cis–trans* forms, the configuration on the side of the ketone group being named first.

It is also convenient for the sake of clarity to use dotted formulas[3] to designate the configuration of the alcohols. Thus of the two possible *cis-syn-*



cis alcohols the compound IX has the hydrogen atom on carbon 9 on the same side of the central ring as the four hydrogen atoms at the points of ring fusion.

The first perhydrophenanthrene derivatives of definite configuration to be discovered were the 9-ketone, m. p. 49°, and the related secondary alcohol, m. p. 119°, prepared by Linstead and Walpole.[1] This ketone, a stable crystalline solid, m. p. 49°, was oxidized to a perhydrodiphenic acid of m. p. 244°. This has now been proved to have the *trans-anti-trans* configuration.[4] Hence the ketone has the same configuration (VIII). Two other compounds which were believed[1] to be 9-keto-perhydrophenanthrenes have now been shown[2] to have a different skeleton structure.

In the present paper we describe the preparation of two new stereoisomeric modifications (*cis-syn-cis* and *trans-syn-cis*) of 9-keto-perhydrophenanthrene. Half of the possible stereoisomeric forms of the perhydrophenanthrene ring have therefore been prepared and orientated.

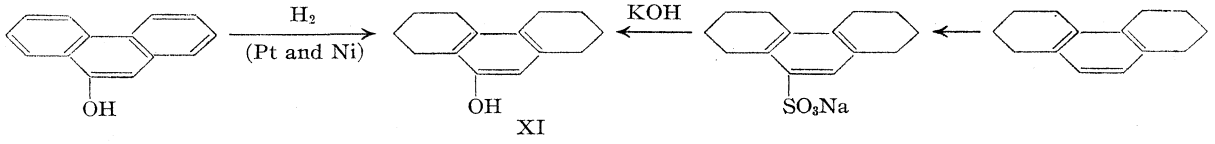
(2) Linstead and Doering, THIS JOURNAL, **64**, 1991 (1942).

(3) Linstead, *Chemistry and Industry*, **56**, 510 (1937); Linstead and Walpole, *loc. cit.*; Ruzicka, Furter and Goldberg, *Helv. Chim. Acta*, **21**, 498 (1938); Linstead, *et al.*, THIS JOURNAL, **64**, 1985 (1942).

(4) Linstead and Doering, *ibid.*, **64**, 2003 (1942); Linstead, Davis and Whetstone, *ibid.*, **64**, 2009 (1942).

The new isomers were obtained in a study of the catalytic hydrogenation over platinum of 9-phenanthrol and of the *as*-octahydro-9-phenanthrols. Marvel and collaborators[5a,5b] have recently made some observations on the perhydrogenation of 9-phenanthrol over nickel. We shall discuss their results later in this paper.

When 9-phenanthrol was hydrogenated over platinum in acetic acid, there were formed (1) *sym*-octahydro-9-phenanthrol (XI), m. p. 135°, (2) a *cis-syn-cis*-perhydro-9-phenanthrol (IX or X), m. p. 111°, and (3) a hydrocarbon fraction. The *sym*-octahydro compound (which was isolated in very small amount) was identical with material prepared by hydrogenating 9-phenanthrol over Raney nickel. The hydrogenation over a different nickel catalyst has already been carried out by von Braun and Bayer[6] who had obtained the same compound. The structure of *sym*-octahydro-9-phenanthrol was proved by its synthesis from Schroeter's *sym*-octahydrophenanthrene[7] by sulfonation and fusion with alkali. The hydrogenation of 9-phenanthrol over Raney nickel is the best preparative method.



XI

The main oxygen-containing product of the platinum hydrogenation of 9-phenanthrol was a perhydro alcohol, m. p. 110–111°. This was easily separated from the octahydro-compound as it was lower boiling and more soluble. On oxidation with nitric acid it yielded *cis-syn-cis* perhydrodiphenic acid, m. p. 289°. This at once proved both its structure and its configuration (apart from the orientation of the hydroxyl group at C_9). We discuss the chemistry of this alcohol more fully below.

It was observed by Linstead and Davis[8] that in the perhydrogenation of *cis*- and *trans*-hexahydrodiphenic acids over platinum the integrity of the already established configuration was preserved, and the subsequent hydrogenation went *syn*- and *cis*-. It was of great interest to see if the same principle held in the tricyclic series. The *cis*- and *trans*-9-keto-*as*-octahydrophenanthrenes recently investigated by J. W. Cook and his collaborators[9] were suitable intermediates for such an investigation. These substances were accordingly prepared essentially by Cook's methods. In confirmation of the earlier results,[9a] we found that the dehydration of 2-phenylcyclohexanol-1-acetic ester, followed by hydrolysis, yielded the β,γ-unsaturated acid, m. p. 93° (probably XII), and that catalytic hydrogenation of this gave almost exclusively a 2-phenylcyclohexane-1-acetic acid of m. p. 170°. The evidence which we present below proves the correctness of Cook's view[9b] that this saturated acid has the *cis*-configuration (XIII). 2-Phenylcyclohexane-1-acetic acid can exist in a second geometrical form, and various reports of this have been made. Cook, Hewett and Lawrence[9a] obtained it in an impure form (m. p. 65–85°) from the mother liquors of the *cis*-acid. They also reported an acid of m. p. 84–85° which was obtained in poor yield by a malonic ester synthesis. Ghose[10] has described an acid of m. p. 69–70°, made by a different method. Cook, Hewett and Robinson[9b] reported that 2-phenylcyclohexylideneacetic acid (XIV, made by dehydrating the hydroxy acid with acetic anhydride) on hydrogenation failed to give the second (*trans*-) saturated acid in useful amount. We can confirm that the α,β-acid (XIV) hydrogenates *cis*- under most conditions. When, however, the hydrogenation is carried out over palladium in benzene solution there is obtained a mixture of saturated acids from which 57% of the *cis*-acid (m. p. 170°) and 33% of an isomer, m. p. 114°,[10a] can be separated without difficulty. The latter is undoubtedly the pure *trans*-2-phenylcyclohexane-1-acetic acid (XV). On cyclization with sulfuric acid, it gives the (*trans*-) 9-keto-*as*-octahydrophenanthrene, m. p. 96°, which Cook[9a] had obtained from his impure acid, m. p. 65–85°. The latter material must therefore have contained the *trans*-acid; the structure of the other low-melting acids described in the literature is doubt-

(5) (a) Marvel and White, THIS JOURNAL, **62**, 2739 (1940); compare (b) Marvel and Patterson, *ibid.*, **63**, 2218 (1941).

(6) von Braun and Bayer, *Ber.*, **58**, 2667 (1925).

(7) Schroeter, *ibid.*, **57**, 1990 (1924).

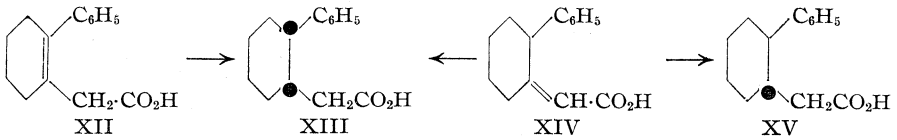
(8) Linstead and Davis, THIS JOURNAL, **64**, 2006 (1942).

(9) (a) Cook, Hewett and Lawrence, *J. Chem. Soc.*, 71 (1936); (b) Cook, Hewett and Robinson, *ibid.*, 168 (1939).

(10) Ghose, *Science and Culture*, **1**, 299 (1935).

(10a) It has just come to our attention that G. Blumenfeld, *Ber.*, **74B**, 524 (1941), recently prepared this acid by a different series of reactions. His acid melts at 112° and gave the same *as*-octahydrophenanthrone, m. p. 96°.

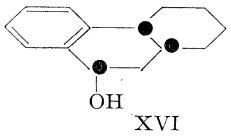
ful. The position of the double bond in the α,β-acid (XIV) was proved by its oxidation by means of alkaline permanganate to 2-phenylcyclohexanone.



XII m. p. 93° XIII m. p. 170° XIV m. p. 169° XV m. p. 114°

The route through phenylcyclohexylideneacetic acid (XIV) provides the best preparative method for the *trans*-acid (XV) but is still unsatisfactory owing to the difficulty of obtaining the α,β-acid. The yield of the latter from the acetic anhydride dehydration of the corresponding β-hydroxy acid, following Wallach, is low. A somewhat better yield is obtained by the use of *n*-butyric anhydride. If the β,γ-acid is equilibrated with alkali the amount of the α,β-isomer formed is very small. This is to be expected, because not only is cyclohexylideneacetic acid unstable with respect to its β,γ-isomer[11] but the γ-phenyl group further stabilizes the β,γ-form.[12]

Cyclization of the two saturated acids (XIII and XV) by means of sulfuric acid gave the two 9-keto-*as*-octahydrophenanthrenes reported by Cook.[9,12a] Catalytic hydrogenation of each of the two ketones yielded the corresponding pair of secondary alcohols. The *cis*-ketone gave almost completely a 9-hydroxy-*as*-octahydrophenanthrene, m. p. 115–116°, evidently identical with the alcohol described by Cook, Hewett and Lawrence.[9a] An epimeric *cis*-octahydro alcohol, m. p. 133°, was isolated from the products of the perhydrogenation of the *cis*-ketone. On the hypothesis of "catalyst hindrance" discussed in Part I,[13] it seems probable that the more easily prepared epimer has the three hydrogen atoms on the asymmetric carbon atoms, located on the same side of the central ring (XVI). The *trans*-ketone gives two epimeric alcohols, m. p.'s 91° and 101°, the proportion of which appears to vary with the method of hydrogenation. Reduction of the *cis*-ketone by means of sodium and alcohol gave a mixture of secondary alcohols from which the 116° epimer was isolated. Reduction with aluminum isopropoxide gave an epimeric mixture.



XVI

The perhydrogenation of the octahydro-ketones and alcohols was difficult because of the ease with which oxygen was eliminated over the active catalysts required to effect the reaction. This is true in particular of hydrogenation using palladium, and using platinum in acetic acid. The use of platinum in alcohol, however, gave a slow hydrogenation with little elimination of oxygen. In this way *cis*-9-keto-*as*-octahydrophenanthrene yielded a complex mixture from which four products were separated. These melted at 110, 114, 133 and 86°, severally. The first of these was identical with the perhydro-alcohol already obtained by the exhaustive hydrogenation of 9-phenanthrol. It is undoubtedly a *cis-syn-cis*-perhydro-9-phenanthrol and has the configuration represented by IX or X, probably the former. The second product was identical with the *cis-as*-octahydro-9-phenanthrol, m. p. 115–116°, described above (XVI). The product of m. p. 133° was the epimer of this. It has almost the same m. p. as *sym*-octahydro-9-phenanthrol (XI), but is not identical with this substance and depresses its melting point by some 35°. The fourth substance, m. p. 86°, crystallized well but was not homogeneous. Analysis indicated that it was a mixture of perhydro- and octahydro- compounds, and the absorption spectrum also showed the presence of aromatic material. After repeated crystallizations had failed to effect a purification, a method was devised (see experimental part) whereby the substance was separated into the three homogeneous products of the reaction, namely, the perhydro alcohol, m. p. 110° (10%), and the two octahydro-alcohols, m. p. 116° (10%) and m. p. 133° (30%).

Catalytic hydrogenation of the *cis-as*-octahydro-9-phenanthrol, m. p. 116°, over Adams catalyst in alcohol gave mainly the same *cis-syn-cis*-perhydrophenanthrol, m. p. 110°, and a little of the mixture, m. p. 86°.

Very interesting results were obtained from a study of the oxidation of the *cis-syn-cis*-perhydro-alcohol. When this compound was treated with a mixture of chromic and acetic acids at room temperature, it yielded a 9-keto-perhydrophenan-

(11) Linstead, *J. Chem. Soc.*, 355 (1927).

(12) Linstead and Williams, *ibid.*, 2735 (1926).

(12a) The assignment of the *cis*- and *trans*-configuration to these is proved by the evidence reported in the preceding paper (Part V).

(13) Linstead, Doering, Davis, Levine and Whetstone, THIS JOURNAL, **64**, 1985 (1942).

threne, m. p. 44°. This ketone formed a rather unstable oxime, m. p. 150°. It is undoubtedly *cis-syn-cis*-9-keto-perhydrophenanthrene (I) because on catalytic hydrogenation with platinum in ethyl alcohol it reformed the parent alcohol, m. p. 110°, and on oxidation with nitric acid it yielded *cis-syn-cis*-perhydrodiphenic acid, m. p. 289°. On the other hand, when the same alcohol was oxidized with chromic and acetic acids on the steam-bath a stereoisomeric ketone was obtained. This melted at 57°, depressed the m. p. of the 44° ketone and gave an oxime, m. p. 225°, from which it could be regenerated. Catalytic hydrogenation of the ketone yielded a perhydro-alcohol of m. p. 88–89° and oxidation with nitric acid gave *cis-syn-trans*-perhydrodiphenic acid, m. p. 199°. The new ketone has therefore been formed by inversion of the configuration of one asymmetric carbon atom, and clearly this must be the one adjacent to the carbonyl group. It must therefore have the *trans-syn-cis* configuration (III), and so must the derived alcohol, m. p. 88–89°.

These two ketones are precisely analogous to the α-decalones, studied by Hückel and his collaborators.[14] The *cis-syn-cis* ketone is easily inverted by heat, alkali, and to some extent in the formation of the usual carbonyl derivatives. The fact that the inversion only proceeds at one ring fusion, *i. e.*, to *trans-syn-cis* and not to *trans-syn-trans*, provides clear evidence that it proceeds through an enolization of the carbonyl group from the hydrogen atom on the neighboring bridgehead. The below summarizes the properties of the *cis-syn-cis* ketone in comparison with those of *cis* α-decalone.

	cis-syn-cis-9-Keto-perhydrophenanthrene	*cis*-α-Decalone[14]
Preparation	Cold CrO_3 on secondary alcohol	Same
Catalytic hydrogenation	Reforms the alcohol without inversion	Same
Nitric acid	Oxidizes without inversion	Same
Vacuum distillation	Unchanged	Same
High temperatures	Inverted at 200°	Inverted at 227°
Oxime	Gives (unstable) *cis-syn-cis*-derivative, m. p. 150°	Gives *trans*-derivative
2,4-Dinitrophenylhydrazone	Gives *trans-syn-cis*-derivative, m. p. 236°	...
Alcoholic alkali	Inverted	Inverted

(14) Hückel and Brinkmann, *Ann.*, **441**, 21 (1925); Hückel, Danneel, Gross and Naab, *ibid.*, **502**, 99 (1933).

The formation of *cis-syn-cis*-perhydrodiphenic acid by the nitric acid oxidation of the *cis-syn-cis* ketone (and alcohol) shows the reliability of this method in the determination of configuration. There could have been no reversible enolization and inversion under the experimental conditions and the ketone, in spite of the instability of its configuration, yielded the corresponding acid.

We are now in a position to review the results of Marvel and White[5a] on the hydrogenation of 9-phenanthrol over nickel. They obtained a perhydro-alcohol as a waxy solid, m. p. 67°. This on oxidation with chromic acid, finally on the steam-bath, yielded a ketone of m. p. 57° which was later prepared by another method.[5b] The ketone yielded an oxime, m. p. 219–220°, and a dinitrophenylhydrazone, m. p. 232–233°. On oxidation it gave an acid of m. p. 174°, which Linstead and Doering[2] have shown to be a dimorphous form of *cis-syn-trans*-perhydrodiphenic acid. It is therefore very probable that the ketone of Marvel and White is identical with our *trans-syn-cis* ketone which has the same m. p., and very similar m. p.'s for the derivatives. The configuration of the original hydrogenation product, m. p. 67°, of Marvel and White is, however, uncertain. It may be a *cis-syn-cis*, or a *trans-syn-cis* alcohol, because the conditions of oxidation were such that an inversion was possible. It is obviously not identical with any of our alcohols but there are vacancies for one epimer in each series.

Some preliminary work has been carried out on the perhydrogenation of *trans-as*-octahydrophenanthrene derivatives, but it has not yet reached a stage suitable for report.

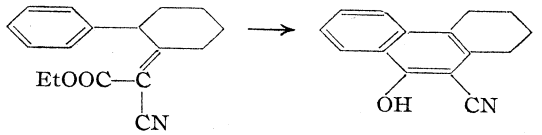
The present state of knowledge of the 9-substituted hydrophenanthrenes of known structure is summarized.

Ketones	Alcohols
	sym-Octahydro-9-phenanthrone, m. p. 133° (B.B., L.W.L.)
9-Keto-*as*-octahydrophenanthrenes	*as*-Octahydro-9-phenanthrols
cis liquid (C.H.L., L.W.L.)	m. p. 116° (C.H.L., L.W.L.)
	m. p. 133° (L.W.L.)
trans m. p. 96° (C.H.L., L.W.L.)	m. p. 91° (L.W.L.)
	m. p. 101° (L.W.L.)
9-Keto-perhydrophenanthrenes	Perhydro-9-phenanthrols
cis-syn-cis m. p. 44° (L.W.L.)	m. p. 111° (L.W.L.)
	.....

Ketones 9-Keto-perhydrophenanthrenes		Alcohols Perhydro-9-phenanthrols
trans-syn-cis m. p. 57° (M.W., L.W.L.)		m. p. 89° (L.W.L.)
		? m. p. 67° (M.W.)
trans-anti-trans m. p. 49° (L.W.)		m. p. 119° (L.W.)

References: B.B. = von Braun and Bayer[6]
L.W.L. = Linstead, Whetstone and Levine, this paper
C.H.L. = Cook, Hewett and Lawrence[9a]
M.W. = Marvel and White[5a]
L.W. = Linstead and Walpole[1]

An interesting incidental observation was made during attempts to find a better method for the preparation of *trans*-2-phenylcyclohexaneacetic acid. 2-Phenylcyclohexanone was condensed with cyanoacetic ester and the 2-phenylcyclohexylidenecyanoacetic ester (XVII) so formed was reduced, both by aluminum amalgam and catalytically, and subsequently hydrolyzed. The acid isolated in this way was the common (*cis*) 2-phenylcyclohexaneacetic acid, m. p. 169–170° (XIII). The method therefore was of no preparative value as the yield was worse than that obtained by the Reformatsky procedure. The feature of interest was that the initial product of the cyanoacetic ester condensation always deposited a small amount of a crystalline solid on standing and that its analytical values were high both in carbon and hydrogen. It was found that the same solid could be formed by heating the unsaturated cyano ester at 210°. The solid gave figures corresponding to the formula $C_{15}H_{13}ON$, *i. e.*, to those required for the unsaturated cyano ester less the elements of ethyl alcohol. It yielded a sodium salt with sodium carbonate, a mono-benzoate and a picrate. It is accordingly assigned the structure 1,2,3,4-tetrahydro-10-cyano-9-phenanthrol (XVIII)



XVII XVIII

Analogous ring-closures have been observed by McRae and Marion,[15] and by Cope and his collaborators.[16]

(15) McRae and Marion, *Can. J. Research*, **15B**, 480 (1937); Marion and McRae, *ibid.*, **18B**, 265 (1940).

(16) Cope, Hofmann, Wyckoff and Hardenbergh, THIS JOURNAL, **63**, 3452 (1941).

Experimental[17]

1. Hydrogenation of 9-Phenanthrol.[18]—9-Phenanthrol was prepared essentially by the method of Fieser, Jacobsen and Price.[19] It was found that very poor yields were obtained unless the sodium (or potassium) acetate was omitted from the reaction mixture. The phenanthrol (9.5 g.) in 200 cc. of glacial acetic acid was hydrogenated in a Parr apparatus using 1.74 g. of Adams catalyst. The theoretical uptake of hydrogen was reached after 188 hours. The product was evaporated to small bulk under reduced pressure in a stream of nitrogen, the residual acid was neutralized and the oil isolated by means of ether. Vacuum distillation separated the product into 4.54 g. of a low fraction (b. p. 120–125° (3 mm.)), 3.22 g. boiling between 150–160° (3 mm.) and 0.54 g. of a residue. Careful fractional distillation of the low fraction yielded a liquid with b. p. 121° (3 mm.), $d^{26.5}_4$ 0.9587, $n^{26.5}_D$ 1.5088. This material, which is undoubtedly a highly hydrogenated phenanthrene, awaits further investigation.

The high-boiling fractions from the above slowly deposited crystals. Fractional crystallization from hexane yielded *cis-syn-cis*-**perhydro-9-phenanthrol** (IX or X), white needles, m. p. 110.5–111°. The yield of this material from a total of 14.4 g. of 9-phenanthrol was 1.26 g.

Anal. Calcd. for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.82; H, 11.61.

The alcohol (125 mg.) was added to a mixture of 0.75 cc. of fuming nitric acid and 2.2 cc. of concentrated nitric acid. The mixture was at first warmed gently and then heated on the steam-bath for five minutes. The product was poured into water (15 cc.) and extracted with benzene. The benzene layer was then extracted with sodium carbonate solution. Acidification of the sodium carbonate gave a solid which was purified by a second extraction with sodium carbonate and was then crystallized from acetic acid. The white crystals melted at 278–283° alone, and at 282–285° in admixture with *cis-syn-cis*-perhydrodiphenic acid.

The further investigation of the *cis-syn-cis*-alcohol is described later.

The highest boiling fraction of the original hydrogenation, and the residue, on crystallization from hexane (charcoal) yielded *sym*-**octahydro-9-phenanthrol** (XI). This crystallized from hexane in needles and melted at 134.5–135° (von Braun and Bayer[6] give 133°).

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.22; H, 9.19.

9-Phenanthrol (5 g.) was hydrogenated with 2 cc. of Raney nickel made up to 20 cc. with alcohol, at 120° and an initial pressure of 123 atmospheres. The hydrogen uptake was about 20% above the theoretical for the formation of the octahydro compound. The alcoholic solution of the product turned dull red on exposure to the air. From it there was isolated *sym*-octahydro-9-phenanthrol, m. p. 132–134°, which did not depress the m. p. of the product obtained in the hydrogenation over platinum.

(17) All melting points corrected. Analyses by Miss Eleanor Werble.

(18) The experiments described in the first paragraph were carried out by Mr. D. P. J. Goldsmith, to whom our thanks are due.

(19) Fieser, Jacobsen and Price, THIS JOURNAL, **58**, 2163 (1936).

sym-Octahydrophenanthrene was prepared from tetralin by Schroeter's method,[7] and converted into the sodium salt of the 9-sulfonic acid.[7] The salt was fused with potassium hydroxide at 290–300° in the usual manner. The efficiency of the reaction was greatly reduced by secondary decomposition and the escape of organic vapors (possibly the desired product). At the end, the alkali was dissolved in water neutralized with acid, and the product was extracted with chloroform. The solution was clarified with charcoal, dried and freed from solvent. The residue was crystallized from hexane containing a little activated clay and then deposited *sym*-octahydro-9-phenanthrol, m. p. 133.5–135°. An attempt to carry out the same fusion in an autoclave failed. The phenol is very difficult to free from colored impurities. It separates from pale solutions in shades ranging from light brown to black. The best method of removing the color is to boil a solution in ligroin (b. p. 90–120°) with activated clay.

2. 2-Phenylcyclohexaneacetic Acids.—2-Phenylcyclohexanone was condensed with bromoacetic ester following Cook, Hewett and Lawrence.[9a] The hydroxy ester, obtained in 80% yield, was dehydrated by refluxing it (90 g.) for three and a half hours with 60 g. of phosphorus pentoxide and 300 cc. of benzene. A 77% yield of unsaturated ester, b. p. 146–153° (3 mm.), was obtained. This was hydrolyzed with alkali to the β,γ-acid (XII), yield 93%; b. p. 180–190° (3 mm.); m. p. 80–85° (crude); 92–93° after one crystallization from light petroleum (lit., 93°).[9a] The crude unsaturated acid (18 g.) in 75 cc. of glacial acetic acid was hydrogenated with 0.5 g. of palladium catalyst.[20] After eighteen hours at atmospheric pressure, the uptake of hydrogen corresponded to 1.12 mols. The solution was filtered, heated to boiling and diluted with water. The average yield was 63% of the pure *cis*-2-phenylcyclohexaneacetic acid (XIII), m. p. 168–170° (lit., 169–170°).[9a] The mother liquors from this acid, containing the *trans*-isomer, were used in the crude state for the preparation of *trans*-9-keto-*as*-octahydrophenanthrene.

2-Phenylcyclohexanol-1-acetic ester was hydrolyzed with boiling alkali. The corresponding hydroxy acid, obtained in 75% yield, melted at 128–129°. The acid was converted into 2-phenylcyclohexylidene-acetic acid (XIV) following Cook, Hewett and Robinson.[9b] The yield of the pure α,β-acid, m. p. 168–170°, was only 17%. The by-products of this reaction are still under investigation. When the hydroxy acid was refluxed with *n*-butyric anhydride for one and one-quarter hours, the α,β-acid was obtained in 35% yield. Both the β,γ- and α,β-acids readily decolorized permanganate in sodium carbonate solution. When the carbonate solutions of the acids were treated with iodine in potassium iodide,[21] the β,γ-acid reacted immediately but the α,β-acid showed no sign of reaction. This difference is in keeping with the structures assigned by Cook.[9] The structure of the α,β-acid was proved by oxidizing 450 mg. of it in sodium carbonate solution with potassium permanganate. The product yielded 220 mg. of 2-phenylcyclohexanone, identified by m. p. and mixed m. p.

The α,β-acid (210 mg.) in 10 cc. of benzene was hydrogenated over 120 mg. of palladium catalyst. In four hours 1.1 mols of hydrogen was taken up. The product was fractionally crystallized from benzene–hexane. It yielded 120 mg. of the *cis*-acid (XIII), m. p. 158–164°; followed by 70 mg. (33%) of a solid melting at 110–114°. Three crystallizations of the latter from hexane gave *trans*-**2-phenylcyclohexaneacetic acid** (XV) as thin plates, m. p. 113.5–114.5°.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.33; H, 8.38.

Cyanoacetic Ester Condensations.—Following the general technique of Cope,[22] a mixture of 3.0 g. of 2-phenylcyclohexanone, 2.5 g. of cyanoacetic ester, 0.5 g. of ammonium acetate, 0.75 g. of acetic acid and 5 cc. of benzene was heated in a bath at 140–160° for six hours, the benzene being continually replaced. The product was taken up in ether, washed with water and 5% aqueous sodium hydroxide. The solvent was removed and the residue distilled, yield 2.4 g. (52%) of a colorless viscous oil, b. p. 167–174° (3 mm.). The product did not decolorize bromine in carbon tetrachloride but reduced permanganate in acetone. The redistilled product boiled at 174° (4 mm.) and analysis showed that it was mainly **2-phenylcyclohexylidenecyanoacetic ester** (XVII).

Anal. Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11. Found: C, 76.46; H, 7.37.

The last drops obtained in the distillation of the above ester solidified to a mass of crystals of **1,2,3,4-tetrahydro-10-cyano-9-phenanthrol** (XVIII), and some of the same solid slowly separated when the original reaction mixture was allowed to stand in the cold. It was also obtained by acidifying the alkaline extracts from the cyano ester. The total yield of the by-product was 8%. It could be prepared by heating the unsaturated cyano ester (XVII) for one and three-quarters hours at 200–220°. It crystallized from benzene in fine white needles, m. p. 230–231°. It was sparingly soluble in alcohol, ether and benzene, and insoluble in sodium bicarbonate solution. With 5% aqueous sodium carbonate it gave an insoluble sodium salt. It gave no color with ferric chloride. Sundry attempts to hydrolyze it failed.

Anal. Calcd. for $C_{15}H_{13}ON$: C, 80.72; H, 5.83; N, 6.28. Found: C, 81.16; H, 5.79; N, 6.19.

The **benzoate,** made by the Schotten-Baumann procedure, crystallized from benzene–hexane in needles, m. p. 183–184°.

Anal. Calcd. for $C_{22}H_{17}O_2N$: C, 80.71; H, 5.24. Found: C, 80.61; H, 5.23.

When warmed with alcoholic picric acid, the cyanophenol yielded a **picrate,** which separated in yellow crystals, m. p. 185–190°, with decomp.

Anal. Calcd. for $C_{21}H_{16}O_8N_4$: C, 55.75; H, 3.56. Found: C, 55.77; H, 3.37.

The picrate regenerated its components when heated with alcohol.

The unsaturated cyano ester (XVII, 1.68 g.) was hydrogenated in alcohol over Adams catalyst, the uptake of hydrogen being 1.03 mols in seven hours. The product was refluxed with 20 cc. of concentrated hydrochloric acid and 5 cc. of water for thirty-six hours. The bulk of the

(20) Shriner and Adams, THIS JOURNAL, **46**, 1683 (1924).

(21) See Bougault, *Ann. chim.*, [8] **14**, 145 (1908); Linstead and May, *J. Chem. Soc.*, 2565 (1927).

(22) Cope and Hoyle, THIS JOURNAL, **63**, 733 (1941).

ester survived hydrolysis; the acid formed melted at 165–168° and was identified as *cis*-2-phenylcyclohexaneacetic acid. Another portion of the unsaturated cyano ester was reduced with aluminum amalgam in moist ether for three days. Hydrolysis as before gave the *cis*-acid, again in poor yield.

3. Derivatives of the *as*-Octahydrophenanthrenes.—*cis*-2-Phenylcyclohexane-1-acetic acid (12.0 g.) was cyclized by means of sulfuric acid following Cook.[9] *cis*-9-Keto-*as*-octahydrophenanthrene (average yield 96%) was obtained as a colorless liquid, b. p. 162–163° (5 mm.).

The ketone (3.5 g.) in 25 cc. of alcohol was treated with 1 mol of hydrogen over Adams catalyst. The product yielded 3.3 g. (93%) of soft, feathery crystals which dried to a chalky mass, m. p. 112–114°. Two recrystallizations from cyclohexane raised the melting point of the *cis*-**octahydro-9-phenanthrol** to 115–116° (lit., 114–115°).[9] The ultraviolet absorption spectrum was measured in alcohol by Mr. J. J. Leavitt. It had two bands of equal intensity at 266 and 273 mμ with log $\epsilon_{max.}$ 2.54.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.10; H, 8.90.

Reduction of the ketone with sodium in alcohol yielded a product melting initially at 60–69°. After a number of crystallizations from cyclohexane this gave some of the same octahydro-alcohol, m. p. 115–116°. Reduction of the ketone with aluminum isopropoxide in isopropyl alcohol gave a solid melting at about room temperature, from which no pure alcohol could be isolated. The ketone (6.0 g.) was hydrogenated over 0.62 g. of palladium catalyst in alcohol, 1.95 mols of hydrogen being taken up in three hours. A small amount (200 mg.) of the 115° alcohol was isolated from the product, but the bulk was a hydrocarbon (4 cc.) which distilled at 121–122° (4–5 mm.) and was presumably *cis-as*-octahydrophenanthrene. The reported boiling point of the latter is 129° (6 mm.).[23]

The isolation of the second epimeric form of the *cis*-alcohol is described below under the perhydrogenations.

trans-**9-Keto-*as*-octahydrophenanthrene.**—The combined mother liquors from the crystallization of *cis*-2-phenylcyclohexylacetic acid were evaporated to a red sirup (25 cc.). This was treated with sulfuric acid as before and the neutral product was crystallized first from light petroleum and then several times from alcohol. The yield of *trans*-ketone was 4.3 g.; m. p. 95–96°, in agreement with Cook, Hewett and Lawrence.[9a] The same ketone was obtained in 74% yield by cyclization of the pure *trans*-acid, m. p. 114°.

The *trans*-ketone (610 mg.) in alcohol, over 120 mg. of Adams catalyst took up 1.0 mole of hydrogen in nineteen hours at atmospheric pressure. Crystallization of the product from hexane and cyclohexane yielded 400 mg. (63%) of a *trans-as*-**octahydro-9-phenanthrol,** sturdy needles melting at 90–91°, and a few milligrams of an *epimer* which formed cotton-like fibers, m. p. 100–101°. A mixture of the two alcohols melted at 84–88°. When a larger preparation was carried out over the same catalyst under a pressure of 3 atmospheres for four days, the proportions of the two alcohols were reversed, the ratio of 101° to 91° form being about 2:1.

(23) Durland and Adkins, THIS JOURNAL, **60**, 1501 (1938).

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found (m. p. 90–91°): C, 83.29; H, 9.19; (m. p. 100–101°): C, 83.06; H, 9.12.

4. Derivatives of Perhydrophenanthrene.—Hydrogenation of the aromatic ring in the *cis*-octahydro compounds was carried out by means of Adams catalyst in alcoholic solution. The use of acetic acid as a solvent led to elimination of the oxygen atoms. This occurred even when very little acetic acid was present, as is shown by the following experiment. The *cis*-octahydro-9-phenanthrol, m. p. 116°, (2.1 g.) in 15 cc. of acetic acid and 185 cc. of alcohol took up 2.9 mols of hydrogen in five days under an initial pressure of 50 lb. The product was mainly a liquid hydrocarbon but yielded a little solid which on crystallization from hexane gave needles of *cis-syn-cis*-perhydro-9-phenanthrol (100 mg.). This melted at 110–111° alone or in admixture with that prepared from 9-phenanthrol.

Anal. Calcd. for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.63; H, 11.54.

The hydrocarbon boiled at 109–111° (4 mm.), failed to solidify, and was insoluble in cold concentrated sulfuric acid. Hence it was presumably a perhydrophenanthrene.

cis-9-Keto-*as*-octahydrophenanthrene (10.7 g.) in alcohol was hydrogenated over 0.9 g. of catalyst added in three portions. The uptake of hydrogen was 3.4 mols in eight days. Removal of the solvent and catalyst, followed by crystallization from hexane, yielded 7 g. of solid melting at about 70–85°. On fractional crystallization from cyclohexane, 2.9 g. of the *cis*-octahydro alcohol, m. p. 112–114°, was obtained. The residue was crystallized from ether, which yielded 2.4 g. of the *cis-syn-cis*-perhydro alcohol, m. p. 108–110°. These substances were identified by mixed m. p. determinations. The ethereal mother liquors deposited 0.2 g. of the epimeric *cis-as*-**octahydro-9-phenanthrol,** m. p. 126–128°, which after repeated crystallization from hexane gave fine needles, m. p. 132.5–133.5°. A mixture of this with the *cis-as*-octahydro alcohol (m. p. 115–116°) melted at 95–100°. A mixture with *sym*-octahydro-9-phenanthrol (m. p. 133°) melted at 95–105°. The new *cis-as*-octahydro alcohol differs from the isomeric *sym*-octahydro phenol of the same m. p. in that it is readily obtained and kept in a pure white crystalline form. The *sym*-octahydro phenol discolors very readily, as already noted.

Anal. Calcd. for $C_{14}H_{18}O$ (alcohol, m. p. 132.5–133.5°): C, 83.12; H, 8.97. Found: C, 82.94; H, 8.82.

The mother liquor from the original 7 g. of solid slowly deposited a further 1.4 g. of solid, which crystallized in rosets of thick spikes, m. p. 85–87°. Repeated crystallization from alcohol, ether and hydrocarbon solvents failed to alter this. This substance, however, gave analytical figures (C, 81.08; H, 10.41) intermediate between those required for an octahydro and a perhydro alcohol. The ultraviolet absorption spectrum (for which we are indebted to Mr. J. J. Leavitt) showed the two equal bands, with maxima at 266 and 273 mμ which are present in the spectrum of *cis-as*-octahydro-9-phenanthrol. The intensity (log $\epsilon_{max.}$ 2.2) corresponded to the presence of about 50% of this compound. The solid, m. p. 85–87°, was dissolved in acetic acid and the solution diluted with small portions of water. Crude *cis-syn-cis* perhydro alcohol

(10% of solid) then separated, and, after crystallization from ether, melted at 108–110°. Further dilution of the acetic acid gave the common *cis-as*-octahydro alcohol (10%), which melted at 115–116° after crystallization from cyclohexane. Removal of the acetic acid left an oil which was hydrolyzed with cold 10% alcoholic potash for forty-eight hours. Acidification and crystallization of the solid product yielded the epimeric *cis-as*-octahydro alcohol, m. p. 133°, (30%). The three components were identified by mixed m. p. determinations.

The *cis-as*-octahydro-9-phenanthrol of m. p. 112–114° was hydrogenated over platinum in alcohol in the same way. It yielded 47% of *cis-syn-cis*-perhydro-9-phenanthrol, m. p. 108–110°, and 10% of the mixture of m. p. 85–87°.

cis-syn-cis-**9-Keto-perhydrophenanthrene.**—Chromic acid (1.0 g.), dissolved in 5 cc. of 80% acetic acid, was added to an ice-cooled solution of 2.3 g. of *cis-syn-cis*-perhydro-9-phenanthrol, m. p. 110–111°, in 30 cc. of glacial acetic acid. The mixture was left overnight at room temperature, poured into water and extracted with ether. The ether was washed with water and sodium carbonate solution. Evaporation of the dried ether solution *in vacuo* left 2.0 g. (87%) of an oil which crystallized to a solid, m. p. 35–38°. The material could be distilled unchanged at about 130° (3 mm.). Six crystallizations from cold petroleum ether gave short needles of the *cis-syn-cis*-perhydro ketone, m. p. 43–44°.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.69; H, 10.42.

The **oxime** was obtained by leaving the ketone in cold aqueous alcoholic solution with hydroxylamine hydrochloride and sodium acetate for four hours. The crystals so obtained melted at 150–151° and were rendered less pure by crystallization, presumably owing to the occurrence of inversion. For analysis the first precipitated crystals were washed with water and petroleum ether and dried.

Anal. Calcd. for $C_{14}H_{23}ON$: C, 75.97; H, 10.47. Found: C, 76.24; H, 10.28.

Recrystallization from hot alcohol lowered the m. p. to 143–146°. When an alcoholic solution was boiled for three hours, the crystals which separated melted at 135–141°.

The 2,4-dinitrophenylhydrazone formed orange plates from hot alcohol, m. p. 236–238°, decomp. The semicarbazone melted at 195–205° without crystallization, at 205–220° after one crystallization from hot alcohol, and at 210–218° after four hours of boiling with alcohol.

The ketone (200 mg.) was heated for fifteen minutes on the steam-bath with 3 cc. of a mixture of 5 cc. concentrated and 3 cc. fuming nitric acid. The product was poured on ice, the yellow resin taken up in ether. The ethereal solution was extracted four times with saturated aqueous sodium bicarbonate. The extract was acidified, the acid isolated by means of ether, boiled with charcoal in acetone and crystallized from benzene. *cis-syn-cis*-Perhydrodiphenic acid (10 mg.) separated, m. p. 275–280°, mixed m. p. 279–284°. The identity was confirmed by converting the acid (3 mg.) into the dimethyl ester, which melted at 66–69° alone and at 71–73° in admixture with authentic material.

Catalytic hydrogenation of the ketone over Adams catalyst in alcohol yielded the *cis-syn-cis*-perhydro-9-phenanthrol of m. p. 110°.

trans-syn-cis-**9-Keto-perhydrophenanthrene.**—*cis-syn-cis*-Perhydro-9-phenanthrol, m. p. 110°, was oxidized with chromic and acetic acids in the manner described above with the difference that after the initial reaction, the mixture was heated on the steam-bath for fifteen minutes. The *trans-syn-cis*-ketone, isolated in the same way as its isomer, crystallized from petroleum ether in needles, m. p. 56.5–57.5°. A mixture of the two ketones was liquid at room temperature.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.65; H, 10.80.

The same perhydro alcohol (1.9 g.) was oxidized following Oppenauer's method by refluxing it for eight hours with 1.4 g. of aluminum *t*-butoxide in a mixture of acetone and benzene. The product was a mixture of the two ketones melting at about 25° and not easily separable by crystallization. It was accordingly heated in an atmosphere of nitrogen at 200° for one and three-quarters hours. The product was the nearly homogeneous *trans-syn-cis* ketone, m. p. 48–52°, identified by a mixed m. p. determination. The same inversion was achieved by refluxing the mixed ketone, m. p. 25°, with alcoholic sodium ethoxide for one and one-half hours.

The **oxime** of the *trans-syn-cis* ketone formed immediately at room temperature and crystallized in fine needles, m. p. 224–225°. A mixture with the *cis-syn-cis* oxime (m. p. 150–151°) melted over the range 143–180°.

Anal. Calcd. for $C_{14}H_{23}ON$: C, 75.97; H, 10.47. Found: C, 76.25; H, 10.38.

When the oxime was boiled for six hours with 5% sulfuric acid, it regenerated the *trans-syn-cis* ketone, m. p. 57°.

The 2,4-dinitrophenylhydrazone formed red plates from hot alcohol, m. p. 236–237°, decomp. The color was more intense than that of the corresponding derivative made from the *cis-syn-cis* ketone but the mixed m. p. was the same (236–237° decomp.) and it is probable that both ketones give the same derivative.

The ketone (200 mg.) was oxidized with nitric acid as described for the *cis-syn-cis*-isomer. The product yielded 30 mg. of *cis-syn-trans*-perhydrodiphenic acid, m. p. 196–198° alone, and 197–198° in admixture with an authentic sample (m. p. 198–199°). Hydrogenation of the ketone (130 mg.) over Adams catalyst in alcohol led to a theoretical uptake of hydrogen. The *trans-syn-cis*-**perhydro-9-phenanthrol** so obtained was crystallized first from hexane and then from ether, from which it separated in rosets of long prisms, m. p. 88–89°.

Anal. Calcd. for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.19, 80.21; H, 11.38, 11.33.

Summary

Catalytic hydrogenation of 9-phenanthrol over platinum yields *cis-syn-cis*-perhydro-9-phenanthrol, m. p. 111°, together with a small amount of *sym*-octahydro-9-phenanthrol. The latter substance was also obtained over nickel at 120°. Its structure was proved by its synthesis from *sym*-octahydrophenanthrene.

cis-9-Keto-*as*-octahydrophenanthrene yields two secondary alcohols, m. ps. 116° and 133°. The isomeric *trans*-ketone also yields two epimeric alcohols, m. ps. 91° and 101°.

Hydrogenation of *cis*-9-keto-*as*-octahydrophenanthrene over platinum in alcohol gives *cis-syn-cis*-perhydro-9-phenanthrol and the two octahydro alcohols. Hydrogenation of *cis-as*-octahydro-9-phenanthrol gave the same *cis-syn-cis*-perhydro alcohol. When the *cis-syn-cis*-perhydro alcohol was oxidized by chromic acid at 0–25° it yielded *cis-syn-cis*-9-keto-perhydrophenanthrene. However, when the same oxidation was completed at 100° the product was the isomeric ketone with the *trans-syn-cis* configuration, presumably identical with a ketone isolated by Marvel and coworkers. The inversion of the *cis-syn-cis* ketone has been studied and is correlated with that of *cis*-α-decalone.

The *cis-syn-cis*-perhydro alcohol and ketone were oxidized by nitric acid to *cis-syn-cis*-perhydrodiphenic acid. The *trans-syn-cis* ketone yielded *cis-syn-trans*-perhydrodiphenic acid on nitric acid oxidation and a new perhydro alcohol on catalytic hydrogenation.

Three forms of the perhydrophenanthrene ring have therefore been made and oriented.

Pure *trans*-2-phenylcyclohexaneacetic acid has been obtained, m. p. 114°. When heated to 200°, 2-phenylcyclohexylidenecyanoacetic ester spontaneously cyclizes to tetrahydro-10-cyano-9-phenanthrol.

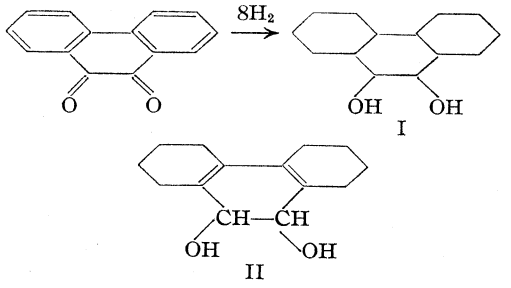
CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 30, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Stereochemistry of Catalytic Hydrogenation. VII. The Complete Hydrogenation of Phenanthraquinone

BY R. P. LINSTEAD AND PHILIP LEVINE

The catalytic hydrogenation of 9,10-phenanthraquinone has already been investigated by von Braun and Bayer[1] and by Skita,[2] but they did not succeed in bringing about the complete hydrogenation of the molecule. Skita observed a reduction over colloidal platinum to *sym*-decahydro-9,10-dihydroxyphenanthrene (II). von Braun and Bayer, working with a nickel catalyst at high temperatures, also observed a preferential hydrogenation of the lateral rings, but their products suffered a partial or complete removal of the oxygen atoms.



We find that phenanthraquinone can be completely hydrogenated both over platinum at room temperature and over Raney nickel at 160° without loss of oxygen. Eight molecular proportions of hydrogen are taken up and the products are perhydro-9,10-dihydroxyphenanthrenes (I). Four beautifully crystalline stereoisomers of this structure have been obtained.

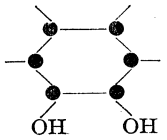
When the hydrogenation was carried out under about 4 atmospheres pressure over Adams platinum oxide in acetic acid solution, a homogeneous glycol, m. p. 174°, was obtained. Over Raney nickel in ethanol at 160° and about 170 atmospheres the reaction yielded principally two isomeric glycols, melting at 174 and 155°, respectively, together with a very small amount of a fourth isomer of m. p. 184°. The glycol of m. p. 174° obtained over nickel differed in crystalline form from that of the same m. p. obtained by the use of platinum, depressed its melting point, and gave a different dibenzoate. All the four products gave analyses corresponding to the perhydroglycol structure, $C_{14}H_{24}O_2$, and yielded distinct dibenzoates. They gave positive Criegee tests for 1,2-glycols.[3]

Corresponding to the six inactive stereoisomeric forms of the fundamental perhydrophenanthrene skeleton[4] there are twenty inactive 9,10-glycols. Each of the *cis-cis* and *trans-trans*

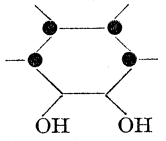
(1) von Braun and Bayer, *Ber.*, **58**, 2667 (1925).
(2) Skita, *ibid.*, **58**, 2685 (1925).
(3) Criegee, *ibid.*, **64**, 260 (1931).
(4) Linstead and Walpole, *J. Chem. Soc.*, 842 (1939); Linstead, Whetstone and Levine, THIS JOURNAL, **64**, 2014 (1942).

forms (*i. e.*, the *cis-syn-cis*, *cis-anti-cis*, *trans-syn-trans* and *trans-anti-trans* configurations) can give rise to *three* glycols (see III below). The remaining two perhydrophenanthrene structures (*cis-syn-trans* and *cis-anti-trans*) can give rise to four glycols each. The extra isomer comes from the fact that both when the two hydroxyl groups are *cis* and when they are *trans*, two forms are possible (see IV below). These possibilities are outlined below for the cases of the *cis-syn-cis* and *cis-syn-trans* series. Only the central ring is shown, for brevity.

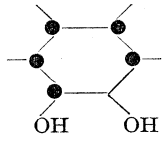
III *c.s.c.* series



(a) Meso

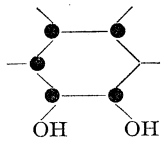


(b) Meso

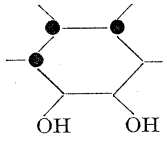


(c) Racemic

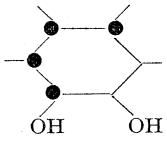
IV *c.s.t.* series



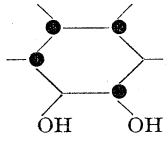
Racemic



Racemic



Racemic



Racemic

[The dots represent hydrogen atoms *above* the plane of the ring.[4]]

To determine the configuration of the perhydrophenanthrene skeleton, the oxidation of the four glycols to the corresponding perhydrodiphenic acids was studied. The configurations of the latter are known.[5] The following reagents were successful for this purpose: lead tetraacetate, potassium periodate, Beckmann's mixture, chromic and acetic acids, and peracetic acid. The following reagents failed: potassium permanganate, nitric acid and potassium hypobromite. In no case was the yield particularly good. The same product was obtained from the three easily obtained glycols (Pt 174°, Ni 174°, Ni 155°). This was the *cis-syn-cis*-perhydrodiphenic acid, m. p. 289°,[6] and in each case was identified by direct comparison and by conversion into the dimethyl ester, m. p. 73°.

It is thus established that these three glycols have the same skeletal configuration and differ only in the orientation of the hydroxyl groups. They therefore correspond with the three formulas III (a), (b), and (c) given above, and all the possible members of this series (*c.s.c.*) have been prepared.

The rare glycol, m. p. 184°, obtained in small amount from the hydrogenation over nickel, was oxidized by chromic and acetic acids to *cis-syn-trans*-perhydrodiphenic acid,[5,6] m. p. 198–200° This was further identified by conversion into the anhydride,[6] m. p. 104°.

As far as the evidence from the isolated products is concerned, therefore, it may be deduced that phenanthraquinone is hydrogenated *cis-syn-cis* over platinum, and almost completely *cis-syn-cis* over nickel. A small amount of *cis-syn-trans* hydrogenation occurs under the conditions of our experiments over the latter catalyst.

In view of the work of Tiffeneau[7] (compare Bartlett[8]) on cyclohexane-1,2-diols, it appeared that it might be possible to dehydrate the glycols obtained from phenanthraquinone into 9-ketoperhydrophenanthrenes. For example, Tiffeneau has shown that *cis*-cyclohexane-1,2-diol yields cyclohexanone when its vapor is passed over alumina at 250–300°. Attempts were therefore made to carry out a parallel dehydration of the reduction products of phenanthraquinone, using both activated alumina and a precipitated alumina catalyst prepared according to Adkins and Krause.[9] In all cases the yield of carbonyl compound was very low. A positive test was obtained by means of Brady's reagent but no oxime or semicarbazone could be isolated. Neither could a ketone be obtained by dehydration with potassium bisulfate, and further experiments in this direction were abandoned.

When the hydrogenation of phenanthraquinone over Raney nickel was carried out at a temperature of 120°, the main product was an incompletely hydrogenated glycol, apparently identical with that of Skita,[2] to which he assigns the decahydro-9,10-dihydroxyphenanthrene structure (II).

Experimental[10]

Phenanthraquinone.—For the purpose of hydrogenation, the quinone was prepared and purified as follows.[11] To a

(5) Linstead and Doering, THIS JOURNAL, **64**, 2003 (1942).

(6) Linstead and Doering, *ibid.*, **64**, 1991 (1942); Linstead and Walpole, *J. Chem. Soc.*, 850 (1939).

(7) Tiffeneau and Tchoubar, *Compt. rend.*, **199**, 1624 (1934); **202**, 1931 (1936).

(8) Bartlett and Rosenwald, THIS JOURNAL, **56**, 1990 (1934).

(9) Adkins and Krause, *ibid.*, **44**, 385 (1922).

(10) All melting points are corrected, unless otherwise stated.

(11) Compare Oyster and Adkins, THIS JOURNAL, **43**, 208 (1921).

hot mixture of 500 cc. of concentrated sulfuric acid and 1500 cc. of water in a 4-l. beaker, 100 g. of crude phenanthrene was added. Potassium dichromate (300 g.) was then added slowly with mechanical stirring and the mixture subsequently stirred for one hour. The product was diluted to *ca.* 4 l. and the crude quinone collected and washed. The products from two such reactions were united and re-oxidized using 1300 cc. of water, 500 cc. of sulfuric acid and 350 g. of potassium dichromate. The final product was worked up as before and dried, yield 185 g. from 200 g. of crude phenanthrene.

This crude quinone was purified through the bisulfite addition product, by heating 75 g. with 1500 cc. of saturated sodium bisulfite solution. The product was filtered and decomposed with an excess of a concentrated aqueous solution of sodium hydroxide. This regenerated phenanthraquinone (58 g.) which was filtered, washed and crystallized from acetic acid (charcoal), yield 47 g., m. p. 205–207°. As a further precaution, in the case of the hydrogenation over platinum, the quinone was again recrystallized from xylene–acetic acid, and from acetic acid before hydrogenation.

Hydrogenation over Platinum.—The quinone (7.5 g.) in 190 cc. of acetic acid was shaken with 1 g. of Adams platinum oxide under about 4 atmospheres of hydrogen. At first the pressure fell very rapidly, and the orange color changed to a blue fluorescence. The reaction later became slower and an additional gram of catalyst was added on the second day. The theoretical amount of hydrogen was taken up on the fifth day. On exposure to air the resulting solution turned yellow and then a deep red. Removal of the solvent left an intensely red residue, which on crystallization from either benzene or toluene gave colorless crystals (2.3 g.). After several crystallizations from toluene *α-cis-syn-cis*-**perhydro-9,10-dihydroxyphenanthrene** was obtained as bold colorless needles, m. p. 173.9–174.4°.

Anal. Calcd. for $C_{14}H_{26}O_2$: C, 74.93; H, 10.80. Found: C, 74.92; H, 10.79.

A mixture of 0.3 g. of the α-glycol, 4 cc. of dry pyridine and 0.6 cc. of benzoyl chloride was heated at 50° for one week. The mixture was poured into dilute acid and extracted with chloroform. The extract was washed with aqueous sodium carbonate and with water, warmed with charcoal, and dried with sodium sulfate. The solvent was removed and the residue crystallized from hexane. The yield of the *α*-**dibenzoate** was 0.5 g., m. p. 153.5–154°.

Anal. Calcd. for $C_{28}H_{32}O_4$: C, 77.71; H, 7.46. Found: C, 77.40; H, 7.53.

Hydrogenation over Nickel.—A preliminary experiment indicated that at 110° and 80 atmospheres, the hydrogenation of phenanthraquinone over Raney nickel came to a stop after about two hours when about 60% of the theoretical amount of hydrogen had reacted. This would correspond approximately to the formation of Skita's compound (II) which involves the reaction of 6 of the total 8 mols of hydrogen (75%). On raising the temperature to 160° the reaction was resumed and the full amount of hydrogeu was taken up in just under two days.

The preparation was accordingly carried out as follows. A steel bomb of 1-l. capacity was charged with a mixture of 26 g. of pure phenanthraquinone, 150 cc. of absolute alcohol and 6 cc. of Raney nickel. The hydrogenation was allowed to proceed at 160° and 170 atmospheres and took nearly thirty-six hours. The resulting solution turned dark brown on exposure to air. It was diluted to about 200 cc. with alcohol and filtered hot through a column of charcoal and alumina. This removed almost all the color. The filtrate deposited 3.75 g. of crystals, m. p. 170–172°. Two crystallizations of this material from benzene yielded pure *β-cis-syn-cis*-**perhydro-9,10-dihydroxyphenanthrene,** m. p. 173.9–174.4°. The crystals are denser and more massive than those of the *α*-isomer. A mixture of the two compounds melts at 142–150°.

The filtrate from the above material was evaporated to 100 cc. and seeded with the *β*-glycol. This yielded a further 2.5 g. of nearly pure *β*-glycol. On further evaporation a little more *β*-glycol separated together with a second product which crystallized in large, clear prisms. These were separated partly mechanically and partly by taking advantage of the fact that the *β*-glycol dissolved faster in warm alcohol. The prisms melted at 148–152° and after three recrystallizations from benzene yielded the pure *γ-cis-syn-cis*-**perhydro-9,10-dihydroxyphenanthrene,** m. p. 154.5–155°.

The final residue from the fractional crystallizations was submitted to vacuum distillation. After removal of a viscous liquid boiling up to 180° (8 mm.) (which is probably partially de-oxygenated), the main portion distilled at 198–200° and set to a glassy solid. Crystallization of this from benzene with suitable seeding yielded more of the *β*- and *γ*-glycols.

The fraction boiling between 180 and 198° was mixed with hexane and allowed to stand. A crystalline solid was slowly deposited. The first crop was recrystallized from benzene. The crystals so obtained (60 mg.) melted at 179–183° and after two further crystallizations from benzene gave pure *α-cis-syn-trans*-**perhydro-9,10-dihydroxyphenanthrene,** long clear prisms, m. p. 184–184.5°. Further fractional crystallization of the remainder of the material led to the separation of more of all three forms (*β*- and *γ-cis-syn-cis*, m. p.'s 174 and 155°, and *α-cis-syn-trans*, m. p. 184°).

The total yield of crystalline glycols was 7.54 g. of the *β*-form, m. p. 174°, 3.96 g. of the *γ*-form, m. p. 155°, and 138 mg. of the *cis-syn-trans* form, m. p. 184°.

Anal. Calcd. for $C_{14}H_{24}O_2$: C, 74.93; H, 10.80. Found—for the *β*-glycol: C, 74.86; H, 10.94; for the *γ*-glycol: C, 75.05; H, 10.91; for the *cis-syn-trans*-glycol[12]: C, 74.81; H, 10.56.

By the method described above for the *α*-glycol, the *β*- and *γ*-glycols were converted into their dibenzoates. These melted at 115.5–116° (*β*), and 114.2–115° (*γ*), respectively. A mixture melted at 102–106°.

Anal. Calcd. for $C_{28}H_{32}O_4$: C, 77.71; H, 7.46. Found— for the *β*-dibenzoate: C, 77.46; H, 7.55; for the *γ*-dibenzoate: C, 77.50; H, 7.53.

Oxidation of the Glycols. (a) *α-cis-syn-cis*-**Glycol (m. p. 174°).**—This glycol (500 mg.) and 1.20 g. of lead tetraacetate were added to 50 cc. of benzene. The solid gathered in a lump which was crushed. After a few minutes the product was filtered and the insoluble solid washed with benzene. The filtrate and washings were freed from

(12) Analysis by Miss Eleanor Werble.

solvent and the oily residue was allowed to stand for two days at 4° with 3 cc. of 33% hydrogen peroxide and 5 cc. of 10% aqueous sodium hydroxide. The product was extracted with ether and the aqueous layer acidified. This precipitated a gummy mass, which was boiled with benzene and the insoluble portion crystallized from alcohol. This yielded *cis-syn-cis*-perhydrodiphenic acid (10 mg.), m. p. 273–280°, mixed m. p. 280–285°. The acid was further identified by conversion into the dimethyl ester, m. p. 69–71°, mixed m. p. 71–73°.

An attempt at the oxidation of the same glycol with potassium permanganate in acetone and with nitric acid at 50° failed to yield a solid acid.

(b) *β-cis-syn-cis*-**Glycol (m. p. 174°).**—The glycol (500 mg.) was dissolved in 50 cc. of hot benzene and the solution treated at 34° with 1.25 g. of lead tetraacetate. A very small temperature rise occurred. The mixture was allowed to stand overnight, filtered and the filtrate treated with alkaline hydrogen peroxide as described above. *cis-syn-cis*-Perhydrodiphenic acid was isolated in the manner already described, yield 30 mg., m. p. 275°, mixed m. p. 280°. The dimethyl ester had m. p. 72–73°, mixed m. p. 73–74°.

The same glycol (250 mg.) was shaken with potassium periodate (230 mg.) and dilute methanol, and then left at 55° overnight. Most of the methanol was removed, a solution of bromine in potassium hydroxide was added, and the product was extracted with ether. Acidification of the alkaline solution gave 40 mg. of acid melting at about 250°, and after one crystallization at 260–267°.

The β-glycol (300 mg.) was dissolved in acetic acid (10 cc.) and a solution of 900 mg. of chromic acid in a little water was added slowly. The solution was divided in half. The first half was allowed to stand at 0° for two hours, and the second half was kept at 75° for the same time. On dilution with water both portions gave *cis-syn-cis*-perhydrodiphenic acid [m. p. (crude) 275–277°] but the yield from the cold oxidation (30 mg.) was twice that from the reaction at 75°.

A very small yield of the same acid was obtained by oxidizing the β-glycol with Beckmann's mixture. No solid acid could be isolated by oxidations from potassium hypobromite.

(c) *γ-cis-syn-cis*-**Glycol (m. p. 155°).**—The glycol (100 mg.) was suspended in 1 cc. of acetic acid and a solution of chromic acid (120 mg.) in 2 cc. of dilute acetic acid was added during one hour at room temperature. The product was warmed on the steam-bath for five minutes. Addition of 10 cc. of water precipitated 18 mg. of *cis-syn-cis*-perhydrodiphenic acid, m. p. 270–274°. The identity was confirmed by the preparation of the dimethyl ester, m. p. 67–70°, mixed m. p. 70–72°.

The same acid was obtained by the oxidation of the 152° glycol (109 mg.) with peracetic acid (1.5 g. of 11.2%) for two months at room temperature. Evaporation of the solvent left a gum and a small amount of crystalline solid. The gum was removed by washing with cold benzene. There remained 5 mg. of *cis-syn-cis*-perhydrodiphenic acid, which was identified by m. p. and mixed m. p. Oxidation of the γ-glycol with lead tetraacetate or with potassium periodate did not yield a crystalline acid.

(d) *α-cis-syn-trans*-**Glycol (m. p. 184°).**—The glycol (100 mg.) was dissolved in glacial acetic acid (4 cc.) and a solution of 130 mg. of chromic acid in 1 cc. of acetic acid and 1 cc. of water was added slowly. The solution was allowed to stand at 4° overnight, diluted to 20 cc. with water and extracted four times with 5-cc. portions of ether. The ether was extracted with aqueous sodium hydroxide and the alkaline extract acidified and again extracted with ether. The ether was removed and the residual acetic acid solution was diluted with water. This yielded 41 mg. of *cis-syn-trans*-perhydrodiphenic acid, m. p. 197.5–199.5°, either alone or in admixture with authentic material. The second crop of acid was identical and equally pure. The identity was confirmed by the preparation of the anhydride, m. p. and mixed m. p. 103–104°.

Dehydration of the Glycols.—The method used was essentially that of Tiffeneau.[7] None of the three *cis-syn-cis* glycols yielded a ketone in sufficient amount to permit of the isolation of an oxime or semicarbazone, although indications of a positive reaction with 2,4-dinitrophenylhydrazine were obtained.

The γ-glycol, m. p. 155°, (150 mg.) was heated with 600 mg. of fused potassium bisulfate for four hours at 150–160°. The product was partitioned between chloroform and water. Evaporation of the chloroform layer left a mixture of an oil and a crystalline solid, which was washed with cold methanol. The methanol solution gave a very small amount of an oxime in the cold; this melted at 190–200° without crystallization. The residual crystals were almost insoluble in boiling alcohol, but easily soluble in hexane and benzene. After three crystallizations from ethyl acetate a pure *compound* was isolated which analyzes to $C_{14}H_{22}O$, or a polymer of this. It melts at 202–203° and is not affected by bromine in chloroform. This last property and the high m. p. do not agree with the decahydro-9-phenanthrol structure suggested by the analysis. A bimolecular structure with two ethereal oxygen atoms is possible, but the solubility in hydrocarbons seems high for so large a molecule.

Anal.[12] Calcd. for $C_{14}H_{22}O$: C, 81.49; H, 10.75. Found: C, 81.53; H, 10.55.

sym-**Decahydro-9,10-dihydroxyphenanthrene.**—Phenanthraquinone (3 g.) and 0.8 cc. of Raney nickel were treated with 20 cc. of alcohol and hydrogenated at 120°. Nearly exactly 5 mols of hydrogen was taken up. The resulting solution turned brown and later red in air. The solvent was removed under reduced pressure and the product crystallized from hexane. Fine white needles of the decahydro-glycol separated, m. p. 135–136° (Skita[2] gives m. p. 136°), yield 1.5 g. A mixture with *sym*-octahydro-9-phenanthrol (m. p. 135°) melted at 110–125°. Acetylation with sodium acetate and acetic anhydride gave a product of m. p. 160–161°. Skita[2] describes the diacetate as melting at 160°. Attempts to convert the decahydro-glycol to *sym*-octahydro-9-phenanthrol by means of potassium bisulfate and *p*-toluenesulfonic acid were unsuccessful. Oxidation of the decahydro-glycol with peracetic acid by Böeseken's method failed to yield an octahydrodiphenic acid.

Summary

The possibilities of stereoisomerism among the perhydro-9,10-dihydroxyphenanthrenes are indicated.

Phenanthraquinone is per-hydrogenated over platinum at 25° to a perhydro-9,10-dihydroxyphenanthrene, m. p. 174°, and over nickel at 160° to a mixture of three stereoisomers of the above, with m. p.'s 174° (not identical with the platinum product), 155 and 184°, respectively. The first three products have the *cis-syn-cis* configuration and may be oxidized to *cis-syn-cis*-perhydrodiphenic acid. The glycol of m. p. 184°, which is obtained in very small yield, has a *cis-syn-trans* configuration as it gives the *cis-syn-trans*-perhydrodiphenic acid on oxidation. The three *cis-syn-cis* glycols differ in the orientation of their hydroxyl groups and represent all the forms with this skeletal configuration which are theoretically possible. Over nickel at 120°, phenanthraquinone yields mainly Skita's decahydro-9,10-dihydroxyphenanthrene.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 30, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

O-Pentaacetyl-*d*-gluconates of Polyhydric Alcohols and Cellulose[1]

BY M. L. WOLFROM AND P. W. MORGAN[2]

To our knowledge, only the methyl[3] and ethyl[4] esters of *d*-gluconic acid pentaacetate have been reported. The object of the present investigation was to prepare and characterize the O-pentaacetyl-*d*-gluconates of polyhydric alcohols and cellulose. Such esters were prepared from ethylene glycol, propanediol-1,3 (trimethylene glycol), bis-(2-hydroxyethyl) ether (diethylene glycol), glycerol, (*dextro*)-sorbitol, *d*-mannitol, α-methyl-*d*-glucoside, mercerized cotton linters and a modified cellulose acetate by reaction of these substances with an excess of *d*-gluconyl chloride pentaacetate in pyridine solution.

Ethylene glycol, propanediol-1,3 and bis-(2-hydroxyethyl) ether formed crystalline di-esters. Glycerol, (*dextro*)-sorbitol, *d*-mannitol and α-methyl-*d*-glucoside yielded fully esterified products in the form of colorless, amorphous powders. This lack of crystallizing power is not surprising, as the molecular weights of these esters are very high. Thus the ethylene glycol derivative has a molecular weight of 839 and the hexitol derivative ($C_{102}H_{134}O_{72}$, shown below) has a molecular weight of 2512.

$$\begin{array}{l} H_2COCO(HCOCOCH_3)_4CH_2OCOCH_3 \\ | \\ (HCOCO(HCOCOCH_3)_4CH_2OCOCH_3)_4 \\ | \\ H_2COCO(HCOCOCH_3)_4CH_2OCOCH_3 \end{array}$$

In the case of mercerized cotton linters, pyridine was found unsatisfactory as a reaction medium because the intense coloration developed by the acid chloride and pyridine, even at room temperature, was very strongly adsorbed on the fibers. Of several other tertiary bases tried as a substitute for pyridine in the reaction with cellulose, triethylamine in an inert solvent was found most satisfactory for the elimination of color. Using triethylamine as the base, a cream-colored, fibrous cellulose O-pentaacetyl-*d*-gluconate was obtained containing 0.45 O-pentaacetyl-*d*-gluconyl group per anhydroglucose unit. In pyridine, a modified cellulose acetate (1.72 acetyl group per anhydroglucose unit) yielded a mixed ester containing 0.75 O-pentaacetyl-*d*-gluconyl group per anhydroglucose unit, while with triethylamine in chloroform a product with 0.33 O-pentaacetyl-*d*-gluconyl groups was produced. The former was obtained as a cream-colored powder that was acetone and chloroform soluble and formed brittle films. The latter product was colorless, was acetone and chloroform soluble, and formed strong, flexible, transparent films.

Experimental

Preparation of the O-Pentaacetyl-*d*-gluconates of Several Polyhydric Alcohols.—The anhydrous polyhydric alcohol (0.5 g.) was dissolved in dry pyridine (50 cc.). Gluconyl chloride pentaacetate[4b] (9 g.) was quickly ground and added in approximately 1-g. portions to the solution with shaking. The mixture became warm and slowly turned deep orange in color. A crystalline water-soluble pyridine-complex separated after a few minutes. After standing overnight, the reaction mixture was diluted to incipient turbidity with water and the material crystallized. More water was added gradually until the volume was about 1 liter. This procedure was followed for the

(1) Presented in essentially the present form before the Division of Cellulose Chemistry at the 101st Meeting of the American Chemical Society, St. Louis, Missouri, April 9, 1941.

(2) Du Pont Cellulose Research Fellow.

(3) G. B. Robbins and F. W. Upson, THIS JOURNAL, **62**, 1076 (1940).

(4) (a) F. Volpert, *Ber.*, **19**, 2622 (1886); (b) R. T. Major and E. W. Cook, THIS JOURNAL, **58**, 2474, 2477 (1936).

TABLE I

O-PENTAACETYL-*d*-GLUCONATES OF POLYHYDRIC ALCOHOLS

Substance, (O-pentaacetyl-*d*-gluconate)	Formula	State	M. p., °C.	$[\alpha]^{25}D$, *c* 4, abs. $CHCl_3$	Yield,[a] g., pure product	Analyses, % Calculated C	Calculated H	Calculated Saponification value[b]	Found C	Found H	Found Saponification value[b]
Ethylene glycol di-	$C_2H_4O_2(C_6H_6O_6(COCH_3)_5)_2$	crystalline	94–95	+15°	5.2	48.69	5.53	14.3	48.50	5.63	14.3
Propanediol-1,3 di-	$C_3H_6O_2(C_6H_6O_6(COCH_3)_5)_2$	crystalline	88–89	+18.5	4.5	49.30	5.68	14.1	49.22	5.84	14.2
Bis(2-hydroxyethyl) ether di-	$C_4H_8O_3(C_6H_6O_6(COCH_3)_5)_2$	crystalline	111–112	+12	3.8	48.98	5.71	13.6	48.70	5.78	13.7
Glycerol tri-	$C_3H_5O_3(C_6H_6O_6(COCH_3)_5)_3$	white powder	58–65[c]	+20	4.5	48.74	5.45	14.3	48.66	5.60	14.3
(*dextro*)-Sorbitol hexa-	$C_6H_8O_6(C_6H_6O_6(COCH_3)_5)_6$	white powder	65–78[c]	+30	4.0	48.75	5.38	14.3	49.02	5.29	14.3
d-Mannitol hexa-	$C_6H_8O_6(C_6H_6O_6(COCH_3)_5)_6$	white powder	65–78[c]	+37	2.0	48.75	5.38	14.3	48.68	5.33	14.3
α-Methyl-*d*-gluco-pyranoside tetra-	$C_7H_{10}O_6(C_6H_6O_6(COCH_3)_5)_4$	white powder	68–72[c]	+57	2.0	48.86	5.42	13.7	49.01	5.41	13.7

[a] From 0.5 g. of the polyhydric alcohol. [b] Method of A. Kunz and C. S. Hudson, THIS JOURNAL, **48**, 1982 (1926); recorded as cc. 0.1 *N* NaOH per 100 mg. of substance. [c] Softening point.

first three products of Table I, where the alcohols were ethylene glycol, trimethylene glycol (propanediol-1,3) and diethylene glycol (bis-(2-(hydroxyethyl) ether). Crystalline products were obtained in each case and were purified by recrystallization from ethanol (decolorizing charcoal) and methanol–water. It was found that the addition of ethylene glycol to a solution of gluconyl chloride pentaacetate in pyridine gave no water-insoluble product and the solution became nearly black in color.

For the last four products of Table I (esters of glycerol, *dextro*-sorbitol, *d*-mannitol and α-methyl-*d*-glucopyranoside), the final products were obtained in the form of white, amorphous powders that resisted crystallization but were of analytical purity. These substances were isolated by pouring the reaction mixture through a small orifice into 800 cc. of a rapidly stirred mixture of ice and water. Purification was effected by solution in acetone (decolorizing charcoal) and precipitation by the addition of water. Colloidal solutions sometimes formed which were easily broken by the addition of a small amount of electrolyte. Drying was carried out slowly and below 45°. The esters of mannitol and of α-methyl-glucoside were purified from methanol (decolorizing charcoal)–water. In the case of mannitol, the reaction mixture was heated initially to 50° for five minutes and was then kept at room temperature overnight. The α-methyl-glucoside reaction mixture was kept at room temperature for seven days. All of the esters were soluble in the common solvents except petroleum ether and water.

Cellulose O-Pentaacetyl-*d*-gluconate.—High viscosity cotton linters[5] (0.5 g.) were mercerized for one hour at 20° in 25 cc. of 18% sodium hydroxide solution. The fibers were washed with water until free of alkali and placed in 50 cc. of dry nitrobenzene after solvent interchange with acetone and nitrobenzene. Triethylamine (0.7 cc.) and gluconyl chloride pentaacetate (5.2 g.) were added and the mixture heated at 80° for sixteen hours. The fibers were well dispersed but undissolved at the end of this time. The liquor showed no turbidity when diluted with large amounts of ethanol. The fibrous product was collected, thoroughly washed with acetone, water and ethanol, and then dried; yield 0.70 g. It was cream colored and resembled the original linters in texture.

(5) Furnished by the courtesy of the Hercules Powder Co., Hopewell, Va.

A saponification was made according to the procedure of Malm and Clarke[6] for cellulose acetate. A blank was run on the solvent and on gluconic acid pentaacetate and corrections were made for a small absorption of alkali by the cellulose. The material was prepared for analysis by drying at 100° for three hours. The saponification equivalents found were 124.3 and 125.0 (8.04 cc. and 8.00 cc. of 0.1 *N* NaOH per 100 mg.). These correspond to 0.45 and 0.44 O-pentaacetyl-*d*-gluconyl group per anhydroglucose unit.

Cellulose Acetate O-Pentaacetyl-*d*-gluconate. Procedure A.—Cellulose acetate[7] (1.72 acetyl groups per anhydroglucose unit, 1.0 g.) was dissolved in 50 cc. of dry pyridine with 6.0 g. of gluconyl chloride pentaacetate and then kept at room temperature for one hundred and twenty hours. Upon pouring the mixture into rapidly stirred, cold water, a flesh-colored precipitate was obtained. The product was purified by precipitation with water from acetone solution and from pyridine solution (decolorizing charcoal), giving a cream-colored, amorphous powder; yield 1.53 g., spec. rot. +2.5° (24°, D line, *c* 3, $CHCl_3$), spec. rot. −10° (21°, *c* 1.5, dry pyridine). The substance was soluble in acetone, pyridine, glacial acetic acid, chloroform and warm tetrachloroethane. It was incompletely soluble in warm 75% ethanol. It formed dark yellow, brittle films. The original cellulose acetate was insoluble in acetone and chloroform, but was easily soluble in pyridine and warm 75% ethanol, and its specific rotation was −13° (24°, D line, *c* 3, dry pyridine).

The saponification equivalents[6] determined in acetone were 84.1 and 84.0 (11.89 cc. and 11.91 cc. 0.1 *N* NaOH per 100 mg.). These values correspond to 0.75 O-pentaacetyl-*d*-gluconyl group per anhydroglucose unit.

Procedure B.—Another sample of the same cellulose acetate (1.0 g.) was placed in 60 cc. of absolute chloroform with 1.0 cc. of triethylamine and 5.2 g. of gluconyl chloride pentaacetate and heated for forty-two hours at 60°. The mixture became orange in a short time and the cellulose acetate slowly went into solution. The solution was filtered and poured into 300 cc. of absolute ethanol, giving a gelatinous precipitate, which, after thorough washing with ethanol and water, dried to a colorless, amorphous powder;

(6) C. J. Malm and H. T. Clarke, THIS JOURNAL, **51**, 274 (1929).

(7) Furnished through the courtesy of the Du Pont Rayon Co., Waynesboro, Va.

yield 1.22 g., spec. rot. +1° (24°, D line, *c* 3.5, $CHCl_3$) and −9° (23°, D line, *c* 3.5, dry pyridine).

The product was soluble in acetone, chloroform, glacial acetic acid, pyridine, warm dioxane and benzene. It dissolved somewhat in warm 75% ethanol accompanied by strong swelling. It formed strong, flexible, colorless films from acetone or chloroform solutions.

The saponification equivalents[6] determined in acetone were 99.1 and 99.7 (10.09 cc. and 10.03 cc. 0.1 *N* NaOH per 100 mg.). These values correspond to 0.33 and 0.29 O-pentaacetyl-*d*-gluconyl groups per anhydroglucose unit. Repeated esterification of cellulose acetate under conditions similar to those described above did not raise the substitution above 0.37 O-pentaacetyl-*d*-gluconyl group per anhydroglucose unit.

Summary

1. Crystalline di-(O-pentaacetyl-*d*-gluconates) of ethylene glycol, propanediol-1,3 and bis-(2-hydroxyethyl) ether have been prepared by the reaction of the corresponding glycol with *d*-gluconyl chloride pentaacetate in pyridine.

2. Under similar conditions glycerol, (*dextro*)-sorbitol, *d*-mannitol and α-methyl-*d*-glucoside formed fully esterified O-pentaacetyl-*d*-gluconates in the form of colorless, amorphous powders.

3. Mercerized cotton linters were esterified in the presence of triethylamine and nitrobenzene, forming a fibrous product containing 0.4 O-pentaacetyl-*d*-gluconyl group per anhydroglucose unit.

4. A modified cellulose acetate (1.72 acetyl groups per anhydroglucose unit) in pyridine gave a mixed ester containing 0.7 O-pentaacetyl-*d*-gluconyl group per anhydroglucose unit and in chloroform and triethylamine, a mixed ester containing 0.3 O-pentaacetyl-*d*-gluconyl group per anhydroglucose unit was formed.

COLUMBUS, OHIO RECEIVED APRIL 6, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLORADO UNIVERSITY]

The Glyoxalines. II. A Study of the Reaction between Benzamidine and Phenylglyoxal

BY RICHARD C. WAUGH,* JOHN B. EKELEY AND ANTHONY R. RONZIO

A reaction between benzamidine and phenylglyoxal was reported by Kunckell and Bauer[1] in which a compound described as "phenacal benzamidine" (m. p. 224°) was isolated. When repeated by us the reaction proceeded exactly as described by them. The product obtained, recrystallized from ethyl alcohol, melted at 225°. Nitrogen analyses, however, failed to check the value for "phenacal benzamidine." The value obtained (13.65%) was so close to the value for kyanphenin (13.60%) that a melting point of the mixture was taken. The melting point found was 228° (m. p. of pure kyanphenin 230–231°). The solubilities and physical appearance of "phenacal benzamidine" and kyanphenin were also identical. The experiment was repeated many times with the same result. Hence, the work of Kunckell and Bauer was considered to be in error and the reaction between benzamidine and phenylglyoxal was re-investigated.

The products obtained from the reaction between benzamidine and phenylglyoxal under different conditions are shown in Chart I. Compound I was formed when the two reactants were treated with base in cold alcohol solution. Recrystallized from ethyl acetate, the product gave analyses corresponding to the formula $C_{17}H_{18}O_3N_2$. Since the compound formed readily in cold solution, it appeared likely that it was a simple addition product. The compound contains one-half molecule of ethyl acetate of crystallization.

Compound I is converted to Compound II by dissolving in basic solution, heating for a short time, then carefully neutralizing with acid. Recrystallized from dioxane, the analyses correspond to a compound $C_{17}H_{16}O_2N_2$.[2] The compound contains one-half molecule of dioxane of crystallization as proved by a cryoscopic determination.

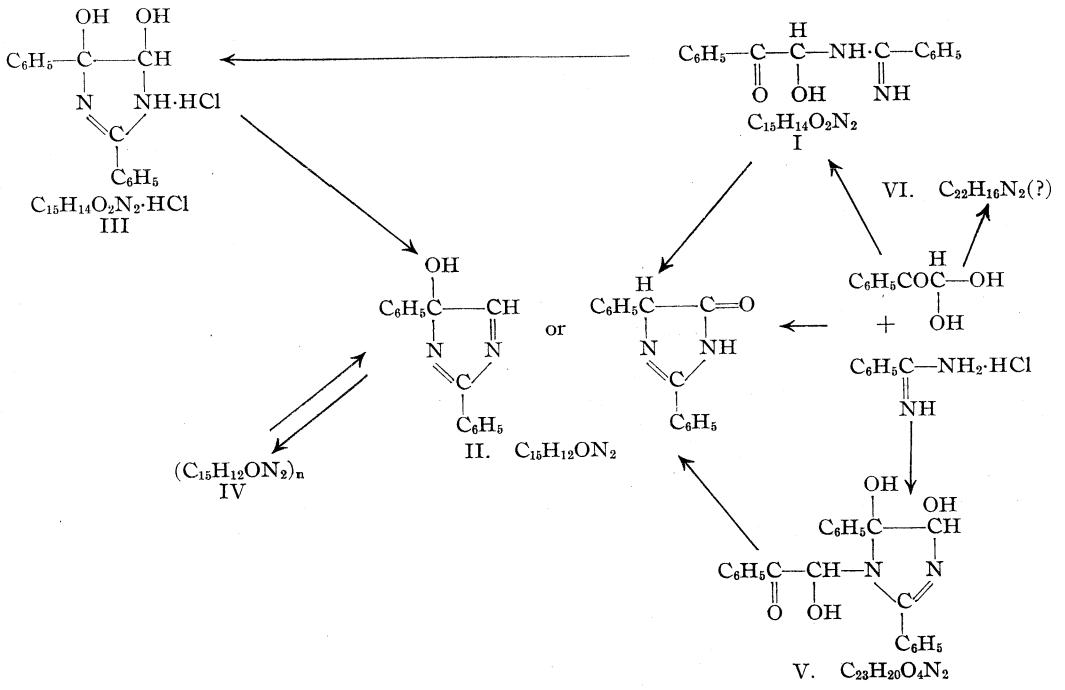
When a basic solution of either Compound I or II is treated with an excess of hydrochloric acid, a voluminous precipitate of the hydrochloride of Compound III is formed. This compound is very unstable in the absence of acids. Analyses gave results corresponding to the formula $C_{15}H_{14}O_2N_2 \cdot HCl$.

* Now with Eastman Kodak Co.

(1) Kunckell and Bauer, *Ber.*, **34**, 3029 (1901).

(2) In the first paper of this series [Fisher, Ekeley and Ronzio, THIS JOURNAL, **64**, 1434 (1942)] it has been shown that phenylglyoxal and urea react to form 4-phenyl-hydantoin. Should a similar reaction take place when benzamidine is used instead of urea, the formula for Compound II, would then be the second structure shown on Chart I.

CHART I



Upon standing in solvents containing traces of base, Compound II changes to Compound IV. This compound was insoluble in all the solvents tried. Analyses gave results corresponding to the empirical formula $C_{15}H_{12}ON_2$. It will be seen that this formula is identical to the formula for Compound II without any solvent of crystallization. The analyses and insolubility indicate that Compound IV is a polymer of Compound II.

Phenylglyoxal and benzamidine hydrochloride dissolved in a strong water solution of sodium acetate yields Compound V as an orange powder. When this powder is dissolved in hot alcohol, it almost instantly separates as yellow needles of Compound II. Analyses gave values which could not be formulated into any logical structure. The results were, however, close to those given by a reaction between two molecules of phenylglyoxal and one molecule of benzamidine. It is probable that the orange powder is Compound V mixed with a small amount of Compound II.

A compound of unknown structure (VI) giving analyses for $C_{22}H_{16}N_2$ was obtained by boiling benzamidine hydrochloride together with phenylglyoxal for several hours. Since a strong odor of ammonia was noted, it is probable that the product is formed from fragments of benzamidine and phenylglyoxal.

Experimental

Compound I. Hydroxyphenacylbenzamidine.—Concentrated potassium hydroxide was added to a cooled 95% alcohol solution containing 3 g. (0.02 mole) of phenylglyoxal hydrate and 3.8 g. (0.02 mole) of benzamidine hydrochloride until the solution was distinctly basic. The precipitated potassium chloride was filtered off and the filtrate was cooled in an ice–salt mixture.

Dropwise addition of water precipitated a colorless compound which was filtered off, dried and recrystallized from ethyl acetate containing just enough absolute ethyl alcohol to dissolve the compound. The compound must be dried *in air*. Either heat or a drying agent cause decomposition. The compound is soluble in acids, bases, alcohol, acetone and dioxane; insoluble in ether, hydrocarbons and chloroform; m. p. 112–115° with decomp., yield, 2.4 g. (40%).

Anal. Calcd. for $2(C_{15}H_{14}O_2N_2)\cdot CH_3\text{-}COO\text{-}C_2H_5$: C, 68.60; H, 6.05; N, 9.30. Found: C, 68.83; H, 5.99; N, 9.40.

Compound II. 2,4-Diphenyl-4-hydroxyglyoxaline (or **2,4-Diphenyl-5-ketodihydroglyoxaline**).—Three grams of phenylglyoxal hydrate (0.02 mole) and 3.8 g. of benzamidine hydrochloride (0.02 mole) were dissolved in 200 ml. of warm water. The addition of 1 ml. of 50% potassium hydroxide and boiling caused a deep brown color to form. After fifteen minutes the solution was cooled and carefully neutralized, whereupon a flocculent yellow solid formed. Recrystallized from dioxane, the sparkling yellow needles melted at 251–252°; the yield was 64%.

Anal. Calcd. for $2(C_{15}H_{12}ON_2)\cdot C_4H_8O_2$: C, 72.90; H, 5.72; N, 10.00. Found: C, 72.80; H, 5.80; N, 10.03.

A molecular weight determination by the method of Smith and Young[3] gave a value of 189. Calcd. for $2(C_{15}$-

(3) J. Smith and W. Young, *J. Biol. Chem.*, **75**, 289 (1927).

$H_{12}ON_2)\cdot C_4H_5O_2$: mol. wt., 189. The compound is soluble in base, alcohol, dioxane and ethyl acetate; insoluble in ether, acetone and the hydrocarbons; soluble in acids but reprecipitates in a short time. A basic alcohol solution of the compound shows a blue fluorescence upon the addition of ether.

The same compound may be prepared by dissolving Compound I in hot base, followed by neutralization of the solution with acid.

A portion of this compound boiled with acetic anhydride yielded a gummy solid, which, recrystallized from a mixture of dioxane and water, yielded colorless plates of the monoacetyl derivative melting at 174°.

Anal. Calcd. for $C_{17}H_{14}O_2N_2$: C, 73.40; H, 5.05; N, 10.07. Found: C, 73.50; H, 5.00; N, 9.95.

Compound III. 2,4-Diphenyl-4,5-dihydroxydihydroglyoxaline.—A solution of 3 g. (0.02 mole) of phenylglyoxal hydrate and 3.8 g. (0.02 mole) of benzamidine hydrochloride in 50 ml. of glacial acetic acid was refluxed. Within ten minutes a white precipitate began to form. After being heated for an hour the mixture was cooled and filtered. The solid gave a positive chloride test. The product was recrystallized from glacial acetic acid containing enough concentrated hydrochloric acid to prevent the formation of a yellow color. The colorless needles obtained in this manner melted at 282° after darkening at 260°; the yield was 62%.

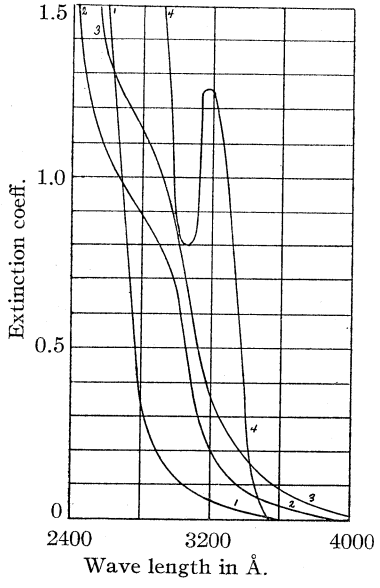


Fig. 1.

The compound was also prepared by adding a large excess of concentrated hydrochloric acid to a basic solution of either Compound I or Compound II. This method of preparation is less convenient.

In the absence of acid the compound quickly forms Compound II.

Anal. Calcd. for $C_{15}H_{14}O_2N_2\cdot HCl$: C, 62.00; H, 5.17; N, 9.65. Found: C, 61.90; H, 5.20; N, 9.50.

Compound III refluxed with acetic anhydride yielded a gummy product which, when recrystallized from dioxane–water mixture, yielded colorless plates of the diacetyl derivative which melted at 181° after three recrystallizations.

Anal. Calcd. for $C_{19}H_{18}O_3N_2$: C, 70.85; H, 5.95; N, 8.70. Found: C, 70.90; H, 5.65; N, 8.85.

Compound IV $(C_{15}H_{12}ON_2)_x$.—When an alcohol or dioxane solution of Compound II containing a trace of base was allowed to stand, it gradually lost its yellow color and a white powder was deposited. Insoluble in the solvents tried, the powder was washed successively with boiling alcohol, ethyl acetate, methyl alcohol, dioxane and acetone. After this treatment the compound darkened at 250° and melted at 262°.

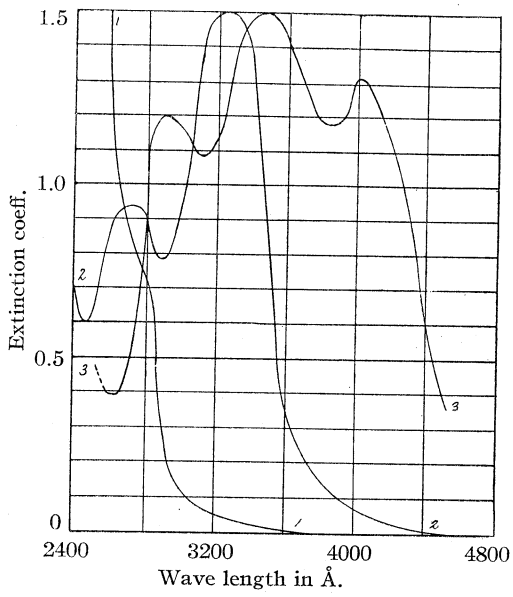


Fig. 2.

Attempts at acetylation produced an unrecrystallizable gum. Solution in hot base regenerated Compound II which was precipitated upon neutralization.

Anal. Calcd. for $(C_{15}H_{12}ON_2)_x$: C, 76.30; H, 5.08; N, 11.80. Found: C, 76.20; H, 4.73; N, 11.85.

Compound V. 2,4-Diphenyl-4,6-dihydroxy-3-(β-hydroxyphenacyl)-dihydroglyoxaline.—A water solution made by dissolving 3.8 g. (0.02 mole) of benzamidine hydrochloride, 3 g. (0.02 mole) of phenylglyoxal hydrate and 10 g. of sodium acetate in 200 ml. of water was allowed to stand for three days at room temperature. A brilliant orange powder was formed which defied all attempts at recrystallization; weight 3.3 g. (87%). The compound dissolved easily in alcohol, then, upon standing about one minute, yellow needles of Compound II precipitated out. The only purification that could be carried out was solution in benzene followed by precipitation of the compound by adding petroleum ether. The melting point of the product thus purified was 73–80°.

Anal. Calcd. for $C_{23}H_{20}O_4N_2$: C, 71.10; H, 5.16; N, 7.23. Found: C, 72.80; H, 5.14; N, 7.50.

Partial decomposition to Compound II is the only explanation which can, at present, be offered for these anomalous results.

Compound VI, $C_{22}H_{16}N_2$.—When 3 g. (0.02 mole) of phenylglyoxal hydrate and 3.8 g. (0.02 mole) of benzamidine hydrochloride in 300 ml. of water were boiled for three hours, a gummy substance formed which was filtered from the hot solution and recrystallized three times from ethyl alcohol. The colorless needles obtained melted at 170–172°. The yield was less than 1%.

Anal. Calcd. for $C_{22}H_{16}N_2$: C, 85.70; H, 5.19; N, 9.09. Found: C, 85.83; H, 5.38; N, 9.18.

No structure could be assigned to fit the formula and which would explain its formation. It would appear that the compound is the result of reaction between decomposition fragments.

TABLE I

ABSORPTION SPECTRA CURVES (1-CM. CELL)

Plate	Compound	Formula	Wt. used, g.	Solvent, ml.	Curve
I	IV	$(C_{15}H_{12}ON_2)_x$	0.00277	50 1% KOH	1
I	II	$2(C_{15}H_{12}ON_2)\cdot C_4H_8O_2$	.00250	50 1% KOH	2
I	III	$C_{15}H_{14}O_2N_2\cdot HCl$	.00266	50 1% KOH	3
I	VI	$C_{22}H_{16}N_2$	.00338	50 abs. EtOH	4
II	I	$2(C_{15}H_{14}O_2N_2)\cdot C_4H_8O_2$	.00250	50 abs. EtOH	1
II	III	$C_{15}H_{14}O_2N_2\cdot HCl$	.00112	50 EtOH contg. 5 ml. concd. HCl	2
II	II	$2(C_{15}H_{12}ON_2)\cdot C_4H_8O_2$	.00198	50 abs. EtOH	3

Absorption spectra data were obtained using a Hilger E3 spectrograph, Hilger Sector photometer and Eastman Wrattan and Wainwright Panchromatic plates. An under-water spark served as a light source.

It may be seen that Curves II and III, Plate I, and Curve I, Plate II are identical. This clearly demonstrates the formation of Compound II when base is added to a solution of either Compound I or Compound III.

Summary

1. The reaction between benzamidine and phenylglyoxal has been studied and found to yield a 2,4-diphenyl-4-hydroxyglyoxaline (or 2,4-diphenyl-5-keto-dihydroglyoxaline).

2. Intermediate, unstable compounds have been isolated and studied, and formulas proposed for them.

3. Absorption spectra curves in the ultraviolet and visible have been obtained for the compound studied.

BOULDER, COLORADO RECEIVED JUNE 16, 1942

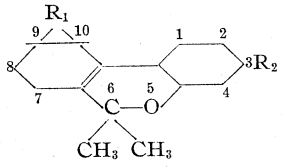
[CONTRIBUTION FROM THE WILLIAM G. KERCKHOFF LABORATORIES OF THE BIOLOGICAL SCIENCES, CALIFORNIA INSTITUTE OF TECHNOLOGY, PASADENA, AND THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Some Analogs of Synthetic Tetrahydrocannabinol

BY GORDON A. ALLES, ROLAND N. ICKE AND GEORGE A. FEIGEN

The recent elucidation of the structure of cannabinol by Adams and co-workers,[1] and the discovery of marihuana activity in synthetic tetrahydrocannabinol[2a] and hexahydrocannabinol[2b] has opened the field for study of relationships between chemical constitution and this type of physiological action. The optically active tetrahydrocannabinols and hexahydrocannabinols derived by isomerization of cannabidiol[3] are of considerable interest in this connection, though their exact structure is in some doubt. Similarly, pulegone-5-*n*-alkylresorcinol products studied by Todd and co-workers,[4] and by Adams and co-workers[5] are of much interest, though the composition of such products is not yet certain.

Several series of compounds of known structure that are analogs or homologs of synthetic tetrahydrocannabinol and hexahydrocannabinol have been prepared by Adams and co-workers,[5,6] by Todd and co-workers[4,7] and by Bembry and Powell.[8] The object of the present work was to prepare and study the physiological activity of a series of analogs of synthetic tetrahydro*nor*-cannabinol[5,7,8] (Series I) and of tetrahydrocannabinol (Series II) that lack a hydroxyl group in the 1-position.



Series I, $R_1 = H$
Series II, $R_1 = CH_3$

The series of compounds were prepared in which the R_2 group in the 3-position was amyl, methyl, hydroxy, butyloxy, butyroxy, ethoxy and acetoxy. Of these, the hydroxy and acetoxy com-

(1) (a) Adams, Baker and Wearn, THIS JOURNAL, **62**, 2204 (1940); (b) Adams and Baker, *ibid.*, **62**, 2401 (1940).

(2) (a) Adams and Baker, *ibid.*, **62**, 2405 (1940); (b) Adams, Loewe, Pease, Cain, Wearn, Baker and Wolff, *ibid.*, **62**, 2566 (1940).

(3) (a) Adams, Pease, Cain and Clark, *ibid.*, **62**, 2402 (1940); (b) Adams, Cain, McPhee and Wearn, *ibid.*, **63**, 2209 (1941).

(4) Ghosh, Todd and Wright, *J. Chem. Soc.*, 137 (1941).

(5) (a) Adams, Smith and Loewe, THIS JOURNAL, **63**, 1973 (1941); (b) Adams, Loewe, Smith and McPhee, *ibid.*, **64**, 694 (1942).

(6) Adams, Loewe, Jelinek and Wolff, *ibid.*, **63**, 1971 (1941).

(7) (a) Ghosh, Todd and Wilkinson, *J. Chem. Soc.*, 1121 (1940); (b) Russell, Todd, Wilkinson, MacDonald and Woolfe, *ibid.*, 826 (1941).

(8) (a) Bembry and Powell, THIS JOURNAL, **63**, 2766 (1941); (b) Bembry, Columbia Univ. Dissertation (1941).

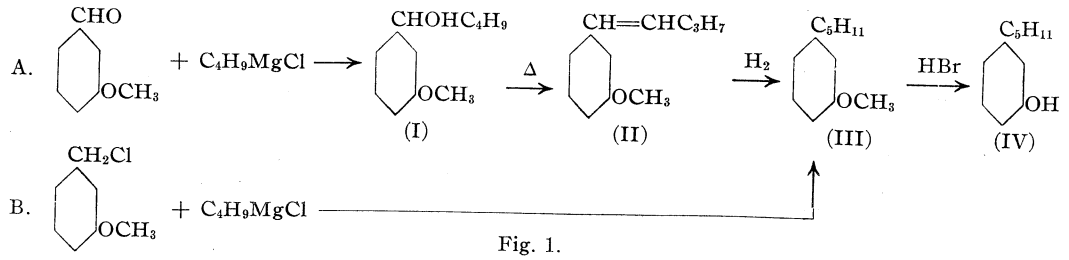


Fig. 1.

pounds had been previously prepared[7a] and reported to be inactive in the rabbit up to a dosage of 5 mg. per kg. intravenously, but were included in the present work for testing in dogs and extension of the rabbit testing. Synthetic tetrahydrocannabinol was prepared for use as a physiological test standard by making 1-hydroxy-3-*n*-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone following the method of Adams and Baker,[1b] then converting this pyrone into the desired 6,6-dimethylpyran by the method of Ghosh, Todd and Wilkinson.[7a]

Fig. 2. The corresponding butyloxy pyrans were prepared both from the butyloxy pyrones and by direct butylation of the hydroxy pyrans.

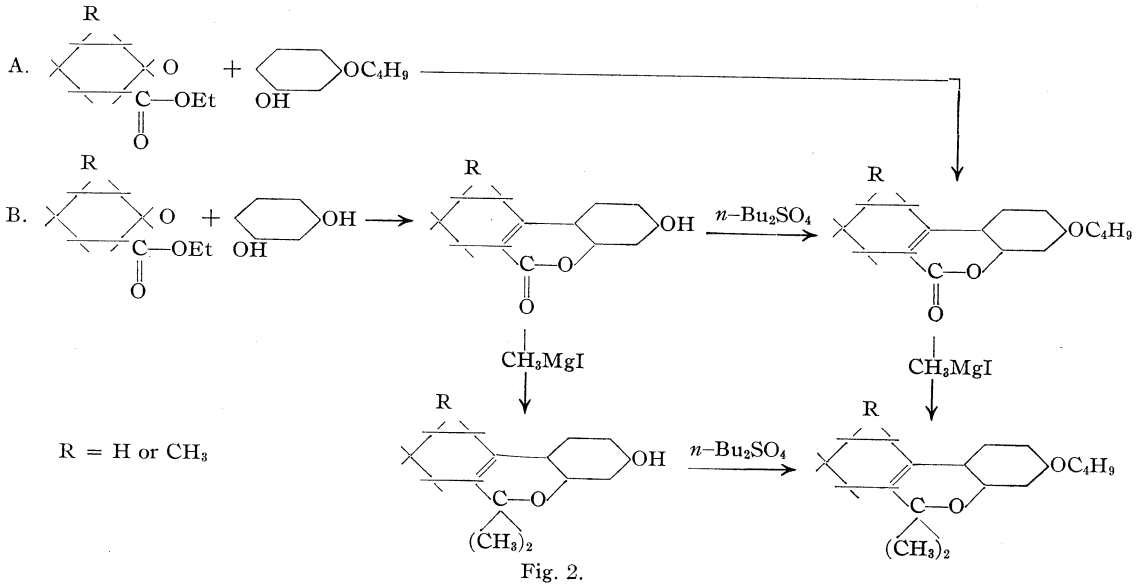


Fig. 2.

The synthesis of 3-*n*-amyl-6,6-dimethyl-7,8,9,-10-tetrahydro-6-dibenzo-pyran (VI) and 3-*n*-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (VIII) required the previously unknown 3-*n*-amylphenol (IV), which was prepared by two different routes, as shown in Fig. 1.

The amyl pyrones were prepared by the condensation of 3-*n*-amylphenol (IV) with the properly substituted cyclohexanone-2-carboxylate in accord with Sen and Basu.[9]

The butyl ethers of the hydroxy pyrones were prepared by two different methods as outlined in

(9) Sen and Basu, *J. Indian Chem. Soc.*, **5**, 467 (1928).

Experimental

3-Methoxyphenyl-*n*-butylcarbinol (I).—A solution of 69.5 g. of 3-methoxybenzaldehyde in 150 ml. of ether was added slowly to a Grignard reagent prepared from 25 g. of magnesium and 101.5 g. of *n*-butyl chloride in 300 ml. of ether. After refluxing for one-half hour, the solution was poured into an excess of ice–sulfuric acid. On distillation, there was obtained 90.8 g. (92% yield) of a viscous, colorless oil, b. p. 115–125° (1 mm.). Redistillation gave, with very little loss, the product b. p. 128.5–129° (5 mm.), d^{25}_4 1.009.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.16; H, 9.34. Found: C, 74.2; H, 9.50.

1-(3-Methoxyphenyl)-amylene-1 (II).—A mixture of 54 g. of I and 10 g. of finely powdered potassium bisulfate was heated in an oil-bath at 135–160° for one hour. After all the water, which readily split out during the heating, had been removed, the product was distilled without further treatment, yielding 33.7 g. of a colorless liquid, b. p. 92–99° (1 mm.), d^{25}_4 0.985.

3-Methoxy-*n*-amylbenzene (III).—A.—A solution of 29.3 g. of II in 100 ml. of ethanol with 100 mg. of palladium oxide catalyst was reduced at room temperature under 3 atmospheres pressure of hydrogen, absorbing nearly the theoretical quantity in twenty minutes. After filtering off

the catalyst and distilling the ethanol, there was obtained 24.1 g. (81.5% yield) of a colorless liquid, b. p. 97–98° (3 mm.), d^{25}_4 0.947.

B.—3-Methoxybenzyl alcohol was prepared by Raney nickel and hydrogen reduction of the aldehyde at 90° under 90 atmospheres pressure. Treatment of 138 g. of the alcohol with 200 ml. of concentrated hydrochloric acid and 30 g. of anhydrous calcium chloride yielded 3-methoxybenzyl chloride, b. p. 75° (2 mm.), 78.3 g. of this in 100 ml. of dry benzene was added to a Grignard reagent prepared from 24.3 g. of magnesium, 92.5 g. of *n*-butyl chloride and 200 ml. of anhydrous ether. After distilling the ether and adding 200 ml. of dry benzene, the mixture was refluxed for thirty hours, then decomposed with ice–sulfuric acid. The benzene extract was separated, washed with dilute alkali, then water, and finally distilled to yield 15.2 g. of a colorless liquid, b. p. 96–99° (3 mm.), d^{25}_4 0.947.

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.8; H, 10.17. Found: C, 79.6; H, 10.11.

Preparations A and B were demethylated separately and in each case the resultant phenol had the same properties.

3-*n*-Amylphenol (IV).—A mixture of 22 g. of III and 100 g. of 30% hydrobromic acid in glacial acetic acid was sealed in a bomb tube and heated for 3.5 hours in a boiling water-bath. The mixture became homogeneous during the heating period. After cooling, five volumes of water and about 5 g. of sodium bisulfite were added, then the solution was neutralized with sodium bicarbonate. Ether was added, the ether extract washed well with water, then the phenol extracted with excess 10% potassium hydroxide solution. Ether extraction of the alkali extract after acidification yielded 10 g. of a colorless viscous liquid, b. p. 103–108° (2 mm.). Upon redistillation this gave a main fraction, b. p. 99–100° (1 mm.), d^{25}_4 0.964. Yields by demethylating with constant boiling hydriodic acid were practically the same and the product identical.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.35; H, 9.81. Found: C, 79.94; H, 9.73.

The 3,5-dinitrobenzoate, recrystallized from isopropanol, melted at 70°.

Anal. Calcd. for $C_{18}H_{18}N_2O_6$: C, 60.5; H, 5.06. Found: C, 60.7; H, 5.12.

Excepting this dinitrobenzoate, all the preceding compounds proved to be difficult to analyze, since all had a tendency to explode during combustion.

3-*n*-Amyl-7,8,9,10-tetrahydro-6-dibenzopyrone (V).—To a mixture of 8.2 g. of IV and 8.7 g. of ethyl cyclohexanone-2-carboxylate cooled below 0°, was added slowly 40 ml. of concentrated sulfuric acid (also cooled to 0°), keeping the temperature below 25° by means of an ice-bath during the addition. The solution was allowed to stand for two hours in the cold-bath, poured onto crushed ice, and the salmon-colored viscous oil extracted with benzene. The benzene solution was washed with water, any unreacted phenol was extracted with 10% potassium hydroxide solution and washed again with water until the washings were neutral to litmus. After drying over magnesium sulfate, the benzene was removed, the unreacted ester (about 3 g.) was recovered under reduced pressure and, finally, the product was distilled under a mercury vapor pump vacuum (10 μ) with 180–185° oil-bath. A yield of 3.72 g. of pale yellow viscous liquid was obtained.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.99; H, 8.20.

3-*n*-Amyl-6,6-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (VI).—To a Grignard reagent prepared in the usual manner from 5.1 g. of magnesium and 30.2 g. of methyl iodide in anhydrous anisole was added a solution of 3.7 g. of V in 50 ml. of anisole. This solution was heated at 100° for eight hours with continuous mechanical stirring, cooled, poured onto ice containing 50 ml. of 12 *N* sulfuric acid and the anisole steam distilled. The residue was extracted with ether; the ether extract was washed with dilute sodium bicarbonate and then with water, dried over magnesium sulfate, and after removal of the solvent the product was distilled under 0.5 μ with a 140–145° bath, obtaining 3.5 g.(90% yield) of a pale yellow viscous liquid.

Anal. Calcd. for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found: C, 83.93; H, 9.86.

3-*n*-Amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone (VII).—This compound was prepared in the same manner as V from 10.8 g. of IV, 14.7 g. of ethyl 5-methyl-cyclohexanone-2-carboxylate, and 40 ml. of concentrated sulfuric acid. The yield was 5.9 g. of a viscous, pale yellow liquid, distilling at 3 μ with 200–205° bath.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.28; H, 8.54.

3-*n*-Amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (VIII).—This compound was prepared by the same method as VI in 88% yield, distilling at 2 μ with a 155–160° bath.

Anal. Calcd. for $C_{21}H_{30}O$: C, 84.51; H, 10.13. Found: C, 84.50; H, 10.35.

3-Methyl-7,8,9,10-tetrahydro-6-dibenzopyrone (IX)[9] **and 3,9-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyrone (X)** were prepared in the same manner as the amyl pyrones. Product X melted at 105–106°.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.93; H, 7.07. Found: C, 78.94; H, 7.60.

3,6,6-Trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (XI) and **3,6,6,9-tetramethyl-7,8,9,10-tetrahydro-6-dibenzopyran (XII)** were made by the same method as the amyl pyrans. XI distilled at 0.5 μ with a 100–105° bath.

Anal. Calcd. for $C_{16}H_{20}O$: C, 84.10; H, 8.83. Found: C, 83.80; H, 8.55.

XII distilled at 10 μ with 130–135° bath.

Anal. Calcd. for $C_{17}H_{22}O$: C, 84.24; H, 9.15. Found: C, 84.40; H, 9.11.

3-Hydroxy-7,8,9,10-tetrahydro-6-dibenzopyrone (XIII) and **3-hydroxy-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone (XIV)** were made by Adams and Baker's[2a] modification of the method of Ahmad and Desai,[10] in yields of 86 and 80%, respectively.

3-Hydroxy-6,6-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (XV) and **3-hydroxy-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (XVI)** were made by the method of Todd and co-workers,[7a] except that the hydroxy pyrones, rather than the acetates, were converted into the pyrans.

(10) Ahmad and Desai, *J. Univ. Bombay*, **6**, Pt. II, 89 (1937).

3-*n*-Butyloxy-7,8,9,10-tetrahydro-6-dibenzopyrone (XVII)—A.—Ethyl cyclohexanone-2-carboxylate and resorcinol mono-*n*-butyl ether, obtained in 65% yield,[11] were condensed with phosphorus oxychloride in dry benzene.[2a] The product boiled at 240–243° under 3 mm. pressure and crystallized in the condenser. Crystallization from 95% ethanol gave fine white needles, m. p. 86–87°.

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 75.02; H, 7.41. Found: C, 75.4; H, 7.31.

B.—Slightly more than 0.01 mole of di-*n*-butyl sulfate[12] was added to a mechanically stirred solution of 0.01 mole of XIII dissolved in 6 ml. of 2 *N* sodium hydroxide solution. After warming in an oil-bath at 90–110° for 1.5 hours, the mixture was allowed to cool slowly with continued rapid stirring. The excess sulfate was destroyed with concentrated ammonium hydroxide solution, and the precipitate was filtered off and crystallized from 95% ethanol in long, white, glistening needles. The yield was 2.2 g. of product, m. p. 87–88°. A mixture of this product with that from method **A**, m. p. 86–88°.

Anal. Calcd. (Same as **A**). Found: C, 74.4; H, 7.41.

3-*n*-Butyloxy-6,6-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (XVIII).—To a Grignard reagent, prepared from 2.8 g. of magnesium and 16.5 g. of methyl iodide in 25 ml. of anisole, was added 4.5 g. of XVII. This solution was heated at 100° with continuous stirring for eight hours and then worked up in the same manner as VI. The yield was 3.4 g. of colorless viscous liquid distilling at 1 μ with a 133–134° bath.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.52; H, 9.24.

3-*n*-Butyloxy-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (XIX).—A solution of 2.44 g. of XVI in 10 ml. of 2 *N* sodium hydroxide solution was heated with 2.1 g. of di-*n*-butyl sulfate in an oil-bath at 90–110° for 1.5 hours with continuous mechanical stirring. The solution was cooled, extracted with ether, the extract washed well with water, and dried over magnesium sulfate. The yield was 2.9 g. of viscous yellow oil, distilling at 5 μ with 162–168° bath.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 80.65; H, 9.15.

3-*n*-Butyroxy-6,6-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (XX).—To 2.3 g. of XV was added 6.3 g. of *n*-butyric anhydride. Upon the addition of one drop of concentrated sulfuric acid, the hydroxypyran went into solution with a slight amount of spontaneous warming. After standing at room temperature for one hour the mixture was heated at 100° for 1.5 hours, cooled, considerable water added, and the organic layer separated. Any unreacted anhydride was hydrolyzed in accordance with Smith, Bryant and Mitchell's[13] pyridine–sodium iodide method. The resulting solution was cooled, diluted with 4 volumes of water and acidified with 4 *N* hydrochloric acid. The organic layer was separated with the aid of some ether, washed with water, and finally dried over magnesium sulfate. The yield was 2.1 g. of colorless, viscous liquid, distilling at 1 μ with 155–160° bath.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.06. Found: C, 76.04; H, 8.49.

3-*n*-Butyroxy-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (XXI).—This was prepared in the same way as XX from 2.44 g. of XVI and 6.33 g. of *n*-butyric anhydride. The yield was 2.6 g. of colorless, viscous liquid, distilling at 2 μ with 160–165° bath.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.60; H, 8.56.

3-Ethoxy-6,6-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (XXII).—This was prepared in the same manner as XIX, except that ethyl sulfate was used. The product, a pale yellow viscous liquid, was obtained in 91% yield, distilling at 5 μ with 120–125° bath.

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 78.96; H, 8.56. Found: C, 78.32; H, 8.50.

3-Ethoxy-6,6,9-trimethyl-7,8,9,10-tetrahydro-7-dibenzopyran (XXIII).—This was also prepared by the same method as for XIX. The product, a viscous yellow liquid, was obtained in 78.6% yield, distilling at 10 μ with 145–150° bath.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 78.70; H, 8.82.

3-Acetoxy-6,6-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (XXIV) and **3-acetoxy-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (XXV)** were prepared from XV and XVI by treatment with acetic anhydride and pyridine, yielding products corresponding to those of Todd and coworkers,[7a] which melted at 65–66° and 59–60°, respectively.

These pyrans that were synthesized in this work were tested for their marihuana activity in dogs by the method of Dixon.[14] Oral administration of each of the compounds of both Series I and II in doses of 50 and 100 mg. per kg. was tried, without the production of ataxia or the other symptoms of marihuana activity. In these same animals 8 mg. per kg. orally of synthetic tetrahydrocannabinol did produce notable ataxia.

The same pyrans were tested for their ability to produce corneal anesthesia in rabbits, following the method of Gayer[15] for testing of marihuana activity. Intravenous administration of each of the compounds of both Series I and II in 10% solution in acetone in doses of 10 and 20 mg. per kg. was tried, without the production of corneal anesthesia. These findings of inactivity in rabbits with regard to XV, XVI, XXIV and XXV extend the similar observations on these compounds made by Ghosh, Todd and Wilkinson.[7a] The testing of different preparations of synthetic tetrahydrocannabinol with doses of 1, 2, 4, 8, 16 and 32 mg. per kg. intravenously, each given to two different animals, did not cause any corneal anesthesia, though with the highest dosages there was some sluggishness of response. Ghosh, Todd and Wright[4] reported this compound to be active at 1 mg. per kg. intravenously in rabbits, and we are unable to explain the discrepancy between

(11) Klarmann, Gatyas and Shternov, THIS JOURNAL, **53**, 3404 (1931).

(12) "Organic Syntheses," **19**, 27 (1939).

(13) Smith, Bryant and Mitchell, THIS JOURNAL, **63**, 1700 (1941).

(14) Dixon, *Brit. Med. J.*, **2**, 1354 (1899); and *Pharm. J.*, 705 (1905).

(15) Gayer, *Arch. exp. Path. Pharmakol.*, **129**, 312 (1928).

these findings. Two different lots of synthetic tetrahydrocannabinol were prepared, and the rabbits used were shown to be responsive on subsequent days to fresh extracts of charas made with ethanol, evaporated, and taken up with acetone for testing.

We are indebted to Dr. C. E. Redemann for the analyses reported in this paper, and wish to thank him for many helpful suggestions made during the course of this work.

Summary

1. 3-*n*-Amylphenol has been prepared by two methods.

2. Derivatives of 6,6-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyran substituted in the 3-position by *n*-amyl, methyl, hydroxy, butyloxy, butyroxy, ethoxy and acetoxy groups have been prepared.

3. Corresponding derivatives of 6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran have also been prepared.

4. Neither of these two series of pyrans exhibits any significant degree of marihuana activity in dogs or rabbits.

PASADENA, CALIFORNIA RECEIVED MAY 12, 1942

[CONTRIBUTION FROM THE LABORATORY OF PHYSIOLOGICAL CHEMISTRY, UNIVERSITY OF MINNESOTA, MINNEAPOLIS]

The Optical Configuration of Glutamic Acid Isolated from Casein Hydrolyzates by Six Procedures[1]

BY JEANETTE C. OPSAHL AND L. EARLE ARNOW[2]

Kögl, *et al.*,[3,4,5] have claimed that the modification of the Foreman procedure employed by Chibnall, *et al.*,[6] isolates preferentially *l*(+)-glutamic acid, leaving much of the *d,l*-glutamic acid in the mother liquor. For example, they[5] isolated 2.472 g. of *l*(+)-glutamic acid from 23.4 g. of pig kidney protein by Chibnall's procedure. Two grams of *d,l*-glutamic acid then was added to the mother liquor, and the isolation was repeated. 1.290 g. of glutamic acid was isolated; the sample was found to contain 0.9335 g. of *l*(+)-glutamic acid and 0.3569 g. of *d*(−)-glutamic acid. The interpretation of this type of experiment is complicated by the possibility that the original isolation might not have been quantitative. In other words, the material recovered in the second isolation conceivably might have reflected more or less accurately the composition of the glutamic acid present in the mother liquor. Chibnall and his collaborators[6] isolated small amounts of *d,l*-glutamic acid from both normal and malignant tissue protein hydrolyzates by their procedure. However, they did not report experiments in which *d,l*-glutamic acid had been added to the hydrolyzate prior to isolation.

Graff, Rittenberg and Foster[7] added *d,l*-glutamic acid to protein hydrolyzates, and found that the material isolated by their modified Foreman procedure contained both optical forms of glutamic acid. However, they were investigating the optical composition of the glutamic acid in the hydrolyzates by means of an isotope (N^{15}) dilution method, and the percentages of *d*(−)-glutamic acid in the material actually isolated were not given in their paper.

It has been shown in several laboratories[8,9,10] that glutamic acid slowly racemizes in boiling hydrochloric acid solutions. Several reports describing the isolation of glutamic acid containing small percentages of *d*-isomer have been recorded.[6,11,12,13] This latter finding casts some doubt on the accuracy of the isotope dilution method as employed by Graff, *et al.*[7] If the figure reported by these workers for the *d*-isomer content of the glutamic acid of tissue protein hydrolyzates (not more than 0.5 ± 0.5%) is accepted, it then becomes necessary to assume that the methods

(1) The data presented in this paper were taken from a thesis submitted by Jeanette C. Opsahl to the Graduate Faculty of the University of Minnesota in partial fulfillment of the requirements for the M.S. degree.

(2) Present address: Medical-Research Division, Sharp & Dohme, Glenolden, Pa.

(3) F. Kögl and H. Erxleben, *Nature*, **144**, 111 (1939).

(4) F. Kögl, H. Erxleben and A. M. Akkerman, *Z. physiol. Chem.*, **261**, 141 (1939).

(5) F. Kögl and H. Erxleben, *ibid.*, **264**, 198 (1940).

(6) A. C. Chibnall, M. W. Rees, E. F. Williams and E. Boyland, *Biochem. J.*, **34**, 385 (1940).

(7) S. Graff, D. Rittenberg and G. L. Foster, *J. Biol. Chem.*, **133**, 745 (1940).

(8) L. E. Arnow and J. C. Opsahl, *ibid.*, **133**, 765 (1940).

(9) J. M. Johnson, *ibid.*, **134**, 459 (1940).

(10) O. K. Behrens, F. Lipmann, M. Cohn and D. Burk, *Science*, **92**, 32 (1940).

(11) J. M. Johnson, *J. Biol. Chem.*, **132**, 781 (1940).

(12) G. E. Woodward, F. E. Reinhart and J. S. Dohan, *ibid.*, **138**, 677 (1941).

(13) B. W. Town, *Biochem. J.*, **35**, 417 (1941).

TABLE I

GLUTAMIC ACID HYDROCHLORIDE ISOLATED FROM CASEIN BY VARIOUS PROCEDURES

Method, with preliminary	Total crude yield, g.	Final yields, g.	C,[a] %	H,[a] %	N,[a] %	$[\alpha]_D$[b]	*d*-Isomer, %	Calcd. final yields, %
1: clarification with Cu_2O	...	1.782	32.79	5.57	7.70	+28.4	5.1	46
2: pptn. as Ca salt	2.330	1.979	32.53	5.61	7.62	+29.9	2.7	51
3: pptn. as Ba salt	3.302[c]	1.715	[d]	[d]	7.58	+29.0	4.1	44
4: extn. with butanol	1.750	1.129	32.50	5.54	7.54	+30.0	2.5	29
5: clarification with ZnO	...	1.300	32.73	5.75	7.63	+27.7	6.2	34
6: sepn. as pyrrolidone-carboxylic acid	2.697	2.389	33.13	5.51	7.58	+29.9	2.7	62

[a] Theoretical: C, 32.71%; H, 5.49%; N, 7.63%. Carbon and hydrogen analyses were done by the Organic Microanalytical Laboratory, University of Minnesota. [b] Theoretical: +31.6°, calculated for free *l*(+)-glutamic acid in 9% hydrochloric acid. [c] Grossly contaminated with barium chloride. [d] This sample accidentally lost prior to carbon and hydrogen analyses.

employed by others preferentially concentrate the *d*-isomer. Since the *d,l*-form is about twice as soluble as the *l*-form in the hydrochloric acid solution usually used for crystallization,[4,7] it seems unlikely that such a preferential concentration occurs, at least in cases in which seeding is not employed.

Experimental Plan and Results

In the first group of experiments, glutamic acid was isolated from aliquots of a single casein hydrolyzate by means of the 6 different procedures listed in Table I. The results indicate that casein hydrolyzates contain small percentages of *d*(−)-glutamic acid. The figures recorded for the *d*-isomer contents of the isolated samples cannot be explained by assuming a large experimental error in the determinations of specific optical rotations. The figures obtained by us for the specific optical rotation of pure *l*(+)-glutamic acid (in 9% hydrochloric acid) have ranged from +31.0 to +32.5°. The average figure obtained in a large number of determinations was +31.6°.

The possibility that drying the casein at 110° might have caused some racemization of the combined glutamic acid was investigated. A sample of casein was heated at 110° for one week. The glutamic acid subsequently isolated by the pyrrolidone-carboxylic acid method was found to contain only 2.5% of *d*-isomer. This is essentially the same figure as that obtained after a much shorter period of drying (Table I).

In calculating the yields listed in Table I (last column), it has been assumed that the hydrolyzate prepared from 100 g. of thoroughly dried casein contains 21.77 g. of glutamic acid. This figure was reported by Foreman[14]; and figures approximating this have been obtained also with the butyl alcohol extraction method[15] and by the pyrrolidone-carboxylic acid method.[16]

In this Laboratory, the pyrrolidone-carboxylic acid method has given the highest yields of pure material. Moreover, the initial crude material obtained with this procedure contains smaller amounts of contaminants than is the case for any of the other methods used. Since the pyrrolidone-carboxylic acid procedure involves prolonged heating in aqueous solution at 100°, it might be supposed that some racemization would occur. However, numerous experiments with solutions of *l*(+)-glutamic acid have demonstrated that no detectable racemization occurs. It has been found also that samples isolated from glutamic acid solutions by this method reflect accurately the optical composition of the original racemic mixture. For example, a sample composed of 25 parts of *l*(+)-glutamic acid hydrochloride and 75 parts of *d,l*-glutamic acid hydrochloride was partly neutralized with sodium hydroxide until the resulting solution was green to brom cresol green (approximately, *p*H 5). At this *p*H, as Wilson and Cannan[17] have shown, the conversion to pyrrolidone-carboxylic acid is not complete. After boiling for fifty hours, extraction with ethyl acetate, and isolation of the hydrochloride, the material obtained consisted of 26% *l*(+)-glutamic acid hydrochloride and 74% *d,l*-glutamic acid hydrochloride. Therefore, even though conditions purposely were adjusted so that recovery was far from complete (yield, 37%), nevertheless, within experimental error, the recovered glutamic acid hydrochloride had the same optical composition as the original sample.

(14) F. W. Foreman, *Biochem. J.*, **8**, 463 (1914).

(15) H. D. Dakin, *ibid.*, **12**, 1290 (1918).

(16) H. B. Vickery, *Carnegie Inst. Washington Yearbook*, **35**, 308 (1936).

(17) H. Wilson and R. K. Cannan, *J. Biol. Chem.*, **119**, 309 (1937).

TABLE II

GLUTAMIC ACID HYDROCHLORIDE ISOLATED FROM CASEIN + *d,l*-GLUTAMIC ACID BY VARIOUS PROCEDURES

Method[a]	Total crude yields, g.	Final yields, g.	Nitrogen (theory, 7.63%), %	$[\alpha]_D^a$	*d*-Isomer, %	Average *d*-Isomer, %	Total final yields, g.	Calcd. final yields, %
1	5.184	2.896	7.60	+22.7	14.1	18.1	3.233	53
		0.337	7.67	− 1.4	52.2			
2	4.198	2.970	7.65	+23.9	12.2	16.4	3.311	54
		0.341	7.56	− 2.1	53.3			
3	4.107	1.593	7.69	+28.7	4.6	17.7	2.714	44
		0.572	7.69	+14.6	26.9			
		0.549	7.55	+ 2.3	46.3			
4	3.083	1.821	7.55	+22.6	14.2	15.4	1.959	32
		0.138	7.68	+11.5	31.8			
5	3.056	1.285	7.65	+24.0	12.0	10.7	1.638	27
	0.431[b]	0.353[b]	7.71	+27.9	5.9			
6	3.980	2.803	7.68	+24.1	11.9	18.8	3.510	57
		0.418	7.68	+ 6.1	40.3			
		0.289	7.60	− 3.0	54.8			

[a] See Table I. [b] Isolated from "insoluble fraction."

The data recorded in Table II were obtained by isolating glutamic acid hydrochloride from a casein hydrolyzate to which had been added a known amount of *d,l*-glutamic acid. Since 12 g. of dry *d,l*-glutamic acid was added to hydrolyzate equivalent to 95 g. of dry casein, the theoretical *d*-isomer content of the glutamic acid in the mixture was 18.4%. This calculation involves the assumption that no *d*-isomer was formed during the hydrolysis. If it is assumed that the hydrolysis caused a racemization of 10% of the glutamic acid originally present, the theoretical content of *d*-isomer becomes 21.5%. Foreman's figure for the glutamic acid content of casein has been used for these calculations.

It appears justifiable, therefore, to assume that the *d*-isomer content of the glutamic acid in the casein hydrolyzate was something between 18.4 and 21.5%. The data recorded in Table II indicate that the methods yielding samples most closely approximating the theoretical value were the pyrrolidone-carboxylic acid method and the cuprous oxide (Abderhalden–Fuchs) method. The two variations of the Foreman procedure used in this investigation (methods 2 and 3) yielded samples containing, respectively, 76–89% and 82–96% of the calculated theoretical *d*-isomer content. The least efficient method was the zinc oxide procedure, which yielded a sample containing only 50–58% of the calculated amount of *d*-isomer.

Chibnall and his collaborators[6] have claimed that the cuprous oxide method preferentially isolates *d,l*-glutamic acid; *i. e.*, that the first fraction crystallizing from the clarified hydrolyzate contains a higher percentage of *d*-isomer than do subsequent fractions. The data in Table II appear to indicate that the initial material isolated by this method does contain a higher percentage of *d*-isomer than do the first samples isolated by the Foreman or pyrrolidone-carboxylic procedures. However, in our experience, invariably it has been found that the first purified fractions obtained from hydrolyzates clarified with cuprous oxide contain less *d*(−)-glutamic acid than do fractions isolated from the original mother liquor. For example, the first fraction isolated from the hydrolyzate to which had been added *d,l*-glutamic acid contained 14.1% *d*-isomer. A crystalline fraction isolated subsequently from the mother liquor had a much higher *d*-isomer content (52.2%). Seeding has not been employed in our isolations.

It is possible that the type of results obtained with casein would not have been obtained if crude tissue protein had been used. In other words, substances absent from casein, but present in tissue, may influence the yield of *d*-isomer. We plan to investigate this possibility.

Experimental

Preparation of Hydrolyzates.—A sample of casein (Hoffman–LaRoche) was dried for thirty-six hours in an oven (105°). Ninety-five grams of the dry protein was mixed with a liter of 20% hydrochloric acid, and the mixture was boiled gently under reflux for twenty hours. After the removal of the majority of the hydrochloric acid

by several distillations under reduced pressure, the hydrolyzate was diluted to a volume of 200 cc. Thirty cc. aliquots then were used for each of the procedures summarized in Table I.

A second sample of the dry casein (95 g.) was treated as just described, except that 12 g. of dry *d,l*-glutamic acid was added to the hydrolyzate before final dilution to a volume of 200 cc. Thirty-cc. aliquots of this hydrolyzate were employed in obtaining the results listed in Table II.

The *d,l*-glutamic acid was prepared from *l*(+)-glutamic acid by the method of Arnow and Opsahl.[18]

Isolation of Glutamic Acid Hydrochloride. Method 1.—The modification of the Abderhalden–Fuchs procedure[19] employed by Kögl, Erxleben and Akkerman[4] was used, except that crystallization was allowed to proceed without seeding.

Method 2.—The method used was that of Chibnall, *et al.*[6] No attempt was made to isolate aspartic acid.

Method 3.—Graff, *et al.*[7,20] did not publish the details of their procedure. The procedure used by us is illustrated by the following description of the isolation of glutamic acid hydrochloride from the hydrolyzate to which had been added *d,l*-glutamic acid.

Thirty cc. of hydrolyzate was added to 100 cc. of water. A slight excess of barium hydroxide was added with stirring, and the volume of the alkaline solution was made to 185 cc.; 925 cc. of 95% alcohol was added with stirring, and the mixture was placed in the refrigerator for four days. The insoluble material then was filtered off, and dissolved in warm water (volume now 310 cc.); 1550 cc. of 95% alcohol was added with stirring, and the mixture allowed to remain in the refrigerator for three days. The insoluble barium salts were filtered off and dissolved in warm water containing sufficient hydrochloric acid to cause complete solution. Barium then was removed with sulfuric acid. The precipitated sulfate was washed several times with hot water, and the washings were combined with the amino acid solution. The combined solutions were evaporated to a small volume (approximately 20 cc.) under reduced pressure. This concentrated solution was saturated with dry hydrogen chloride gas at ice-bath temperature, and was stored at 0° for several days. The precipitated glutamic acid hydrochloride was filtered off (sintered glass filter); washed successively with cold concentrated hydrochloric acid, absolute alcohol, and ether; and dried in a desiccator over calcium chloride and potassium hydroxide. After its weight had been recorded, it was recrystallized from a minimum quantity of 20% hydrochloric acid. The other fractions listed in Table II were isolated from the mother liquor filtrates.

Method 4.—Thirty cc. of hydrolyzate was diluted with 10 cc. of water, and solid calcium hydroxide was added until the *p*H of the solution reached 6.1, as indicated by the glass electrode. This solution was extracted in a continuous extractor with butyl alcohol for seventy-four hours. The butanol-insoluble fraction was filtered (*p*H of solution now 8.0), and was freed of calcium with oxalic acid solution. The calcium-free solution was concentrated under reduced pressure to a volume of approximately 20 cc., and was saturated with cold hydrogen chloride gas at ice-bath temperature. After the solution had remained for several days at 0°, glutamic acid hydrochloride was isolated and purified in the usual way.

Method 5.—The procedure will be illustrated by a brief description of the isolation of the material recorded in Table II.

Thirty cc. of hydrolyzate and 20 g. of zinc oxide were added to 100 cc. of water. The mixture was heated to boiling for a few minutes, after which it was allowed to remain at 0° for one week. The insoluble material was filtered off, and washed with hot water. (This precipitate was saved for further investigation.) Zinc was removed from the filtrate and washings with hydrogen sulfide, and the filtrate was evaporated under reduced pressure to a volume of approximately 20 cc. After the addition of 5 cc. of concentrated hydrochloric acid, the solution was heated under reflux for two hours (to convert any pyrrolidone-carboxylic acid present to glutamic acid). After saturation of the solution with dry hydrogen chloride gas at ice-bath temperature, and storage of the concentrated hydrochloric acid solution in the refrigerator for several days, glutamic acid hydrochloride was isolated in the usual manner.

The original insoluble material (see above) was dissolved in 10% acetic acid. After removal of the zinc with hydrogen sulfide, it was evaporated to dryness under reduced pressure (to remove acetic acid). The residue was dissolved in 20 cc. of 9% hydrochloric acid; 5 cc. of concentrated hydrochloric acid was added; and the solution was heated under reflux for two hours. The small fraction of glutamic acid indicated in Table II was isolated and purified as already described.

Method 6.—This procedure was based on the suggestive experiments of Wilson and Cannan[17] and of Pucher and Vickery.[21] It will be illustrated by a brief description of the isolation of the material listed in Table II.

Thirty cc. of hydrolyzate was diluted with 30 cc. of water. The *p*H of this solution was adjusted to 3.3 (glass electrode) with 15 *N* sodium hydroxide. This neutralized solution was boiled gently under reflux for fifty hours (to convert glutamic acid to pyrrolidone-carboxylic acid). After concentration to a volume of about 30 cc., insoluble material was filtered off and washed with a small amount of cold water. The combined filtrate and washings were adjusted to *p*H 2.5 (glass electrode) with hydrochloric acid, after which pyrrolidone-carboxylic acid was removed by extracting with ethyl acetate for fifty hours. Further extraction for fifty hours did not increase the yield. Ethyl acetate was removed from the crude pyrrolidone-carboxylic acid by evaporation on a water-bath. The crude material was dissolved in 40 cc. of 9% hydrochloric acid, and the solution was heated under reflux for two hours (to convert pyrrolidone-carboxylic acid to glutamic acid hydrochloride). The condenser was removed, and heating was continued until the volume of the solution was approximately 20 cc. After saturation with hydrogen chloride gas at ice-bath temperature and storage at 0°, glutamic acid hydrochloride was isolated and purified.

(18) L. E. Arnow and J. C. Opsahl, *J. Biol. Chem.*, **134**, 649 (1940).

(19) E. Abderhalden and D. Fuchs, *Z. physiol. Chem.*, **57**, 339 (1908).

(20) S. Graff, *J. Biol. Chem.*, **130**, 13 (1939).

(21) G. W. Pucher and H. B. Vickery, *Ind. Eng. Chem., Anal. Ed.*, **12**, 27 (1940).

Nitrogen Analysis.—The nitrogen contents of the isolated samples were determined by the method of Cavett.[22] Each recorded nitrogen value represents the average of at least two independent determinations.

This investigation was financed in part by a grant from the Cancer Institute Fund, University of Minnesota.

Summary

1. Glutamic acid hydrochloride was isolated from hydrolyzed casein by six different procedures. The percentages of *d*-isomer in the isolated samples varied from 2.5 to 6.2%.

2. The isolations were repeated, using this time a casein hydrolyzate to which had been added a known amount of *d,l*-glutamic acid. The methods yielding samples having *d*-isomer contents closest to the theoretical content were the pyrrolidone-carboxylic acid procedure and the cuprous oxide procedure. Two modifications of the Foreman procedure yielded samples containing, respectively, 76–89 and 82–96% of the theoretical content of *d*-isomer. The poorest percentage yields of *d*-isomer were obtained with the zinc oxide procedure.

3. Methods for isolating glutamic acid by the pyrrolidone-carboxylic acid procedure and the zinc oxide clarification procedure, and modifications of the barium salt and butyl alcohol extraction procedures are described.

(22) J. W. Cavett, *J. Lab. Clin. Med.*, **17**, 79 (1931).

GLENOLDEN, PA. RECEIVED MAY 8, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY]

Products from the Wurtz Reaction and the Mechanism of their Formation[1]

BY ALFRED SAFFER AND T. W. DAVIS

The combination of methyl radicals with each other does not seem to occur under conditions where other combinations proceed readily.[2] The symmetrical approach of two methyl groups according to calculations of Kimball[3] and of Kassel[4] leads to a product of very short life. There is a possibility that methyl and ethyl radicals, being unlike, may combine more readily than like radicals, in which event the cross combination would result in a preponderant formation of propane, for example, in a Wurtz synthesis involving a methyl and an ethyl compound. The Wurtz reactions seem to offer a way to generate free radicals in any desired proportions so that one may study the relative probability of particular free radical combinations. The results of such a study are reported in this paper.

Von Hartel and Polanyi[5] found the reaction of methyl iodide with sodium vapor to proceed with zero energy of activation, and the reaction ought to go at every collision, therefore, regardless of the temperature. But below 300°, there is no measurable reaction because of the low vapor pressure of the metal. Above 300° with pressures of iodide in the neighborhood of 100 mm., the reaction with methyl or ethyl iodide proceeds at a convenient rate. Our experiments were conducted at 320° and in the absence of solvent because the compounds used as solvents in the ordinary Wurtz syntheses often enter into the reactions.[6] Consequently, in undertaking a study of mixed free radical reactions, we have found it convenient and desirable to depart markedly from the conventional details of the Wurtz synthesis.

Experimental

Method.—The apparatus for this study was used in the following way. About nine grams of sodium was placed in the large bulb of the addition tube, D, and the open end, E, was sealed off. The system was evacuated and the sodium melted by heating with a flame until it flowed into the lower and smaller bulb, where it was further melted and allowed to run into the reaction vessel, C.

During a run, the sodium was kept at 320° by means of the furnace, B. The reactant vapors were introduced by dropping liquid from the

(1) Presented at the Atlantic City meeting of the American Chemical Society, Sept. 10, 1941. Original manuscript received November 5, 1941.

(2) (a) Davis, Jahn and Burton, THIS JOURNAL, **60**, 10 (1938); (b) H. A. Taylor and M. Burton, *J. Chem. Phys.*, **7**, 675 (1939); (c) Burton, Taylor and Davis, *ibid.*, **7**, 1080 (1939); (d) A. Gordon and H. A. Taylor, THIS JOURNAL, **63**, 3435 (1941).

(3) G. E. Kimball, *J. Chem. Phys.*, **5**, 310 (1937).

(4) L. S. Kassel, *ibid.*, **5**, 922 (1937); *cf.* E. Teller, *Annals New York Academy of Sciences*, **41**, 173 (1941).

(5) H. v. Hartel and M. Polanyi, *Z. physik. Chem.*, **B11**, 97 (1930).

(6) Hückel, Kraemer and Thiele, *J. prakt. Chem.*, N. F. **142**, 207 (1935); W. E. Bachmann and T. H. Clarke, THIS JOURNAL, **49**, 2089 (1927); A. A. Morton and F. Fallwell, *ibid.*, **59**, 2387 (1937); R. B. Richards, *Trans. Faraday Soc.*, **36**, 956 (1940); Whitmore, Popkin, Bernstein and Wilkins, THIS JOURNAL, **63**, 124 (1941); P. Schorigin, *Ber.*, **41**, 2711 (1908); A. A. Morton and I. Hechenbleikner, THIS JOURNAL, **58**, 2599 (1936).

dropping funnel, A, into the trap maintained above 100°. The vapors passed into the reaction vessel, spattering molten sodium over the walls. The alkyl iodide remained in contact with the sodium for ten minutes at a pressure of about 200 mm. Then on opening stopcock F, the products and unreacted iodide were drawn over into trap G, which was cooled in liquid nitrogen. This batch treatment was continued until enough halide had been sent through the apparatus in the course of several hours to produce on complete reaction an anticipated two liters of gaseous product, but under such circumstances reaction was only 10 to 40% complete as determined by Volhard titration of the sodium iodide formed.

The gaseous products volatile at liquid nitrogen temperatures were removed by a mercury piston and analyzed in a gas analysis apparatus of the Orsat type. The condensed material was warmed in turn to −131, −78 and −45° and the vapors released at the several temperatures were pumped off for analysis. The following table shows the products withdrawn from the condensate at the several temperatures.

TABLE I

FRACTIONATION OF PRODUCTS FROM REACTION MIXTURES

Refrigerating agent	Temp., °K.	Products released from mixture			
Liquid nitrogen	77	H_2	CH_4		
s-Butyl chloride mush	142	CH_4	C_2H_4	C_2H_6	(C_2H_2)
Dry-ice + toluene	195	C_2H_4	C_2H_6	C_3H_6	C_3H_8
Chlorobenzene mush	228	C_3H_6	C_3H_8	C_4H_8	C_4H_{10}

The gas analyses were carried out in the usual way. The unsaturated hydrocarbons were dissolved in fuming sulfuric acid. The hydrogen (which appeared only in the fraction uncondensed by liquid nitrogen) and saturated hydrocarbons were estimated by burning with excess oxygen. It was assumed in compiling the data that the unsaturated components in any sample of gas had the same average number of carbon atoms per molecule as the saturated gases in the same sample, for the boiling points of unsaturated hydrocarbons are fairly close to the boiling points of the corresponding alkanes. Complete identification of the alkenes could be accomplished by catalytic hydrogenation of the samples followed by combustion and carbon dioxide determination but, since the proportion of these products is so low, the more lengthy procedure was not adopted.

The results of the parallel analyses of gas from the reaction mixtures, as recorded in Table III, indicate the general consistency of the analytical results. To check further on the gas analysis methods, a mixture of tank gases was made up, mixed with about the quantity of methyl iodide used in our experiments and was fractionated in the usual manner. The tank gases were themselves analyzed before use. The results appear in Table II. There is clearly some uncertainty, amounting to about 15 to 30 ml. total, in the butane and propane figures. This arises largely from the solubility of these heavier gases in the methyl iodide, from which they cannot be completely recovered. The magnitude of the uncertainty, however, is not so large as to modify seriously the interpretation of the reaction.

TABLE II

ANALYSES OF KNOWN GAS MIXTURES

Gas	Mixture I		Mixture II	
	Taken, ml.	Found, ml.	Taken, ml.	Found, ml.
C_2H_4	6	6		
C_2H_6	191	192		
C_3H_6	18	16	9	9
C_3H_8	91	93	168	146
C_4H_8	1	5	2	9
C_4H_{10}	96	62	148	146
Total	403	374	327	310

The consistent trends in the values of n in successive samples of gas drawn from the various mixtures give basis for confidence in the combustion methods for analyzing the heavier hydrocarbons, where n is the average number of carbon atoms per molecule of alkane gas. With pure propane or pure butane, combustion gave the expected values of 3 and 4, respectively, for n.

Materials.—Methyl and ethyl iodides to be used in the experiments were prepared by treating the corresponding alcohols with red phosphorus and iodine. The crude products were dried over calcium chloride and fractionally distilled. Their final boiling points of 42.2–42.7° and 71.5–72.1° are in agreement with accepted values.

Results

The analyses of the products secured from typical reactions of sodium with methyl iodide and ethyl iodide, both singly and in equimolecular mixture, are shown in Table III.

The large amount of methane from the methyl iodide is relatively unexpected as is the appearance of hydrogen, methane and propane in the gases from the ethyl compound. We have noted the formation of carbon in all of these experiments.

TABLE III

DISTRIBUTION OF PRODUCTS FROM WURTZ REACTIONS

Halide used	CH_3I	C_2H_5I	$CH_3I + C_2H_5I$	$CH_3I + C_2H_5I$
Expt. no.	20	14	15	24
% H_2	7.0	5.5	2.3	4.5
% CH_4	64.1	3.9	42.7	42.9
% C_2H_4	1.9	12.7	8.3	6.8[a]
% C_2H_6	27.0	51.1	20.3	19.9
% C_3H_6		2.7	1.7	0.8
% C_3H_8		15.2	16.1	12.5
% C_4H_8		1.3	0.9	0.8
% C_4H_{10}		7.6	7.7	11.8
Total gaseous products,[b] ml.	591.2	226.9	666.2	1231.5
Black residue, mg.	96.4	35.2	93.4	173.4
NaI formed, g.	6.290	2.255	7.173	12.71
% reaction	23.5	8.4	26.8	47.5

[a] In this experiment acetylene was determined by absorption in ammoniacal silver nitrate solution. It made up 1.3% of the sample. This is included in the figure for % C_2H_4. [b] At S. T. P.

When all the volatile products had been distilled from the reaction vessel, methyl alcohol was added to the residual sodium iodide and excess sodium. The alcohol extract was always observed to contain much suspended material resembling carbon in appearance. This product was not introduced as an impurity in the sodium, for sodium melted into the apparatus, but not exposed to the halide vapors, yielded no carbon at all. Several of the black suspensions were filtered and the insoluble material was dried and weighed. The product had no observable solubility in ethyl alcohol, diethyl ether, tetralin, acetone or benzene and certainly is not to be confused with methylene polymer.

The carbon and hydrogen contents of some of the dried carbon samples were determined in a micro-combustion apparatus.[7] The ratio of the two elements varied fairly widely, not only from specimen to specimen, but different samples from a single specimen were sometimes in bad agreement with each other. The ratios varied from $C_{0.9}H_1$ to C_4H_1. Evidently the carbon had adsorbed fairly large and variable amounts of hydrocarbon gases.

While the color of iodine vapors was not observed in any of our experiments, a dark liquid, not easily volatile, condensed in the leads above the reaction vessel. This fluid probably consisted of polyiodide containing some dissolved iodine. The excess and unreacted halide collected with the reaction products was distilled after the hydrocarbon gases had been removed for analysis. While the material boiled at the temperature of the original reactants, there may have been present several per cent. of some higher iodide or hydrocarbon that would not be detected in our procedure.

In an effort to check on the completeness with which the chief reaction products were recovered, and to gain some idea of the nature of any missing products, a materials balance was set up for some of the runs. From the amount of sodium iodide formed, the quantities of carbon and hydrogen expected in the products may be computed, assuming further that in the mixture runs equimolecular amounts of the two halides enter into the original reaction. The detailed data for Experiments 15 and 24 appear in Table IV. The

TABLE IV

MATERIALS BALANCE IN WURTZ REACTIONS

Expt.	15	24
C expected, g.	0.861	1.526
H expected, g.	.190	0.339
C in gases	.664	1.229
H in gases	.161	0.305
C in black residue	.085	.119
H in black residue	.008	.0025
C recovered, %	87.6	88.5
H recovered, %	89.0	90.6

incomplete recovery of butane is sufficient to account for most of the hydrogen and carbon deficiencies, but possibly the formation of higher monohalides and hydrocarbons also contribute a little to the deficiency. Some of these products may arise from reactions like

$$CH_2I + C_2H_5I \longrightarrow C_3H_7I + I \qquad (1)$$

or by hydrogen exchange reactions.[8] These calculations are important in eliminating from the reaction scheme chain-producing reactions[9] of the type

$$CH_3 + CH_3I \longrightarrow CH_4 + CH_2I$$
$$CH_2I + CH_3I \longrightarrow CH_2I_2 + CH_3, \text{ etc.} \qquad (2)$$

Were such chain reactions a source of appreciable amounts of free radicals, the hydrogen and carbon content of the recovered products would be more than equivalent to the sodium iodide remaining in the reaction flask, for if the dihalide formed in reaction (2) contains a greater percentage of iodide than the original reactant, its appearance

(7) We are indebted to Dr. R. Bruce Van Order for these analyses.

(8) A. O. Allen [THIS JOURNAL, **63**, 708 (1941)] found these reactions to be of importance during the photolysis of acetone in the presence of propane.

(9) P. Fugasi and F. Daniels [*ibid.*, **60**, 771 (1938)] observed no chains in ethyl bromide decomposition at 395°.

in the products would correspond to additional amounts of both carbon and hydrogen brought into the reaction but not accompanied by an equivalent production of sodium iodide. Other experiments not reported here indicate that the dihalides react about as readily with sodium as the monohalides at 320°.

Mechanism

Methyl Iodide.—There is little doubt that the initial reaction involves the formation of sodium iodide and methyl radicals at the surface of the metal. Some of the radicals are doubtless held on the surface, but the instability of the sodium alkyls[10] makes unlikely the confining of the reaction to the sodium surface.

The most obvious second step in the reaction course is the union of the free radicals, but the multiplicity of products and their unexpected distribution indicates that such a picture is too simple, and a calculation of free radical concentrations shows that reactions between two alkyls are probably unimportant. Assuming the uniform production of the radicals and uniform distribution throughout the reaction vessel, and that the free radicals disappear in a chemical change with the alkyl iodide involving an energy of activation of 16 kcal., a steric factor of 0.1 and ordinary collision diameters, the partial pressure of the methyls will reach a steady state concentration of about 3×10^{-4} mm., when by contrast the pressure of halide is about 200 mm. If the bimolecular free radical reactions, either associations or disproportionations,[11] require an appreciable energy of activation, they will not contribute largely to the final products. On the other hand, the more probable free radical–molecule reactions lead to new free radicals which will meet halide molecules more frequently than any other species in the system. The occurrence of reaction chains of any considerable length, however, is not expected.[8] The chains must be interrupted either by unimolecular decomposition to give unreactive fragments or by two-radical reactions of some sort. It becomes a matter of some importance to observe not only whether the principal products can be accounted for in terms of reactions that are inherently probable, but also to find some reasonable way to account for the termination of the reaction chains.

On collision with methyl iodide, methyls can capture another methyl, an iodomethyl, a hydrogen atom or an iodine atom as shown by the equations

$$CH_3 + CH_3I \longrightarrow CH_3CH_3 + I \quad (3)$$
$$CH_3 + CH_3I \longrightarrow CH_3CH_2I + H \quad (4)$$
$$CH_3 + CH_3I \longrightarrow CH_4 + CH_2I \quad (5)$$
$$CH_3 + CH_3I \longrightarrow CH_3I + CH_3 \quad (6)$$

Probably all of these reactions proceed with an energy of activation around 16 kcal, with the exception of (4) which, because of its endothermal character, will require a greater activation energy. Reaction (5) should be favored over (3) on steric grounds in the ratio of 3 to 1 approximately, which is roughly the proportions of the stable products, CH_4 and C_2H_6. If hydrogen atoms are formed at all, they would probably yield molecular hydrogen in a combination on the walls. The iodine atoms for the most part end up as sodium iodide and the iodomethyls may either lose iodine at the surface of the sodium (the reaction going more easily than the original iodide–sodium reaction) or may unite to form ethylene and molecular iodine. If the CH_2I loses iodine at the sodium surface, the CH_2's apparently react there

$$\left.\begin{aligned} CH_2 + CH_2 &\longrightarrow CH_4 + C \\ CH_2 + CH_2 &\longrightarrow 2C + 2H_2 \end{aligned}\right\} \quad (7)$$

The carbon is almost certainly formed on the surface for, at the conclusion of the reactions, it is found intimately mixed with the sodium. The reacting vapors never appeared smoky as they would if the carbon was formed in the gas phase. Usually carbon is formed only at rather high temperatures and as a result of slow reactions; its appearance at such low temperatures is uncommon. Several investigators, however, have mentioned in passing the appearance of carbon from reactions of iodide near these temperatures[12] without discussing the manner of its formation.

Ordinarily methylene does not react to give free carbon[13] but at higher temperatures such reactions may be important, as in the decomposition of ketene at 530° as suggested by Williamson.[14] The general scheme proposed for the

(10) W. H. Carothers and D. D. Coffman, THIS JOURNAL, **52**, 1254 (1930); *ibid.*, **51**, 588 (1929).

(11) Disproportionation probably requires a higher energy of activation than combination, *cf.* C. E. H. Bawn, *Trans. Faraday Soc.*, **35**, 898 (1939); and J. C. Jungers and H. S. Taylor, *J. Chem. Phys.*, **6**, 325 (1938).

(12) Horn, Polanyi and Style, *Trans. Faraday Soc.*, **30**, 189 (1934); E. W. R. Steacie and R. D. McDonald, *Can. J. Res.*, **10**, 591 (1934); H. P. Meissner and H. J. Schumacher, *Z. physik. Chem.*, **A185**, 435 (1940).

(13) W. F. Ross and G. B. Kistiakowsky, THIS JOURNAL, **56**, 1112 (1934); Burton, Davis, Gordon and Taylor, *ibid.*, **63**, 1956 (1941).

(14) A. T. Williamson, *ibid.*, **56**, 2216 (1934).

reaction accounts for all the observed products by means of reasonable intermediate reactions.

Ethyl Iodide and Mixed Halides.—The possibilities in the ethyl iodide reaction are much more numerous than with methyl iodide alone. The ethyl radical on colliding with ethyl iodide may combine with hydrogen (from either of the two carbon atoms in ethyl iodide), with iodine, methyl, iodomethyl, iodoethyl, or ethyl groups. None of these reactions can be eliminated as completely impossible. The formation of propane and butane is indicated by the equations

$$C_2H_5 + CH_3CH_2I \longrightarrow C_3H_8 + CH_2I$$
$$C_2H_5 + C_2H_5I \longrightarrow C_4H_{10} + I$$

These reactions are expected to be about equally probable. Unsaturated products, including carbon, arise as before from CH_2I. The appearance of a little methane in the gases collected from the ethyl iodide reaction means either that the C–C chain is broken in the original reaction or, what is more likely, in a subsequent reaction of the type shown in equation (8) below.

$$C_2H_5 + C_2H_5I \longrightarrow C_2H_5CH_2I + CH_3 \quad (8)$$

That the propane is not formed by union of methyl and ethyl radicals is shown by the experiments with the mixed halides where the greatly increased concentration of methyls does not result in any appreciable increase in propane. That the propane production is not diminished by addition of methyl iodide to ethyl iodide means that methyls can enter into some propane-producing reaction with ethyl iodide, and ethyls can enter into a propane-producing reaction with methyl iodide, the most obvious suggestions being

$$CH_3 + C_2H_5I \longrightarrow C_3H_8 + I$$
$$C_2H_5 + CH_3I \longrightarrow C_3H_8 + I$$

There is no evidence for the union of either like or unlike alkyl radicals under the conditions of our experiments and it is possible in certain other reaction systems where saturated hydrocarbons have been attributed to this kind of process, that alternative sources are responsible.

Acknowledgment.—The authors express their thanks to Dr. Milton Burton for helpful discussion of many aspects of the work reported in this paper.

Conclusions and Summary

On the basis of a free radical mechanism, one would expect a gas phase Wurtz reaction to be very complicated, and this is found to be true experimentally. The reaction of methyl iodide or ethyl iodide or a mixture of the two at a pressure of about 200 mm. at 320° produces hydrogen, free carbon, saturated and unsaturated hydrocarbons and possibly smaller amounts of higher halides. The character of the products is in harmony with current views concerning free radical reactions.

Combinations of two alkyl radicals to give saturated molecules seem not to occur in this system. Most of the primarily formed free radicals disappear by reaction with excess halide molecules, and the secondary radicals containing iodine disappear either by reacting with each other or by reaction with sodium.

UNIVERSITY HEIGHTS, NEW YORK

RECEIVED JUNE 3, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Alkylation of α-Naphthoquinones with Esters of Tetravalent Lead

BY LOUIS F. FIESER AND FREDERIC C. CHANG[1]

This investigation originated in a chance observation made by one of us in attempting to improve a known procedure[2,3] for converting butadiene-toluquinone (I) into 2-methyl-1,4-naphthoquinone. Treatment of the isomerization product II with silver oxide affords the highly sensitive quinone III, and powerful oxidizing agents lead to some destruction. With chromic anhydride, as in comparable cases,[4] II can be converted into IV in about 50% yield.

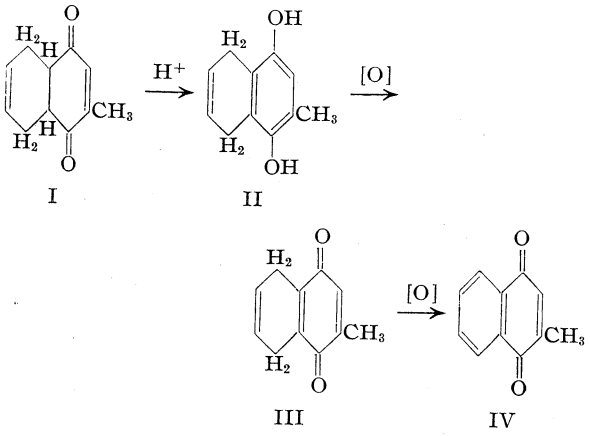
The use of lead tetraacetate was thought to offer a possibility for improvement, for the intermediate quinone III might undergo acetoxylation in one of the activated methylene groups or give a glycol diacetate by an addition to the double bond, and either intermediate should lose acetic acid readily with the formation of IV. When the hydroquinone II was warmed on the steam-bath

(1) On leave of absence from the Department of Chemistry, Lingnan University, Canton, China.

(2) Fieser, Tishler and Wendler, THIS JOURNAL, **62**, 2861 (1940).

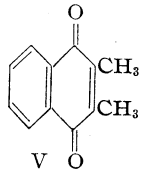
(3) Tishler, Fieser and Wendler, *ibid.*, **62**, 2866 (1940).

(4) Fieser, Campbell and Fry, *ibid.*, **61**, 2206 (1939).



I II III IV

in acetic acid with just two moles of lead tetraacetate, there was obtained a crystalline product which melted slightly above the melting point of pure 2-methyl-1,4-naphthoquinone (m. p. 106–107°) and seemed reminiscent of the intermediate yellow products of unknown nature isolated on partial oxidation of other 5,8-dihydro-1,4-naphthohydroquinones with chromic acid.[4] Since these intermediates are convertible to the naphthoquinones by further oxidation, the experiment was repeated with three moles of lead tetraacetate, all of which was consumed. The reaction product melted at 126.5–127.5°, and analyses of the substance and of its sharply melting hydroquinone diacetate pointed to the formula $C_{12}H_{10}O_2$, whereas methylnaphthoquinone is $C_{11}H_8O_2$. The Craven test[5] was found to be completely negative, indicating the absence of a free position in the quinonoid ring, and the substance was identified by direct comparison as 2,3-dimethyl-1,4-naphthoquinone (V).



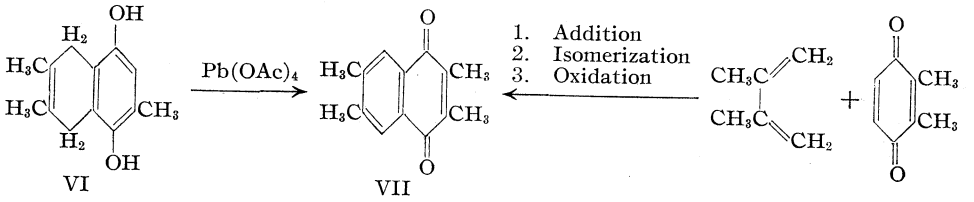
V

The action of excess lead tetraacetate on 2-methyl-5,8-dihydro-1,4-naphthohydroquinone thus involves a remarkable methylation reaction.

(5) Craven, *J. Chem. Soc.*, 1605 (1931).

It was ascertained that the result is the same when the hydroquinone II is first oxidized with silver oxide to the quinone III, and this is then treated with lead tetraacetate. When either II or III is employed as the starting material, the reaction with lead tetraacetate in acetic acid at the steam-bath temperature is characterized by a rapid evolution of gas containing carbon dioxide in amounts corresponding to approximately 1.4 moles per mole of hydroquinone II. When methylnaphthoquinone was submitted to similar treatment (thirty-six hours), there was no gas evolution or consumption of the reagent, and the starting material was recovered unchanged. It was observed also that when the quinone III is refluxed with lead tetraacetate in benzene solution it is converted in moderate yield into methylnaphthoquinone (IV), and affords none of the dimethyl compound V.

In a further investigation of the unusual reaction, the action of lead tetraacetate on 5,8-dihydro-1,4-naphthohydroquinone was found to give a small amount of 2,3-dimethyl-1,4-naphthoquinone. 2,6,7-Trimethyl-5,8-dihydro-1,4-naphthohydroquinone (VI) was prepared by the isomeri-



VI VII

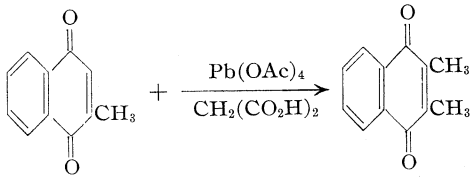
zation of the addition product from 2,3-dimethylbutadiene and toluquinone and treated with excess lead tetraacetate. The reaction product corresponded in melting point with 2,3,6,7-tetramethyl-1,4-naphthoquinone (VII), as described by Bergmann and Bergmann,[6] and its identity was established by comparison with a sample of this substance synthesized by adding 2,3-dimethylbutadiene to *o*-xyloquinone and oxidizing the isomerized product with chromic acid. The oxidation was also conducted with lead tetraacetate, and in this case the reaction proceeded normally and likewise yielded the tetramethylnaphthoquinone VII. The methylation of the trimethyl compound VI in the lead tetraacetate reaction bears some resemblance to the conversion of 2,6,7-trimethyl-1,4-naphthoquinone to the 2,3,6,7-tetramethyl compound VII by the action of diazomethane, observed by Bergmann and Berg-

(6) E. Bergmann and F. Bergmann, *J. Org. Chem.*, **3**, 125 (1938).

mann.[6,7] The resemblance is superficial, however, for the latter reaction very probably proceeds through the formation and decomposition of a pyrazoline, as in the example studied in this Laboratory.[8]

That the methyl group introduced in the course of the curious reaction comes from lead tetraacetate was initially discounted because of the observation that the reagent is without action on methylnaphthoquinone at the same temperature (steam-bath). That the 5,8-dihydride III under the same conditions enters into a brisk reaction, suggested that it may serve the dual rôle of providing the carbon substituent, through an allylic intermediate,[9] as well as acting as acceptor of the methyl group.

In an attempt to separate the two functions, malonic acid was selected as a component having an activated methylene group, and methylnaphthoquinone was employed as an acceptor which itself is not attacked under the conditions of the experiment. When an acetic acid solution of approximately equivalent amounts of methylnaphthoquinone and malonic acid was heated on the steam-bath and treated with successive portions of lead tetraacetate, a steady gas evolution ensued, nearly five moles of reagent were consumed, and the reaction product proved to be 2,3-dimethyl-1,4-naphthoquinone. Since the product is



easily isolated in a pure condition and the yield is 45–50% of the theoretical amount, this constitutes a practical method of methylation. The fact that no reaction occurred in the absence of malonic acid seemed to indicate that this substance had functioned as the methylating agent even though it is itself attacked by lead tetraacetate, probably in a reaction analogous to the conversion of malonic ester into acetylmalonic ester.[10,11]

Other active-hydrogen components were tried with varying results. Ethyl acetoacetate was found to function about as satisfactorily as malonic acid, but when diethyl malonate was employed the starting material was recovered unchanged. In experiments conducted under the same conditions (90–95°), triphenylmethane, cyclopentadiene, acenaphthene and dimethylmalonic acid proved ineffective in comparison with malonic acid, and at least a large part of the starting material was recovered. Methylmalonic acid was then tried and found to promote a characteristic gas evolution and to afford a transformation product in yield as high as that obtained with malonic acid. If the alkyl group introduced is derived from the malonic acid, methylmalonic acid should afford 2-methyl-3-ethyl-1,4-naphthoquinone. The product obtained, however, proved to be the 2,3-dimethyl compound (V). Therefore, although the active-hydrogen component promotes the alkylation, it is not the alkylating agent. This conclusion was confirmed by the observation that methylnaphthoquinone can be converted into the 2,3-dimethyl derivative by the action of lead tetraacetate in combination with C-ethyl ethyl acetoacetate as promoter.

A method of testing the possibility that lead tetraacetate functions as the methylating agent was to attempt the introduction of higher alkyl groups by means of appropriate esters of tetravalent lead. Thus lead tetrapropionate would be expected to afford an ethyl substituent. Since preformed lead tetraacetate is not required in typical oxidations with this reagent but can be replaced by a combination of red lead and acetic acid,[12] we adopted this method of operation both as a matter of convenience and in order to extend the scope of experimentation. Thus methylnaphthoquinone was dissolved in propionic acid, an equivalent amount of ethyl acetoacetate was added as a promoter, and red lead was added in portions, with heating and stirring. A smooth reaction ensued, affording in 49.5% yield a product melting at 72–72.6° and having the composition of the methylethyl compound. Karrer and Epprecht[13] observed the melting point 73° for a sample of 2-methyl-3-ethyl-1,4-naphthoquinone (VIII) synthesized from α-β-methyltetralin. As a possible means of obtaining a sample for direct comparison, we attempted the methylation of 2-ethyl-1,4-naphthoquinone (IX) with lead tetraacetate in the presence of malonic acid. The re-

(7) We do not agree with the interpretation which these authors advance of the nature of the product obtained from 2,6-dimethyl-1,4-naphthoquinone and diazomethane by Fieser and Seligman, THIS JOURNAL, **56**, 2690 (1934).

(8) Fieser and Hartwell, THIS JOURNAL, **57**, 1479 (1935).

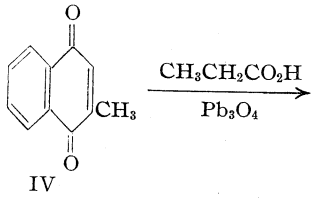
(9) Fieser, *ibid.*, **61**, 3467 (1939).

(10) Dimroth and Schweizer, *Ber.*, **56**, 1375 (1923).

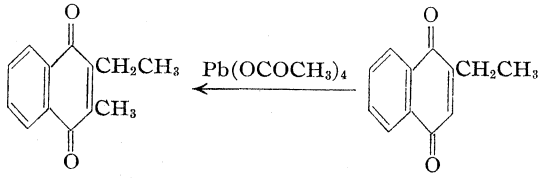
(11) Bak, *Ann.*, **537**, 291 (1938).

(12) Ward, THIS JOURNAL, **60**, 325 (1938); Fieser and Cason, *ibid.*, **62**, 432 (1940); Scanlan and Swern, *ibid.*, **62**, 2305 (1940).

(13) Karrer and Epprecht, *Helv. Chim. Acta*, **23**, 272 (1940).



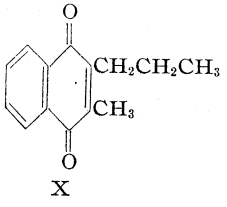
IV



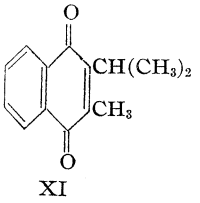
VIII IX

action proceeded satisfactorily and the product obtained proved to be identical with that resulting from the ethylation experiment. The organometallic ester is thereby identified as the alkylating agent.

The behavior of methylnaphthoquinone under the same conditions with red lead in combination with *n*-butyric acid and with isobutyric acid was then investigated. Each reaction yielded a different, fully substituted quinone (negative Craven test), and these melted at 65° and 112°, respectively, and had the expected composition of the methylpropyl compounds. It was established that these substances have the structures X and XI, respectively, corresponding to normal alkyla-



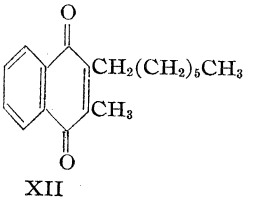
X



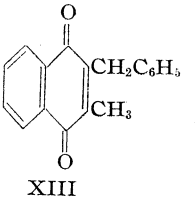
XI

tions, and that the substituent does not suffer isomerization in the course of the reaction, by the above expedient of introducing the groups in the alternate order. 2-*n*-Propyl-1,4-naphthoquinone,[4] when treated with lead tetraacetate and malonic acid, afforded a product identical with the lower melting isomer, obtained in the propylation experiment employing *n*-butyric acid. One of the two routes to the disubstituted compound shows that it contains a normal propyl group in the quinonoid ring, and the other indicates the presence of a similarly situated methyl group; the structure X therefore is fully established. Evidence was likewise obtained in support of formula XI for the isomer. A small sample of β-isopropylnaphthalene was oxidized with chromic acid and the crude, oily quinone obtained was methylated with lead tetraacetate; this afforded a product identical with the higher melting methylpropyl compound. In the preparation of these comparison samples, it was observed that the methylation reaction proceeds less readily when the quinonoid ring carries an ethyl or propyl substituent than when a 2-methyl group is initially present. A higher temperature is required, and the yields are lower.

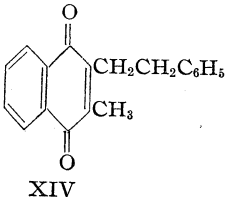
No comparable limitation was observed with respect to the introduction of higher alkyl groups into 2-methyl-1,4-naphthoquinone. The above ethylation and propylation reactions proceeded as smoothly as the methylation of this compound, giving yields as high as 59%, and alkylation of the same quinone with *n*-caprylic acid and red lead was conducted with success. When a stirred mixture of the quinone, the fatty acid and malonic ester was treated with red lead at 120–130°, the oxide dissolved steadily if slowly, and the reaction afforded in 34% yield a quinone of composition and properties consistent with the structure of 2-methyl-3-*n*-heptyl-1,4-naphthoquinone (XII). Quinones of this type heretofore have been obtainable only in a rather elaborate sequence of synthetic operations.[13,14] By a similar process,



XII



XIII



XIV

phenylacetic acid afforded in 65% yield a product which was fully identified as the 2-methyl-3-benzyl compound XIII by direct comparison with a sample of the substance obtained previously in this Laboratory by another synthesis.[15] An alkylation utilizing hydrocinnamic acid yielded a new quinone which, in analogy with the other examples of the reaction, can be assigned the probable structure of 2-methyl-3-β-phenylethyl-1,4-naphthoquinone (XIV). Attempted alkylation

(14) Fernholz, Ansbacher and MacPhillamy, THIS JOURNAL, **62**, 430 (1940).

(15) Fieser, Campbell, Fry and Gates, *ibid.*, **61**, 3216 (1939).

with γ-phenylbutyric acid thus far has been unsuccessful.

The alkylation of naphthoquinones with esters of tetravalent lead is at least a fairly general phenomenon, and it is evident that the alkyl group introduced is derived from an acyl radical of the ester. The carbon dioxide evolved evidently is derived from the same source, and it appears that under certain conditions lead tetraacetate suffers decomposition to lead acetate, carbon dioxide and either actual or potential methyl radicals. Of significance in this connection is the early observation by Dimroth and Schweizer[10] that when lead tetraacetate is heated with acetic acid and acetic anhydride at the reflux temperature a small amount of an inflammable gas is evolved, which presumably is ethane. A consideration of the mechanism of the breakdown of the lead tetraacetate molecule will be deferred to reports of further investigations being conducted by other workers in this Laboratory. An observation made by R. C. Clapp and W. H. Daudt suggested the possibility of initiating the alkylation reaction without the use of an active-hydrogen promoter, and it was found that, although methylnaphthoquinone is recovered unchanged after a prolonged period of warming with lead tetraacetate and acetic acid on the steam-bath, alkylation sets in, with evolution of carbon dioxide, if the temperature is raised to the point of refluxing. The 2,3-dimethyl compound is thus obtainable without the use of a promoter, although malonic acid or similar reagent definitely facilitates the reaction. Criegee[16] found that the velocity of the cleavage of glycols by lead tetraacetate in acetic acid solution is accelerated enormously by the addition of another solvent such as methanol or water. Following an observation by S. T. Putnam that the activating effect applies to still other reactions of lead tetraacetate, we discovered that methanol can be used to promote the alkylation reaction at 90–95°. When acetic acid is employed as the sole solvent, crystals of added lead tetraacetate remain colorless and undissolved until the reaction is initiated by adding a promoter or by raising the temperature to the boiling point. Although the alkylation appears to be subject to catalysis, it seems from the present results to require being maintained in progress, as well as being initiated.

It is now evident that, in the initial experiment which led to the discovery of the remarkable alkylating action of lead tetraacetate, the unsaturated compound II played the dual role of providing a source of methylnaphthoquinone and of functioning as a promoter of the methylation reaction.

(16) Criegee, *Ber.*, **73**, 563 (1940).

Experimental Part[17]

Action of Lead Tetraacetate on 2-Methyl-5,8-dihydro-1,4-naphthohydroquinone, II (L. F. F.).—In a first trial, 0.18 g. of II[2] (m. p. 173–174°) in 5 cc. of acetic acid was treated with 0.95 g. of lead tetraacetate, and the mixture was warmed until solution was complete and allowed to stand for two days, when the test for tetravalent lead was negative. The product, when crystallized from methanol, melted at 107–110.5° and showed a depression (*ca.* 90°) when mixed with 2-methyl-1,4-naphthoquinone. In another experiment a solution of 0.70 g. of II in 10 cc. of acetic acid was heated on the steam-bath and treated in the course of about four hours with a total of 5.54 (3.1 equivalents) of lead tetraacetate, added in portions. The reagent was all consumed, and on adding water there was precipitated a slightly sticky solid, m. p. 117–119°. One crystallization from methanol gave yellow needles, m. p. 124–125°, and after four more crystallizations the substance melted constantly at 126.5–127.5°; the Craven test was negative. In another experiment, 1.4 g. of II in 25 cc. of acetic acid took up a total of 13.9 g. (3.92 equivalents) of reagent under similar conditions and the once crystallized product (0.38 g.) melted at 124–126°. The fully purified material melted at 126.5–127.5° and gave no depression when mixed with **2,3-dimethyl-1,4-naphthoquinone.** Analyses of the two preparations were carried out with the following results.

Anal. Calcd. for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.37, 77.36; H, 5.66, 5.82.

The **hydroquinone diacetate,** prepared by reductive acetylation of the quinone with zinc dust, acetic anhydride and pyridine, melted initially at 189.5–190.5°. The substance crystallized from alcohol in the form of diamond-shaped, laminated plates, m. p. 190–190.5°.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.70; H, 6.16.

The following experiments were run in parallel at the steam-bath temperature. In the first, 0.70 g. of II in 15 cc. of acetic acid was heated with 7.08 g. (4 equiv.) of lead tetraacetate. Carbon dioxide was evolved steadily and the starch–iodide test was negative only after four hours, when 0.5 g. more reagent was added. The test was negative after three hours, and the product was precipitated with water, extracted with ether and crystallized from methanol. The yield of 2,3-dimethyl-1,4-naphthoquinone, m. p. 124–125°, was 0.21 g. (28%). In the second experiment, 0.70 g. of II in 15 cc. of dry ether was shaken for one-half hour with 2 g. of silver oxide and magnesium sulfate, and the yellow solution was filtered and evaporated. The residue was a bright yellow, light-sensitive solid, m. p. 86–87°, consisting of the quinone III. This was dissolved in 15 cc. of acetic acid and treated as above with 5.32 g. (3

(17) Microanalyses by Lyon Southworth and E. Werble. All melting points are corrected.

equiv.) of lead tetraacetate. Gas was evolved at first and tetravalent lead was still present after heating for seven hours. After destroying the excess reagent by the addition of 3 drops of glycerol, the product was precipitated and worked up as above. The once crystallized product, m. p. 124.5–125.5°, was identified as the 2,3-dimethyl compound by mixed melting point determination; yield 0.16 g. (22%).

Another 0.70-g. lot of II was oxidized with silver oxide to the quinone and a solution of this in 15 cc. of benzene was refluxed with 5.32 g. of lead tetraacetate for fifteen hours. The mixture was filtered and the solution shaken with dilute hydrochloric acid until the precipitated lead dioxide was dissolved. The crude product (0.7 g.) obtained on evaporation afforded, on crystallization from methanol, 0.20 g. of yellow needles, m. p. 103–104°. The recrystallized material melted at 106–107° and did not depress the m. p. of 2-methyl-1,4-naphthoquinone. Treatment of 0.70 g. of II in acetic acid with a slight excess of chromic anhydride afforded 0.40 g. of methylnaphthoquinone, m. p. 102–103°. When pure methylnaphthoquinone (0.69 g.) was heated on the steam-bath in acetic acid with one equivalent of lead tetraacetate, there was no gas evolution, and unconsumed reagent was still present after thirty-six hours. The collected product proved to be unchanged starting material, m. p. 106–106.5°.

Extension of the Experiments.—Some improvements were made in the preparation of the starting material. The addition of butadiene (16 g.) to toluquinone (20 g., steam distilled) was conducted in the presence of benzene (20 cc.) in a capped bottle at 70° for six hours. The resulting solution was clarified with Norit, concentrated and diluted with ligroin (70–90°). The addition product I which crystallized was obtained after washing with ligroin as pale yellow crystals, m. p. 80–81°; yield 24.4 g. (84%). When this substance was heated with lead tetraacetate in acetic acid, there was no gas evolution, and no dimethylnaphthoquinone could be isolated. Isomerization to 2-methyl-5,8-dihydro-1,4-naphthohydroquinone was accomplished satisfactorily by the method reported[2] only when working with small quantities. With larger amounts it was found best to reflux the addition product for a few minutes in acetic acid containing about 1% of concentrated hydrochloric acid and a trace of stannous chloride; a colorless crystalline product invariably resulted, and either separated from the boiling medium or crystallized on dilution with water. A typical methylation experiment conducted with four equivalents of lead tetraacetate afforded 2,3-dimethyl-1,4-naphthoquinone in 28% yield; the hydroquinone diacetate melted at 190.5–191.5°.

Approximate determinations of the amount of carbon dioxide evolved in the course of the reaction were made. In one experiment with 3.1600 g. of II, the net weight of carbon dioxide evolved was 1.0910 g., whence the ratio moles CO_2/moles II = 1.38. In another run, 2.1397 g. of II gave rise to 0.7526 g. of carbon dioxide, corresponding to the molecular ratio 1.41:1.

Methylation of 5,8-Dihydro-1,4-naphthohydroquinone.—The starting material[18] was obtained by isomerization of the corresponding addition product with boiling acetic acid containing hydrochloric acid and stannous chloride; the substance crystallized on dilution in elongated prisms, m. p. 212–214°. A solution of 1.62 g. of the hydroquinone was treated with 16 g. (3.6 equivalents) of lead tetraacetate at 90°. Rapid gas evolution had ceased after one hour, although the test for oxidizing agent was negative only after four hours. The collected product was an oil which partially crystallized. Washing with methanol afforded 0.1 g. (5%) of brown crystals, m. p. 112–115°, and the recrystallized material melted at 122–124° and did not depress the melting point of 2,3-dimethyl-1,4-naphthoquinone.

2,3,6,7-Tetramethyl-1,4-naphthoquinone, VII. (a) **By the Methylation Reaction.**—For the preparation of the starting material, 8.6 g. of toluquinone was refluxed with 13.5 cc. of 2,3-dimethylbutadiene in 15 cc. of alcohol for four hours. The product[6] which separated on ice cooling was recrystallized once from alcohol and afforded 9.3 g. (67%) of material melting at 91–92°; this was isomerized by the method described above to **2,6,7-trimethyl-5,8-dihydro-1,4-naphthohydroquinone**[6] (VI), m. p. 214–215°. Methylation of 1.43 g. of VI was accomplished by treatment with lead tetraacetate as in the previous experiments. The sticky solid obtained as the crude reaction product on crystallization from methanol gave 0.32 g. (21%) of the tetramethyl compound VII in two crops (m. p. 164–165.5°). Recrystallization afforded well-formed yellow crystals melting at 167–168.5°. Bergmann and Bergmann[6] report the melting point 167–168°.

(b) **By Synthesis.**—*o*-Xyloquinone was prepared from *o*-xylidine by oxidation with manganese dioxide.[19] A mixture of 1.65 g. of the quinone, 4 cc. of 2,3-dimethylbutadiene, and 5 cc. of absolute alcohol was refluxed for eight hours. The addition product, **2,3,6,7-tetramethyl-5,8,9,10-tetrahydro-1,4-naphthoquinone,** separated on cooling as small, colorless needles, m. p. 105–106.5°; yield 2.22 g. (80%).

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.87; H, 8.24.

This was isomerized in the usual way to 2,3,6,7-tetramethyl-5,8-dihydro-1,4-naphthohydroquinone, which when purified from dioxane–ligroin melted at 269–270.5° (Bergmann and Bergmann[6] obtained in a different way a substance melting at 232° which they regarded as having this structure).

Oxidation of the hydroquinone with chromic acid in acetic acid gave a product which crystallized from methanol in yellow leaflets melting at 169.5–170°, and this did not depress the melting point of the quinone obtained by method (a). Oxidation of the hydroquinone with lead tetraacetate likewise afforded VII (m. p. 166–168°). Samples of the quinone prepared by methods (a) and (b) were submitted to reductive acetylation and in each case afforded a colorless **hydroquinone diacetate** melting at 216–217°; the samples when mixed showed no depression.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.84; H, 6.54.

Action of Lead Tetraacetate on 2-Methyl-1,4-naphthoquinone, IV, (a) with Malonic Acid.—A solution of 0.86 g. (0.005 mole) of IV and 0.6 g. of malonic acid in 15 cc. of

(18) Diels and Alder, *Ber.*, **62**, 2361 (1929).

(19) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1935, p. 228.

acetic acid was treated with 5 g. of lead tetraacetate and heated on a water-bath to 50–60°, when a brownish solid soon began to separate from the upper part of the solution and gas bubbles began to appear. After heating for about one hour, the precipitate had lightened in color and appeared as a curdy white solid which filled the entire solution. The same substance is formed in the absence of methylnaphthoquinone and probably is a lead salt of malonic acid. After heating for another hour at 75° the solid had all dissolved, no more gas was evolved, and the test with starch–iodide paper was negative. When an additional 2-g. portion of lead tetraacetate was added it was consumed rather rapidly, with further gas evolution. When the reaction slackened, another 2-g. portion was added. This process was repeated until, at the end of six and one-quarter hours (total), no more gas was evolved, the solution was of a clear, golden color, and excess reagent was present; a total of 10.5 g. (4.7 equivalents) of lead tetraacetate had been used. The excess reagent was destroyed with glycerol (6 drops) and the solution was poured into water. The crystalline yellow precipitate on one crystallization from methanol yielded 0.45 g. (49%) of yellow needles, m. p. 118–125°. On recrystallization, the sample melted at 122–124° and was identified by mixed melting point determination as 2,3-dimethyl-1,4-naphthoquinone. A trace of starting material (m. p. 102–104°) was recovered from the aqueous filtrate by extraction with ether and crystallization. In later experiments conducted at the steam-bath temperature, no starting material was detected and the yield of methylated product was better.

(b) **With Ethyl Acetoacetate.**—In an experiment with 0.86 g. of IV and 0.6 cc. of acetoacetic ester in 15 cc. of acetic acid, heated on the steam-bath, no solid intermediate appeared, but gas was evolved and a total of 4.16 equivalents of lead tetraacetate was consumed. The product was identified as the 2,3-dimethyl compound. Other experiments indicated that the results are better when a full molecular equivalent of the promoter is used than with 0.4 equivalent.

(c) **With C-Ethyl Ethyl Acetoacetate (L. F. F.).**—The following rapid procedure gave good results with this promoter but was less satisfactory when malonic acid or acetoacetic ester was used. A mixture of 0.86 g. of IV, 8.8 g. (3.7 equiv.) of lead tetraacetate, and 10 cc. of acetic acid was heated on the steam-bath and a solution of 1.03 g. (1.3 equiv.) of C-ethyl ethyl acetoacetate in 5 cc. of acetic acid was run in from a dropping funnel in the course of one-half hour, during which time gas was evolved steadily. A few remaining crystals of lead tetraacetate subsequently dissolved, but after heating for one and one-half hours excess reagent was still present. This was discharged with glycerol (4 drops) and the solution was diluted and extracted with ether. The ethereal extract was washed with dilute nitric acid and with sodium carbonate solution and shaken with aqueous sodium hydrosulfite solution to effect reduction of the quinone. The hydroquinone was then extracted with three portions of 5% potassium hydroxide containing 2% of sodium hydrosulfite and the yellow vat solutions were drawn off under ether, combined and acidified. [20] The hydroquinone was extracted with ether and the solution was washed with soda solution, dried, shaken with silver oxide and magnesium sulfate, filtered and evaporated. The residue was a bright yellow solid, m. p. 120–122° (recrystallized: 124–125°); yield 0.43 g. (46%).

(d) **With Diethyl Malonate.**—In an experiment conducted as in (a) except for the substitution of malonic ester in place of malonic acid, there was but little gas evolution at the steam-bath temperature and after heating for twelve hours a considerable part of the initial 5-g. lot of lead tetraacetate remained unconsumed and crystallized when the solution was cooled. The filtered solution afforded only starting material, m. p. 103–104°.

In another run performed in the same way but at the reflux temperature and with excess lead tetraacetate, methylation proceeded satisfactorily and the dimethyl compound was produced.

(e) **With Methylmalonic Acid.**—This reagent, when employed under the conditions defined for malonic acid (a), gave entirely comparable results and afforded 2,3-dimethyl-1,4-naphthoquinone in good yield. The only difference noticed was that no intermediate white salt precipitated, although at the beginning of the reaction the solution was slightly cloudy.

(f) **With Tartronic Acid.**—When tartronic acid[11] (m. p. 159°, dec.) was used, a curdy white solid at first separated and then dissolved on the addition of more reagent. Dimethylnaphthoquinone again was a product of the reaction.

(g) **With Dimethylmalonic Acid.**—With this reagent,[21] employed under the conditions of (a), about half the usual amount of lead tetraacetate was consumed, there was relatively little gas evolution, and the product after one crystallization melted at 95–100° and after a second at 99–102°. This, apparently, consisted largely of starting material, but on reëxamination it was found to afford after further crystallizations a small amount of material melting at 113–115°; a mixture with the dimethyl compound melted at 115–120°.

(h) **With Methanol.**—A solution of 0.86 g. of the quinone IV in 15 cc. of acetic acid and 5 cc. of methanol was treated at the steam-bath temperature with a total of 9 g. (4.1 equiv.) of lead tetraacetate, added in portions. At the end of the reaction the clear solution was decanted from a small amount of dark precipitate and processed as usual. After two crystallizations the product melted at 120–122° and was identified as the dimethyl compound VII.

(i) **Without a Promoter.**—When a mixture of 5.16 g. of methylnaphthoquinone, 30 cc. of acetic acid, and 25 g. of lead tetraacetate was heated to the reflux temperature, the reaction started promptly, with vigorous gas evolution. As the reagent was used up, further 5-g. portions were added until, when a total of 67 g. (5 equiv.) of lead tetraacetate had been added, the reaction subsided. Refluxing was continued for a total of five hours. The dark brown mixture was poured into water and the product extracted with ether and processed as usual. The solid material obtained from the residual oil when purified afforded 0.42 g. of 2,3-dimethyl-1,4-naphthoquinone, m. p. 123–125°; the mother liquor remained as an oil even on sublimation and yielded no additional product. Better results were

(20) Compare procedure for the isolation of vitamin K_1.[9]

(21) Bartlett, Fraser and Woodward, THIS JOURNAL, **63**, 495 (1941).

obtained in an earlier experiment employing less reagent (4 equiv.) and more acetic acid; the yield was not determined accurately but appeared to be comparable with those in the experiments with added malonic acid.

(j) **With Reactive Hydrocarbons.**—In trials with cyclopentadiene and with acenaphthene as possible promoters, the starting material was recovered unchanged. With triphenylmethane, the reaction seemed to proceed as in the successful methylations, but the only crystalline product isolated from the oily reaction mixture was a colorless solid, m. p. 88–90° (probably triphenylmethyl acetate, m. p. 87–88°).

2-Methyl-3-ethyl-1,4-naphthoquinone. (a) **By Ethylation.**—A solution of 3.44 g. (0.02 mole) of 2-methyl-1,4-naphthoquinone and 3.2 cc. (0.025 mole) of ethyl acetoacetate in 50 cc. of propionic acid was heated with stirring on the steam-bath and 60 g. (4.37 equiv.) of red lead was added in 5-g. portions. The reaction started on the addition of the first lot of oxide, as evidenced by the rapid evolution of gas. After a time the gas evolution noticeably lagged. The first 40 g. of red lead was consumed within forty-five minutes and the remainder had largely disappeared after a total time of about two hours, when the reaction appeared to be at an end. Heating and stirring were continued for a total of three hours. In this and similar alkylations it seems advisable to continue heating for about one hour after evident gas evolution ceases. The mixture, which gave a positive test for tetravalent lead, was cooled somewhat, with continued stirring, and ether was added to extract the product. The ethereal solution was decanted and the semisolid residue containing red lead and lead salts was extracted several times with fresh portions of ether. The combined ethereal solution was washed with saturated sodium bicarbonate solution until neutral, dried with calcium chloride, and evaporated. A voluminous white precipitate of a basic lead salt sometimes appears in the washing with sodium bicarbonate solution; in this case the ethereal solution is acidified, shaken thoroughly with 10% nitric acid, and then washed again with bicarbonate solution. The residual oil obtained from the ether crystallized when cooled and manipulated. The crystalline product was transferred to a Hirsch funnel and washed with methanol, giving 0.75 g. of yellow needles, m. p. 69–70.5°. Concentration of the mother liquor and washings afforded 0.87 g. of material melting at 66–70.5°. The total amount collected represents a yield of 40.5%; additional material is retained in the mother liquor. After two further crystallizations the quinone melted at 72–72.6° and sublimation of the sample produced no change (Karrer, *et al.*,[13] 73°).

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.36, 78.38; H, 6.48, 6.44.

The **hydroquinone diacetate** crystallized from dilute acetic acid in needles melting at 106–108°, and remelting at 116–117°.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.37; H, 6.34. Found: C, 71.69; H, 6.34.

(b) **By Methylation.**—2-Ethyl-1,4-naphthoquinone (1.86 g.) was methylated with lead tetraacetate in acetic acid in the presence of malonic acid (1.3 g.) by the procedure described above. The yield of once crystallized product, m. p. 65–68°, was 0.3 g. (15%). Sublimation, followed by crystallization from ether–petroleum ether raised the melting point to 71.4–72.4° and admixture of the sample with that described in (a) did not depress the melting point. The second crop of crystals from the mother liquor melted below 60° and contained a considerable amount of starting material.

2-Methyl-3-*n*-propyl-1,4-naphthoquinone. (a) **By Propylation.**—The reaction was conducted with 1.72 g. of methylnaphthoquinone, 1.5 g. of malonic acid (1.4 equiv.), 45 cc. of *n*-butyric acid, and 35.7 g. (5.2 equiv.) of red lead. The mixture was poured into water and the viscous oily layer which appeared was washed with water by decantation and extracted with ether. The crude reaction product was obtained as a yellow oil which crystallized on cooling. Crystallization from methanol afforded the following crops of material: 0.07 g. (m. p. 65–65.5°), 0.72 g. (64–64.5°), 0.21 g. (63–64.2°); combined yield 47%. Sublimation at 53–58° at 1 mm. gave quinone melting at 65–65.4°.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.69; H, 6.90.

The **hydroquinone diacetate** was prepared by reductive acetylation of the quinone with acetic anhydride, zinc dust and a trace of pyridine. It separated from methanol in diamond-shaped crystals, m. p. 93.5–95°.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.00; H, 7.11.

(b) **By Methylation.**—The 2-*n*-propyl-1,4-naphthoquinone required as starting material was prepared by hydrogenating a sample of the 2-allyl compound,[4] oxidizing the resulting hydroquinone, crystallizing the quinone from ether–petroleum ether, and finally subliming the sample slowly at 40° and 8 mm. This gave canary-yellow material melting at 40.5–41° (compare 39–39.5°[4]). Methylation with lead tetraacetate (and malonic acid) was first attempted at steam-bath temperature, but the starting material was recovered unchanged. The reaction proceeded successfully, however, when conducted at the boiling point of the acetic acid solution. The crude product melted at 50–55°, and recrystallization gave well formed needles, m. p. 58–60°. Slow sublimation afforded in the terminal fraction material melting at 61–63.5°, and a mixture of this with the sample (a) melted at 63.5–65°.

2-Methyl-3-isopropyl-1,4-naphthoquinone. (a) **By Propylation.**—The alkylation of methylnaphthoquinone (1.72 g.) with isobutyric acid and red lead afforded 1.27 g. (59%) of satisfactory product in two crops, m. p. 106–108° (0.95 g.) and 104–107° (0.32 g.). Recrystallization from methanol and sublimation at 80–85° and 1 mm. afforded canary-yellow material, m. p. 110–111.2°.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.61; H, 6.77.

The **hydroquinone diacetate** crystallized from methanol in colorless, diamond-shaped needles, m. p. 115–116°.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.20; H, 7.03.

(b) **By Methylation.**—The method first tried for the preparation of the required β-isopropylnaphthalene proved unsuccessful. **Dimethyl-β-naphthylcarbinol** was obtained by the reaction of β-acetonaphthalene (24.6 g.) with methylmagnesium iodide (from 3.5 g. of magnesium) in ether; the acid-hydrolyzed and washed ethereal layer was

neutralized with sodium bicarbonate solution, decolorized with Darco, concentrated to about 100 cc., and diluted with petroleum ether, which caused the separation of 19.7 g. (72%) of crystalline carbinol, m. p. 60–63°. Recrystallization from ligroin (70–90°) gave colorless leaflets, m. p. 65–65.5°.

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 84.08; H, 7.88.

Reduction was attempted by refluxing the carbinol in acetic acid and shaking the resulting solution with hydrogen and Adams catalyst,[22] but very little hydrogen was absorbed and the hydrocarbon appeared to have polymerized. Reduction with red phosphorus and potassium iodide[23] likewise gave a polymer.

β-Isopropylnaphthalene finally was prepared by the Friedel and Crafts reaction according to Haworth and coworkers,[24] although the reaction proceeded poorly and afforded a hydrocarbon fraction boiling at 120–135° (8 mm.) in only 14% yield. The crude hydrocarbon (4.5 g.) was oxidized with chromic anhydride[15] and the quinone extracted by the vatting procedure,[9] which afforded 1.5 g. of crude 2-isopropyl-1,4-naphthoquinone as a dark yellow, viscous oil. The entire product was methylated in boiling acetic acid solution with lead tetraacetate and malonic acid. The oily product partially crystallized when cooled, and the crystals when collected and washed with methanol melted at 95–110°. Fractional sublimation gave material melting progressively higher, and the best sample melted at 109–110°. A mixture with the 2-methyl-3-isopropyl-1,4-naphthoquinone described in (a) melted at 108.5–110°, while the substance strongly depressed the melting point both of 1,4-naphthoquinone and its 2-methyl derivative.

2-Methyl-3-*n*-heptyl-1,4-naphthoquinone.—The *n*-caprylic acid used was obtained by fractional distillation of commercial 90% acid; b. p. 120–126° (12 mm.). The alkylation of methylnaphthoquinone (1.72 g.) with *n*-caprylic acid (30 cc.), red lead (35 g.) and diethyl malonate (1.5 cc.) was conducted in an oil-bath maintained at 120–130°. The hot reaction mixture was poured into water and the nearly solid cake which separated was disintegrated by prolonged manipulation with ether and dilute nitric acid (see next section for a better method of processing the reaction mixture). The material recovered from the washed and dried ethereal solution afforded, on crystallization from methanol, 0.55 g. of product, m. p. 77–78°, and 0.36 g., m. p. 75–78°; total yield 34%. Sublimation at 70–76° (1 mm.) gave canary-yellow crystals, m. p. 80.4–80.8°. Malonic acid also was found satisfactory as the promoter.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.22, 80.20; H, 8.55, 8.58.

The **hydroquinone diacetate** separated from methanol as colorless silken needles, m. p. 64–65°.

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.44; H, 8.25.

2-Methyl-3-benzyl-1,4-naphthoquinone.—The reaction was conducted with 1.72 g. of methylnaphthoquinone, 35 g. of phenylacetic acid, 1.7 cc. of ethyl acetoacetate, and excess red lead. The mixture was stirred in an oil-bath kept at 110–120° and toward the end of the reaction benzene was added to facilitate stirring of the otherwise pasty mixture. The addition of a diluent before the melt cools and solidifies also simplifies the processing of the reaction mixture. When benzene has been added as a thinning medium, the mixture can be cooled, with continued stirring, and enough ether added to dissolve the organic material. The solution is then filtered from oxides and salts of lead, washed with 10% nitric acid and then with sodium bicarbonate solution, dried and evaporated. In the present instance the crude product weighed 1.7 g. (65%), m. p. 98–104°. Crystallization from ethanol gave 1.13 g. of product melting at 107–108° but having the odor of phenylacetic acid. The odor was not removed entirely by sublimation at 80° (1 mm.), but two recrystallizations from ether–petroleum ether gave odorless, hexagonal, yellow prisms, m. p. 108–108.5°.

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 82.41; H, 5.38. Found: C, 82.08; H, 5.60.

No depression in the melting point was observed when the material was mixed with a sample of the quinone (m. p. 107.5–108°) prepared by a different method.[15] The **hydroquinone diacetate** crystallized from methanol in clusters of colorless needles, m. p. 163–164.5°.

Anal. Calcd. for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.63; H, 5.50.

2-Methyl-3-β-phenylethyl-1,4-naphthoquinone.—The reaction was carried out with 1.7 g. of methylnaphthoquinone, 25 g. of hydrocinnamic acid, 1.7 cc. of ethyl acetoacetate, and excess red lead in a bath at 120–130° (four hours). The crude product when washed with methanol amounted to 0.40 g. (14.5%), m. p. 72–73° (additional material was retained in the mother liquor but was not recovered). After sublimation and crystallization from ether–petroleum ether, the substance was obtained as yellow crystals, m. p. 73–73.5°.

Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.86. Found: C, 82.46; H, 5.90.

The hydroquinone diacetate formed microcrystals, 140.5–141.2°, from ether–petroleum ether.

Summary

Under certain experimental conditions lead tetraacetate is capable of functioning as a methylating agent. Thus 2-methyl-1,4-naphthoquinone can be converted into 2,3-dimethyl-1,4-naphthoquinone in yields as high as 50% by interaction with this reagent. The reaction can be caused to occur in acetic acid solution by operating at the reflux temperature, but proceeds more smoothly and at a lower temperature in the presence of a promoter such as malonic acid, methylmalonic acid acetoacetic ester or methanol. 2-Methyl-5,8-dihydro-1,4-naphthohydroquinone functions both as acceptor of the methyl group and as a promoter of the alkylative decomposition of lead tetraacetate.

Other alkyl groups can be introduced into the

(22) See procedure of Fieser and Joshel, THIS JOURNAL, **62**, 957 (1940).

(23) Miescher and Billeter, *Helv. Chim. Acta*, **22**, 601 (1939).

(24) Haworth, Letsky and Mavin, *J. Chem. Soc.*, 1790 (1932).

naphthoquinone nucleus by treatment with an acid, a promoter and excess red lead. The 3-ethyl, 3-*n*-propyl and 3-isopropyl derivatives of 2-methylnaphthoquinone were synthesized with the use of propionic, *n*-butyric, and isobutyric acid, respectively, and the structures were established by the preparation of identical substances by the action of lead tetraacetate on 2-ethyl, 2-*n*-propyl, and 2-isopropyl-1,4-naphthoquinone. The 3-*n*-heptyl, 3-benzyl, and 3-β-phenylethyl derivatives of 2-methyl-1,4-naphthoquinone were synthesized by the new method.

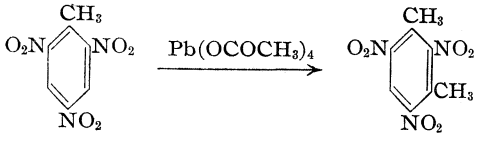
CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 29, 1941

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Methylation of Aromatic Nitro Compounds with Lead Tetraacetate

BY LOUIS F. FIESER, RICHARD C. CLAPP AND WILLIAM H. DAUDT

In an initial experiment, 2,4,6-trinitrotoluene was treated in acetic acid solution with lead tetraacetate in the expectation of introducing an acetoxyl group into the reactive methyl substituent. Much to our surprise, the only pure reaction product isolated proved to be trinitro-*m*-xylene. The reaction appears to constitute a second instance



of the methylating action of lead tetraacetate, observed in this Laboratory as applied to various α-naphthoquinones.[1] In further analogy with the naphthoquinone methylation, it was found that carbon dioxide is evolved copiously in the reaction with trinitrotoluene and that a large excess of lead tetraacetate is consumed. Since an efficient method of methylating nitrohydrocarbons might have practical applications of value in the production of high explosives, an exploratory survey was made to test the applicability and efficiency of the novel reaction.

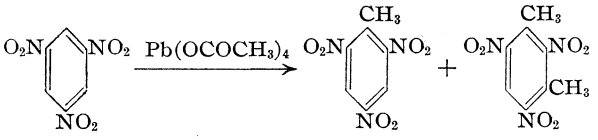
At the time the study was commenced, the parallel work in the quinone field was at a stage where it appeared that the methylating function of lead tetraacetate is evoked only in the presence of an active–hydrogen component such as malonic acid, which is itself attacked by the reagent. We thought at first that a part of the trinitrotoluene might be undergoing acetoxylation in the methyl group and thereby serving as the initiator of the methylation reaction. In the first applications of the reaction to *s*-trinitrobenzene and to *m*-dinitrobenzene, a suitable amount of malonic acid was incorporated in the reaction mixture comprising the nitro compound, lead tetraacetate and acetic acid. Although the reactions proceeded under these conditions, it was subsequently discovered that the malonic acid serves only as a promoter of reactions which can be realized in the absence of this or similar component. The methylation reaction, which becomes quite evident from the gas evolution as well as by a marked darkening of the solution, often can be initiated by brief refluxing of the mixture, or by local heating of the flask with a free flame. Once the reaction has been set in progress, it will proceed briskly at a temperature previously found insufficient to cause it to start promptly. No significant differences, in this respect, were observed between trinitrobenzene and trinitrotoluene. In one experiment with the latter compound which was conducted throughout at the steam-bath temperature, the reaction started only after an induction period of about five hours but then proceeded easily to completion. Malonic acid, added as a promoter, promptly induces reaction at the temperature of the steam-bath, and methanol has the same influence. These reagents, however, seem to have no advantages over the method of initiating the reaction by heat, and they merely consume an additional mount of lead tetraacetate. In several parallel experiments the yields were essentially the same whether or not a promoter was used.

The conversion of trinitrotoluene to trinitro-*m*-xylene constitutes a particularly favorable case for study because the product is much less soluble and higher-melting than the starting material. The dimethyl compound also appears to be an end-product, for lead tetraacetate was found to be without action on trinitro-*m*-xylene in refluxing acetic acid. On treating trinitrotoluene with varying amounts of lead tetraacetate in the ab-

(1) Fieser and Chang, THIS JOURNAL, **64**, 2043 (1942).

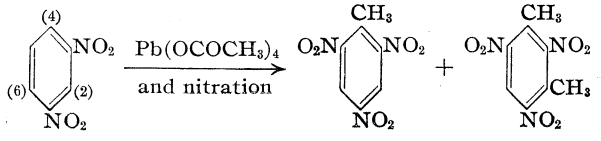
sence of a promoter, no evident stopping point was found and as much as 4.7 equivalents of the reagent was consumed readily. The yield of trinitro-*m*-xylene (19%) was not as high, however, as when a more moderate amount of reagent was used. In three experiments employing 2.5–3 equivalents of lead tetraacetate, yields of 28–32% were obtained, and this appears to be approximately the optimum proportion of reagent for the yield dropped to 20% when but one equivalent was used. The methylation was accomplished also by adding red lead to a warm solution of trinitrotoluene in acetic acid, and by prolonged refluxing of the nitro compound with lead dioxide in acetic acid, but the resulting mixtures were not as easily processed and these methods have no advantages over the use of lead tetraacetate.

The action of lead tetraacetate on 1,3,5-trinitrobenzene was found to result in the formation of both trinitrotoluene and trinitro-*m*-xylene. Be-

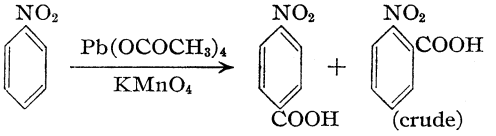


cause of the more complicated nature of the mixture and the less favorable solubility relationships, the yields are less easily determined; orienting experiments indicate merely that the reaction affords more of the monomethyl than of the dimethyl compound, and that the extent of total methylation is perhaps slightly less than found with trinitrotoluene.

In trials with *m*-dinitrobenzene, the reaction mixture was characterized after submitting it to nitration with mixed acid at 120°, for methylation products are thereby nitrated and converted to less soluble products, whereas any starting material is left unchanged. The crude products obtained by the action of lead tetraacetate on the dinitro compound, both with and without the use of a promoter, were nitrated and processed as follows. Crystallization from alcohol–acetone afforded trinitro-*m*-xylene, and addition of β-naphthylamine to the mother liquor gave an easily separated complex of this amine with trinitrotoluene, from which the nitro compound is recoverable by treatment with acid; unchanged *m*-dinitrobenzene was recovered from the acidified mother liquor. The results show that 1,3-dinitrobenzene is converted in part by lead tetraacetate into its 4-methyl and 2,4- or 4,6-dimethyl derivatives. The extent of total methylation appears to be of the same order of magnitude as with the trinitro compounds.

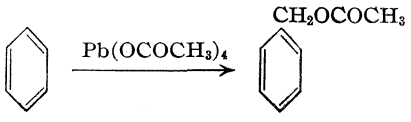


The reaction was found applicable also to nitrobenzene, although this substance is attacked somewhat less readily than the polynitro compounds. In the first trials, carried out both with lead tetraacetate (3 equivalents) and with red lead and acetic acid, the reaction product was characterized subsequent to nitration, and trinitrotoluene was isolated from the final mixture in 4.9% yield through the β-naphthylamine complex. In another experiment, conducted on a large scale with equivalent amounts of nitrobenzene and lead tetraacetate, the bulk of the unchanged starting material was eliminated by fractionation and the slightly higher-boiling terminal fraction was characterized by oxidation with permanganate. *p*-Nitrobenzoic acid was isolated in a pure condition and a second acidic product was characterized as crude *o*-nitrobenzoic acid; the ortho isomer ap-



pears to predominate but the para compound is more easily separated from the mixture. The extent of the reaction, as indicated by the amounts of the two nitrobenzoic acids isolated, represented 4.3% methylation.

We next ventured to try the new reaction on benzene. When a solution of benzene (10 g.) in acetic acid (60 cc.) was refluxed with lead tetraacetate there was little change at first but, after an induction period of four to five hours, a rapid reaction set in and a total of 2.4 equivalents of reagent was consumed. The reaction mixture contained little if any benzene but consisted almost entirely of high-boiling material. The main constituent of the mixture, isolated by a simple and inefficient distillation technique in 18% yield, proved to be essentially pure benzyl acetate. The reaction evidently involves the separate steps of



methylation and acetoxylation. The oxidative step has already been demonstrated, for Dimroth and Schweizer[2] found that toluene can be converted to benzyl acetate by the action of lead tetraacetate in refluxing acetic solution (four hours) under conditions very similar to those employed in the present work. Our yield of the product from benzene is even slightly better than theirs obtained starting with toluene (11.5%). The methylation step, therefore, must have proceeded with particular efficiency. Another point of interest is that Dimroth and Schweizer state that benzene is very stable to lead tetraacetate and cite in evidence an experiment in which a mixture of 15 cc. of benzene and 1 cc. of acetic acid was refluxed with the reagent for five and one-half hours with no more than 1% loss in the oxidation value. That they did not encounter the striking reaction observed in the present investigation, may have been because the refluxing was stopped somewhat short of the end of the induction period. Perhaps of greater importance is the difference in the relative amounts of benzene and acetic acid and the consequent difference in the reflux temperatures; the mixture containing an excess of acetic acid as the solvent would be more favorable for initiation of the reaction. It remains to be determined whether the nature of the solvent is of any consequence beyond controlling the boiling temperature. In past instances in which benzene has been employed as solvent for reactions conducted with lead tetraacetate, some attack of the solvent may well have occurred, only to remain undetected.

Chlorobenzene was found to react in a manner similar to benzene, giving a mixture probably consisting of isomeric chlorobenzyl acetates. After saponification, *p*-chlorobenzyl alcohol was isolated and identified, but no other component of the mixture was characterized. The behavior of naphthalene was different for, under the usual conditions of the methylation reaction, this hydrocarbon was converted in at least 26% yield into 1-acetoxynaphthalene. Thus naphthalene is sufficiently susceptible to oxidative attack to give this reaction precedence over methylation. Still more reactive hydrocarbons such as acenaphthene,[3] anthracene[4] and 3,4-benzpyrene[5] are known to undergo acetoxylation at temperatures well below that at which the methylative action of lead tetraacetate becomes operative.

In completion of this survey of the applicability of the reaction to available starting materials, we tested the action of lead tetraacetate on various mono-, di-, tri- and tetra-nitronaphthalenes, but with invariably unpromising results. The reactions proceeded rather destructively, and a product of methylation was isolated in only one case and in small amounts.

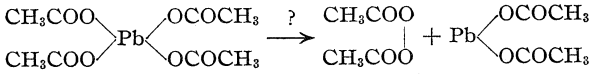
Although any interpretations of the unusual reaction are at present necessarily tentative, it may be noted that the substances which thus far have been found capable of being methylated by lead tetraacetate all conform to the general definition of unsaturated cyclic compounds which are rather resistant to ordinary aromatic substitutions and which do not appear to be susceptible to the acetoxylating action of the reagent. This roughly defined category includes such otherwise widely divergent types as 2-methyl-1,4-naphthoquinone, nitro- and chloro-benzene, the polynitro benzenes and even benzene itself. Toluene and naphthalene fall outside the category, for they are subject to acetoxylation in the side-chain and in the nucleus, respectively. 2-Methyl-1,4-naphthoquinone is associated in behavior with the polynitro compounds in the respect that the yields are favorable and that the methyl group introduced resists subsequent attack. The quinone resembles trinitrobenzene in that the nuclear position undergoing methylation is flanked by unsaturated groups, and a certain similarity is indicated by the fact that a hydroxyl group situated at this position is in each case endowed with pronounced acidic characteristics. The fact that in the series of benzene derivatives the substituting methyl group enters positions ortho and para to the nitro group and the halogen atom, indicates that the reaction is in a class entirely distinct from the usual aromatic substitution.

The reaction has certain other characteristic peculiarities, including the marked induction period frequently noted, and the promoting effect of active-hydrogen compounds and of heat. The evolution of carbon dioxide must be an index of the breakdown of the lead tetraacetate molecule or of some product derived from it, possibly with the direct liberation of methyl radicals. Once this breakdown is initiated, it appears to proceed autocatalytically and to an extent which is excessive in comparison with the amount of methylated

(2) Dimroth and Schweizer, *Ber.*, **56**, 1375 (1923).
(3) Fieser and Cason, THIS JOURNAL, **62**, 432 (1940).
(4) K. H. Meyer, *Ann.*, **379**, 73 (1911).
(5) Fieser and Hershberg, THIS JOURNAL, **60**, 1893, 2542 (1938).

material formed, for the yield is not improved beyond a certain point by increasing the amount of lead tetraacetate, and starting material almost always is recovered. Certain substances of adequate stability, when present at the time of the decomposition, seem capable of acting as acceptors of a certain amount of the actual or potential methyl radicals.

There may be a certain analogy between the catalyzed decomposition of this lead salt of acetic acid to carbon dioxide and possible hydrocarbon radicals and the electrolytic decomposition of sodium acetate in the Kolbe synthesis, and from a consideration of this possible analogy we were led to investigate two other lines of experimentation. One of these was suggested by Dr. A. E. Oxford and has been applied by him in an extension of the parallel work in progress in this Laboratory in the quinone field. Since, according to one of the current views concerning the mechanism of the Kolbe synthesis,[6] the reaction may proceed through the intermediary formation of the acyl peroxide, it might be supposed that lead tetraacetate undergoes decomposition to the same intermediate. In



a trial made of the action of acetyl peroxide (3 equivalents) on trinitrotoluene in acetic acid solution, a reaction set in without delay at 85° and proceeded with steady gas evolution and darkening of the solution, in marked resemblance to the lead tetraacetate reaction. Processing of the reaction mixture afforded trinitro-*m*-xylene in 10.6% yield. The alkylation of quinones with acyl peroxides has been conducted with distinct success in several instances.

The second idea was that methylation might be realized by conducting the electrolytic decomposition of sodium acetate in the presence of a suitable acceptor. Initial trials were made with a solution of trinitrotoluene in acetic acid saturated with sodium acetate placed in a porcelain cell which constituted the anode chamber of the cell. On electrolysis over a period as long as twelve hours, some of the nitro compound was lost by diffusion, but there was little destruction of the material remaining in the anode chamber, and trinitro-*m*-xylene was isolated as a reaction product in yields up to 9%.

(6) Review papers: Fichter, *Trans. Electrochem. Soc.*, **75**, 309 (1939); Glasstone and Hickling, *ibid.*, **75**, 333 (1939).

These few exploratory experiments demonstrate that alkylations of a novel type may be accomplished by three different experimental methods which probably are interrelated and which may involve manifestations of the same general phenomenon. As for possible practical applications, the present survey indicates that methylation with either lead tetraacetate or acetyl peroxide is more likely to find uses in the synthesis of rare chemicals than in the quantity-production of polynitro alkylbenzenes. The electrolytic method of methylation has not been evaluated fully but does not appear promising for practical application.

Experimental Part[7]

Conversion of Trinitrotoluene into Trinitro-*m*-xylene

Identification of the Product.—In an initial experiment carried out by Dr. E. B. Hershberg, a mixture of 3 g. of 2,4,6-trinitrotoluene, 6.2 g. (1 equiv.) of lead tetraacetate and 20 cc. of glacial acetic acid was heated gently at first and then refluxed for one-half hour. The product precipitated with water (1.7 g.) on one crystallization from alcohol afforded 0.6 g. of material, m. p. 145–165°. After six further crystallizations from benzene–hexane, the purified substance melted at 182.7–183.2°, and a mixture with a sample of authentic trinitro-*m*-xylene (m. p. 180.5–182°) melted at 180.5–182°.

Anal. Calcd. for $C_8H_7O_6N_3$: C, 39.84; H, 2.93; N, 17.43. Found: C, 40.34; H, 3.06; N, 17.27.

With Red Lead and Acetic Acid.—Methylation also can be accomplished by the addition of red lead in portions to a stirred solution of trinitrotoluene in acetic acid at 95°, with subsequent gentle refluxing, and the formation of trinitro-*m*-xylene under these conditions was established. The reaction mixture is not as clean as when lead tetraacetate is used, and the processing is therefore less easily accomplished; the separation of lead dioxide from the acetic acid solution makes it difficult to follow the progress of the reaction. For these reasons, lead tetraacetate was employed in most of the exploratory experiments. Preliminary attempts to ethylate trinitrotoluene and trinitrobenzene with lead tetrapropionate or with propionic acid and red lead were unpromising.

With Lead Tetraacetate.—In trial runs made with 1.0, 2.5, and 4.7 equivalents of lead tetraacetate, which in each case was completely consumed, the yields of trinitro-*m*-xylene of comparable purity were 19.8, 28.2, and 18.8%, respectively. The product was more difficult to purify in the experiment utilizing the largest amount of reagent than in the other runs.

The most satisfactory of these experiments was carried out by adding 14.6 g. (0.033 mole) of lead tetraacetate to a solution of 3.0 g. (0.132 mole) of trinitrotoluene (m. p. 80.4–81.8°) in 40 cc. of acetic acid. The reaction was not initiated by heating the mixture on the steam-bath (90–95°), for no gas was evolved, and the originally undissolved lead tetraacetate remained colorless and showed no ten-

(7) Microanalyses by Lyon Southworth and E. Werble.

dency to go into solution. When the mixture was heated to the reflux temperature, however, a yellow coloration soon appeared at one spot in the lead tetraacetate crystals and soon spread over the entire mass, and there was a rapid evolution of gas containing carbon dioxide. After refluxing for about fifty minutes the evolution of gas had ceased and a test with moistened starch–iodide paper was negative. By this time the originally light yellow solution had acquired a rather deep red-orange color. The hot solution was diluted with water and cooled, when 1.4 g. of crude product separated; this melted at 135–165°. Two crystallizations from benzene–hexane (Norit) gave 0.90 g. (28.2%) of yellow needles of trinitro-*m*-xylene, m. p. 174–178°. A further crystallization from alcohol–acetone afforded 0.66 g. (20.7%) of long, light yellow needles, m. p. 178–180°, and the more fully purified material melted at 182.7–183.2° and did not depress the melting point of an authentic sample.

Effect of Promoters.—An experiment parallel to that just described was carried out with the same amounts of reagents (4.7 equiv. of lead tetraacetate) but with the addition of one equivalent of malonic acid. This functioned as a promoter, for the reaction started, as evidenced by the gas evolution, when the mixture was heated on the steam-bath. The reaction proceeded to completion at this temperature, and the test for lead tetraacetate was negative after one hour. The yield was practically the same as when no malonic acid was used. In other trials with varying proportions of lead tetraacetate, the yields tended to be slightly lower with malonic acid present than when no promoter was employed.

Methanol (1 cc. in 40 cc. of acetic acid, 3 equivalents of lead tetraacetate) also functioned as a promoter and induced a prompt reaction at the steam-bath temperature; the yield of trinitro-*m*-xylene, m. p. 177–179.5°, in this case was 28%. When an absolute methanol solution of trinitrotoluene and lead tetraacetate (3 equiv.) was refluxed, reaction set in immediately and was complete in about fifteen minutes. However, only starting material was recovered, indicating that the consumption of reagent was due to oxidation of the solvent.

Conversion at a Moderate Temperature.—A mixture of 1.0 g. of trinitrotoluene, 5.9 g. (3 equiv.) of lead tetraacetate, and 10 cc. of acetic acid was heated on the steam-bath without a promoter and without stirring. After an induction period of about five hours, gas evolution became discernible and the lead tetraacetate began to dissolve. After continued heating overnight on the steam-bath, the reaction was found to have gone to completion. The product which separated on adding water to the light red solution and cooling gave, on crystallization from acetone–alcohol (Norit), 0.37 g. of needles, m. p. 174–177°. Recrystallization afforded 0.34 g. (32%) of trinitro-*m*-xylene, m. p. 176–178.5°. The high yield and quality of the product may be due to the mild conditions of the reaction.

With Lead Dioxide and Acetic Acid.—A suspension of 10 g. (3.2 equiv.) of lead dioxide in a solution of 3 g. of trinitrotoluene in 50 cc. of acetic acid was heated under reflux, when a slow evolution of carbon dioxide was observed. After refluxing for twelve hours, all of the reagent had dissolved and the starch–iodide test was negative. The red-dish solution was filtered from a small amount of black residue and diluted with water. The precipitated material on crystallization afforded 0.54 g. (17%) of trinitro-*m*-xylene, m. p. 175–178°, and from the mother liquor there was recovered 0.64 g. of trinitrotoluene, isolated through the β-naphthylamine complex.

In another trial acetic anhydride was added to a similar reaction mixture. This caused the lead dioxide to dissolve rapidly, and the reaction was completed in a much shorter time; the yield, however, was distinctly lower. The yield was also lower when the above experiment was repeated with the use of a larger excess of lead dioxide.

Stability of Trinitro-*m*-xylene to Lead Tetraacetate.—A solution of 0.5 g. of trinitro-*m*-xylene and 0.92 g. (1 equiv.) of lead tetraacetate in acetic acid was refluxed for four and one-half hours, but there was no pronounced gas evolution, lead tetraacetate was still present at the end of the period of refluxing, and unchanged starting material crystallized from solution on cooling. In another trial an acetic acid solution of equimolecular amounts of trinitro-*m*-xylene and malonic acid was heated on the steam-bath and treated with lead tetraacetate until a total of 4.7 equivalents of the reagent had been consumed. Practically all of the starting material was recovered unchanged.

Methylation with Acetyl Peroxide.—The reagent was prepared essentially according to Gambarjan[8] by adding ice with shaking to a cooled mixture of acetic anhydride, sodium peroxide and petroleum ether, and separating and evaporating the hydrocarbon layer. A solution of 4 g. of trinitrotoluene and 6.2 g. (3 equiv.) of acetyl peroxide in 50 cc. of acetic acid was warmed gradually in a water-bath to a temperature of 85°, when a steady gas evolution was noted. After heating for one hour at 85–95°, and for one hour longer at 95–100°, the evolution of gas had become feeble, and after one hour more at 95–100° it had ceased completely. The orange-red solution was diluted well with water, and the semisolid material which precipitated was collected, dried, and leached with about 100 cc. of warm alcohol. This dissolved the bulk of the material and left 0.32 g. of powdery, light brown solid, m. p. 170–177°. Crystallization of this material from acetone–alcohol gave 0.28 g. of characteristic needles of trinitro-*m*-xylene, m. p. 177–180°, and 0.17 g. of product of the same melting point was recovered from the alcoholic mother liquor; total yield 10.6%. Only a very small amount of trinitrotoluene could be recovered from the mother liquors.

Methylation by Electrolysis.—The electrolysis was conducted in a 400-cc. beaker in which was suspended a 4-inch porcelain cell about 1.5 inches in diameter to contain the anode liquid. The anode and cathode were made of bright platinum foil. A solution of 1 g. of trinitrotoluene in acetic acid saturated with sodium acetate was placed in the anode chamber and the cathode chamber was filled with a concentrated solution of sodium acetate in 50% aqueous acetic acid. The electrolysis was conducted for twelve hours with an average current of about 0.9 ampere and at a temperature maintained with minor exceptions at 35–45° by thorough external cooling with salt-ice. Additional 7–8 cc. portions of acetic acid containing sodium acetate were added after four and nine hours. The anodic solution acquired a light orange-yellow color soon after the reaction

(8) Gambarjan, *Ber.*, **42**, 4003 (1909).

was initiated. The cathodic solution, after remaining essentially colorless for several hours, gradually turned light orange-red, indicating loss of material from the anode compartment.

On pouring the anodic solution into water, there separated rather slowly a solid precipitate weighing 0.24 g. and melting from 80 to 130°. Crystallization from alcohol–acetone afforded 95 mg. (9%) of characteristic needles of trinitro-*m*-xylene, m. p. 155–170°, representing 40% of the material collected. In another experiment, in which electrolysis was continued for only five and one-half hours, the yield was lower but there was less diffusion and considerable starting material was present in undamaged condition. When a lead anode was used there was no gas evolution in the anode chamber and only starting material was recovered.

Other Trials.—Hydrogen peroxide (1.5 cc. of Superoxol, 3.8 equiv.) proved to be without effect on trinitrotoluene (1 g.) in acetic acid solution (10 cc.) at the temperature of the steam-bath. Gas was evolved only very slowly and after six hours the starch–iodide test had become faint. On cooling, 0.8 g. of trinitrotoluene (m. p. 80–82°) crystallized.

Mercuric acetate was tried in place of lead tetraacetate in refluxing acetic acid (twelve hours), but no methylation was observed.

Solutions of trinitrotoluene in acetic acid containing 3 equivalents of tetraethyllead or tetramethyllead were heated on the steam-bath, but although there was some gas evolution and a darkening of the solutions, nearly all of the original trinitrotoluene was recovered unchanged in each case.

Methylation of 1,3,5-Trinitrobenzene

With a Promoter.—A mixture of 2.5 g. of trinitrobenzene (m. p. 122–123°), 1.25 g. of malonic acid, 26 g. (5 equiv.) of lead tetraacetate, and 60 cc. of acetic acid was heated on the steam-bath until all of the solids had dissolved, including a lead salt which formed at first, and until the evolution of carbon dioxide had ceased and the starch–iodide test was negative. On pouring the red solution into water and allowing the mixture to stand for several hours in the cold, 1.85 g. of material separated, m. p. 50–60°. One crystallization from benzene–hexane and two from alcohol (Norit) afforded 0.13 g. of trinitrobenzene as plates, m. p. 120–122° (no depression). Processing of the mother liquor gave a small amount of trinitro-*m*-xylene (needles, m. p. 173–178°, after several crystallizations from alcohol–acetone) and, after several crystallizations, 0.15 g. of trinitrotoluene, m. p. 76.5–78.5°. The mono and dimethyl derivatives were identified by mixed melting point determinations. Additional small amounts of trinitrobenzene were recovered from the mother liquors as the phenanthrene complex (yellow needles, m. p. 155–158°).

Without a Promoter.—A mixture of 2.5 g. of trinitrobenzene, 21.6 g. (4.15 equiv.) of lead tetraacetate, and 60 cc. of acetic acid was heated on the steam-bath for four hours without visible sign of reaction; the colorless crystals of lead tetraacetate remained largely undissolved and no gas was evolved. When the mixture was refluxed, a yellow color soon appeared in one part of the crystal mass and soon spread, the solution turned yellow and then red, and carbon dioxide was evolved. The gas evolution ceased in about one-half hour and the test for tetravalent lead was negative. Precipitation with water gave a total of 1.35 g. of material melting at about 80–130°. Systematic fractional crystallization afforded in all 0.11 g. of trinitro-*m*-xylene needles, m. p. 178–180°, and 0.26 g. of trinitrotoluene plates, m. p. 78–80°. No trinitrobenzene could be recovered, either as such or as the phenanthrene complex.

Methylation of *m*-Dinitrobenzene

In preliminary methylation experiments with twice recrystallized commercial *m*-dinitrobenzene, the reaction mixtures were found to contain small amounts of trinitro-*m*-xylene. Since this may well have arisen from a trace of trinitrobenzene present in the starting material as an impurity, the *m*-nitrobenzene employed in the final experiments was purified carefully by repeated crystallization, when it melted constantly at 89.8–90.5° and had the analysis: C, 42.90; H, 2.43 (calcd.: C, 42.86; H, 2.40). Since the preliminary trials had indicated that the separation of dinitrobenzene and dinitrotoluene presents considerable difficulty, the crude reaction mixtures (which with pure starting material afforded no trinitro-*m*-xylene) were, in subsequent experiments, submitted to nitration before being fractionated.

With a Promoter.—A stirred mixture of 3 g. of pure *m*-dinitrobenzene and 38 g. (4.8 equiv.) of lead tetraacetate in 40 cc. of acetic acid was maintained at 85–90° on the steam-cone and a portion of a solution of 1.9 g. (1 equiv.) of malonic acid in 40 cc. of acetic acid was added slowly by drops. When a little more than half of the solution had been added (in about thirty minutes), a marked deepening in the color of the liquid indicated that the reaction had started and no more malonic acid was added. After stirring at 95° for two and one-quarter hours the lead tetraacetate had all reacted and the solution was consequently poured into ice-water. The powdery precipitate was dissolved in ether and the cloudy aqueous solution was extracted three times with ether. The total ethereal solution was filtered from a trace of flocculent precipitate, washed well with water, dried over calcium chloride, and evaporated to a dark reddish brown, viscous oil. This was dissolved in 20 g. of concentrated sulfuric acid and treated dropwise at 75–95° with a mixture of 5 g. of fuming nitric acid and 30 g. of concentrated sulfuric acid. The temperature was raised to 110° in about twenty-five minutes and held at 110–120° for three and one-quarter hours. The crude, precipitated product (1.65 g.) was a brownish solid, m. p. 55–63°. The first crop from alcohol (0.18 g., m. p. 120–150°) afforded on further purification 80 mg. (1.9%) of crude trinitro-*m*-xylene, m. p. 168–175°. Treatment of the remaining mother liquor with 1.5 g. of β-naphthylamine afforded 0.78 g. of the trinitrotoluene–β-naphthylamine complex as red needles, m. p. 112–113°. Decomposition of the complex with dilute hydrochloric acid gave a total of 0.43 g. (10.6%) of trinitrotoluene, m. p. 77–79°. The mother liquor from the amine complex, after treatment with dilute hydrochloric acid, afforded 0.2 g. of *m*-dinitrobenzene, m. p. 90–92° (6.7% recovery).

Without a Promoter.—In this experiment a solution of 5 g. of analytically pure *m*-dinitrobenzene in 50 cc. of acetic acid was treated with 50 g. (3.9 equiv.) of lead tetraacetate in 5-g. portions, largely at the temperature of the steam-bath. It was discovered that the reaction can be initiated

either by refluxing the mixture for a short time at the outset or by application of localized heat. The reaction then proceeded at the temperature of the steam-bath (but not lower) at a moderate rate (about two bubbles of gas per second). The reaction product was collected and nitrated as described above, giving 2.35 g. of crude yellow solid, m. p. 75–85°. Systematic fractionation from alcohol–acetone afforded in all 0.7 g. of crude trinitro-*m*-xylene, m. p. 160–170°, which when recrystallized formed needles, m. p. 175–178° (no depression). The mother liquor material when processed as above gave 1.05 g. of red needles of trinitrotoluene–β-naphthylamine complex from which 0.53 g. of pure trinitrotoluene was obtained, m. p. 79–80° (no depression). The aqueous acid liquor was extracted with benzene and the solution was washed and concentrated and the residue taken up in alcohol, from which 150 mg. of *m*-dinitrobenzene (m. p. 89–91°) crystallized; a small amount of trinitrotoluene, m. p. 75–78°, was isolated from the mother liquor through the β-naphthylamine complex.

Methylation of Nitrobenzene

In one experiment a mixture of 5 g. of purified nitrobenzene (steam distilled and redistilled), 40 cc. of acetic acid, and 18 g. (1 equiv.) of lead tetraacetate was heated on the steam-cone and, when an attempt to initiate a reaction by local heating with a free flame failed, 0.1 g. of malonic acid was added. Heating on the steam-cone was continued for two hours, but gas was evolved only very slowly. When a second equivalent of reagent was added, however, a steady evolution of gas ensued and the color of the solution deepened to a red-orange. Four hours later, the addition of a third equivalent of lead tetraacetate further accelerated the reaction, and the reagent was all consumed in a total time of twelve hours. The crude product collected by dilution with water and extraction with ether was nitrated in the usual way, giving 2.67 g. of crude solid, m. p. 43–75°. This was treated in alcoholic solution with an equal weight of β-naphthylamine and yielded 0.79 g. of crude trinitrotoluene complex, m. p. 107–111°, which on cleavage with acid afforded 0.45 g. (4.9%) of trinitrotoluene, m. p. 79–81°. The mother liquor from the amine complex yielded, after acid treatment, a total of 1.88 g. (27.5%) of *m*-dinitrobenzene and a very small amount of high-melting material which probably is trinitro-*m*-xylene. The β-naphthylamine complex of trinitrotoluene was also isolated, after nitration, in a methylation experiment carried out with red lead, added in portions to a refluxing solution of nitrobenzene in acetic acid and acetic anhydride.

In another experiment designed to permit characterization of the methylated material as such, a total of 300 g. (0.68 mole) of lead tetraacetate was added in three portions, at intervals of about one hour, to a refluxing solution of 80 g. (0.65 mole) of purified nitrobenzene in 200 cc. of acetic acid. The reaction proceeded rapidly (gas evolution, darkening) at the reflux temperature, and each portion of reagent was consumed in about one hour. The very dark reddish brown solution was poured into water and the organic material extracted with ether and steam distilled (dark, tarry residue). The straw-colored distillate was washed in ether solution with water and with soda solution, and dried. The residual liquid (78 g.) was then fractionated in a 1-meter column packed with glass helices. The first fraction consisted chiefly of 55.7 g. of nitrobenzene, b. p. 102.8–106.3° at 25 mm. Further distillation gave 2.8 g. of material boiling at 106.3–109.5° (25 mm.) before exhaustion of liquid in the boiling flask. This was combined with the hold-up liquid recovered by washing the column, and distillation from a modified Claisen flask yielded 10.7 g. of straw yellow liquid, b. p. 105–112° (17.5 mm.).

Attempted characterization of the liquid by reduction of the nitro group and preparation of acyl derivatives proved unpromising, for mixtures were obtained which could not be separated satisfactorily by fractional crystallization. Oxidation with permanganate provided a more effective means of identification and of obtaining a measure of the extent of methylation. Following a procedure[9] which has been shown to afford *o*-nitrobenzoic acid from *o*-nitrotoluene in 90% yield, a mixture of 2.5 g. of the liquid product and 100 cc. of water containing 5.4 g. of potassium permanganate was stirred on the steam-cone for seven and one-half hours. The aqueous liquor was made alkaline with soda, the manganese dioxide was removed by filtration, and some unoxidized liquid was extracted with ether. Since no precipitate appeared on acidification of the alkaline solution, the product was collected by five extractions with ether. Evaporation of the ether left a white solid which, on crystallization from alcohol, gave in the first crop 0.3 g. of long, flat needles, m. p. 230–236°. Recrystallization raised the melting point to 238–239.5°, and a mixed melting point determination with authentic *p*-nitrobenzoic acid showed no depression. Further crops yielded a total of 0.79 g. of crude needles, m. p. 133–138°. The melting point of this material could not be raised above 138.5–142°, but a mixture of this sample with *o*-nitrobenzoic acid (m. p. 144–145.5°) showed no depression, whereas a mixture with *m*-nitrobenzoic acid (m. p. 138.5–140.5°) melted from 106 to 119°.

The unoxidized material recovered from the ethereal extract of the neutral fraction was reduced with stannous chloride and the crude amine treated with benzoyl chloride. This afforded 0.79 g. of solid which was identified after purification as benzanilide. The amount of this derivative collected corresponds to the presence of 23.7% of nitrobenzene in the product submitted to oxidation. The amounts of the two nitrobenzoic acids isolated indicate the presence in the product of 9.8% of *p*-nitrotoluene and 26.0% of *o*-nitrotoluene. On the basis of the oxidation experiment, the total yield of identified nitrotoluenes produced in the reaction with lead tetraacetate is 3.85 g., representing 4.3% methylation (compare 4.9%, found after nitration).

In view of the low yields in these experiments, it seemed desirable to examine the purified nitrobenzene employed as starting material for the possible presence of nitrotoluenes. For this purpose, 490 cc. of the nitrobenzene used was fractionated through the 1-m. column, when 465 cc. of material distilled at 97.9–98.1° at 20 mm. The tail fraction was recovered from the pot residue and the column by ether extraction. One 5-g. portion of the residual material was nitrated and gave 5.0 g. of crude *m*-dinitrobenzene, m. p. 75–83°; this when recrystallized afforded 2.72 g. of the dinitro compound, m. p. 89.5–90°, and on processing of the

(9) Ullmann and Uzbachian, *Ber.*, **36**, 1799 (1903).

mother liquor with β-naphthylamine no indication was obtained of the presence of trinitrotoluene. Another portion (5 cc.) of the tail fraction was oxidized with permanganate exactly as described above and the alkaline filtrate was acidified and extracted thoroughly with ether; there was no significant residue on evaporation of solution.

Other Actions of Lead Tetraacetate

Conversion of Benzene to Benzyl Acetate.—A mixture of 10 g. of thiophene-free benzene in 60 cc. of acetic acid with 57 g. (1 equiv.) of lead tetraacetate was refluxed for two and one-half hours with but little sign of reaction (light yellow solution), although toward the end of this period a slight evolution of carbon dioxide was noted. An additional 80-g. lot of lead tetraacetate (total = 2.42 equiv.) was added, together with 20 cc. more acetic acid. After a total time of about four hours of refluxing, the gas evolution became somewhat stronger and the color began to deepen. At about five hours, the solution was yellow-orange and the reaction began to proceed very rapidly. Within another half hour the solution had turned dark red-brown and all of the lead tetraacetate was found to have been consumed.

The mixture was drowned and extracted with ether, and the product collected, after washing with water and soda, was distilled at atmospheric pressure from a Claisen flask. Only 1.5 g. of distillate was obtained up to 190°, and the main fraction was taken at 190–250° and consisted of 7.0 g. of a slightly yellow liquid with a pleasant odor; a gummy residue of about 2 g. remained undistilled. The main fraction was redistilled and a cut taken of 3.45 g. (18%) of colorless liquid boiling at 95–110° (20 mm.); most of this distilled at 105–107°. Hydrolysis of this fraction with 10% sodium hydroxide gave a liquid which was identified as benzyl alcohol by the preparation of the α-naphthylurethan; this derivative melted at 131.4–132.0° and did not depress the melting point of an authentic sample. The alkaline solution from the hydrolysis was steam distilled for several hours and then acidified carefully with phosphoric acid and distilled. The Duclaux numbers found by the usual procedure[10] for three fractions were 7.04, 7.40, and 8.05, which demonstrates the presence of acetic acid. The reaction product is thereby identified completely as benzyl acetate.

A check run, in which all of the lead tetraacetate was added at the start, proceeded similarly and afforded benzyl acetate, b. p. 93–104° at 16 mm., in 16.2% yield (the bulk of the product distilled at 102–103°). The undistilled residues from the two runs were combined and hydrolyzed, but the only product recognized was a small additional amount of benzyl alcohol. It was noticed that the acidified aqueous solution obtained after hydrolysis of the main fraction has a phenolic odor, but no test for phenol could be obtained.

Action of Lead Tetraacetate on Chlorobenzene.—A mixture of 10 g. of chlorobenzene, 80 g. (2 equiv.) of lead tetraacetate, and 80 cc. of acetic acid was refluxed until the reagent was consumed; as with benzene, there was an induction period of three to four hours before the reaction became rapid. Distillation of the collected product gave 2.9 g. of material boiling at 115–140° at 12.5 mm., and redistillation of this fraction afforded 2.12 g. (12.9%) of clear, pleasant smelling liquid, b. p. 115–130° at 12.5 mm. (chiefly at 120–123°). Hydrolysis with dilute alcoholic alkali yielded 1.25 g. of material, b. p. 112–117° (11 mm.), which partially crystallized. Crystallization of the distillate from ligroin (70–90°) gave 0.45 g. (3.5%) of irregular plates, m. p. 60–63°, and the recrystallized sample formed flat needles, m. p. 69.4–70.4°. The melting point is close to that of *p*-chlorobenzyl alcohol (m. p. 71–72.5°[11]), but not far from that of the ortho isomer (m. p. 64–65°[11]), and consequently a sample of the alcohol melting at 60–63° was oxidized to the acid with refluxing permanganate solution. This afforded an acid which on recrystallization formed small plates melting at 238–240° and gave no depression when mixed with authentic *p*-chlorobenzoic acid. Since the yield of crystallized para acid was low (10–15%), it is quite possible that more soluble isomers may have been present. Oxidation of the crude product of hydrolysis gave evident mixtures of acids from which, however, only *p*-chlorobenzoic acid was isolated.

Acetoxylation of Naphthalene.—A mixture of 20 g. of naphthalene, 50 g. of lead tetraacetate and 100 cc. of acetic acid was heated with a flame adjusted so as to maintain a steady and moderate gas evolution. When the reagent had been consumed, another 50-g. portion was added (total, 2.9 equiv.) and heating was continued until it had all reacted (very dark solution). After collection of the product by drowning and extraction with ether, distillation at 10 mm. gave 7.8 g. of low-boiling material (to 140°), from which there was obtained 4.1 g. of naphthalene by crystallization. The next fraction taken (140–180° at 10 mm.) was redistilled and a middle fraction, b. p. 150–175° at 10 mm. (insoluble in alkali), was saponified with 10% sodium hydroxide and alcohol. Two distillations of the dark product of hydrolysis gave 4.0 g. of phenolic product, b. p. 140–150° (10 mm.). Crystallization from ether–hexane yielded 2.9 g. (26%) of crude α-naphthol, m. p. 91–94°, and two further crystallizations gave plates, m. p. 94–96°, which gave no depression when mixed with authentic α-naphthol.

Preliminary Trials with Nitronaphthalenes.—Trial experiments carried out essentially as described above with α-nitronaphthalene, 1,5- and 1,8-dinitronaphthalene, 1,3,8- and 1,4,5-trinitronaphthalene, and 1,3,6,8-tetranitronaphthalene gave unpromising results; oxides of nitrogen were evolved in some cases, the reaction mixtures were very dark, and brief processing afforded a pure transformation in only one instance. The reaction mixture from 1,8-dinitronaphthalene and lead tetraacetate yielded a very small amount of crystalline material melting at 207–210°. The substance corresponds in melting point and composition to 1,8-dinitro-2-methylnaphthalene.

Anal. Calcd. for $C_{11}H_8O_4N_2$: C, 56.90; H, 3.47. Found: C, 56.74; H, 3.22.

Summary

Aromatic nitro compounds can be methylated in low or moderate yield by the action of lead tetraacetate in acetic acid solution. The reaction is akin to the recently observed alkylation of

(10) Shriner and Fuson, "Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 120.

(11) Carothers and Adams, THIS JOURNAL, **46**, 1675 (1924).

methylnaphthoquinone by the same reagent and is similarly initiated by the use of active-hydrogen promoters or by heating. By this method trinitrotoluene has been converted in yields as high as 32% into trinitro-*m*-xylene, which appears to be an end product. Trinitrobenzene affords trinitrotoluene and trinitro-*m*-xylene as reaction products, and the same two substances were obtained from *m*-dinitrobenzene by treatment with lead tetraacetate, followed by nitration. Nitrobenzene is converted in low yield into *o*- and *p*-nitrotoluene, identified as the corresponding nitrobenzoic acids.

Under similar conditions, benzene is converted by lead tetraacetate in acetic acid into benzyl acetate in yields up to 18%. Chlorobenzene behaves similarly and yields a mixture which has been characterized as containing *p*-chlorobenzyl acetate. Naphthalene is converted into the 1-acetoxy derivative in 26% yield. The reaction does not appear promising as applied to nitro and polynitronaphthalenes.

Analogies to the electrolytic decomposition of metal salts of carboxylic acids in the Kolbe synthesis have led to the discovery of related methods of alkylation consisting in the treatment of the nitro compound in acetic acid solution with acetyl peroxide and the electrolysis of a solution of the nitro compound in acetic acid containing sodium acetate. Trinitrotoluene was converted by both methods into trinitro-*m*-xylene in low yields.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 29, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Alkylation of Para Quinones with Acyl Peroxides

BY LOUIS F. FIESER AND ALBERT E. OXFORD[1]

In continuation of previous work in this Laboratory on the alkylating action of esters of tetravalent lead,[2,3] a few exploratory experiments were made to see if the reaction of lead tetraacetate with 2-methyl-1,4-naphthoquinone in acetic acid solution to give 2,3-dimethyl-1,4-naphthoquinone can be promoted by the addition of substances other than active-hydrogen reagents and methanol.[2] It was found that a number of solvents, including some which do not themselves appear to be attacked, not only promote the methylation reaction but also, in the absence of a quinone or other methyl acceptor, exert a presumably catalytic effect and promote the decomposition of lead tetraacetate to carbon dioxide and an inflammable gas.

In experiments conducted with 0.005 mole of methylnaphthoquinone in 14 cc. of acetic acid at 90–100° with excess solid lead tetraacetate present throughout, no reaction occurred in the absence of a promoter, as previously observed,[2] but a usually vigorous gas evolution ensued, with darkening of the solution and ultimate production of the 2,3-dimethyl compound, on the addition of 1–3 g. of any one of the following substances: methanol,[2] water, isopropyl alcohol, *t*-butyl alcohol (thirty-minute lag, then gentle effervescence), isopropyl ether, benzene, toluene, cyclohexane (benzene-free), *n*-octane (synthetic). Under the same conditions but in the absence of methylnaphthoquinone, all of these substances except *t*-butyl alcohol brought about a steady if somewhat less vigorous decomposition of lead tetraacetate in the acetic acid solution. The gas evolution was particularly rapid and vigorous in the presence of added benzene, while with toluene as the promoter there was a prolonged induction period followed by a very slow gas evolution. Cyclohexane is a slightly less effective promoter for the decomposition than benzene, and *n*-octane produces, after a brief lag, a still more moderate gas evolution. The cyclohexane employed as a promoter was found to be largely recoverable unchanged after a reaction period of eight hours, in which time a considerable amount of lead tetraacetate had suffered decomposition before the reaction had come to a standstill. Although the action of the hydrocarbon somewhat resembles that of a true catalyst, it is noteworthy that the reaction slows down after a time and that a given quantity of cyclohexane brings about the decomposition of only a limited amount of lead tetraacetate. The

(1) International Fellow of the Rockefeller Foundation on leave of absence from the London School of Hygiene and Tropical Medicine.

(2) Fieser and Chang, THIS JOURNAL, **64**, 2043 (1942).

(3) Fieser, Clapp and Daudt, *ibid.*, **64**, 2052 (1942).

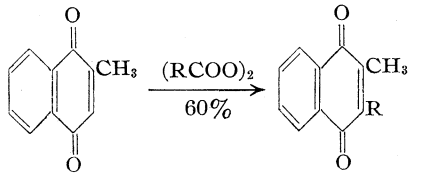
decomposition has been observed to come to a stop with a considerable amount of recoverable cyclohexane still present, and yet to be set in motion again by the addition of a fresh lot of this hydrocarbon. It was found further that the heating of lead tetraacetate with cyclohexane in the absence of acetic acid resulted in no evident decomposition and that methylnaphthoquinone could not be methylated under these conditions. The slowing down of the decomposition in acetic acid–cyclohexane may be due to some extent to the accumulation of lead diacetate, for the addition of this reagent to a mixture of methylnaphthoquinone, acetic acid, toluene and cyclohexane retarded the methylation reaction but did not prevent it.

The gas evolved in the course of the decomposition of lead tetraacetate in the presence or absence of an acceptor contains both carbon dioxide and an inflammable gas not absorbed in alkali. The amount of the neutral gas is often considerable (Table I, Experimental Part) and was found in one experiment conducted in the absence of an acceptor to be approximately 1/2.3 the volume of carbon dioxide, which is close to the ratio to be expected if the gas is pure ethane.

The decomposition therefore appears analogous to the Kolbe reaction. As noted in the second paper of this series,[3] the consideration that diacetyl peroxide is regarded by some as an intermediate in the electrolysis of potassium acetate, coupled with the possibility that lead tetraacetate may initially dissociate to give this substance and lead acetate, led us to attempt the alkylation of quinones with diacyl peroxides in place of esters of tetravalent lead. This indeed can be accomplished; 2-methyl-1,4-naphthoquinone and diacetyl peroxide, for example, afforded 2,3-dimethylnaphthoquinone when warmed together in acetic acid at about 90°. In this and many other instances the reaction proceeds readily and cleanly and under conditions of dilution, solvent and temperature similar to those found favorable for effecting analogous alkylations with the tetravalent lead derivatives. In the reaction with diacyl peroxides, however, no promoter is required, there is no induction period,[3] and one equivalent of the reagent gives better results than a 3–4 fold excess.[2,3] Inferences concerning the mechanisms of the two reactions and the question of a possible correlation between them can best await quantitative studies.

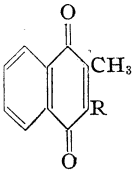
Many instances are on record of the thermal decomposition of diacyl peroxides in the presence of solvents which serve as acceptors of the hydrocarbon residue. This type of reaction has been investigated extensively, particularly as applied to diaroyl peroxides, by the Dutch workers Böeseken, Gelissen and Hermans, *et al.*, and by Wieland and collaborators, as summarized in an excellent review by Hey and Waters.[4] Recent applications to the peroxides of aliphatic acids are reported by Kharasch, Kane and Brown.[5] The present observations appear novel in that the reaction is applied to a type of acceptor so favorable for the reaction that the alkylation can be conducted with equivalent amounts of reactants in a solvent essentially inert to the peroxide.

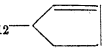
The introduction of higher saturated alkyl radicals is illustrated by the smooth reaction of 2-methyl-1,4-naphthoquinone in ligroin solution with dipalmitoyl and distearoyl peroxide to give the 3-pentadecyl and 3-heptadecyl derivatives I and II. These quinones both melt about 4° lower than 2-methyl-3-octadecyl-1,4-naphthoquinone,



I, R = $C_{15}H_{31}$
II, R = $C_{17}H_{35}$

which has been prepared by a much longer synthesis.[6] As applied to the derivatives of the higher fatty acids, the present method is probably more convenient than the process of alkylation with a mixture of red lead and the fatty acid.[2] Furthermore, it can be employed for the introduction of at least certain types of unsaturated hydrocarbon residues. Thus the peroxides from erucic, chaulmoogric and undecenoic acids were employed successfully for the synthesis of the quinones III–V. 2-Methyl-3-norchaulmoogryl-1,4-naphthoquinone (IV) is of interest because of



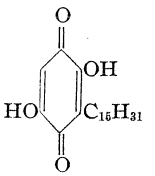
III, R = $-(CH_2)_{11}CH{=}CH(CH_2)_7CH_3$
IV, R = $-(CH_2)_{12}-$ 
V, R = $-(CH_2)_8CH{=}CH_2$
VI, R = $-CH{=}CH(CH_2)_{13}CH_3$

(4) Hey and Waters, *Chem. Rev.*, **21**, 186 (1937).
(5) Kharasch, Kane and Brown, THIS JOURNAL, **63**, 526 (1941).
(6) Karrer and Epprecht, *Helv. Chim. Acta*, **23**, 272 (1940); Fernholz, Ansbacher and MacPhillamy, THIS JOURNAL, **62**, 430 (1940).

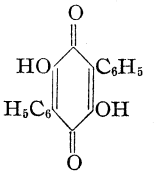
the presence in a structure related to that of the K vitamins of the hydrocarbon residue of an acid employed in the treatment of leprosy. The synthesis has the advantage of convenience and wide scope, since the diacyl peroxides required are obtainable by the action of sodium peroxide on a solution of the acid chloride in petroleum ether, and the examples cited show that a double bond remote from the carboxyl group does not interfere with either the formation or utilization of the peroxides. The α,β-unsaturated 2-heptadecenoic acid likewise afforded a peroxide which on interaction with methylnaphthoquinone gave a product, m. p. 72–73°, having the composition of 2-methyl-3-hexadecenyl(1′)-1,4-naphthoquinone (VI). The substance does not give the Dam–Karrer test[7] with alcoholic alkali and hence the double bond cannot have shifted to the β-position. The quinone is bright yellow, whereas compounds III–V, which are of comparable molecular weight but which do not possess a double bond in the α-position in the side-chain, are very pale yellow, and hence there is some analogy to the relationship between the 3-α-alkenyl (orange) and 3-β-alkenyl (yellow) derivatives of 2-hydroxy-1,4-naphthoquinone.[8]

Paralleling results obtained by the alternate method of alkylation,[2] it was found that a higher alkyl group present at the 2-position of a 1,4-naphthoquinone, in contrast to a methyl group, impedes the introduction of a second alkyl substituent. Thus, although α-naphthoquinone on treatment with diacetyl peroxide afforded only the 2,3-dimethyl derivative in low yield, the reaction of the quinone with dipalmitoyl peroxide provided a satisfactory method for the synthesis of 2-pentadecyl-1,4-naphthoquinone. The applicability of the diacyl peroxide method in the benzoquinone series was established by the conversion of cumoquinone into duroquinone and into 2,3,5-trimethyl-6-pentadecylquinone by interaction with diacetyl peroxide and with dipalmitoyl peroxide, respectively.

On extending the study to quinones having substituents other than alkyl groups, we were surprised to find that 2-methoxy-1,4-naphthoquinone could be recovered unchanged from the attempted reaction with diacetyl peroxide, whereas 2-hydroxy-1,4-naphthoquinone afforded phthiocol in good yield. Similarly 2,5-dihydroxybenzoquinone reacted satisfactorily with dipalmitoyl peroxide in acetic acid solution to give the mono substitution product VII, while under the same conditions the dimethyl ether was largely recovered unchanged. 2,5-Dihydroxy-3-pentadecylbenzoquinone (VII) is a higher homolog of the naturally occurring anthelmintic pigment embelin[9] (R = $C_{11}H_{23}$), to which the same synthesis may be applicable. 2,6-Dimethoxybenzoquinone gave at least a very small amount of the monomethyl derivative, but from the present observations it appears that methoxy quinones are definitely more inert to the products of the thermal decomposition of diacyl peroxides than hydroxy quinones and that the latter are perhaps somewhat more reactive than unsubstituted or alkylated quinones. The one bromoquinone investigated also reacted very readily in an appropriate solvent. Tribromoquinone was converted into tribromotoluquinone in acetic acid solution in about 68% yield but only in poor yield with the use of ligroin. This example of the reaction should offer a particularly favorable case for quantitative study because of the ease with which the high melting and sparingly soluble product can be separated from the reaction mixture. To test the possibility of using bromine to block temporarily nuclear positions and thus expand the scope of the synthetic method, we made a trial of the hydrogenation of tribromotoluquinone in acetic acid in the presence of palladium–barium sulfate and sodium acetate[10] and indeed isolated toluhydroquinone.


VII

Arylation with dibenzoyl peroxide was tried in a few instances with unpromising results. In experiments with methylnaphthoquinone conducted in both acetic acid and ligroin the starting material was consumed but no reaction product could be isolated. 2,5-Dihydroxybenzoquinone, however, afforded in very small yield a substance corresponding in properties to the fungus pigment polyporic acid[11] (VIII). Dicinnamoyl peroxide gave only negative results in attempted reaction with methylnaphthoquinone, while with 2,5-dihydroxybenzoquinone it gave only a trace of material forming lustrous plates and ex-


VIII

(7) Dam, Geiger, Glavind, P. Karrer, W. Karrer, Rothschild and Salomon, *Helv. Chim. Acta*, **22**, 310 (1939).

(8) Hooker, THIS JOURNAL, **58**, 1163 (1936).

(9) Structure: Asano and Yamaguti, *J. Pharm. Soc. Japan*, **60**, 105 (1940) [*C. A.* **34**, 5069 (1940)].

(10) Compare Fieser and Holmes, *ibid.*, **60**, 2553 (1938).

(11) Kögl, *Ann.*, **447**, 78 (1926).

hibiting brilliant colors in ligroin (purple) and in sulfuric acid (green). The poor results may be due in part to the choice of unsuitable experimental conditions; it may also be significant that dibenzoyl and dicinnamoyl peroxide are notably prone to enter into decompositions leading to esters and diaryls.[12]

Experimental Part[13]

Gas Evolution Attending the Decomposition of Lead Tetraacetate.—In the exploratory experiments summarized in Table I the gases were swept from the reaction vessel to an azotometer with a stream of carbon dioxide and the volume of unabsorbed gas measured.

Another experiment (0.6 g. water, 10 g. lead tetraacetate, 7 cc. acetic acid) was carried out in a stream of dry oxygen and the gases collected over water (total, 92 cc.). The carbon dioxide (46 cc.) was then absorbed in strong caustic potash; the oxygen (26 cc.) was absorbed in alkaline pyrogallol and the residual hydrocarbon gas measured (20 cc.).

TABLE I

PRODUCTION OF HYDROCARBON GAS IN THE DECOMPOSITION OF LEAD TETRAACETATE

Experiments conducted in glacial acetic acid solution (14 cc.) at 80–100° for 1.5 hr. or until visible reaction had ceased.

Quinone (0.005 mole)	Promoter, g.	Lead tetraacetate, g. Added	Lead tetraacetate, g. Recovered	Neutral gas, cc.
None	Malonic acid, 0.8	14	none	104
None	Malonic acid, 0.15	14	8.3	79
None	Malonic acid, 0.05	10	6.5	71
None	Water, 1.2	20	trace	155
Methylnaphthoquinone	none	6		none
Methylnaphthoquinone	Malonic acid, 0.15	14	5.4	81
Methylnaphthoquinone	Water, 1.2	20	trace	141
Trimethylbenzoquinone	none	10	8.2	2
Trimethylbenzoquinone	Malonic acid, 0.05	10	6.3	17.5
Benzoquinone	Water, 1.1	19	trace	109

Preparation of the Peroxides.—The various diacyl peroxides were prepared for the most part by vigorously shaking a solution of the acid chloride (usually made by the phosphorus trichloride method) in petroleum ether (b. p. 20–40°) with a solution of sodium peroxide (large excess) in ice-water in a stoppered flask. The upper layer containing the peroxide was separated from the alkaline liquor or soap solution, dried, and allowed to evaporate. Usually the crude peroxide was found to evolve gas upon heating at 90–100° and to give no acid reaction when a cold solution in methanol was tested with moistened litmus paper. In this event, the crude material was regarded as satisfactory for use without further purification. The peroxides were stored and weighed out in the cold room (5°), where they could be safely scraped from a glass dish with a silver spatula.

(12) Wieland and Rasuwajew, *Ann.*, **480**, 157 (1930).

(13) Microanalyses by Miss Eleanor Werble. The melting points are uncorrected.

The following procedure for the preparation of **dipalmitoyl peroxide** is typical. A solution of 3.3 g. of crude palmitoyl chloride in 10 cc. of petroleum ether was added with ice cooling to a solution of 1 g. of sodium peroxide in a few cc. of ice-water. After the addition of a little ice the flask was corked and shaken well for a minute or two. More solid sodium peroxide (1 g.) was added, together with more ice and petroleum ether, and the corked flask was shaken thoroughly for at least ten minutes with the introduction of small amounts of ice from time to time and with short periods of cooling in a freezing bath. The mixture was then transferred with about 100 cc. of added petroleum ether to a separatory funnel, and after shaking for a few minutes a little ether was added to facilitate separation of the layers. The top layer was separated as far as possible, dried over calcium chloride, filtered into a glass dish and allowed to evaporate spontaneously at room temperature. The residue consisted of 1 g. of colorless crystals, m. p. about 65°, and this was used directly for an alkylation. A sample of the peroxide recrystallized from methanol melted at 67–68°.

The crude **distearoyl peroxide** melted at 63–64° and a sample crystallized from methanol, in which it is not very soluble, melted at the same temperature. The crude peroxides from **erucic** and **2-heptadecenoic acid** melted at 30° and 45°, respectively, and that from **undecenoic acid** was liquid at room temperature and solidified in the cold room. An attempted conversion of **chaulmoogric acid** into the chloride with thionyl chloride gave a resin and it was found better to warm the acid with the calculated amount of phosphorus trichloride on the steam-bath, pour off the top layer from the phosphorous acid, and remove hydrogen chloride by evacuation at the water pump. The residue afforded a peroxide melting at 50–55°. **Dicinnamoyl peroxide** was prepared by the above procedure rather than in acetone solution[12]; 5 g. of acid chloride afforded 3.0 g. of peroxide, m. p. 127–130°.

Diacetyl peroxide was prepared best according to Gambarjan[14] from acetic anhydride in ether. With an initial reaction temperature of −5° instead of −15°, the yield was only 5.5 g. (G., 9 g.), and unless the evaporation was carried out in the cold room about half of the volatile peroxide was lost. The yield was much lower when the solvent ether was replaced by petroleum ether, in which acetic anhydride is only sparingly soluble.

Methylation of 2-Methyl-1,4-naphthoquinone.—In parallel experiments conducted to determine the optimum proportion of the reactants, tubes containing 1-g. samples of the quinone in 14 cc. of acetic acid were charged with 0.4 g. (0.6 equiv.), 0.75 g. (1.1 equiv.), and 1.4 g. (2 equiv.) of diacetyl peroxide, respectively, and heated together in the same bath at 90–95° until effervescence ceased. The solutions were cooled, poured into water and the products crystallized from methanol. The first experiment afforded much unchanged starting material and only 0.1 g. of impure 2,3-dimethyl-1,4-naphthoquinone, m. p. 112–118°, after several crystallizations. The second yielded 0.55 g. of the once crystallized dimethyl derivative, m. p. 118–123°, while the third gave a gummy product yielding only 0.1 g. of dimethylnaphthoquinone, m. p. 118–122°, after recrystallization. The ratio 1:1.1 therefore seems to be

(14) Gambarjan, *Ber.*, **42**, 4010 (1909).

TABLE II

ALKYLATION OF QUINONES WITH DIACYL PEROXIDES (1.1–1.3 EQUIVALENTS)

-1,4-naphthoquinone	Diacyl peroxide from	Solvent	Product, -1,4-naphthoquinone	Isolation, % yield	Cryst. from	M. p., °C.	Appearance	Analyses, % C and H
2-Methyl	Palmitic acid	Ligroin	2-Methyl-3-pentadecyl (Formula I)	A, 60	Ligroin (70–100°)	95–97	Very pale yel. needles	$C_{26}H_{38}O_2$: 81.61; 10.02. Found: 81.69; 9.90
2-Methyl	Stearic acid	Ligroin	2-Methyl-3-heptadecyl (Formula II)	A, 60	Ligroin (50–70°)	96	Very pale yel. needles	$C_{28}H_{42}O_2$: 81.89; 10.31. Found: 81.44; 10.19
2-Methyl	Erucic acid	Ligroin	2-Methyl-3-heneicosenyl(12′)- (Formula III)	D, small	Alcohol (six times)	39–81[a]	Yel. cryst. aggregates	$C_{32}H_{48}O_2$: 82.69; 10.42. Found: 82.57; 10.37
2-Methyl	Chaulmoogric acid	Ligroin	2-Methyl-3-norchaulmoogryl- (IV)	C, 40	Methanol (1), alcohol (3)	65–68[b]	Pale yel. needles	$C_{28}H_{38}O_2$: 82.70; 9.43. Found: 82.47; 9.27
2-Methyl	Undecenoic acid	Ligroin	2-Methyl-3-decenyl(9′)- (V)	C, 40	Alcohol	68	Coarse, pale yel. needles	$C_{21}H_{26}O_2$: 81.24; 8.45. Found: 81.29; 8.18
2-Methyl	2-Heptadecenoic acid[c]	Ligroin	2-Methyl-3-hexadecenyl(1′)- (VI)	D, 25	Alcohol, methanol	72–73	Bright canary yel. microcrystals	$C_{27}H_{38}O_2$: 82.17; 9.71. Found: 82.33; 9.71
2-Hydroxy	Acetic acid	AcOH	Phthiocol	Add water, 50	Alcohol	167–169	Golden needles	
α-Naphthoquinone	Palmitic acid	Ligroin	2-Pentadecyl-	D, small	Alcohol	71–72	Pale yel. needles	$C_{25}H_{36}O_2$: 81.46; 9.86. Found: 81.63; 9.94
-1,4-benzoquinone			-1,4-benzoquinone					
Trimethyl	Acetic acid	Ligroin	Tetramethyl (Duroquinone)	B, small	Alcohol	108-111		
Trimethyl	Palmitic acid	Ligroin	2,3,5-Trimethyl-6-pentadecyl	C, 25	Alcohol	74	Pale yel. needles	$C_{24}H_{40}O_2$: 79.93; 11.18. Found: 80.17; 11.04
2,6-Dimethoxy[d]	Acetic acid	AcOH	2-Methyl-3,5-dimethoxy	B, small	CCl_4	123–124[e]	Golden needles	$C_9H_{10}O_4$: 59.31; 5.55. Found: 59.01; 5.61
2,5-Dihydroxy[f]	Benzoic acid	AcOH	3,6-Diphenyl-2,5-dihydroxy (Polyporic acid, VIII)	A, very small	AcOH	Dec. above 280°	Purple-bronze plates	$C_{18}H_{12}O_4$: 73.95; 4.14. Found: 73.53; 4.32
2,5-Dihydroxy	Palmitic acid	AcOH	3-Pentadecyl-2,5-dihydroxy (VII)	A, small	Ligroin; alcohol; $CHCl_3$	136–138	Orange plates[g]	$C_{21}H_{34}O_4$: 71.94; 9.79. Found: 71.82; 10.16

[a] This may be a mixture of the *cis*- and *trans*- forms. The erucic acid used (Eastman Kodak Co.) was not purified but converted directly to the acid chloride by means of thionyl chloride. [b] Softening from 57°. [c] The acid was prepared according to Lauer, Gensler and Miller, THIS JOURNAL, **63,** 1153 (1941). [d] Graebe and Hess, *Ann.*, **340,** 237 (1905). [e] Anslow, Ashley and Raistrick, *J. Chem. Soc.*, 441 (1938), report the m. p. 125° (4,6-dimethoxytoluquinone). [f] Knoevenagel and Bückel, *Ber.*, **34,** 3995 (1901). [g] The quinone gives a light violet color in dilute alkali.

the best. The second experiment was duplicated except that half of the peroxide was added at the beginning and the rest when the first effervescence had ceased; the yield was the same (0.60 g., m. p. 115–119°). In another experiment *n*-propyl alcohol was employed successfully as the solvent.

Methylation of Tribromoquinone.—A mixture of 2.4 g. of tribromoquinone[15] (m. p. 147°), 0.85 g. of diacetyl peroxide and 24 cc. of acetic acid was warmed gently in a water-bath, when solution soon took place, and the temperature was slowly raised to 90° and kept there for one hour and at 100° for one-half hour longer, when effervescence had ceased. Pale yellow plates of tribromotoluquinone had begun to separate from the hot solution and, after cooling, the copious crystallizate was collected and amounted to 1.3 g., m. p. 230°, dec. The material precipitated from the mother liquor with water afforded after crystallization a further 0.4 g. of product, m. p. 210–220°; total yield 68%. A sample recrystallized from alcohol melted at 232–235°, dec. (lit., 235–236°).

Anal. Calcd. for $C_7H_3O_2Br_3$: C, 23.40; H, 0.84. Found: C, 23.85; H, 1.10.

When tribromoquinone (3 g.) was treated with diacetyl peroxide (1.1 g.) in purified ligroin[16] (40 cc., b. p. 95–100°) at 95–100° for one and one-half hours, the reaction mixture afforded only a trace of tribromotoluquinone and consisted largely of brown-red gums and a brown sandy product of indefinite melting point which could not be purified.

For **catalytic hydrogenation,** a solution of 0.65 g. of tribromotoluquinone and 0.65 g. of anhydrous sodium acetate was shaken with hydrogen in the presence of 8 g. of palladium–barium sulfate. The reaction stopped after the absorption of 200 cc. of gas in one-half hour. The solution was filtered and evaporated to dryness in vacuum and the residue extracted with ether in the presence of a little

(15) Sarauw, *Ann.*, **209,** 120 (1881); Datta and Bhoumik, THIS JOURNAL, **43,** 309 (1921).

(16) The solvent was shaken with a solution of potassium permanganate in dilute sulfuric acid and then with a mixture of concentrated sulfuric and nitric acids.

dilute sulfuric acid. Evaporation of the solvent left a dark gum which when dissolved in benzene and treated with petroleum ether afforded crystalline material, m. p. 120–121° (0.15 g.). Recrystallized from benzene–ligroin, the substance formed colorless plates, m. p. 124° (**toluhydroquinone,** m. p. 124–125°). The sample was free from bromine.

Anal. Calcd. for $C_7H_8O_2$: C, 67.69; H, 6.49. Found: C, 67.91; H, 6.56.

Other Alkylations.—The principal results of the synthetic experiments are summarized in Table II. The procedure generally employed for the introduction of higher alkyl and alkenyl groups may be illustrated by the following account of the preparation of **2-methyl-3-pentadecyl-1,4-naphthoquinone.** A solution of 1 g. of dipalmitoyl peroxide in 10 cc. of purified ligroin (95–100°) in a boiling tube was treated with 0.25 g. of methylnaphthoquinone, a chip of porous pot was added, and the mixture was warmed and stirred until the quinone had dissolved. The bath temperature was gradually raised until effervescence set in at 90°, and after one hour the temperature was raised to 100° during thirty minutes and then allowed to fall to 90°, when gas evolution had ceased.

The reaction products were isolated in one of the following ways.

A. Separation as a solid from the cooled solution was followed by recrystallization.

B. When no material crystallized on cooling, other than the fatty acid derived from the peroxide, the solution sometimes was evaporated to dryness and the residue fractionally crystallized (not recommended for quinones with long alkyl side chains).

C. As in B, but the residue was dissolved in alcohol and treated with aqueous sodium hydrosulfite solution according to the procedure of Fieser[17]; the reduced mixture was shaken with ligroin (b. p. 30–60°), when the substituted hydroquinone usually appeared as a white solid at the interface and could be collected by suction filtration. The solid was dried and oxidized with silver oxide in ethereal solution in the presence of sodium sulfate.

D. As in C, except that after reduction the hydroquinone did not separate from the water–ligroin mixture as a solid but remained in the hydrocarbon layer. In this case the ligroin solution was washed with aqueous alkali-hydrosulfite and extracted with Claisen's alkali, etc., exactly as in a procedure described for the isolation of vitamin K_1 from alfalfa concentrates.[17]

Each of the analytical samples of fully substituted quinones gave a negative test with Craven's reagent.[18]

Summary

Both the methylation of quinones by lead tetraacetate in acetic acid solution and the decomposition of the tetraacetate to carbon dioxide and hydrocarbon gas in the absence of an acceptor are promoted by a number of hydroxylic and hydrocarbon solvents.

Diacyl peroxides are excellent agents for the alkylation of *p*-benzo- and 1,4-naphthoquinones having a free position in the quinonoid ring, and a number of new or difficultly accessible quinones have been prepared with ease by this method.

(17) Fieser, THIS JOURNAL, **61**, 3467 (1939).

(18) Craven, *J. Chem. Soc.*, 1605 (1931).

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED AUGUST 14, 1941

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

Relative Acid Strengths of Formic, Acetic, and Propionic Acids in Alcohols and Dioxane–Water Mixtures

BY MARTIN KILPATRICK AND R. DEAN EANES

The determination, in various alcohols, of the acid strengths of substituted benzoic acids relative to benzoic acid, has shown that the logarithm of the acid strength varies linearly with the reciprocal of the dielectric constant of the medium over the range $D = 78.5$ to $D = 24.2$.[1] On the other hand, in dioxane–water mixtures, the logarithm of the acid strength does not vary linearly with the reciprocal of the dielectric constant. The present paper shows that these conclusions are also valid for certain aliphatic acids.

The acetic and propionic acids, free from homologs, were refluxed with the pure anhydrides and fractionally distilled. Formic acid was treated with boric anhydride to remove water and distilled under reduced pressure. The purification of methyl and ethyl alcohol, ethylene glycol, and dioxane and the preparation of the solutions have been described in the earlier papers as has the e. m. f. method by which the experiments were carried out.[2]

Table I gives the ratio of the dissociation constant of formic acid to that of acetic acid in the various solvents containing lithium chloride. The ratio of the dissociation constants is the equilibrium constant, $K_{A_xB_o}$, for the reaction

$$A_x + B_o \rightleftharpoons A_o + B_x \qquad (1)$$

where A_x is formic acid and B_o acetate ion.

(1) For references see Kilpatrick, *Chem. Rev.*, **30**, 159 (1942).

(2) Elliott and Kilpatrick, *J. Phys. Chem.*, **45**, 454, 466, 472, 485 (1941).

TABLE I

RATIO OF THE DISSOCIATION CONSTANT OF FORMIC ACID TO THAT OF ACETIC

Solvent	Dielectric constant	Ionic strength	$K_{A_xB_o}$	Calculated $K_{A_xB_o}$ by eq. (2)
Water	78.5	0.00	10.1[a]	10.4
		.10	10.3[b]	
Ethylene glycol	37.7	.05	14.0	14.0
Methyl alcohol	31.5	.05	17.3	16.4
Ethyl alcohol	24.2	.05	19.6	20.5
Dioxane–water	25	.05	19.4	19.8

[a] From the thermodynamic dissociation constants of Harned and co-workers, ref. 4. [b] Solvent salt potassium chloride.

The logarithm of the ratio of the dissociation constants is plotted against the reciprocal of the dielectric constant in Fig. 1. The results for the pure solvents may be expressed by the equation

$$\log K_{A_xB_o} = 0.887 + \frac{10.3}{D}$$

Values thus calculated are given in column five of Table I. In agreement with our previous findings the relative acid strength in dioxane–water mixtures ($D = 25$) closely approximates that in ethyl alcohol.[2,3] Figure 1 also includes the values

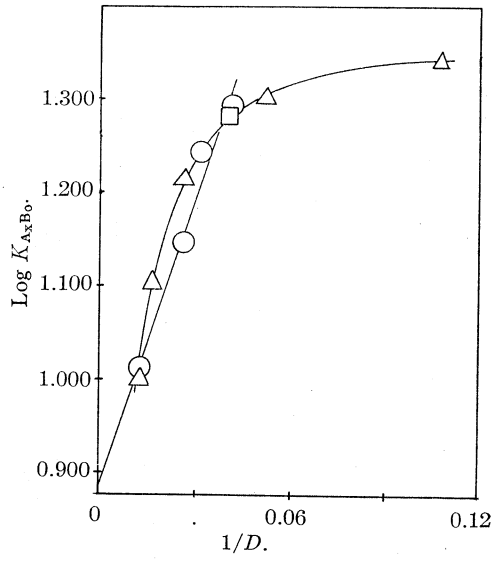


Fig. 1.—Formic acid *vs.* acetic acid: Δ, Harned and co-workers; O, pure solvents, this investigation; □, dioxane–water, this investigation.

of the constant, $K_{A_xB_o}$, calculated from the thermodynamic dissociation constants at 25° of formic and acetic acids in water and dioxane–water mixtures of dielectric constant 60.8, 38.5, 17.7 and 9.3.[4] It is evident that log $K_{A_xB_o}$ is not a linear function of the reciprocal of the dielectric constant, and that we are dealing with the same phenomenon observed in the case of the substituted benzoic acids.[5]

TABLE II

RATIO OF THE DISSOCIATION CONSTANT OF PROPIONIC ACID TO THAT OF ACETIC

Solvent	Dielectric constant	Ionic strength	$K_{A_xB_o}$	Calculated $K_{A_xB_o}$ by eq. (3)
Water	78.5	0.00	0.762[a]	0.773
Ethylene glycol	37.7	.05	.637	.617
Methyl alcohol	31.5	.05	.566	.566
Ethyl alcohol	24.2	.05	.477	.484
Dioxane–water	25	.05	.521	.495

[a] From the results of Harned and co-workers, refs. 4 and 5.

Table II and Fig. 2 present the corresponding results for the ratio of the dissociation constant of propionic acid to that of acetic.

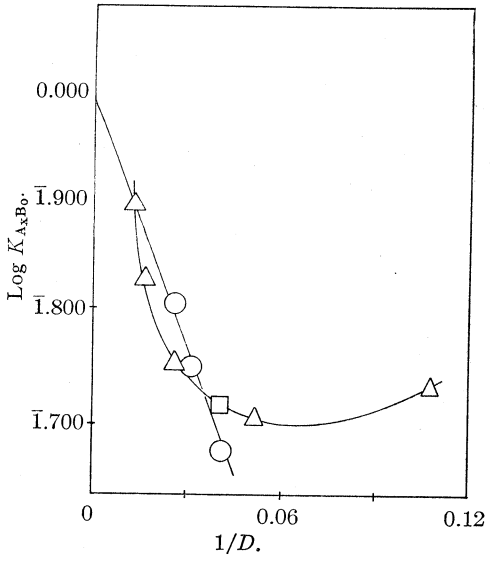


Fig. 2.—Propionic acid *vs.* acetic acid: Δ, Harned and co-workers; O, pure solvents, this investigation; □, dioxane–water, this investigation.

The result for the dioxane–water mixture of dielectric constant 25 lies above the value for the solvent ethyl alcohol, but fits nicely on the smooth curve through the values for the other dioxane–water mixtures calculated from the recent data on the thermodynamic dissociation constant of propionic acid,[6] and that of acetic acid.[4] In the

(3) Minnick and Kilpatrick, *J. Phys. Chem.*, **43**, 259 (1938).

(4) Harned and Ehlers, THIS JOURNAL, **54**, 1351 (1932); Harned and Kazanjian, *ibid.*, **58**, 1912 (1936); Harned and Fallon, *ibid.*, **61**, 2377 (1939); Harned and Embree, *ibid.*, **56**, 1042 (1934); Harned and Done, *ibid.*, **63**, 2579 (1941).

(5) Elliott and Kilpatrick, *J. Phys. Chem.*, **45**, 485 (1941).

(6) Harned and Dedell, *ibid.*, **63**, 3308 (1941).

pure solvents, the results may be expressed by the equation

$$\log K_{A_xB_o} = -0.022 - \frac{7.1}{D}$$

and the values thus calculated are given in column five of Table II.

It should be emphasized that the values of $K_{A_xB_o}$ for the experiments reported in this paper are direct determinations of the equilibrium constant for the reaction

$$C_2H_5COOH + CH_3COO^- \rightleftharpoons CH_3COOH + C_2H_5COO^- \quad (4)$$

and the corresponding reaction for formic acid. The measurements were made in the presence of 0.045 mole per liter of lithium chloride with a 1.0 molar bridge solution of the same salt. For a reaction of the charge type of equation (4), the equilibrium constant would be expected to be independent of ionic strength, for the same solvent salt, and comparable to the thermodynamic equilibrium constant. This is borne out by the results at various ionic strengths given in the following table.

In addition, the value of $K_{A_xB_o}$ calculated from the thermodynamic constants in water given in Table I, agrees with the value in 0.095 molar potassium chloride.

TABLE III

THE EFFECT OF IONIC STRENGTH ON THE EQUILIBRIUM CONSTANT OF THE REACTION

$$HCOOH + CH_3COO^- \rightleftharpoons CH_3COOH + HCOO^-$$

Solvent	$K_{A_xB_o}$ μ = 0.05	0.10	0.20	0.50	1.00	2.00
Water	..	10.3	10.3	10.3	10.3	10.3
Methyl alcohol	17.3	17.8	17.6			
Ethyl alcohol	19.6	19.5	19.8			

The authors would like to take this opportunity to thank the Faculty Research Committee of the University for a grant.

Summary

In dioxane–water mixtures, the logarithm of the acid strength of formic acid relative to acetic, or of propionic relative to acetic, is not a linear function of the reciprocal of the dielectric constant of the medium. In the pure solvents studied—water, ethylene glycol, methyl alcohol and ethyl alcohol—a linear relationship holds. This same phenomenon has been observed in the case of the substituted benzoic acids.

PHILADELPHIA, PENNA. RECEIVED JUNE 22, 1942

[CONTRIBUTION FROM THE GEORGE HERBERT JONES CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO AND THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

Studies on High Molecular Weight Aliphatic Amines and their Salts. VIII. Soluble and Insoluble Films of the Amine Acetates. A. The Surface Tension of Aqueous Solutions of Dodecylamine Acetate

BY EVERETT J. HOFFMAN, G. E. BOYD AND A. W. RALSTON

Introduction

In the fifth paper of this series[1] we reported the results of an investigation of the surface properties of a simple, long chain cationic colloidal electrolyte, namely, dodecylamine hydrochloride. The present paper deals with a study of the surface properties of aqueous solutions of dodecylamine acetate. In this case the time effects of long duration which were observed for dilute solutions of dodecylamine hydrochloride were not found. In the case of 5×10^{-3} N solutions at 25°, constant values of the surface tension were obtained within thirty minutes. No time effects were observed at other temperatures for this same solution. With a solution of concentration 7.5×10^{-3} N (critical micelle concentration = 1.2×10^{-2} N) no time effects were observed at any temperature. In contrast to this behavior, in the case of dodecylamine hydrochloride a steady decrease was observed even after five hours.

The absence of aging effects with unbuffered n-alkylamine acetate solutions may not, however, reflect the behavior in general of solutions containing this type of colloidal electrolyte. Preliminary experiments on a 5×10^{-3} N solution of dodecylamine acetate in the presence of 10^{-2} N acetic acid–sodium acetate revealed an appreciable variation of surface tension with time. It is possible that the surface active species in our experiments consists of free amine in equilibrium with amine acetate in the interior of the solution.

(1) E. J. Hoffman, G. E. Boyd and A. W. Ralston, THIS JOURNAL, 64, 498 (1942).

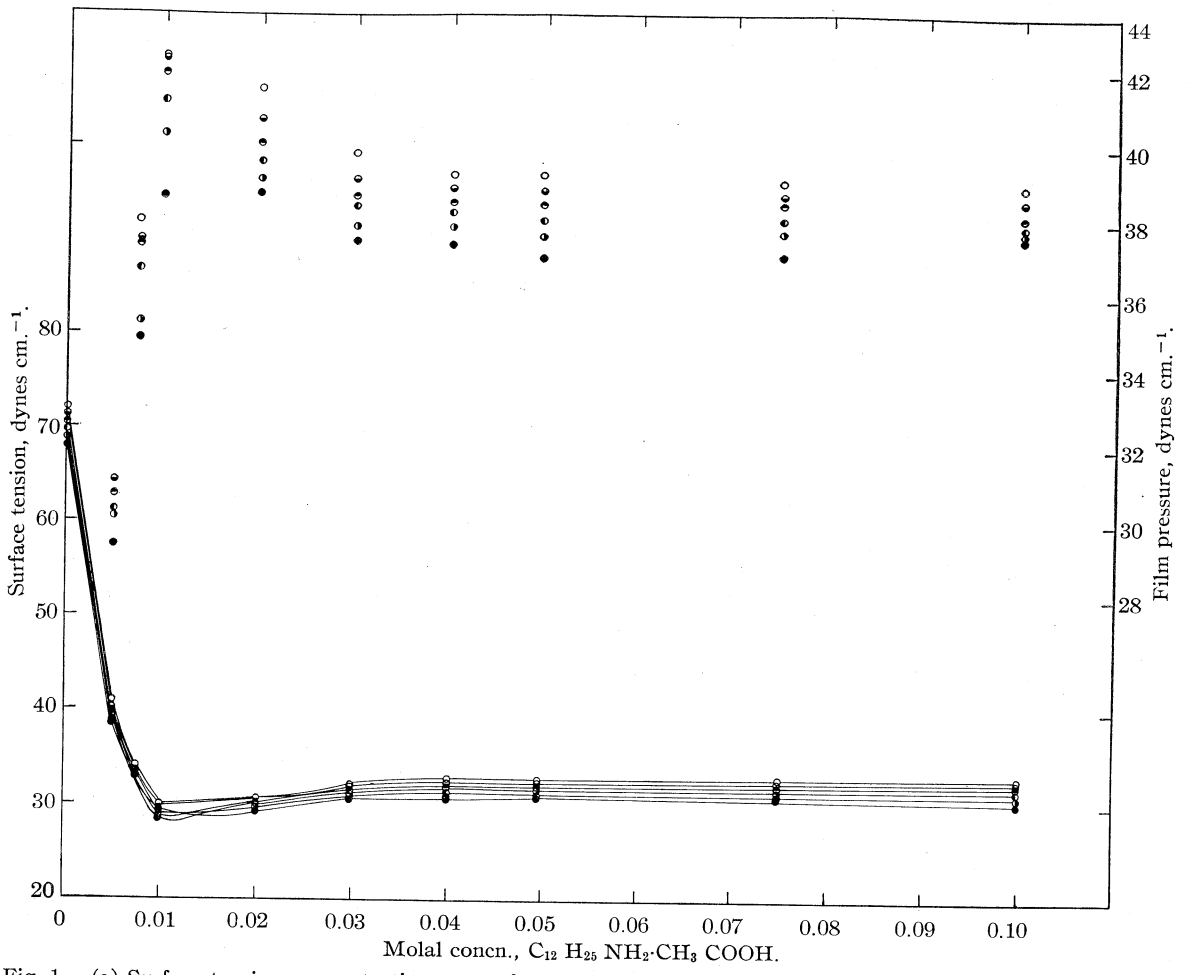


Fig. 1.—(a) Surface tension–concentration curves for aqueous solutions of dodecylamine acetate; (b) film pressure–concentration values for aqueous solutions of dodecylamine acetate: ○, 25°; ◒, 30°; ◓, 35°; ◐, 40°; ◑, 45°; ●, 50°.

Experimental Part

Preparation of Materials. Dodecylamine Acetate.—Dodecylamine acetate was prepared by the method previously described.[2] Solutions were made with triple distilled water as described in an earlier communication.[1] Densities of the solutions were determined by means of a 25-ml. pycnometer by C. W. Hoerr of the Armour Research Laboratories.

Apparatus and Procedure.—Surface tensions were determined at five degree intervals from 25 to 50° by the ring method with the apparatus used by Harkins and Jordan.[3] The ring used was made of platinum–iridium, and its mean radius was 0.6402 cm.; the value of R/r was 45.64, where R is the mean radius of the ring, and r is the mean radius of the wire.

(2) A. W. Ralston, C. W. Hoerr and E. J. Hoffman, THIS JOURNAL, **63**, 2576 (1941).

(3) W. D. Harkins and H. F. Jordan, *ibid.*, **52**, 1751 (1930).

Experimental Results

Surface tension–concentration curves at five-degree intervals from 25 to 50° are shown in Fig. 1. A plot of the film pressure, $\pi = -\Delta\gamma = \gamma_0 - \gamma$, where γ_0 is the surface tension of water and γ is the surface tension of the solution, against concentration is also shown. The latter plot has the advantage that the values are separated so that the effect of temperature is more clearly demonstrated.

Discussion

It is evident from an examination of the curves in Fig. 1 that the surface tension of solutions of dodecylamine acetate of concentrations above that exhibiting a minimum value decreases with increasing temperature. At lower concentrations this is true except for the surface tension at 40°. A slightly deeper minimum is obtained at 40° than at any other temperature investigated. A

similar behavior was observed in the study of the surface tension of aqueous solutions of dodecylamine hydrochloride.[1]

An examination of the values for the film pressure (Fig. 1) shows that at a given concentration it decreases with increasing temperature and that the value of $-\Delta\pi/\Delta T$ is fairly constant in the range 25 to 50°. The fact that, at a constant concentration, the film pressure decreases with increasing temperature shows that adsorption of dodecylamine acetate in the surface is less at higher temperatures. Between concentrations of approximately 3×10^{-2} and 10^{-1} N the film pressure does not change greatly with the concentration although this change is slightly greater at higher temperatures than at 25°.

The surface tension–concentration curves for aqueous solutions of dodecylamine acetate are similar to those obtained by us for dodecylamine hydrochloride[1] and by other investigators for anionic colloidal electrolytes.[4] A comparison of the concentration for minimum surface tension with that for the break in the conductance curve[5] shows that they are essentially the same. This is the so-called critical micelle concentration.

B. Pressure–Area Relations of Docosylamine Acetate Monolayers on Acetic Acid

Introduction

In a previous publication[1] we have reported a systematic study of the effect of inorganic anions on insoluble films of long-chain amines. In 1930, N. K. Adam[6] reported an extensive study of the variation of the character of amine films with pH in which the importance of the nature of the anion was noted. A portion of this investigation dealt with the use of an acetate buffer (pH 4.0) in which the total acetate concentration was 5×10^{-2} N. Adam reports that the insoluble films, even of eicosylamine, were gaseous and that that of hexadecylamine was one of the most perfect gaseous films ever found with insoluble substances. This last statement appears to be erroneous on the basis of our results since the film of octadecylamine acetate was so soluble that satisfactory pressure readings could not be obtained. Several trial runs were made by rapid compression of films of octadecylamine acetate to a constant area and observing the change in pressure with time. There was a continuous decline of pressure with time with an approximately constant final value regardless of the initial pressure. Films spread on sub-solutions from which a film from a previous experiment had been removed by sweeping invariably gave higher pressures than the first film spread on 10^{-1} N acetic acid. In order to eliminate this difficulty, octadecylamine acetate was replaced by docosylamine acetate. The solubility effect was not observed in this case.

Experimental Part

Preparation of Materials. Docosylamine Acetate.—Docosylamine acetate was prepared by Dr. F. M. Garland of the Armour and Co. Research Laboratories by a method similar to that described for the preparation of octadecylamine acetate.[2]

Preparation of Sub-solutions.—Sub-solutions were prepared by diluting glacial acetic acid with double distilled water[1] to a concentration of 10^{-1} N.

Apparatus and Procedure.—The film balance was that described in detail by Nutting and Harkins.[7] One degree of the divided circle corresponded to 0.0634 dyne cm.$^{-1}$ pressure on the float; the circle was read to 0.2°.

Docosylamine acetate (*ca.* 23 mg.) was weighed by means of a semi-micro analytical balance into a calibrated 25-ml. volumetric flask, dissolved in ethanol (95%, *ca.* 4 ml.), and diluted with purified benzene to 25 ml. This solution was stored in a 50-ml. ground-glass stoppered volumetric flask. Solutions were spread from a pipet (0.0722 ml. capacity) of the type described by Harkins and Anderson.[8] A period of fifteen minutes after the spreading of the film was permitted before the experiment was started. Pressure readings were made at one-minute intervals on compression to various areas and also, in separate experiments, as rapidly as possible at a much smaller number of areas. Good agreement of results between these two methods was obtained. This indicates that loss due to solubility was negligible.

Experimental Results

Pressure–area isotherms for films of docosylamine acetate on a 10^{-1} N acetic acid sub-solution at 14.8, 19.9 and 24.9° are given in Fig. 2. At

(4) J. W. McBain and G. F. Mills, "Reports on Progress in Physics," V, 30 (1939).

(5) A. W. Ralston, C. W. Hoerr and E. J. Hoffman, THIS JOURNAL, **64**, 97 (1942).

(6) N. K. Adam, *Proc. Roy. Soc.* (London), **A126**, 526 (1930).

(7) G. C. Nutting and W. D. Harkins, THIS JOURNAL, **61**, 1180 (1939).

(8) W. D. Harkins and T. F. Anderson, *ibid.*, **59**, 2189 (1937)

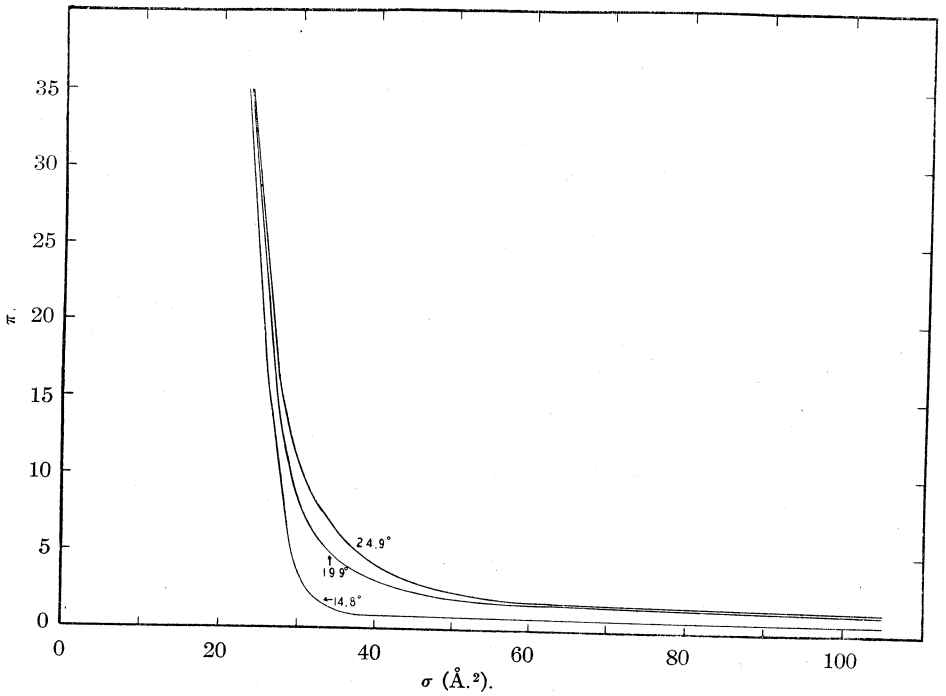


Fig. 2.—Pressure–area isotherms for docosylamine acetate monolayers on 10^{-1} N acetic acid.

large areas per molecule the film is vapor expanded in all three cases, but increased pressure produces condensed films.

The extrapolated area per molecule at zero pressure, at 14.8° is 27.9 sq. Å., at 19.9° it is 29.4 sq. Å. and at 24.9° it is 30.4 sq. Å.

The entropy of spreading is defined by the equation[9]

$$s_s = \frac{q_s}{T} = \left(\frac{\partial S}{\partial \sigma}\right)_T = \left(\frac{\partial \pi}{\partial T}\right)_\sigma$$

A plot of π against T for $\sigma = 35$ sq. Å. gives a value of 0.44 erg cm.$^{-2}$ deg.$^{-1}$ for s_s.

The increase of heat content on spreading may be calculated by use of the equation[9]

$$h_s = \left(\frac{\partial H_s}{\partial \sigma}\right)_T = -\left[\frac{\partial(\pi/T)}{\partial(1/T)}\right]_\sigma$$

At $\sigma = 35$ sq. Å., $h_s = 140$ ergs cm.$^{-2}$. This value is much lower than that obtained for octadecylamine hydrochloride.[1]

Discussion

A comparison of the curves in Fig. 2 shows the effect of temperature on the pressure–area relations of monolayers of docosylamine acetate. They show the normal trend, the film becoming more expanded with increasing temperature. The change between 14.8 and 19.9° is much greater than that in the range 19.9 to 24.9°. The isotherm at 14.8° much more closely approximates that of a true condensed film than does either one of the others.

(9) W. D. Harkins, T. F. Young and G. E. Boyd, *J. Chem. Phys.*, **8**, 954 (1940).

Summary

1. The variation of surface tension of solutions of dodecylamine acetate with concentration has been investigated at a series of temperatures by the ring method.

2. A time effect was observed only at 25° in one solution below the critical concentration for micelle formation. This is in sharp contrast to the behavior of dodecylamine hydrochloride solutions previously reported.

3. It has been pointed out that monolayers of octadecylamine acetate are too soluble to permit investigation by means of the film balance.

4. Insoluble monolayers of docosylamine acetate spread on an acetic acid sub-solution have been investigated by means of the film balance.

5. An increase in temperature causes docosylamine acetate films to become more expanded. The heat of spreading at an area of 35 sq. Å. per molecule was estimated to be 140 ergs cm.$^{-2}$.

CHICAGO, ILLINOIS RECEIVED APRIL 6, 1942

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

The Elimination of Liquid Junction Potentials. IV. The Conditions of Extrapolation[1a]

BY BENTON BROOKS OWEN AND STUART R. BRINKLEY, JR.[1b]

In the preceding communications[2,3,4] of this series it is shown experimentally that accurate thermodynamic information can be derived from cells with heterionic liquid junctions by suitable extrapolations. In each of these investigations the following conditions were fulfilled.

$$\text{Ag, AgCl (s)} \left| \begin{array}{l} \text{AgCl [satd.]} \\ \text{KNO}_3\ [(1-x)m] \\ \text{KCl}\ [xm] \end{array} \right|$$

I. The composition of the liquid systems in contact are so chosen that, in a series of measurements, these systems can be made to approach by extrapolation either absolute identity, or some condition which may be treated by present thermodynamic methods.

II. The ionic strengths of the liquid systems in contact are the same, and the extrapolation is performed at constant ionic strength.

These conditions are the subject of the present communication.

Condition I

The necessity of Condition I scarcely requires comment, but it will be useful to distinguish between and to classify several types of junctions which can fulfill this condition. The classification of junctions will be based upon their characteristics in limiting states attained by extrapolation, because it is ordinarily these characteristics which justify their use in thermodynamic calculations. The concentration of one or more solutes at every junction will be expressed in terms of a variable, x $(1 \geqslant x \geqslant 0)$, which will always be reduced to zero by the extrapolation. Therefore when the properties, or types of any junctions are referred to, it is implied that the condition, $x \rightarrow 0$, has been imposed.

Limiting Liquid Junctions, Type A.—The two liquid systems comprising Type A junctions become absolutely identical in the limit when $x \rightarrow 0$, and their junction potentials are zero. The following cells illustrate this type of junction.

$$\text{H}_2 \left| \begin{array}{l} \text{H}_2\ \text{[satd.]} \\ \text{HCl}\ [m] \end{array} \right| \left| \begin{array}{l} \text{H}_2\ \text{[satd.]} \\ \text{HCl}\ [(1+x)m] \end{array} \right| \text{H}_2 \qquad \text{I}$$

$$\text{Ag, AgCl (s)} \left| \begin{array}{l} \text{AgCl [satd.]} \\ \text{KNO}_3\ [(1-x)m] \\ \text{KCl}\ [xm] \end{array} \right| \left| \begin{array}{l} \text{AgCl [satd.]} \\ \text{KNO}_3\ [m] \end{array} \right| \left| \begin{array}{l} \text{AgCl [satd.]} \\ \text{KNO}_3\ [(1-x)m] \\ \text{AgNO}_3\ [xm] \end{array} \right| \text{AgCl (s), Ag} \qquad \text{II}$$

It is characteristic of such cells that each constituent of the limiting junction solutions, *including soluble components of the electrodes*, is present in both solutions at the same concentration. The electromotive forces of these cells are therefore independent of standard electrode potentials. In other respects such cells may be widely dissimilar. Thus, Cell I is homo-ionic, and its liquid junction potential is thermodynamically defined at *all* values of x. The e. m. f. of this cell is a simple function of transference numbers and activities at all values of x, and is independent of the geometry of the junction. Cell II is heterionic for values of x different from zero, and its junction potential is thermodynamically defined only in the limit.

Limiting Liquid Junctions, Type B. The two liquid systems comprising Type B junctions do not become identical in the limit when $x \rightarrow 0$, but differ only with respect to the soluble components of the two electrodes. The following cells will serve as illustrations.

$$\text{Hg, HgCl (s)} \left| \begin{array}{l} \text{HgCl [satd.]} \\ \text{KCl}\ [m] \end{array} \right| \left| \begin{array}{l} \text{H}_2\ \text{[satd.]} \\ \text{KCl}\ [(1-x)m] \\ \text{HCl}\ [xm] \end{array} \right| \text{H}_2 \qquad \text{III}$$

$$\text{Ag, AgCl(s)} \left| \begin{array}{l} \text{AgCl [satd.]} \\ \text{KCl}\ [xm] \\ \text{KNO}_3\ [(1-x)m] \end{array} \right| \text{KNO}_3\ [m] \left| \begin{array}{l} \text{AgNO}_3\ [xm] \\ \text{KNO}_3\ [(1, x)m] \end{array} \right| \text{Ag} \qquad \text{IV}$$

Although the limiting liquid junction potentials of these cells are not zero, they are of the type which is always present when the so-called "cells without liquid junctions" are used to compare standard electrode potentials. Such junction potentials are neglected in thermodynamic practice, and are therefore integral parts of all measured standard electrode potentials. For example, the replacement of potassium chloride by hydrogen chloride throughout Cell III would lead to the familiar cell

$$\text{Hg, HgCl(s)} \left| \begin{array}{l} \text{HgCl [satd.]} \\ \text{HCl}\ [m] \end{array} \right| \left| \begin{array}{l} \text{H}_2\ \text{[satd.]} \\ \text{HCl}\ [m] \end{array} \right| \text{H}_2 \qquad \text{V}$$

(1a) Presented April, 1941, at the Saint Louis meeting of the American Chemical Society.

(1b) Present address, Mallinckrodt Chemistry Laboratory, Harvard University.

(2) B. B. Owen, THIS JOURNAL, **60**, 2229 (1938).

(3) B. B. Owen and S. R. Brinkley, Jr., *ibid.*, **60**, 2233 (1938).

(4) B. B. Owen and E. J. King, *ibid.*, **63**, 1711 (1941).

without changing the nature[5] of the liquid junction. Note that the Type A junction of Cell II changed to Type B in Cell IV by elimination of the silver chloride from the right-hand electrode and solution.

Limiting Liquid Junctions, Type C.—The following cells give rise to Type C junctions

$$\text{Ag, AgCl(s)} \left| \begin{matrix}\text{AgCl [satd.]} \\ \text{KCl } [xm]\end{matrix} \right| \left| \begin{matrix}\text{AgCl [satd.]} \\ \text{HCl } [xm]\end{matrix} \right| \text{AgCl (s), Ag} \quad \text{VI}$$

$$\text{Ag, AgCl (s)} \left| \begin{matrix}\text{AgCl [satd.]} \\ \text{KNO}_3\ [xm\,(1-y)] \\ \text{KCl } [xmy]\end{matrix} \right| \left| \begin{matrix}\text{AgCl [satd.]} \\ \text{KNO}_3\ [xm]\end{matrix} \right| \left| \begin{matrix}\text{AgCl [satd.]} \\ \text{KNO}_3\ [xm\,(1-y)] \\ \text{AgNO}_3\ [xmy]\end{matrix} \right| \text{AgCl (s), Ag} \quad \text{VII}$$

The variable y ($1 \geqslant y \geqslant 0$) in the last cell is used to express changes in the ratio of the solute concentrations. In this respect, y plays the same rôle in Cell VII that x plays in Cell II, but the conditions of extrapolation in these otherwise similar cells are quite different. In the operation of Cell II, m is kept constant during a given extrapolation to $x \longrightarrow 0$, and the limiting junction becomes two identical solutions of potassium nitrate of concentration, m. In the operation of Cell VII, y and m are kept constant during a given extrapolation to $x \longrightarrow 0$, and the junction consists of two solutions which do not become identical in the limit so long as y is different from zero.

Thus, in general, the solutions composing Type C junctions contain constituents which are not shared by both in common, and this asymmetry is not eliminated by extrapolation. The liquid junction potential produced by this asymmetry when $x \longrightarrow 0$ is not of the type inherent in "cells without liquid junctions," and cannot logically be neglected. Fortunately there are both experimental and theoretical grounds for believing that it is possible to estimate the magnitudes of such residual junction potentials within reasonable limits. This possibility argues the practical utility of cells which lead to this "calculable" type of junction potential, but does not permit the use of such junctions with the same confidence with which Types A and B are employed in thermodynamic calculations. This category can be made to include cells whose limiting junction potentials are partly calculable and partly neglected. For example, if the silver chloride is eliminated from the right hand solution and electrode of Cell VII, extrapolation to $x \longrightarrow 0$ results in a junction with characteristics of both Types C and B. This composite junction might be termed Type CB, but since the asymmetry of the B variety is absorbed in the standard electrode potentials, it will not be necessary to distinguish between Types C and CB in the following discussion.

The estimation of a liquid junction potential, E_j, is based upon the expression[6]

$$-\mathrm{d}\,E_j = \frac{RT}{F} \sum \frac{T_i}{z_i}\,\mathrm{d}\ln m_i\gamma_i \qquad (1)$$

in which T_i, m_i, and γ_i are the transference number, molality and activity coefficient of any ionic constituent, i. The valence, z_i, carries the sign of the charge. The activity coefficients may be disregarded, as the equation will be employed only in the limit, $\mu \longrightarrow 0$. The summation extends over all the ion constituents present, except those produced by dissociation of the solvent.[7]

Ordinarily, the exact values of T_i and m_i are not known at all points throughout the region of the junction, and some assumptions are required before equation (1) can be integrated. For this purpose Planck[8] assumed "constrained diffusion" across the junction, and Henderson[9] assumed a "continuous mixture boundary" which leads to linear concentration gradients. Both of these assumptions, as well as those employed in more elaborate treatments[10,11,12] of the problem, yield values of E_j which are in reasonable agreement (plus or minus a few tenths of a millivolt) with each other and with experiment, if the solutions are dilute and differences in ionic mobilities are not extreme. So long as the objectives do not demand more than this reasonable agreement, it is not necessary to decide which, if any, of these assumptions is strictly valid.

With this in mind, and purely as a matter of

(5) The magnitude of the junction potential would vary to some extent depending upon the properties of the electrolyte at the concentration m, but this variation is also neglected. Thus, in determining the activity coefficient of HCl in salt solutions, the same value of E^0 is used regardless of the nature of the salt. Since E^0 contains the junction potential of Cell V at $m = 0$, the calculated activity coefficient contains the variation of this junction potential with the composition of the solutions at finite concentrations.

(6) D. A. MacInnes, "The Principles of Electrochemistry," Reinhold Publishing Corp., New York, N. Y., 1939, pp. 220–245.

(7) F. O. Koenig [*J. Phys. Chem.*, **44**, 101 (1940)] has shown that the quantities T_i in equation (1) are properly the Hittorf transference numbers, corrected for the conductivity of the solvent.

(8) M. Planck, *Wied. Ann.*, **40**, 561 (1890); H. Pleijel, *Z. physik. Chem.*, **72**, 1 (1910).

(9) P. Henderson, *Z. physik. Chem.*, **59**, 118 (1907); **63**, 325 (1908); M. Gouy, *J. chim. phys.*, **14**, 185 (1916).

(10) P. B. Taylor, *J. Phys. Chem.*, **31**, 1478 (1927); K. Sitte, *Z. Physik*, **91**, 622 (1934).

(11) J. J. Hermans, Dissertation, Leiden, 1937.

(12) F. O. Koenig, *J. Phys. Chem.*, **44**, 101 (1940).

convenience, the Henderson assumption will be used in the present discussion because it leads to the relatively simple expression

$$-E_j^0 = \text{Lim}\ \frac{RT}{F}\frac{\Sigma(\lambda_i^0/z_i)(m_i'' - m_i')}{\Sigma\lambda_i^0(m_i'' - m_i')} \qquad (2)$$

at infinite dilution. This choice does not imply that the authors can dispose of the theoretical objections[11] to the general application of this assumption to heterionic junctions. The primes and double primes in equation (2) refer to concentrations in the immediate neighborhood of the left and right hand electrodes, respectively, and λ_i^0 is the limiting conductance of the i-ions.

In order to evaluate the limit appearing in this equation, the ionic concentrations m_i', m_i'', etc., may be expressed as fractions

$$\rho_i' \equiv m_i'/m', \quad \rho_i'' \equiv m_i''/m'', \text{ etc.} \qquad (3)$$

of the total ionic concentrations, m' and m''. In the limit, as $x \rightarrow 0$

$$\frac{m'' - m'}{m'' + m'} = 0 \qquad (4)$$

for the Type A and C junctions. The application of this equation to Type B and CB junctions can only be considered permissible in view of the *convention* of disregarding the soluble constituents of the electrodes in cells containing these junctions.

Combination of equations (2), (3) and (4) leads to the following result at infinite dilution.

$$-E_j^0 = \frac{RT}{F}\frac{\Sigma(\lambda^0/z_i)(\rho_i'' - \rho_i')}{\Sigma\gamma_i^0(\rho_i'' - \lambda_i')}\ln\frac{\Sigma\lambda_i^0\rho_i''}{\Sigma\lambda_i^0\rho_i'} \qquad (5)$$

For Type A junctions, $\rho_i' = \rho_i''$, etc., and the logarithmic factor is zero. According to the convention referred to above, this factor is also zero for Types B and CB junctions. For the simplest Type C junctions (Cell VI), equation (2) reduces to the familiar equation of Lewis and Sargent.[13]

MacInnes and Yeh[14] investigated cells of Type VI which contained pairwise combinations of the chlorides of hydrogen, ammonium and the alkali metals. Unfortunately, only two concentrations (0.1 and 0.01) were used, but the values of E_j^0 obtained by linear extrapolation for all combinations (except those involving potassium chloride) are in reasonable agreement with equation (5) the average deviation being 0.11 mv. For the potassium salts the disagreement is of the order of 1.2 mv. Data are available which can be used for a similar "two point" (m = 0.05 and 0.03) extrapolation for the system KCl (m) | KBr (m), and this also is not in accord with equation (5). The disagreement in this case amounts to 0.25 mv.

In order to determine whether the discrepancies obtained with potassium salts represent a failure of the equation or of the "two point" extrapolation, the family of straight lines shown in Fig. 2 of the first paper of this series[2] has been used to obtain interpolated values of $E - 2k\log(xmy) + 2k\alpha\sqrt{\mu}$ which would be applicable to Cell VII. The constants k = 0.05915 and α = 0.506 at 25°. The addition of $k\log K$ (= −0.5768) to these values yields the values of $k\log\gamma_{Cl}\gamma_{Ag} + 2k\alpha\sqrt{\mu} + E_j$ which are plotted as ordinates in Fig. 1.

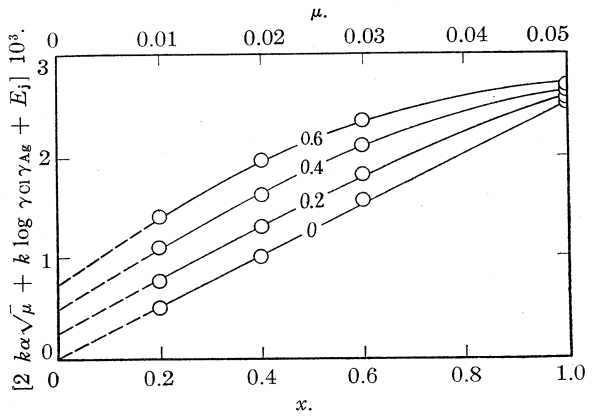


Fig. 1.—Extrapolation of the results for Cell VII. Values of y are indicated on the curves; m is constant and equal to 0.05 mole per kg. of water. The intercepts, E_j^0, were calculated by equation (5).

The abscissa is expressed in terms of x at the bottom, and μ at the top of the figure. Two important conclusions may be drawn from this plot. First, for all values of y greater than zero the plots are not linear, and as the system KCl|$AgNO_3$ is approached (y = 1), a very pronounced curvature appears in the neighborhood of μ = 0.025. Second, the extrapolated portions of the curves have been drawn to intercepts, E_j^0, calculated by equation (5) without producing any apparent discontinuity with the experimental curves. These results supply a reasonable explanation of the discrepancies referred to above, and appear to justify the use of equation (5) in estimating E_j^0 for practical purposes. The rigorous validity of this equation is, of course, a question which cannot be decided by such curved extrapolations from so few data.

(13) G. N. Lewis and L. W. Sargent, THIS JOURNAL, **31**, 363 (1909).

(14) D. A. MacInnes and Y. L. Yeh, *ibid.*, **43**, 2563 (1921).

The classification of liquid junctions according to their limiting characteristics ($x \rightarrow 0$) is helpful in determining the propriety of using a given cell for thermodynamic purposes.

The use of Type A junctions assumes the possibility of a suitable extrapolation to $x \rightarrow 0$. If the accuracy of this extrapolation is not inferior to that of the data upon which it is based, the extrapolated quantity is subject to rigorous thermodynamic treatment. The accuracy of such extrapolations appears to fulfil this condition, but only one system with Type A junctions has been investigated.[2]

The extrapolation required for Type B junctions is similar to that for Type A, and appears equally accurate,[3,4] but the extrapolated quantity derived from a Type B junction contains an unknown residual junction potential. Although this unknown potential is disregarded in the use of all of the so-called "cells without liquid junctions," this convention does not always permit a rigorous thermodynamic interpretation of the data. For example, the values of E^0 and the activity coefficients calculated from the electromotive forces of Cell V are somewhat ambiguous for this reason.[5] On the other hand, the modern electrometric determination of ionization constants of weak electrolytes is free from this defect, because the residual junction appears twice in the procedure (in the extrapolations for E^0 and for K) and cancels out.

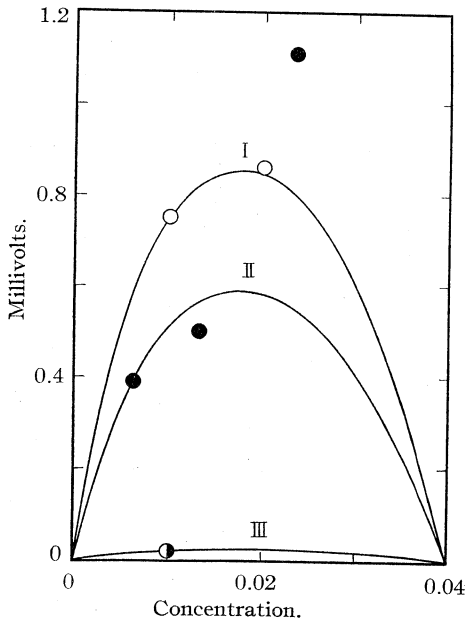


Fig. 2.—Departures of several extrapolations from linearity in dilute solutions. I. Cell VIII: abscissa, chloride (or silver) molality: potassium nitrate concentration constant, 0.01 molal. II. Cell IX: abscissa, total iron wt. normality: hydrochloric acid concentration constant, 0.05 wt. normal. III. Cell III: abscissa, hydrochloric acid normality: ionic strength constant, 0.1 normal.

The extrapolations which result in Types A and B are practically linear when performed at constant ionic strength.[2,3,4] Type C (CB) junctions are produced by extrapolation to zero ionic strength, and may depart widely from linearity, as in Fig. 1. In addition to the uncertainty caused by this curvature, the use of Type C (CB) junctions is under the disadvantage of requiring an estimate of E_j^0. Furthermore, all of the equations proposed for this purpose involve some extra-thermodynamic assumption that is difficult to justify *per se*, and attempts to verify the equations may have to contend with non-linear extrapolations such as those encountered in systems containing potassium salts. These considerations make it undesirable to employ Type C (CB) junctions for any purpose for which Types A and B, or cells "without liquid junctions" can be utilized, and leave room for doubt that condition I is rigorously fulfilled by Type C (CB) junctions.

Condition II

While the extrapolations ($x \rightarrow 0$) are not necessarily performed at constant total ionic strength, it appears that this condition must be fulfilled if a *linear* extrapolation is to be obtained, or even approximated. In the three systems investigated by the authors[2,3] and E. J. King,[4] the deviations of the experimental results from linearity are of the order of the reproducibility of the electromotive forces (0.05 mv.). The liquid junction potentials in these systems were small because of the choice of ions with nearly equal mobilities,[2,4] and the use of buffers[3] when acids were present. In cells containing high liquid junction potentials, there is evidence of only a slight departure from linearity. For example, the available data[15] on Cell III ($m = 0.1$; $x = 0.1$, 0.5, and 1.0) show a maximum deviation of 0.25 mv. from a straight line drawn through the points corresponding to $x = 0$ and $x = 1$. This curvature is illustrated by curve III in Fig. 2, which was constructed as follows: (1) a large-scale plot of the function $E - k \log (mx)$ against mx was made from measurements on Cell III, (2) a smooth curve was drawn through these ex-

(15) A. Unmack and E. A. Guggenheim, *Kgl. Danske Videnskab. Selskab. Math.-fys. Medd.*, **X**, 8 (1930).

perimental results, and extrapolated to the limit, $mx = 0$, (3) a chord was drawn from $mx = 0$ to $mx = 0.04$, and (4) vertical distances between this chord and the curve were scaled off at several values of mx, and plotted as the ordinates of Curve III, in Fig. 2, against mx as abscissa. Curve III therefore represents the departure of the experimentally determined function, $E - k \log (mx)$, from linearity at acid concentrations (mx) between 0 and 0.04 mole per liter. In this particular case the ionic strength is constant (0.1 mole per liter at 18°), and the departure from linearity is very small.

On the other hand, the upper curves[16] in Fig. 2 illustrate the relatively enormous curvatures encountered when the extrapolation is not performed at constant ionic strength. Curve I shows the departures of the function, $E - 2k \log (xm) + 2k\alpha\sqrt{\mu}$, from linearity for the cell

Ag, AgCl (s)	AgCl [satd.] KCl [xm] KNO_3 [m_0]	AgCl [satd.] KNO_3 [$xm + m_0$]	AgCl [satd.] $AgNO_3$ [xm] KNO_3 [m_0]	AgCl (s), Ag	VIII

at a constant concentration of potassium nitrate ($m_0 = 0.01$). These results were obtained graphically from the family of straight lines given in Fig. 2 of the first paper in this series.[2] The temperature is 25°, and $m = 0.05$ molal. It is evident that this extrapolation at varying ionic strength is almost useless for practical purposes, although the ionic strength is uniform throughout the cell [equation (4)], and the mobilities of all of the ions are very nearly equal. In this case the departure from linearity is obviously due to variations in activity coefficients, rather than to large changes in E_j.

Curve II in Fig. 2 shows the departures of the function, $E + k \log (c_{Fe^{+++}}/c_{Fe^{++}})$, from linearity for the cell

H_2	H_2 [satd.] HCl [m_0]	$FeCl_2 + FeCl_3$ [m] HCl [m_0]		Pt	IX

used by Popoff and Kunz.[17] The constant acid concentration, m_0, is 0.05 mole per kilo of solution, and the total iron concentration, m, is here expressed in *equivalents* per kilo of solution to reduce the concentration range covered by the plot.[18] The temperature is 25°. The curvature in this case is probably due to considerable variations in E_j as well as in the activity coefficients.

Summary and Conclusions

In the elimination of liquid junction potentials by extrapolation, it is useful to classify junctions according to their characteristics in the limit obtained by extrapolation. This depends upon the fact that a given pair of junction solutions may lead to quite different limiting cell potentials depending upon the nature of the electrodes employed and the manner in which the limit is approached. Thus, the limiting potential of the liquid–liquid system KNO_3, KCl | KNO_3, $AgNO_3$ can be Type A ($E_j^0 = 0$, as in Cell II), Type B (E_j^0 neglected, as in Cell IV), or Types C and CB (E_j^0 calculable, as in Cell VII as written, or modified by elimination of silver chloride from the right-hand electrode).

New evidence (Fig. 1) is produced to show that the Henderson equation yields values of E_j^0 in reasonable agreement with experiment. An explanation is suggested for the previous failure of this equation in some systems involving the potassium salts.

The practical necessity of performing the extrapolations at constant ionic strength is illustrated by means of graphs (Fig. 2).

NEW HAVEN, CONN. RECEIVED DECEMBER 31, 1941

(16) The construction of Curves I and II is analogous to that just described for Curve III, but differs in the nature of the plotted experimental functions.

(17) S. Popoff and A. H. Kunz, THIS JOURNAL, **51**, 382 (1929).

(18) If the *molar* concentration of iron had been used the maximum of Curve II would have been over twice as high. The experimental point at 0.025 normal was disregarded in drawing the curve because it was inconsistent with the data at higher concentrations.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Electric Moments of Inorganic Halides in Dioxane. II. Chlorides of Boron, Aluminum, Iron, Silicon, Germanium and Tin[1]

BY T. J. LANE, P. A. MCCUSKER AND B. COLUMBA CURRAN

In the first paper[2] of this series, the degree of coördination of phosphorus, arsenic and antimony halides with dioxane was estimated from electric moment data. Further similar studies on the chlorides of some other trivalent elements and some of the tetravalent elements of Group IV B have been made. The number of compounds suitable for such study was limited either by low solubility in dioxane or by the occurrence of reactions other than coördination between the halide and dioxane. Whereas the chlorides of boron and aluminum caused no decomposition of dioxane, the corresponding bromides were found to react with this solvent to form decomposition products, the reaction with boron bromide taking place violently. In the case of titanium tetrachloride electric moment data of sufficient accuracy were unobtainable due to the low solubility of the dioxanate in dioxane.

Experimental

Preparation and Purification of Compounds.—Boron chloride was prepared from boron fluoride and aluminum chloride by the method of Gamble, Gilmont and Stiff.[3] The product was purified by several distillations and was finally absorbed in weighed amounts of cold dioxane, the composition of each solution being checked by analysis for chlorine. All manipulations were carried out under conditions which effectively prevented absorption of moisture.

Anhydrous aluminum chloride, a Baker C. P. product, was resublimed three times in a current of carbon dioxide, using an all-glass apparatus. The final product was sublimed directly into weighing bottles and anhydrous dioxane added.

Anhydrous ferric chloride was prepared by passing dry chlorine over heated standard iron wire in an all-glass apparatus. The apparatus was so designed that the product could be sublimed in an atmosphere of chlorine, without removal from the apparatus, through two glass wool plugs in series directly into weighing bottles. The chlorine atmosphere in the receivers was replaced by drawing a slow current of dry air over the sublimate. Analysis for chlorine indicated a purity of 99.8% for the product. Samples were prepared by direct addition of dioxane.

Silicon tetrachloride was prepared and purified by a standard method.[4] The product was fractionally distilled and a middle fraction boiling at 57° was used in sample preparation.

Germanium tetrachloride was obtained by the purification of a sample furnished through the courtesy of the Eagle–Picher Lead Company. Dissolved chlorine was removed by treatment with mercury and the chlorine-free liquid fractionally distilled through a glass-helix packed column. The middle fraction, boiling at 83.6° at 751 mm., was used in sample preparation. Analysis of this fraction for chlorine by the method of Baxter and Cooper[5] indicated a purity above 99%.

Anhydrous stannic chloride, a Baker C. P. product, was fractionally distilled several times in an atmosphere of carbon dioxide and a sample of the distillate sealed off in a glass tube. Absorption of moisture was prevented by opening the glass tube and making up the dioxane solutions in a dry-atmosphere chamber fitted with long-sleeved rubber gloves.

Dioxane for all purposes was purified by refluxing the commercial product over sodium for twenty-four hours and fractionally distilling.

Measurements and Calculations.—Densities and dielectric constants were measured as previously described.[2] The solute polarizations at infinite dilution were calculated by the method of Hedestrand.[6] The $\Delta\epsilon/C_2$ ratio for the dioxane solutions of boron chloride, germanium tetrachloride and stannic chloride showed a slight variation with concentration. The average value of this ratio, rather than an extrapolated value, was used in calculating the total polarization of each compound. The difference in the moments calculated from the average ratio and from that for the most dilute solution is in every case within the limit of accuracy indicated in Table II.

The distortion polarizations listed in Table II were determined in the following manner. The value for germanium tetrachloride is the polarization of the pure liquid.[7] The values for boron chloride and stannic chloride are the total polarizations at infinite dilution in benzene solution.[8] The value for silicon tetrachloride is the molar refraction for the sodium D line in the vapor state,[9] plus ten per cent. The values for aluminum chloride and ferric chloride are the molar refractions for the sodium D line determined in water solution,[10] plus ten per cent.

Attempts to measure the dielectric constants of dioxane solution of boron bromide gave values which changed continuously with time. That decomposition of dioxane results from its interaction with boron bromide was shown by the incomplete precipitation of bromine, as silver bromide, from the hydrolyzed solutions.

Dielectric constants and densities are listed in Table I.

(1) Presented in part at the Atlantic City meeting of the American Chemical Society, September, 1941.

(2) McCusker and Curran, THIS JOURNAL, **64**, 614 (1942).

(3) Gamble, Gilmont and Stiff, *ibid.*, **62**, 1257 (1940).

(4) Biltz, Hall and Blanchard, "Laboratory Methods of Inorganic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1928, p. 80.

(5) Baxter and Cooper, *J. Phys. Chem.*, **28**, 1049 (1924).

(6) Hedestrand, *Z. physik. Chem.*, **B2**, 428 (1929).

(7) Miller, THIS JOURNAL, **56**, 2630 (1934).

(8) Ulich and Nespital, *Z. Elektrochem.*, **37**, 559 (1931).

(9) Goldschmidt and Holemann, *Z. physik. Chem.*, **B24**, 199 (1934).

(10) Limann, *Z. Physik*, **8**, 13 (1922).

The calculated polarizations and electric moments are listed in Table II. Electric moments are expressed in Debye units.

TABLE I

DIELECTRIC CONSTANTS AND DENSITIES OF DIOXANE SOLUTIONS AT 25°

c_2	ϵ	d
	Boron Chloride	
0.00000	2.211	1.0279
.01158	2.599	1.0355
.01342	2.674	1.0368
.01880	2.880	1.0408
	Aluminum Chloride	
0.00000	2.211	1.0280
.00805	2.264	1.0352
.01045	2.284	1.0373
.01291	2.297	1.0395
.01510	2.309	1.0414
	Ferric Chloride	
0.00000	2.211	1.0279
.00556	2.232	1.0350
.01378	2.257	1.0452
.01601	2.267	1.0479
	Silicon Tetrachloride	
.00000	2.223	1.0279
.01618	2.228	1.0369
.02242	2.230	1.0430
	Germanium Tetrachloride	
0.00000	2.213	1.0280
.01031	2.224	1.0394
.01930	2.228	1.0494
.02530	2.231	1.0567
	Stannic Chloride	
0.00000	2.214	1.0279
.00504	2.337	1.0391
.00646	2.358	1.0419
.00654	2.360	1.0425
.00859	2.394	1.0471

TABLE II

POLARIZATIONS AND ELECTRIC MOMENTS

	$P_{2\infty}$	P_{E+A}	μ
Boron chloride	517	24.5	4.86 ± 0.07
Aluminum chloride	112	27.0	2.02 ± .05
Ferric chloride	67	33.0	1.27 ± .05
Silicon tetrachloride	30	31.9	0.0
Germanium tetrachloride	47	37.1	0.67 ± .08
Stannic chloride	345	42.5	3.82 ± .15

Discussion

The symmetrical planar configuration of boron chloride in inert solvents, as evidenced by its zero moment in benzene,[8] gives way to a tetrahedral complex in donor solvents. The value obtained by Ulich and Nespital[8] for the moment of the etherate of boron chloride, $(C_2H_5)_2O{\cdot}BCl_3$, is 5.98 D. Assuming that the ether moment vector, 1.2, makes an angle of 125° with the $^+O\text{-}B^-$ bond, the sum of the $^+O\text{-}B^-$ bond moment and the resultant of the three B–Cl dipoles is 5.2. This value should be equal to the moment of the dioxanate of boron chloride, $C_4H_8O_2{\cdot}BCl_3$. Comparison of the observed moment of boron chloride in dioxane, 4.86, and the moment calculated for the complex, 5.2, indicates that coördination of boron chloride with dioxane is almost complete.

A similar calculation for aluminum chloride from the moment of its etherate,[8] 6.54, yields a value of 5.6 for the moment of $C_4H_8O_2{\cdot}AlCl_3$. The observed moment of aluminum chloride in dioxane is 2.02. This low moment indicates either that the extent of coördination is small, or that in a large number of the complexes two dioxane molecules coördinate with each aluminum atom to form trigonal bipyramids having the three chlorine atoms in the equatorial plane. Such complexes would have zero moments. Since aluminum chloride may be expected to exist as a dimer in completely inert solvents, indications of interaction were sought in cryoscopic measurements on the solutions listed in Table I. These measurements indicated that aluminum chloride is monomolecularly dispersed in dioxane solution. It is difficult to understand how dioxane could break up the aluminum chloride dimers without at the same time forming coördinate bonds with aluminum.

The apparent lack of coördination between ferric chloride and dioxane, as evidenced by the low moment, 1.27, is surprising. The structure of the isolated ferric chloride molecule is not known. The magnetic moment of this compound in the solid state[11] indicates five unpaired electrons. The most probable bond types for a ferric chloride molecule with five unpaired electrons are sp^2 and dsp, the former resulting in a trigonal planar structure having a zero moment, and the latter in an unsymmetrical planar structure having a low moment. Coördination complexes of ferric chloride and dioxane having various configurations are possible, most of which would have large moments. It appears from the observed low moment that only a small percentage of ferric chloride molecules coördinate with dioxane in solution.

The complete lack of coördination between dioxane and silicon tetrachloride, as evidenced by

(11) Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, p. 107.

the zero moment of this compound in dioxane, is of importance in connection with the mechanism of the hydrolysis of silicon tetrachloride. This reaction has been interpreted[12] as resulting from the formation of $^{+}O\text{-}Si^{-}$ bonds with the subsequent splitting off of hydrogen chloride. A mechanism involving the formation of Cl–H bonds would appear more probable unless the smaller size of the water molecule, compared to dioxane, makes the formation of an $^{+}O\text{-}Si^{-}$ bond possible in this special case.

The low moment of germanium tetrachloride in dioxane reveals that only a small amount of interaction takes place between these compounds in solution. Efforts to isolate a solid dioxanate of germanium tetrachloride have been unsuccessful and this confirms the view that very little tendency exists for germanium to expand its valence shell in forming coördinate bonds with dioxane. A comparison of the behavior of germanium and titanium tetrachlorides toward dioxane is of interest. While the solubility of the complex of titanium tetrachloride in dioxane is too small to permit determination of its moment in dioxane, the existence of the crystalline complex indicates that coördination readily occurs, at least in the solid state. The greater size of the titanium atom is probably responsible for the difference in the behavior of titanium and germanium tetrachlorides.

The effect of atomic radius is further shown in the case of stannic chloride. A solid coördination complex having the composition $SnCl_4 \cdot 2C_4H_8O_2$ has previously been reported.[13] That coördination persists in solution is evident from a comparison of the zero moment obtained for stannic chloride in benzene[8] with the value, 3.82, in dioxane. The values[14] reported for $(C_2H_5)_2O \cdot SnCl_4$ and $2(CH_3)_2CO \cdot SnCl_4$ are 3.60 and 7.7, respectively. The possible arrangements of the chlorine atoms and dioxane molecules in the octahedral complexes would permit various configurations having moments ranging from 0 to about 6. For this reason it is not possible to estimate from the data the degree of coördination of stannic chloride with dioxane, but it is evident that dioxane coördinates to a greater extent with stannic chloride than with germanium tetrachloride.

(12) Sidgwick, *J. Chem. Soc.*, **125**, 2672 (1924).

Summary

Electric moments have been determined for boron chloride, aluminum chloride, ferric chloride, silicon tetrachloride, germanium tetrachloride and stannic chloride in dioxane. Coördination between dioxane and boron chloride in solution is almost complete. Ferric chloride appears to interact only slightly with dioxane. The extent of coördination of the group IV B elements increases with increasing size of the central atom, silicon tetrachloride having a zero moment and stannic chloride a moment of 3.8 in dioxane.

(13) Rheinboldt and Boy, *J. prakt. Chem.*, **129**, 268 (1931).

(14) Ulich, Hertel and Nespital, *Z. physik. Chem.*, **B17**, 21 (1932).

NOTRE DAME, INDIANA RECEIVED JUNE 26, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WAYNE UNIVERSITY]

The Effect of Temperature on the Surface Tension and Density of Some Halogen Substituted Acetic Acids

BY JOSEPH J. JASPER AND LEWIS ROSENSTEIN

In a recent investigation carried out in this Laboratory, accurate surface tension–temperature data were required for the comparison of certain physico-chemical properties of the halogen substituted acetic acids. Search of the literature revealed the apparent unavailability of such data for most of the compounds involved. To supply this deficiency, the surface tension–temperature data for monobromoacetic acid and monoiodoacetic acid were determined over an appreciable temperature range in their molten states.

Experimental

Materials.—The compounds were Eastman Kodak Company reagent quality. The melting point of the monobromoacetic acid was 49.7° and that of monoiodoacetic acid 81.9°. No decomposition of the latter was observed below 130° during the measurements. The decomposition of this compound below its boiling point is believed to be dependent upon traces of mineral acids and moisture present[1]; therefore, great care was used to prevent traces of those impurities from reaching the molten monoiodoacetic acid.

(1) Eastman Kodak Company, private communication.

Procedure.—Because of the relative simplicity of the process and the necessity of excluding moisture from the molten compounds, the capillary rise method was employed for the surface tension measurements. The apparatus used was a slight modification[2] of that described by Richards and Coombs.[3] To ensure a plane reference liquid surface, the dimensional specifications suggested by Richards and Carver[4] were adopted. The diameter of the reference surface was 45 mm. The capillary tube of the apparatus was calibrated according to the method suggested by Harkins and Brown,[5] in which the focusing method described by Wolff, Shoemaker and Briggs[6] was employed, using a "cold" fluorescent light source. The radius of the capillary was found to be 0.019168 cm.

Density determinations were made with a 20-ml. Pyrex pycnometer, which was provided with an expansion bulb and a ground-glass stopper. This was calibrated with mercury.

The constant-temperature system consisted of a thick-wall Pyrex jar of eighteen liters capacity and an electronic relay controlled by a mercury regulator having a bulb of 250-ml. capacity. The Pyrex jar was insulated with magnesia-asbestos, one inch thick. Two small openings in the insulation, cut diametrically opposite, provided the necessary observation windows. Petroleum oil, the liquid medium of the bath, was found to provide a slower heat transfer than water. Although this effect was largely overcome by increasing the efficiency of stirring, the best temperature precision obtainable was $\pm 0.2°$.

The capillary rise was measured with a short range cathetometer. To ensure thermal equilibrium between the measured liquid and the surrounding oil-bath, at least thirty minutes were allowed. During this time the apparatus was agitated constantly. To equalize the pressure within the system with that of the prevailing atmosphere, the stopcock with which the apparatus was equipped was opened to the air from time to time through a calcium chloride drying tube. Between readings, the capillary was wet by drawing the liquid to the full length of the bore and allowing it to recede spontaneously to its static equilibrium position.

Experimental Results

The equation[7]

$$\gamma = \frac{(h + (r/3))(d_l - d_a)gr}{2}$$

was used to calculate the surface tension γ. In this equation, h is the capillary rise, r the capillary radius, and d_l and d_a, respectively, the densities of the liquid and air during the experiment. Each recorded measurement is the average of ten to fifteen readings. Experimental results are presented in Tables I and II.

TABLE I

DENSITY AND SURFACE TENSION DATA FOR MOLTEN MONOBROMOACETIC ACID

Temp., °C.	Density, g./ml.	$(h + (r/3))$, cm.	$(d_l - d_a)$	Surface tension, dynes/cm.
55	1.9017	2.2561	1.9007	40.30
70	1.8778	2.1870	1.8768	38.57
85	1.8531	2.1230	1.8522	36.96
100	1.8286	2.0454	1.8277	35.13
120	1.7955	1.9648	1.7947	33.14
145	1.7542	1.8446	1.7535	30.40
170	1.7123	1.7237	1.7117	27.72

TABLE II

DENSITY AND SURFACE TENSION DATA FOR MOLTEN MONOIODOACETIC ACID

Temp., °C.	Density, g./ml.	$(h + (r/3))$, cm.	$(d_l - d_a)$	Surface tension, dynes/cm.
85	2.2694	1.8119	2.2685	38.63
90	2.2606	1.7908	2.2597	38.03
95	2.2519	1.7653	2.2510	37.35
100	2.2430	1.7488	2.2421	36.85
110	2.2250	1.7161	2.2242	35.87
120	2.2070	1.6659	2.2062	34.54
130	2.1893	1.6278	2.1886	33.41

These data give straight line relationships. Using the method of least squares, the equations for the best curves were calculated and are given in the following:

For monobromoacetic acid

$$d = 1.93302 - 0.0016482t \quad (1)$$
$$\gamma = 46.20552 - 0.10901t \quad (2)$$

For monoiodoacetic acid

$$d = 2.42118 - 0.0017837t \quad (3)$$
$$\gamma = 48.35779 - 0.11483t \quad (4)$$

The average deviation of the data from these curves is as follows: (1) 0.024%; (2) 0.15%; (3) 0.024%; (4) 0.14%.

Summary

The effect of the temperature on the density and the surface tension of monobromoacetic acid and monoiodoacetic acid in the molten state was determined over an appreciable temperature range. The data obtained gave straight line relationships. The equations were calculated by using the method of least squares.

DETROIT, MICHIGAN RECEIVED JULY 2, 1942

(2) J. R. Bright and J. J. Jasper, THIS JOURNAL, **63**, 3486 (1941).
(3) T. W. Richards and L. B. Coombs, *ibid.*, **37**, 1656 (1915).
(4) T. W. Richards and E. K. Carver, *ibid.*, **43**, 827 (1921).
(5) W. D. Harkins and F. E. Brown, *ibid.*, **41**, 499 (1919).
(6) Wolff, Shoemaker and Briggs, *Bull. Bureau of Standards*, **12**, 432 (1915).
(7) N. E. Dorsey, "National Research Council Bull.," No. 69, p. 56.

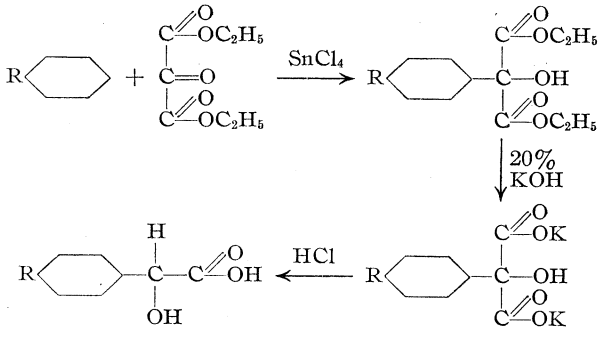
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DEPAUW UNIVERSITY]

The Preparation of Substituted Mandelic Acids and their Bacteriological Effects. III

BY J. L. RIEBSOMER, DALE STAUFFER, FRANCIS GLICK AND FREDERICK LAMBERT

Up to the present publication in this series,[1,2] we have confined our attention essentially to the preparation of halogen and alkyl substituted mandelic acids in which substitution has been on the benzene ring. This paper not only extends the series of ring substituted compounds but also describes eight compounds in which the hydroxy groups of certain mandelic acids have been changed to acetyl or propionyl. This type of compound was considered of interest because its efficacy as a bacteriocide might give some indication concerning the bacteriological significance of the hydroxyl group in the original molecule.

The Ando synthesis which may be summarized as follows



was used with a number of aromatic compounds such as diphenylmethane, diphenyl, β-methylnaphthalene, α-methylnaphthalene, triphenylmethane, fluorene, acenaphthene and anthracene, hoping to prepare the corresponding hydroxy acetic acids. While the acids prepared from these more complex hydrocarbons may require a stretch of the rules of nomenclature to regard them as derivatives of mandelic acid, yet it seems appropriate to consider them here. Of the eight hydrocarbons listed above, only the first two of the series reacted as expected.

Experimental

The method used for the preparation of the nuclear substituted mandelic acids was the same as previously described.[1,2] The same method was used for β-methylnaphthalene and the other more complex hydrocarbons except that a solvent (usually chloroform) was used either to make a suspension or solution of the solid hydrocarbons.

To prepare the acetyl or propionyl derivatives the appropriate mandelic acid and twice the theoretical amount of acid chloride were refluxed gently for ten to twelve hours. The resulting mixture was cooled and poured into cracked ice. In most cases a solid separated at once. The solid was filtered, dried and crystallized from benzene or benzene–petroleum ether mixtures. Table I summarizes the properties, yields, analyses and bacteriological data for the substituted mandelic acids. The bacteriological activity of each acid is compared with mandelic acid as unity. These tests were made *in vitro* on *B. coli*.

The intermediates for the *p*-benzyl, 2,4-, 3,4- and 2,5-dimethyl mandelic acids boiled under a pressure of 4–5 mm. at 225–230, 150–155, 157–160, and 154–156°, and were obtained in yields of 51, 47, 51, and 47%, respectively. The intermediate from the *p*-phenyl derivative was not distilled, so its yield could not be ascertained.

It will be noticed that no mention is made in Table I of derivatives from α-methylnaphthalene, β-methylnaphthalene, acenaphthene, fluorene, anthracene or triphenylmethane. When α-methylnaphthalene was subjected to the usual reaction conditions, the mixture turned almost black. Upon washing with water and distilling, 7 g. of a viscous oil was produced, b. p. 180–230° at 2 mm. pressure, which apparently was the expected intermediate, but upon saponification and subsequent acidification only a thick oil was formed from which no crystals could be obtained. Essentially the same observations were made with acenaphthene. β-Methylnaphthalene gave a very low yield of an acid, m. p. 146.5–147.5°, neutralization equivalent 217.8, and a carbon–hydrogen analysis which corresponded with a β-methylnaphthylhydroxyacetic acid. We were unable to prove the identity of this product.

In the cases of fluorene and anthracene the mixtures became deep purple in color when stannic chloride was added but none of the expected

(1) Riebsomer, Irvine and Andrews, THIS JOURNAL, **60**, 1015 (1938).

(2) Riebsomer, Baldwin, Buchanan and Burkett, *ibid.*, **60**, 2974 1938).

TABLE I

Mandelic acid derivative	Bacteriological activity (mandelic acid = 1)	Yield of acid, %	M. p. of acid, °C.	Neut. equiv. Calcd.	Neut. equiv. Found	Combustion analyses, % Calcd. Carbon	Calcd. Hydrogen	Found Carbon	Found Hydrogen
2,4-Dimethyl	3.5	44	113–115	180.1	180.6	66.6	6.7	67.1	6.8
3,4-Dimethyl	3.5	37	135	180.1	179.3	66.6	6.7	66.4	6.8
2,5-Dimethyl	3.5	37	116.5–117	180.1	180.0	66.6	6.7	66.4	6.8
p-Phenyl	0	63	192	228.1	229.3	73.7	5.3	73.7	5.6
p-Benzyl	< 1	26	133.5–134.5	242.1	238.6	74.4	5.8	74.3	6.4
Acetyl	1	94	76–76.5	194.1	192.6	61.8	5.2	61.5	5.3
Acetyl-2,4-dimethyl	0.5	74	92	222.2	222.0	64.8	6.4	65.3	6.4
Acetyl-2,5-dimethyl	< 1	72	112–113	222.2	221.2	64.8	6.4	64.5	6.4
Acetyl-*p*-phenyl	< 1	63	133	270.2	269.9	71.1	5.2	70.6	5.1
Acetyl-*p*-methyl	0.5	71	104–105	208.2	207.0	63.5	5.8	63.2	5.9
Propionyl	2	55	58	208.2	208.0	63.5	5.8	63.9	5.9
Propionyl-2,5-dimethyl	< 1	89	86	236.2	236.2	66.1	6.8	66.0	6.7
Propionyl-*p*-phenyl	0	64	107	284.2	284.0	71.8	5.6	72.3	5.6

products were obtained. The appearance of this purple color is typical of many of these reactions which do proceed as desired.

When triphenylmethane was run through the usual reaction routine, an acidic compound which crystallized from benzene (m. p. 90–95°) was formed but we were unable to get a product with a sharp melting point upon further crystallizations. The neutral equivalent was 335.5; calculated for the expected compound, 318.2, This material discolored upon standing. Its identity was not established.

The structures of the three dimethylmandelic acids described in Table I were determined previously[3] by careful permanganate oxidation to the corresponding dimethylbenzoic acids. The 2,4- and 3,4-dimethylmandelic acids were previously prepared by Ando but not tested bacteriologically.

The mandelic acid prepared from diphenyl was oxidized with dilute permanganate and produced diphenyl-4-carboxylic acid, m. p. 228°, thus indicating this product to be *p*-phenylmandelic acid. The compound prepared from diphenylmethane was shown to be *p*-benzylmandelic acid by permanganate oxidation to *p*-benzylbenzoic acid, m. p. 154–155°.

Discussion

The mixture of isomeric dimethylmandelic acids, which may be obtained using a commercial xylene mixture in the Ando synthesis, shows the same bacteriological activity as the pure isomers (3.5). This mixture would therefore appear to be better than mandelic acid in treating urinary tract infections, especially since its cost of production could be relatively low. Unfortunately, when the mixture of isomers was injected intravenously into rabbits it proved to be somewhat more toxic than mandelic acid. Accordingly its use in medicine is prohibited.

It was hoped that converting the hydroxy group of some of these mandelic acids to the acetyl or propionyl group would throw some light on the significance of the hydroxy group in the bacteriological activity of mandelic acids. It is obvious from the results shown in Table I that the data are conflicting and that no conclusions are justifiable.

The authors wish to express their indebtedness to Dr. R. S. Shelton of the William S. Merrell Co., who kindly carried out the bacteriological and pharmaceutical studies. The funds to support this work were partially provided from the William M. Blanchard Memorial Research Fund.

Summary

1. The synthesis and bacteriological activity of thirteen mandelic acids are reported.

2. Only the dimethyl derivatives show markedly greater activity than mandelic acid, but they proved to be too toxic to be used medicinally.

(3) Riebsomer and Burkett, *Indiana Acad. Sci.*, **48**, 75 (1939).

GREENCASTLE, IND. RECEIVED JUNE 17, 1942

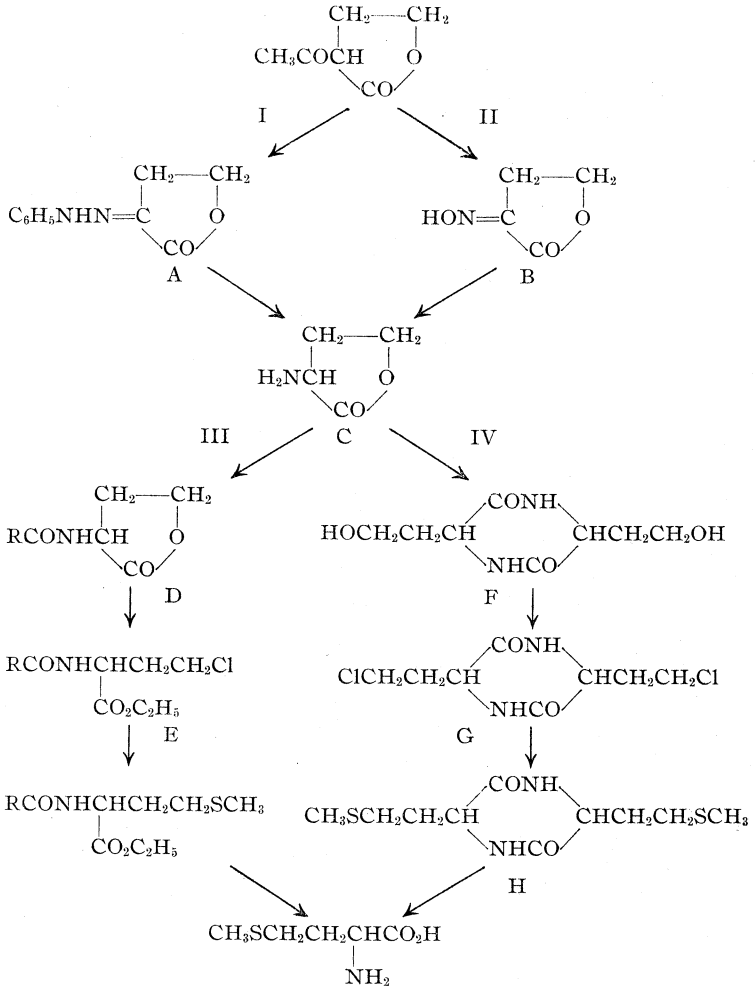
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A Convenient Synthesis of *dl*-Methionine

BY H. R. SNYDER, JOHN H. ANDREEN, GEORGE W. CANNON AND CARL F. PETERS

The synthesis of *dl*-methionine from the benzoyl derivative of α-amino-γ-butyrolactone, described by Hill and Robson,[1] does not require the use of the strongly vesicant β-chloroethylmethyl sulfide employed in the syntheses of Windus and Marvel[2] and of Barger and Weichselbaum.[3] However, α-amino-γ-butyrolactone has been difficult to prepare and consequently has not been much used in the preparation of methionine. Recently, certain derivatives of α-amino-γ-butyrolactone have been prepared from the easily available α-aceto-γ-butyrolactone.[4] Feofilaktov and Onishchenko[5] have obtained the hydrochloride of the aminolactone by reduction of α-oximino-γ-butyrolactone with tin and hydrochloric acid. They reduced the phenylhydrazone of α-keto-γ-butyrolactone in the same manner and obtained the hydrochloride of α-amino-γ-hydroxybutyric acid. The oxime and phenylhydrazone[6] were prepared by the action of nitrous acid and benzenediazonium chloride, respectively, on α-aceto-γ-butyrolactone.

The availability of α-amino-γ-butyrolactone from these reactions suggested a re-examination of the use of its acyl derivatives in the synthesis of *dl*-methionine. However, a possible route to *dl*-methionine involving the conversion of the aminolactone to 3,6-*bis*-(β-hydroxyethyl)-2,5-diketopiperazine was considered more attractive. Fischer and Blumenthal[7] have observed that the aminolactone readily changes to the diketopiperazine. In the accompanying scheme path III (R = C_6H_5) represents the synthesis of Hill and Robson,[1] who employed α-aminobutyrolactone prepared by a more tedious method; path IV represents the projected synthesis by way of the diketopiperazine.



In the present study the phenylhydrazone of α-keto-γ-butyrolactone (A) was prepared by the method of Harradence and Lions[6] and was subjected to catalytic reduction. When the reduction was carried out in ethanol over Raney nickel, temperatures of 100–150° were required and the product was not the aminolactone (C) but the diketopiperazine (F). When the reduction was carried out in ethyl acetate containing acetic an-

(1) Hill and Robson, *Biochem. J.*, **30**, 246 (1936).

(2) Windus and Marvel, THIS JOURNAL, **52**, 2575 (1930).

(3) Barger and Weichselbaum, "Organic Syntheses," **XIV**, 58 (1934).

(4) Knunyantz, *Compt. rend. acad. sci.* (U. R. S. S.), N. S. **1**, 312 (1934).

(5) Feofilaktov and Onishchenko, *J. Gen. Chem.* (U. S. S. R.), **9**, 304, 314 (1939).

(6) Previously prepared by Harradence and Lions, *J. Proc. Royal Soc. N. S. Wales*, **72**, 221 (1938).

(7) Fischer and Blumenthal, *Ber.*, **40**, 111 (1907).

hydride, a mixture of acetanilide and α-acetamino-γ-butyrolactone (D, R = CH_3) was produced. It was possible to separate these by water extraction and distillation and thus to obtain α-acetamino-γ-butyrolactone in yields of about 30%. When this substance was treated with hydrogen chloride and ethanol according to the method of Hill and Robson[1] for the corresponding benzamino derivative, the acetyl group was removed and the hydrochloride of α-amino-γ-butyrolactone was produced; none of the desired ethyl α-acetamino-γ-chlorobutyrate (E) was isolated.

α-Oximino-γ-butyrolactone (B) was prepared from ethyl nitrite and α-aceto-γ-butyrolactone in methanol solution. The oxime was hydrogenated over either Raney nickel or palladium-charcoal in methanol or ethanol solution. The resulting solution, after removal of the catalyst, was heated under reflux for twenty-four hours to effect the conversion of α-amino-γ-butyrolactone (C) to the dihydroxydiketopiperazine (F). This substance was obtained from the oxime in yields of 55–60%. It was identical with the diastereoisomeric modification previously obtained by Fischer and Blumenthal.[7] It was converted to 3,6-*bis*-(β-chloroethyl)-2,5-diketopiperazine (G), in yields of 90–95%, by treatment with excess thionyl chloride. 3,6-*bis*-(β-Methylthiolethyl)-2,5-diketopiperazine (H) was obtained in 63% yield from the reaction of the chloro derivative with sodium methylmercaptide. Hydrolysis of this diketopiperazine gave *dl*-methionine in 85–95% yield. These reactions constitute a convenient and economical method for the preparation of the amino acid.

Experimental

1. Hydrogenation of the Phenylhydrazone of α-Keto-γ-butyrolactone in Ethanol.—Acetobutyrolactone was prepared by the method of Knunyantz.[4] It was converted to the phenylhydrazone of α-keto-γ-butyrolactone by the procedure described by Harradence and Lions.[6] The crude phenylhydrazone was washed with water until the washings were free of halide ion, then dried and extracted with boiling ethanol or ethyl acetate to remove colored impurities. In one reduction 70 g. of the phenylhydrazone and 250 cc. of absolute ethanol were placed in a bomb with Raney nickel. Hydrogen under 1700 lb. pressure was admitted and the bomb was heated to 100° for four hours. During this period hydrogen was absorbed slowly, so the temperature was raised to 150° for eight hours. The ethanol was removed from the filtered solution by distillation under diminished pressure. The residue was a mixture of an oil (aniline) and a white solid (the diketopiperazine). The oil was removed by extraction with ether and the residual solid was crystallized from ethanol; it melted at 178–180°. The yield was 20 g. (54%). However, in other runs in which the temperature was kept constant at various temperatures between 100° and 150° the yield did not exceed 20%.

2. Hydrogenation of the Phenylhydrazone of α-Keto-γ-butyrolactone in the Presence of Acetic Anhydride.—A mixture of the phenylhydrazone (115 g.), acetic anhydride (170 cc.), and ethyl acetate (350 cc.) was placed in the bomb with Raney nickel and heated at 125° until hydrogen (initial pressure, 2000 lb.) was no longer absorbed. The solution contained nickel salts which were removed by treatment with hydrogen sulfide. The solvent was removed from the filtered solution by evaporation under 20 mm. pressure from a water-bath maintained at 90°. The residue was added to 500 cc. of cold water and the mixture was stirred rapidly and warmed to 40°. The aqueous solution was separated from the undissolved acetanilide (m. p. 113°) and evaporated to dryness under 20 mm. pressure. The sirupy residue was distilled and the fraction boiling at 175–178° (2 mm.) was collected as a pale yellow sirup which crystallized on standing; m. p. 82–84°. The yield was 29 g. or 30%.

Anal. Calcd. for $C_6H_9O_3N$: C, 50.35; H, 6.30; N, 9.79. Found: C, 50.43; H, 6.40; N, 9.72.

3. Reaction of α-Acetamino-γ-butyrolactone with Ethanol and Hydrogen Chloride.—The procedure of Hill and Robson[1] was used, except that an equivalent weight of α-acetamino-γ-butyrolactone was substituted for the benzamino derivative. The sirup remaining after evaporation of the ethanol was insoluble in ether. After crystallization from acetone it melted at 200–201° (lit.,[5] 201°) and analysis showed it to have the composition of α-amino-γ-butyrolactone hydrochloride; the yield was 40%.

4. Preparation of α-Oximino-γ-butyrolactone.—To a cold (0 to −5°) solution of 256 g. (2 moles) of acetobutyrolactone in 500 cc. of methanol was added 300 g. (4 moles) of ethyl nitrite prepared from hydrochloric acid, sodium nitrite and ethanol.[8] The reaction flask was packed in ice–salt and allowed to stand for fifteen to twenty hours, during which time the ice melted and the temperature of the reaction mixture reached that of the room. The mixture was cooled and the crystalline solid was collected on a filter. The filtrate was concentrated under diminished pressure and the dark-colored residue was heated on the steam-bath with 100 cc. of *n*-butyl alcohol. The mixture was cooled and filtered. The two crops of crystals were combined, washed twice with 100-cc. portions of cold *n*-butyl alcohol and then with ether. The α-oximino-γ-butyrolactone weighed 196–209 g. (85–91%) and melted at 183–185° (lit.,[5] 192°).

5. 3,6-*bis*-(β-Hydroxyethyl)-2,5-diketopiperazine.—Solutions of the oxime in methanol (about 4 cc. per g.) were hydrogenated over a palladium catalyst. The catalyst was prepared by evaporating to dryness a mixture of charcoal, previously washed with nitric acid, and aqueous palladium chloride. Quantities were chosen so that the dry catalyst contained the equivalent of 5% of metallic

(8) Evidently the reaction is catalyzed by a trace of hydrogen chloride, for reactions employing ethyl nitrite made from sulfuric acid have been found to proceed very slowly unless a small amount of an acid is added. For these observations the authors are indebted to Dr. E. E. Howe of Merck and Co., Inc., Rahway, N. J.

palladium. Two grams of the impregnated charcoal was used for each 100 cc. of methanol. The reductions were carried out at low pressure (50 lb. at start). They proceeded very rapidly (thirty minutes for a 25-g. run) and with the evolution of heat. When the hydrogen absorption was complete the catalyst was removed and the solution was heated under reflux for forty-eight hours, then stored in a refrigerator overnight. The crystalline solid was collected and washed with cold alcohol and cold ether; it melted at 186° with decomposition (lit.,[7] 189°). The yields were from 55–60%.

6. 3,6-*bis*-(β-Chloroethyl)-2,5-diketopiperazine.—The following procedure has given the best yields. In a 500-cc. flask fitted with a stirrer and reflux condenser 110 cc. of thionyl chloride was cooled to 0 to −5°, and 15 g. of 3,6-*bis*-(β-hydroxyethyl)-2,5-diketopiperazine was added in one lot. The mixture was stirred and allowed to come to room temperature slowly. The flask was then immersed in a water-bath which was very slowly warmed until the thionyl chloride began to reflux. The mixture was cooled and diluted with 75 cc. of dry ether. The solid was collected on a filter and washed twice with ether, then twice with water. Drying of the product may be facilitated by washing with alcohol and ether. The dry product was a very light yellow or white solid of m. p. 230–231°; the yield was 15.8–17 g. (90–95%). The substance can be recrystallized from ethanol or acetic acid, but the amount of solvent required is large (about 50 cc. per g.) and the melting point is not changed.

Anal. Calcd. for $C_8H_{12}O_2N_2Cl_2$: N, 11.7. Found: N, 11.4.

Larger runs have been made in the same way, but there is danger of uncontrollable boiling of the thionyl chloride when the reaction sets in. Addition of thionyl chloride to the hydroxyl compound suspended in an inert solvent, such as chloroform, gave lower yields and the product was of a dark color. The use of thionyl chloride and pyridine resulted in very poor yields.

7. 3,6-*bis*-(β-Methylthiolethyl)-2,5-diketopiperazine.—The chloro compound was mixed with a solution containing a 10% excess of sodium methylmercaptide (2.2 moles per mole of chloro compound) in absolute ethanol. Absolute ethanol was added until the total volume was about three liters per mole of chloro compound. This mixture, in a flask provided with a reflux condenser, was heated cautiously on the steam-bath. As soon as the reaction began the steam was turned off. Refluxing continued for about ten minutes without external heating; when boiling subsided steam was again applied until the total period of reflux was one hour. The boiling solution was filtered through a heated funnel and the filtrate was cooled in ice-water. The crystals were collected and the mother liquor was used for a second hot extraction of the original residue. The total yield from three such extractions was 63%. The material could be freed of a yellow-colored impurity, which was sometimes present, by washing with water, and the white diketopiperazine so produced melted at 225–226°. It could be recrystallized from ethanol to yield a product melting at 231–232°, but the crude material is satisfactory for the next step.

Anal. Calcd. for $C_{10}H_{18}O_2N_2S_2$: C, 45.9; H, 6.9. Found: C, 46.0; H, 7.0.

8. *dl*-Methionine.—The 3,6-*bis*-(β-methylthiolethyl)-2,5-diketopiperazine was mixed with concentrated hydrochloric acid (15 cc. per g.). The clear solution which resulted when the mixture was warmed was heated under reflux for three hours. The solution was evaporated to dryness under diminished pressure and the residue was dissolved in boiling absolute ethanol (20 cc. per g. of diketopiperazine used). This solution was clarified with charcoal and, while still hot, was treated with pyridine (1–2 cc. per g. of diketopiperazine) until an excess was present. Crystallization of *dl*-methionine began immediately. The mixture was allowed to stand in a refrigerator (0–5°) overnight and the product was collected, washed with cold absolute alcohol and then with absolute ether. The yield of *dl*-methionine was 85–95%.

Summary

A convenient and economical synthesis of *dl*-methionine is described. α-Aceto-γ-butyrolactone is converted to α-oximino-γ-butyrolactone by treatment with ethyl nitrite in the presence of a trace of mineral acid; the α-oximino-γ-butyrolactone is reduced catalytically to α-amino-γ-butyrolactone which changes to 3,6-*bis*-(β-hydroxyethyl)-2,5-diketopiperazine; 3,6-*bis*-(β-chloroethyl)-2,5-diketopiperazine is prepared by the action of thionyl chloride on the corresponding hydroxy compound and is converted to the anhydride of methionine by treatment with sodium methylmercaptide; *dl*-methionine is obtained by acid hydrolysis of the anhydride.

URBANA, ILLINOIS RECEIVED JUNE 29, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Behavior of Pyrogallol Trimethyl Ether and 3,4,5-Trimethoxybenzonitrile toward Grignard Reagents

BY CHARLES D. HURD AND H. E. WINBERG

Recently Haller and Schaffer[1] investigated the course of reaction between isobutylmagnesium bromide and 3,4,5-trimethoxybenzonitrile at the refluxing temperature of toluene. In addition to the expected 3,4,5-trimethoxyphenyl isobutyl ketone there was obtained a phenolic ketone and a second neutral ketone. On the basis of the reactions of these compounds, analytical data, and the known reactivity of the methoxyl group in the 4-position of trimethylpyrogallol derivatives, it was suggested that they were 3,5-dimethoxy-4-hydroxyphenyl isobutyl ketone and a 3,5-dimethoxy-4-butylphenyl isobutyl ketone.

At Dr. Haller's suggestion we continued this problem. We confirmed the observations of Haller and Schaffer and have obtained additional evidence for cleavage of the vicinal ether linkage. By increasing the molar ratio of the Grignard reagent from two and one-half to four-fold excess and the reaction time from three to five hours at a temperature of 110°, the yield of hydrolysis products may be greatly increased at the expense of the trimethoxy ketone. However, at 40° and with the longer reaction period cleavage of the ether linkage does not occur, the only product being the trimethoxy ketone.

The cleavage of ethers by Grignard reagents usually requires a reaction temperature of the order of 200°[2] but with more active linkages as in phenyl allyl ether cleavage occurs at 50 to 75°.[3] In trimethylpyrogallol derivatives the methoxyl group in the 4-position can be replaced with hydrogen[4] or hydrolyzed by sulfuric acid[5,6] to the corresponding dimethoxy phenol. It may be anticipated that at 110° Grignard reagents would cause a cleavage of the activated ether linkage.

The structure of the phenolic product resulting from the action of isobutylmagnesium bromide on 3,4,5-trimethoxybenzonitrile was shown to be the suggested 3,5-dimethoxy-4-hydroxyphenyl isobutyl ketone by hydrolysis of 3,4,5-trimethoxyphenyl isobutyl ketone with sulfuric acid to yield the same phenol obtained from the Grignard reaction. Oxidation of the phenol with chromic anhydride in glacial acetic acid produced the known 2,6-dimethoxybenzoquinone, showing the location of the phenolic group. Several attempts were made to oxidize the neutral ketone to 3,5-dimethoxyterephthalic acid,[7] but only intractable tars resulted.

The formation of a phenol is the characteristic reaction in the cleavage of an aryl alkyl ether by a Grignard reagent but in the case of trimethylpyrogallol cleavage may occur at the aryl-oxygen linkage, accounting for the formation of the neutral ketone in which a butyl group has apparently replaced the methoxyl group. When pyrogallol trimethyl ether was heated at 110° with methylmagnesium iodide the only product was 2,6-dimethoxyphenol, obtained in 84% yield. Possibly an activating group in the para position is necessary to sufficiently weaken the aryl-oxygen to cause its cleavage.

Experimental

Trimethoxygallic acid was prepared in 91% yield by methylation of alkaline sodium gallate with methyl sulfate.[8] The acid chloride was prepared readily with phosphorus pentachloride by heating equimolar amounts of the two reagents for fifteen minutes at 100°, whereas attempts to bring about this conversion with thionyl chloride gave far less satisfactory yields. In the former case, phosphorus oxychloride and unused pentachloride were distilled off at 18 mm. and an excess of concentrated ammonium hydroxide was added to the residue. The amide, m. p. 177°, was prepared in 81% yield. It was converted in 93% yield to 3,4,5-trimethoxybenzonitrile, m. p. 86–89°, by heating in benzene solution with phosphorus pentachloride. Neither vacuum distillation nor crystallization from aqueous alcohol was effective in raising the melting point of this material, but isopropyl ether proved to be an efficient solvent. After one crystallization from it, the material melted at 90–92° (literature, 93°).

Reaction of 3,4,5-Trimethoxybenzonitrile with Isobutylmagnesium Bromide

First Experiment.—Haller and Schaffer's[1] conditions were duplicated, starting with 19.3 g. of the nitrile (0.1

(1) Haller and Schaffer, THIS JOURNAL, **61**, 2175 (1939).

(2) Grignard, *Compt. rend.*, **151**, 322 (1910); Simonis and Remmert, *Ber.*, **47**, 269 (1914); Späth, *ibid.*, **47**, 766 (1914); Späth, *Monatsh.*, **35**, 319 (1914); Hirao, *J. Chem. Soc. Japan*, **54**, 991 (1933), and earlier articles; Grignard and Ritz, *Bull. soc. chim.*, **3**, 1181 (1936); Challenger and Miller, *J. Chem. Soc.*, 894 (1938).

(3) Lüttringhaus, Sääf and Hauschild, *Ber.*, **71**, 1673 (1938).

(4) Houben, "Die Methoden der organischen Chemie," pt. 3, 1930, p. 179.

(5) Alimchandani, *J. Chem. Soc.*, **125**, 539 (1924).

(6) Asahina and Kusaka, *Ber.*, **69**, 454 (1936).

(7) Brunner, *Monatsh.*, **50**, 224 (1928).

(8) "Organic Syntheses," Vol. VI, 1926, p. 96.

mole) and 0.25 mole of isobutylmagnesium bromide. Refluxing in toluene solution, after displacement of the ether as solvent, was for three hours. The yield of 3,4,5-trimethoxyphenyl isobutyl ketone, b. p. 164–166° at 6 mm., was 3.8 g. Haller and Schaffer reported its b. p. as 147–150° (1 mm.) and did not observe its solidification. On standing, our product crystallized spontaneously. These crystals melted at 37–39°. The yield of phenolic product, 3,5-dimethoxy-4-hydroxyphenyl isobutyl ketone, m. p. 93–93.5°, was 4.5 g.

Second Experiment.—The points of difference in procedure were a greater excess of Grignard reagent and a longer period of refluxing. The mixture of 19.3 g. of nitrile and 0.4 mole of Grignard reagent (from 55 g. of isobutyl bromide) was made in ether as before, then the solvent ether was replaced by toluene, and the mixture refluxed for five hours. Only 1.50 g. of 3,4,5-trimethoxyphenyl isobutyl ketone was isolated, but 10.0 g. of 3,5-dimethoxy-4-hydroxyphenyl isobutyl ketone was formed. From the toluene solution there was obtained 6.18 g. of oil boiling at 163–167° (5 mm.) and 1.58 g. boiling at 167–177° (5 mm.). This is presumably 3,5-dimethoxy-4-isobutylphenyl isobutyl ketone. Its semicarbazone melted at 183–184°.[1]

Third Experiment.—By carrying out the reaction at 40° only the trimethoxy ketone was obtained. To the Grignard reagent prepared from 17.1 g. (0.125 mole) of isobutyl bromide in 65 cc. of ether and 3.04 g. (0.125 mole) of magnesium in 100 cc. of ether was added 19.3 g. (0.100 mole) of the nitrile dissolved in 200 cc. of dry toluene. The mixture was maintained at 40° for five hours. It was then poured onto ice containing 30 cc. of concentrated hydrochloric acid. The organic layer was separated, washed with water, and dried over sodium sulfate. Evaporation of the solvents gave 9.26 g. of the unreacted nitrile. The water layer was refluxed for two hours, cooled, and then the resulting oil extracted with ether. The extract was washed with 5% sodium hydroxide, with water, and dried over sodium sulfate. After removal of the solvent the residue boiled at 163–168° (7 mm.) and solidified at room temperature. The yield was 10.7 g. The sodium hydroxide extract contained no alkali-soluble material; hence, hydrolysis to 3,5-dimethoxy-4-hydroxyphenyl isobutyl ketone had not taken place during the reaction.

Oxidation of 3,5-Dimethoxy-4-hydroxyphenyl Isobutyl Ketone to 2,6-Dimethoxybenzoquinone.—To 0.5 g. of the phenol dissolved in 20 cc. of glacial acetic acid was gradually added 1.25 g. of chromic anhydride. After the reaction had subsided, the solution was heated on the water-bath for fifteen minutes, cooled, and 35 cc. of water was added. The resulting solution was extracted three times with chloroform and the extract dried over sodium sulfate. After removal of the solvent, the oil was treated with a small quantity of ether and the insoluble material removed by filtration. The precipitate was recrystallized from glacial acetic acid; m. p. 253–254°. When mixed with an authentic sample of 2,6-dimethoxybenzoquinone[9] there was no depression of the melting point.

3,5-Dimethoxy-4-hydroxyphenyl Isobutyl Ketone from 3,4,5-Trimethoxyphenyl Isobutyl Ketone.—One gram of the trimethoxyphenyl isobutyl ketone was dissolved in 4 cc. of concentrated sulfuric acid. The solution was maintained at 35–40° for twenty hours and then poured onto ice. The resulting mixture was extracted with ether and the extract washed with 5% sodium hydroxide. The alkaline solution was acidified, then extracted with ether and the ether solution dried over sodium sulfate. Evaporation of the ether gave 0.80 g. of the phenol. After one recrystallization from 50% ethanol, it melted at 93°. A mixed melting point with the phenol obtained from the Grignard reaction on the nitrile showed no depression.

Reaction of Pyrogallol Trimethyl Ether with Methylmagnesium Iodide.—To the Grignard reagent prepared from 85.2 g. (0.60 mole) of methyl iodide in 110 cc. of ether and 14.6 g. (0.60 mole) of magnesium in 175 cc. of ether was added 25.2 g. (0.15 mole) of pyrogallol trimethyl ether dissolved in 200 cc. of dry toluene. The reaction mixture was then heated in an oil-bath and the ether removed by distillation, toluene being added gradually to maintain the original volume. After all of the ether had been replaced with toluene, the mixture was refluxed for ten hours with constant stirring. The reaction mixture was then poured on ice containing 80 cc. of concentrated hydrochloric acid. The organic layer was separated, the water saturated with sodium chloride and extracted with ether. The combined organic solution was extracted with 5% sodium hydroxide and dried over sodium sulfate. Evaporation of the solvents left no residue. The alkaline extract was acidified, the water saturated with sodium chloride and extracted with ether. After drying over sodium sulfate, removal of the ether gave 19.4 g. of 2,6-dimethoxyphenol, b. p. 106–108° (4 mm.). When recrystallized from butyl ether the melting point was 55–56°. When treated with benzoyl chloride in pyridine the phenol gave a benzoate[10] melting at 116–117° and with picric acid formed a picrate[11] melting at 61°.

Summary

In the reaction of isobutylmagnesium bromide and 3,4,5-dimethoxybenzonitrile, the yield of abnormal products (3,5-dimethoxy-4-hydroxyphenyl isobutyl ketone and 3,5-dimethoxy-4-isobutylphenyl isobutyl ketone) is favored by a 4:1 excess of Grignard reagent and by a prolonged reaction time at 110°. At 40°, only the normal product (3,4,5-trimethoxyphenyl isobutyl ketone) was obtained.

The structure of 3,5-dimethoxy-4-hydroxyphenyl isobutyl ketone was established by oxidizing it to 2,6-dimethoxybenzoquinone.

Conversion of 3,4,5-dimethoxyphenyl isobutyl ketone into 3,5-dimethoxy-4-hydroxyphenyl isobutyl ketone was effected by the action of sulfuric acid.

Methylmagnesium iodide reacted with pyrogallol trimethyl ether at 110°, to yield 2,6-dimethoxyphenol.

EVANSTON, ILLINOIS RECEIVED JUNE 11, 1942

(9) Graebe and Martz, *Ann.*, **340**, 221 (1905).

(10) Hahn and Wasmuth, *Ber.*, **67**, 701 (1934).

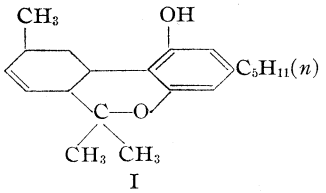
(11) Graebe and Haas, *Ann.*, **340**, 236 (1905).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND FROM THE DEPARTMENT OF PHARMACOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE, IN COLLABORATION WITH THE TREASURY DEPARTMENT, NARCOTICS LABORATORY, WASHINGTON, D. C.]

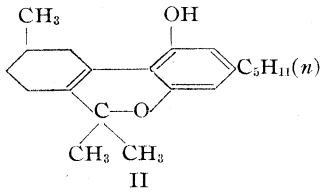
Optically Active Synthetic Tetrahydrocannabinols; *d*- and *l*-1-Hydroxy-3-*n*-amyl-6,9,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrans. XIV[1]

BY ROGER ADAMS, C. M. SMITH AND S. LOEWE

The tetrahydrocannabinol resulting from the isomerization of cannabidiol has been postulated as having structure I and is optically[2] active. A synthetic, racemic tetrahydrocannabinol obtained by the condensation of ethyl 5-methylcyclohexanone-2-carboxylate with olivetol, followed by treatment of the resulting pyrone with excess methylmagnesium iodide has the formula II.[3]



I



II

Compound II has about one-seventh the potency of I, which was derived from a natural source.

This investigation was undertaken to prepare the optically active forms of II and to compare them in physiological activity. Optically active *d*- and *l*-3-methylcyclohexanone were obtained and subjected to the same series of reactions previously used for converting the *dl*-modification to *dl*-tetrahydrocannabinol. Pulegone, upon hydrolysis according to the procedure of Wallach,[4] yielded *d*-3-methylcyclohexanone in what appears to be optical purity. The *l*-form is much less accessible and was finally obtained by the resolution of the *dl*-form through the 1-menthydrazone.[5] The less soluble menthydrazone was the *l,l*-modification, which was readily hydrolyzed to *l*-3-methylcyclohexanone of rotation only slightly lower than that observed for the *d*-form from pulegone. The intermediates in the preparation of the tetrahydrocannabinols derived from the *d*- and *l*-3-methylcyclohexanones showed essentially parallel rotations, but the final products differed considerably. The *l*-pyran happened to be a little more highly colored than usual and was decolorized by refluxing in ethanol with activated charcoal for a longer period than was used in the case of the *d*-form. This apparent racemization was checked using a sample of the *d*-pyran, $[\alpha]^{25}D$ +147° in ethanol. After prolonged refluxing in ethanol with activated charcoal, this substance had $[\alpha]^{28}D$ +123°. It is not improbable that either disproportionation or an actual dehydrogenation may take place. Assuming the *d*-tetrahydrocannabinol to be optically pure, the *l*-modification finally obtained was 87% pure.

Pharmacological tests revealed that the *d*-form is about 40% as active as the racemic and that the *l*-form has between four and five times the physiological potency of the *d*-form. The precise results are shown in Table I.

TABLE I

POTENCY OF OPTICALLY ACTIVE TETRAHYDROCANNABINOLS[a]

	Number of expts.	Potency	Range of variation
dextro-Pyran (II) $[\alpha]^{20}D$ +155	11	0.38	±0.025
levo-Pyran (II) $[\alpha]^{26}D$ −114	9	1.66	± .21

[a] *dl*-Tetrahydrocannabinol was used as standard.

It is pertinent that both the tetrahydrocannabinol (I) from cannabidiol and the purified active fractions from red oil of hemp are[6,7] levorotatory.

Before this investigation was complete, Leaf, Todd and Wilkinson[8] published a description of the *d*-form of the tetrahydrocannabinol (II), made in essentially the same way as herein reported. On the basis of their pharmacological results, using the Gayer test, they estimate the *d*-form to be one-sixth to one-eighth as active as the racemic modification. This discrepancy in their results and ours (about one-third the potency) lies prob-

(1) For previous paper see Adams, Loewe, Smith and McPhee, THIS JOURNAL, **64**, 694 (1942).

(2) Adams, Loewe, Pease, Cain, Wearn, Baker and Wolff, *ibid.*, **62**, 2566 (1940).

(3) Adams and Baker, *ibid.*, **62**, 2405 (1940).

(4) Wallach, *Ann.*, **289**, 340 (1896).

(5) Woodward, Kohman and Harris, THIS JOURNAL, **63**, 122 (1941).

(6) Adams, Pease, Cain and Clark, *ibid.*, **62**, 2402 (1940).

(7) Wollner, Matchett, Levine and Loewe, *ibid.*, **64**, 26 (1942).

(8) Leaf, Todd and Wilkinson, *J. Chem. Soc.*, 185 (1942).

ably in the method of testing. The Gayer test used by these investigators, in our hands, has been much less quantitative and less reliable an index of potency than the dog-ataxia method used by us for determining the activity of these substances.

In this recent paper of Leaf, Todd and Wilkinson, exception is taken to a previous statement made by us[9] that migration of a double bond from conjugation with a benzene nucleus is without precedent. They consider this statement ill-advised in view of the numerous cases of deconjugation in the literature. They cite as references merely well-known cases of deconjugation in the terpene series which can hardly be considered refutatory to our statement about molecules of the type under consideration, where the double bond is conjugated to a benzene ring and no other group is present in the molecule to which the double bond might conjugate preferably.

Experimental

***d*-3-Methylcyclohexanone.**—The details for the preparation of this product from pulegone are described since Wallach gave none.

From 200 g. of pulegone and 160 cc. of water, heated at 250° for six hours, an organic layer was obtained which was shaken with saturated aqueous sodium bisulfite until solidification occurred. The cake was broken up, about one-third of its volume of ether added, and the whole was shaken, water being added gradually until the bisulfite compound just dissolved. Treatment of the aqueous layer with one-half its volume of saturated sodium carbonate solution yielded 39 g. of *d*-3-methylcyclohexanone or 26.5% of the theoretical. The constants observed were b. p. 164–168°; $n^{20}D$ 1.4445; d^{20}_4 0.9179.

Rotation. $\alpha^{20}D$ +12.21° (pure liquid); *l*, 1; $[\alpha]^{20}D$ +13.3°. Wallach reported $[\alpha]^{15}D$ +13.38°.

The semicarbazone purified from ethanol had a m. p. 181° (cor.); Wallach reported 180°.

Rotation. 0.3625 g. made up to 25 cc. with ethanol at 20° gave αD −0.60°; *l*, 2; $[\alpha]^{20}D$ −20.7°.

***d*-3-Methylcyclohexanone-*l*-menthydrazone.**—A mixture of 1.5 g. of *d*-3-methylcyclohexanone, 3.0 g. of 1-menthydrazide, 0.2 g. of sodium acetate, 0.1 cc. of acetic acid and 20 cc. of ethanol was refluxed for two hours, diluted with water and the product allowed to crystallize. It was purified from 50% ethanol; white needles, softening at 126–130° and melting at 130–136° (cor.).

Anal. Calcd. for $C_{18}H_{32}O_2N_2$: C, 70.06; H, 10.46. Found: C, 70.00; H, 10.39.

Rotation. 0.2700 g. made up to 5 cc. with ethanol at 25° gave αD −3.31°; *l*, 1; $[\alpha]^{25}D$ −61.3°. The product from the mother liquors from the last crystallization gave the same rotation.

***l*-3-Methylcyclohexanone.**—By following the procedure just described, 162 g. of *dl*-3-methylcyclohexanone and 310 g. of *l*-menthydrazide in 400 cc. of ethanol gave a product which after filtering and recrystallizing from 1800 cc. of 65% ethanol, amounted to 195 g. This was recrystallized several times from the same solvent, then repeatedly from petroleum ether (b. p. 60–110°). When much of the more soluble derivative was present, the latter solvent could not be used as the substance tends to separate as a gel. It was found desirable not to heat the compound too much in the solvent and to remove the solvent under diminished pressure. After twenty crystallizations, there was obtained 13 g. of product of very nearly constant rotation, m. p. 146° (cor.).

Anal. Calcd. for $C_{18}H_{32}O_2N_2$: C, 70.06; H, 10.46. Found: C, 70.18; H, 10.94.

Rotation. 0.298 g. made up to 5 cc. with ethanol at 25° gave αD −1.90°; *l*, 1; $[\alpha]^{25}_4$ −31.3°.

Hydrolysis by warming with 10% sulfuric acid followed by steam distillation gave 3.7 g. of ketone; b. p. 164–168°; $n^{20}D$ 1.4449; d^{20}_4 0.9133; d^{25}_4 0.9108.

Anal. Calcd. for $C_7H_{12}O$: C, 74.94; H, 10.79. Found: C, 74.84; H, 10.69.

Rotation. $\alpha^{20}D$ −11.54° (pure liquid); *l*, 1; $[\alpha]^{20}D$ −12.64°.

The semicarbazone, purified from ethanol, melted at 181° (cor.).

Rotation. 0.1154 g. made up to 10 cc. with ethanol at 27° gave αD +0.24°, *l*, 1; $[\alpha]^{27}D$ +20.8°.

***d*- and *l*-Ethyl 5-Methylcyclohexanone-2-carboxylate.**—A solution of 5.95 g. of sodium in 120 cc. of absolute ethanol was cooled to 3° in an ice-bath and with stirring a mixture of 29 g. of *d*- or *l*-3-methylcyclohexanone and 38 g. of pure ethyl oxalate was added gradually. The temperature was maintained at 3–5° during the addition and for an hour thereafter. After standing overnight at room temperature, the reaction mixture was hydrolyzed by pouring onto a mixture of 15 cc. of sulfuric acid and cracked ice. The pale yellow oil was separated and the aqueous solution extracted with chloroform. The combined oil and extracts were washed with water plus a little sodium bicarbonate solution until neutral to congo red, dried and distilled in the presence of powdered soft glass and a trace of iron powder.

The *d*-product boiling at 100–140° (24–28 mm.) was collected and fractionated. The large middle fraction, b. p. 122–124° (15 mm.) was colorless, weighed 29 g. (61%) and had $n^{20}D$ 1.4722; d^{20}_4 1.040.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.18; H, 8.76. Found: C, 64.93; H, 8.68.

Rotation. $\alpha^{20}D$ +94.4° (pure liquid); *l*, 1; $[\alpha]^{20}D$ +90.8°.

After standing two months, this material had $[\alpha]^{28}D$ +73°. This decrease in rotation was probably due to re-establishment of the keto–enol equilibrium, since the value of +90.8° was obtained on freshly distilled material.

Gardner, Perkin and Watson[10] prepared the *d*-modification of this compound from an optically impure sample of *d*-3-methylcyclohexanone by carboxylation of the ketone with sodamide and carbon dioxide followed by esterification; they reported $[\alpha]D$ +84.2 in ethanol. Leaf, Todd and Wilkinson used a sample $[\alpha]^{19}D$ +79.2° (pure liquid).

(9) Adams, Smith and Loewe, THIS JOURNAL, **63**, 1973 (1941).

(10) Gardner, Perkin and Watson, *J. Chem. Soc.*, **97**, 1768 (1910).

Assuming the ester has a maximum rotation of +90.8°, this product corresponds to 93% purity.

The *l*-product was collected at 126–130° (17 mm.); $n^{20}D$ 1.4730; d^{20}_4 1.043.

Anal. Calcd. for $C_{19}H_{16}O_3$: C, 65.18; H, 8.76. Found: C, 65.41; H, 8.69.

Rotation. $\alpha^{20}D$ −88.26° (pure liquid); *l*, 1; $[\alpha]^{20}D$ −84.6°.

***d*- and *l*-1-Hydroxy-3-*n*-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone.**—These were prepared from the previously described *d*- and *l*-ethyl 5-methylcyclohexanone-2-carboxylates in a synthesis identical with that for the *dl*-modification.[3]

The *d*- and *l*-products were purified from methanol, m. p. 177° (cor.) in each case.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.03. Found: (dextro form) C, 75.97; H, 7.98; (levo form) C, 76.17; H, 8.13.

Rotation. (*d*-form) 0.3936 g. made up to 25 cc. with ethanol at 28° gave αD +4.20°; *l*, 2; $[\alpha]^{27}D$ +133°. 0.0205 g. made up to 5 cc. with chloroform at 25° gave αD +0.56°; *l*, 1; $[\alpha]^{25}D$ +137°. Leaf, Todd and Wilkinson[8] gave $[\alpha]^{24}D$ +130.3° in chloroform. (*l*-form) 0.1214 g. made up to 25 cc. with ethanol at 27° gave αD −1.23°; *l*, 2; $[\alpha]^{27}D$ −127°.

***d*- and *l*-1-Hydroxy-3-*n*-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran.**—These were prepared from the optically active pyrones with rotations given above by use of excess methylmagnesium iodide as previously described for the *dl*-modification.

The *d*-form had a b. p. of 175–185° (0.1 mm.), bath temp. 205–210°; $n^{20}D$ 1.4550; the *l*-form had identical b. p. and index of refraction.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.20; H, 9.62. Found: (*d*-form) C, 80.01; H, 9.63. (*l*-form) C, 80.07; H, 9.67.

Rotation. (*d*-form) 0.1742 g. made up to 5 cc. with ethanol at 20° gave αD +5.41°; *l*, 1; $[\alpha]^{20}D$ +155°. 0.1456 g. of a sample which had $[\alpha]^{25}D$ +147° in ethanol, made up to 5 cc. with chloroform at 25° gave αD +4.32°; *l*, 1; $[\alpha]^{25}D$ +147.5°. Leaf, Todd and Wilkinson[8] report $[\alpha]^{20}D$ +134.8°. (*l*-form) 0.0873 made up to 5 cc. with ethanol at 26° gave αD −1.99°; *l*, 1; $[\alpha]^{26}D$ −114°.

Pharmacological Tests.—These were performed by the dog-ataxia method as described in previous papers.[7,11,12]

Summary

1. The *d*- and *l*-forms of 3-methylcyclohexanone have been synthesized; the former was prepared by hydrolysis of pulegone; the latter by resolution of the *dl*-methylcyclohexanone through the *l*-menthydrazone.

2. These were converted to the active ethyl 5-methyl-cyclohexanone-2-carboxylates, which were condensed with olivetol to form the *d*- and *l*-pyrones. By the action of excess methylmagnesium iodide, the *d*- and *l*-1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrans resulted.

3. The *l*-modification had four to five times the marihuana activity of the *d*-form.

(11) Loewe, *J. Pharm. Exper. Therap.*, **66**, 23 (1939); *J. Am. Pharm. Soc.*, **28**, 427 (1939).

(12) Matchett and Loewe, *ibid.*, **30**, 130 (1941).

URBANA, ILLINOIS RECEIVED JULY 6, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. CLI. Rearrangement of 17,21-Dibromo-*allo*-pregnan-3(β)-ol-20-one Acetate[1]

BY RUSSELL E. MARKER, HARRY M. CROOKS, JR., R. B. WAGNER AND EMERSON L. WITTBECKER

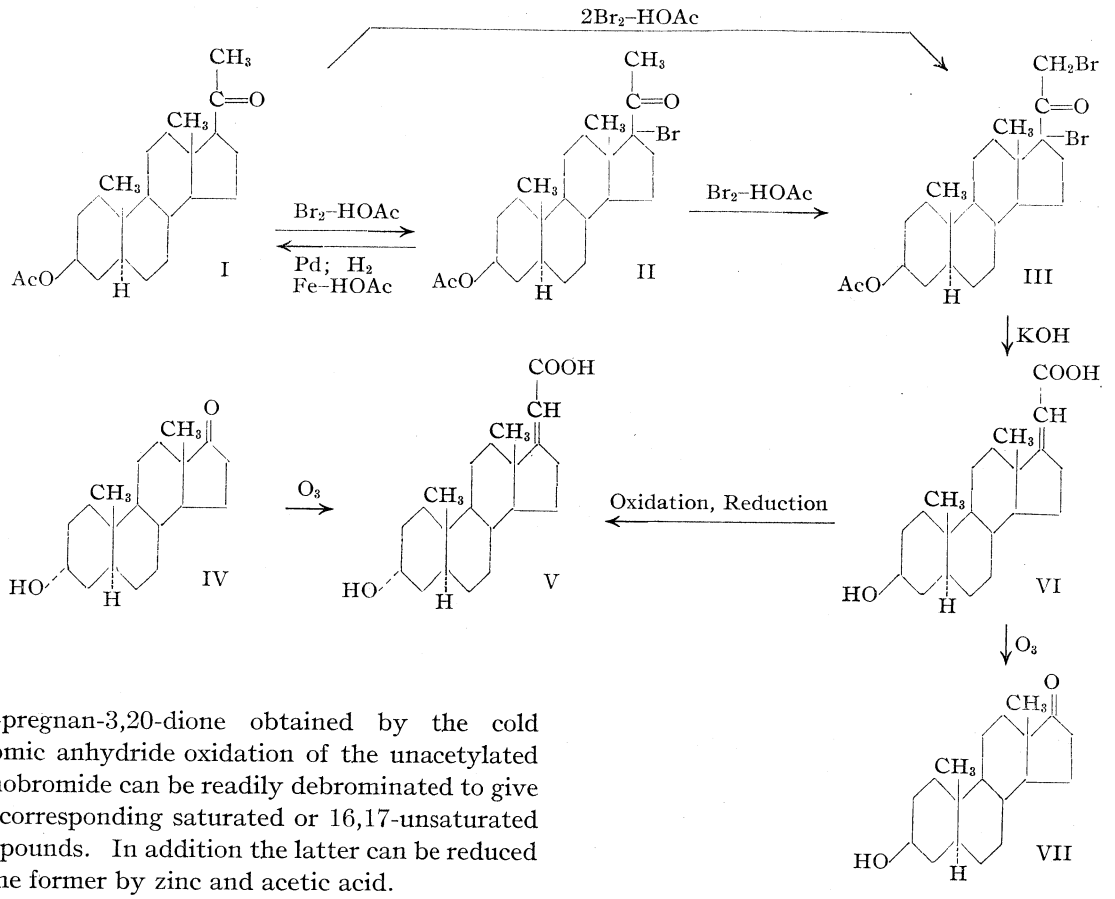
Recently,[2] we have shown that an equimolecular quantity of bromine with 20-keto-pregnane compounds introduces a bromine atom at C-17. Further bromination of these compounds substitutes a second bromine atom at C-21. Studies with these compounds have shown them to be particularly susceptible to rearrangement. The monobromo derivative[3] treated with methanolic potassium bicarbonate rearranges to place methyl and carbomethyoxyl groups at C-17. The 17,21-dibromo derivatives[2] under more vigorous alkali treatment yield Δ^{17-20}-pregnen-21-oic acids. The latter rearrangement products are particularly interesting since they can be degraded easily to the etio-cholane series. This fact has given support for their structure. We have now extended some of these reactions to *allo*-pregnan-3(β)-ol-20-one as a further study of the 17,21-dibromo-20-keto-pregnane rearrangement in the *allo* series.

allo-Pregnan-3(β)-ol-20-one or its acetate (I) with an equimolecular quantity of bromine readily forms a 17-monobromide (II) which can be reconverted to the parent compound or converted to 16-*allo*-pregnen-3(β)-ol-20-one by reactions described before.[2] In the same manner 17-bromo-

(1) Original manuscript received July 16, 1941.

(2) Marker and co-workers, THIS JOURNAL, **64**, 210, 213, 817, 822 (1942).

(3) Marker and Wagner, *ibid.*, **64**, 216, 1273 (1942).



allo-pregnan-3,20-dione obtained by the cold chromic anhydride oxidation of the unacetylated monobromide can be readily debrominated to give the corresponding saturated or 16,17-unsaturated compounds. In addition the latter can be reduced to the former by zinc and acetic acid.

allo-Pregnan-3(β)-ol-20-one acetate (I) with twice the molecular quantity of bromine forms 17,21-dibromo-pregnan-3(β)-ol-20-one acetate (III). The latter can be formed equally well by the treatment of the monobromide (II) with an equimolecular quantity of bromine.

By the same alkali treatment used for the rearrangement of its C-5 isomer,[2] the dibromide (III) rearranges to give 3(β)-hydroxy-Δ^{17-20}-*allo*-pregnen-21-oic acid (VI). Oppenauer oxidation of the latter followed by a Meerwein reduction of the resulting keto-acid gives the epimeric pregnenoic acid (V). The structures of these acids are now established by ozonolysis. The 3(β)-hydroxy acid (VI) yields isoandrosterone (VII) and the 3(α)-hydroxy acid (V) yields androsterone (IV). As early as 1913 Faworskii[3] showed that 3-methyl-1,3-dibromobutan-2-one reacting with alcoholic potassium hydroxide readily undergoes a rearrangement to give β,β'-dimethylacrylic acid. As a model experiment we have shown that the corresponding dibromide of methyl cyclohexyl ketone in a like manner is converted to cyclohexylidene acetic acid. The pregnenoic acids are analogous to this acid and to that obtained by Faworskii.[4]

The reactions are summarized in the accompanying chart.

We thank Parke, Davis and Company for their generous assistance.

Experimental Part

17-Bromo-*allo*-pregnan-3(β)-ol-20-one Acetate (II).—To a solution of 11 g. of *allo*-pregnan-3(β)-ol-20-one acetate (I) in 500 cc. of acetic acid was added 31 cc. of molar bromine in acetic acid solution, dropwise at room temperature. The solution was allowed to stand for one hour. Ice and cold water were added, and the monobromide was extracted with ether. The ethereal layer was washed successively with water, dilute sodium carbonate solution and water. The solvent was removed and the monobromide acetate was crystallized three times from methanol, m. p. 155°; yield 6.0 g.

Anal. Calcd. for $C_{23}H_{35}O_3Br$: C, 62.9; H, 8.0. Found: C, 62.6; H, 8.0.

17-Bromo-*allo*-pregnan-3(β)-ol-20-one.—To a solution of 17 g. of *allo*-pregnan-3(β)-ol-20-one in 1 l. of acetic acid was added dropwise 54 cc. of molar bromine in acetic acid solu-

(4) Faworskii, *J. Russ. Phys.-Chem. Soc.*, **44**, 1358 (1913); *J. prakt. Chem.*, [2] **88**, 658 (1913).

tion at room temperature. The solution was allowed to stand ten minutes, and then 1 l. of water was added. The monobromide was extracted with ether. The ether layer was washed well with water and evaporated. The monobromide was crystallized once from dilute methanol and then from ether–pentane, m. p. 93–96°; yield 9 g.

Anal. Calcd. for $C_{21}H_{33}O_2Br$: C, 63.5; H, 8.4. Found: C, 63.6; H, 8.1.

***allo*-Pregnan-3(β)-ol-20-one Acetate from 17-Bromo-*allo*-pregnan-3(β)-ol-20-one.**—A mixture of 2 g. of the bromo compound (II) in 500 cc. of methanol–dioxane mixture and 3 cc. of pyridine was hydrogenated at 40 pounds pressure for two hours using 2 g. of palladium catalyst. The catalyst was filtered off and the filtrate concentrated. An ethereal solution of the residue was washed successively with water, dilute hydrochloric acid solution and water, and then evaporated. The residue was crystallized from methanol, m. p. and mixed m. p. with *allo*-pregnan-3(β)-ol-20-one acetate (I), 142–144°; yield 1 g.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.6; H, 10.1. Found: C, 76.4; H, 10.0.

Reduction of 17-Bromo-*allo*-pregnan-3(β)-ol-20-one with Iron.—A mixture of 0.20 g. of the bromo compound (II), 1 g. of powdered iron and 10 cc. of glacial acetic acid was heated on a steam-bath for two hours. After filtering, water was added and the product extracted with ether. After evaporation of the solvent, the residue was crystallized from methanol, m. p. and mixed m. p. with *allo*-pregnan-3(β)-ol-20-one, 193–194°; yield 0.12 g.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 78.9; H, 10.8.

Catalytic Reduction of 17-Bromo-*allo*-pregnan-3(β)-ol-20-one.—A mixture of 0.50 g. of the bromo compound (II), 5 cc. of pyridine, 50 cc. of dioxane and 1 g. of palladium–barium sulfate catalyst was shaken with hydrogen for three hours at 40 pounds pressure. The catalyst was filtered and the filtrate was vacuum distilled. An ethereal solution of the residue was washed well with water and evaporated. The product was crystallized from methanol, m. p. and mixed m. p. with *allo*-pregnan-3(β)-ol-20-one, 193–194°; yield 0.26 g.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.0; H, 10.7.

16-*allo*-Pregnen-3(β)-ol-20-one Acetate from 17-Bromo-*allo*-pregnan-3(β)-ol-20-one Acetate.—A mixture of 1 g. of the bromo compound (II) and 5 cc. of pyridine was refluxed for five hours. Water was added and the mixture was extracted with ether. The ether layer was washed with water, dilute hydrochloric acid and water. The solvent was removed and the residue was treated with Norite in methanol. It was crystallized, m. p. and mixed m. p. with 16-*allo*-pregnen-3(β)-ol-20-one acetate, 163–165°; yield 0.6 g.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 77.0; H, 9.2.

Treatment of 17-Bromo-*allo*-pregnan-3(β)-ol-20-one with Pyridine.—A mixture of 0.50 g. of 17-bromo-*allo*-pregnan-3(β)-ol-20-one and 5 cc. of pyridine was refluxed for six hours. The product was extracted with ether, washed with dilute hydrochloric acid and crystallized from methanol, m. p. and mixed m. p. with 16-*allo*-pregnen-3(β)-ol-20-one, 202–204°; yield 0.25 g.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.6; H, 10.1.

***allo*-Pregnan-3(β)-ol-20-one Acetate from 16-*allo*-Pregnen-3(β)-ol-20-one Acetate.**—A mixture of 3 g. of the unsaturated acetate and 6 g. of zinc dust in 150 cc. of acetic acid was heated on the steam-bath for two hours. The zinc was filtered and water was added to the filtrate. This was then extracted with ether. The ethereal solution was washed with water, dilute sodium carbonate solution and again with water. The solvent was removed and the residue was crystallized from methanol and from acetone, m. p. and mixed m. p. with *allo*-pregnan-3(β)-ol-20-one acetate, 143°; yield 2.6 g.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.6; H, 10.1. Found: C, 77.0; H, 9.9.

Oxidation of 17-Bromo-*allo*-pregnan-3(β)-ol-20-one.—To a solution of 3 g. of the bromo compound in 50 cc. of acetic acid was added a solution of 1.5 g. of chromic anhydride in 15 cc. of 80% acetic acid at room temperature. After standing for thirty minutes, water was added and the product was extracted with ether. The acetic acid was washed out. Attempts to crystallize the product gave material with a melting point range.

(a) To a solution of 0.5 g. of the above product was added 10 cc. of dry pyridine and the mixture was refluxed for six hours. Water was added and the product was extracted with ether. The pyridine was removed and the residue was crystallized from ether, m. p. and mixed m. p. with 16-*allo*-pregnen-3,20-dione, 210–212°; yield 0.3 g.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.1; H, 9.6. Found: C, 80.1; H, 9.7.

(b) A solution of 0.50 g. of the crude bromo product in 25 cc. of acetic acid was refluxed for two hours with 1 g. of anhydrous potassium acetate. The solvent was removed and the residue was extracted with ether. Upon concentration, it crystallized, m. p. and mixed m. p. with 16-*allo*-pregnen-3,20-dione, 211–212°; yield 0.30 g.

(c) A solution of 0.50 g. of the crude bromo product was heated on a steam-bath for two hours with 1 g. of iron dust and 20 cc. of acetic acid. It was filtered and the filtrate was extracted with ether. The ethereal solution was washed with water and evaporated. The residue was crystallized from acetone, m. p. and mixed m. p. with *allo*-pregnan-3,20-dione, 200°; yield 0.27 g.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.6; H, 10.0.

***allo*-Pregnan-3,20-dione from 16-*allo*-Pregnen-3,20-dione.**—A solution of 0.50 g. of 16-*allo*-pregnen-3,20-dione in 20 cc. of acetic acid was heated with 1 g. of zinc dust on a steam-bath for one hour. The zinc was filtered and water was added to the filtrate. The solid was filtered and crystallized from acetone, m. p. and mixed m. p. with *allo*-pregnan-3,20-dione, 200°; yield 0.35 g.

17,21-Dibromo-*allo*-pregnan-3(β)-ol-20-one Acetate (III).—To a solution of 18 g. of 17-bromo-*allo*-pregnan-3(β)-ol-20-one acetate (II) in 1 l. of acetic acid was added 41.0 cc. of molar bromine in acetic acid at 40°. Water was added and the dibromide was extracted with ether. The ether layer was washed with water, dilute sodium

carbonate solution and water. The solvent was removed and the dibromide acetate was crystallized from methanol, m. p. 174°; yield 12 g.

Anal. Calcd. for $C_{23}H_{34}O_3Br_2$: C, 53.4; H, 6.6. Found: C, 53.0; H, 6.7.

3(β)-Hydroxy-Δ$^{17-20}$-*allo*-pregnen-21-oic Acid (VI).—A solution of 1.5 g. of 17,21-dibromo-*allo*-pregnan-3(β)-ol-20-one acetate (III) in 200 cc. of methanol was heated with 5 g. of potassium hydroxide on the steam-bath for two hours. After adding water, the mixture was extracted with ether. The aqueous layer was acidified and the organic acid (VI) was extracted with ether and crystallized from methanol, m. p. 249°; yield 0.8 g.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.8; H, 9.7. Found: C, 75.7; H, 9.5.

Isoandrosterone (VII) from 3(β)-Hydroxy-Δ$^{17-20}$-*allo*-pregnen-21-oic Acid (VI).—A chloroform solution of 6.7 g. of the acetate of 3(β)-hydroxy-Δ$^{17-20}$-*allo*-pregnen-21-oic acid (VI) was treated with oxygen containing about 6% ozone at the rate of 30 liters of oxygen per hour for three hours. The chloroform solution was poured into 300 cc. of water and stirred for forty-five minutes. The chloroform was distilled on a steam-bath and the water layer extracted with ether. The ether was evaporated and the residue hydrolyzed with 6 g. of potassium hydroxide in 200 cc. of methanol for twenty minutes. Water was added and the mixture extracted with ether. The ether layer was washed with water and then evaporated. The residue was dissolved in 200 cc. of ethanol and refluxed with 4 g. of semicarbazide hydrochloride and 5 g. of sodium acetate in 10 cc. of water for one hour. Water was added and the precipitate was filtered and washed with water and ether. The semicarbazone was crystallized twice from ethyl alcohol–chloroform mixture, m. p. 260–262° dec.; yield 2.1 g.

Anal. Calcd. for $C_{20}H_{33}O_2N_3$: C, 69.1; H, 9.6. Found: C, 69.2; H, 9.6.

A mixture of 0.2 g. of the above semicarbazone in 50 cc. of alcohol was refluxed for an hour with 50 cc. of alcohol containing 5 cc. of concd. sulfuric acid and 10 cc. of water. Water was added and the product was extracted with ether. The ether was evaporated and the residue was crystallized from aqueous methanol, m. p. and mixed m. p. with isoandrosterone (VII), 173–174°; yield 0.1 g.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4. Found: C, 78.2; H, 10.3.

3(α)-Hydroxy-Δ$^{17-20}$-*allo*-pregnen-21-oic Acid (V).—A mixture of 3 g. of 3(β)-hydroxy-Δ$^{17-20}$-*allo*-pregnen-21-oic acid (VI), 10 g. of aluminum tertiary-butoxide, 100 cc. of dry toluene and 25 cc. of dry acetone was refluxed for six hours. Ether and hydrochloric acid were added. The ether layer was washed with water and evaporated. The residue was refluxed with 200 cc. of dry isopropyl alcohol and 10 g. of aluminum isopropylate overnight. The solvent was then slowly distilled off over a period of five hours. Ether and hydrochloric acid were added. The ether layer was washed with water and evaporated. The 3(α)-hydroxy acid (V) was dissolved in ether and crystallized. It appears to be much more soluble than the β-form. It was also crystallized from ethyl acetate and finally again from ether, m. p. 232–235°. It gave a depression of 18° when mixed with a sample of 3(β)-hydroxy-Δ$^{17-20}$-*allo*-pregnen-21-oic acid (VI). It did not precipitate with digitonin.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.8; H, 9.7. Found: C, 75.8; H, 9.7.

Androsterone (IV) from 3(α)-Hydroxy-Δ$^{17-20}$-*allo*-pregnen-21-oic Acid (V).—A solution of 1 g. of the above acid in 200 cc. of chloroform was treated with ozone and the product worked up as described for the β-acid. It gave a semicarbazone, m. p. 260–264° dec.; yield 0.4 g.

Anal. Calcd. for $C_{20}H_{33}O_2N_3$: C, 69.1; H, 9.6. Found: C, 69.4; H, 9.5.

A solution of 0.4 g. of the above semicarbazone was refluxed for one hour with 50 cc. of ethanol containing 5 cc. of sulfuric acid and 10 cc. of water. Water was added and the product was extracted with ether. The ether was evaporated and the residue was crystallized from aqueous methanol, m. p. 182–183°. There was no depression in melting point when mixed with an authentic sample of androsterone (XI).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4. Found: C, 78.4; H, 10.4.

Cyclohexylidene-acetic Acid from Methyl Cyclohexyl Ketone.—To 31.5 g. of methyl cyclohexyl ketone was added 8.0 g. of bromine at 0°. To this mixture was added a solution of 80 g. of potassium hydroxide in 1 l. of absolute ethanol. This was allowed to stand at room temperature overnight. Water was added and the mixture was then extracted with ether. The water layer was acidified and the acid was extracted with ether. The ether was evaporated and the residue was distilled. The cyclohexylidene acetic acid was solid and was crystallized from dilute methanol, m. p. 89–91°.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.5; H, 8.6. Found: C, 68.8; H, 8.7.

Summary

The 17-monobromide (II) of *allo*-pregnan-3(β)-ol-20-one and its acetate (I) has been prepared and its dehalogenation reactions studied.

The 17,21-dibromide (III) of *allo*-pregnan-3-(β)-ol-20-one acetate (I) has been shown to undergo a Faworskii rearrangement to give 3(β)-hydroxy-Δ$^{17-20}$-*allo*-pregnen-21-oic acid (VI). The structure has been established by conversions to isoandrosterone (VI) and androsterone (V).

STATE COLLEGE, PENNA. RECEIVED JUNE 11, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. CLII. Rearrangement of 16,17-Dibromopregnan-3(β)-ol-20-one[1]

BY RUSSELL E. MARKER, R. B. WAGNER AND EMERSON L. WITTBECKER

During the course of our recent studies of bromopregnan-20-keto compounds, we found that 17,21-dibromopregnan-3(β)-ol-20-one acetate[2] under vigorous alkali treatment yields 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid. We now find that 16,17-dibromopregnan-3(β)-ol-20-one acetate undergoes a rearrangement to give this same product and the corresponding methyl ester.

Bromination of 16-pregnen-3(β)-ol-20-one acetate (I) in acetic acid solution gives a good yield of the 16,17-dibromide (II). That the formation of the latter was not attended by any rearrangement was shown by the simple debromination of the product (II) with methanolic sodium iodide to give the original olefinic compound (I) in almost quantitative yield. The debromination was effected equally well with boiling pyridine. Since the dibromo compound (II) was easily converted to 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid (IV) under exactly the same conditions as those required for the formation of IV from 17,21-dibromopregnan-3(β)-ol-20-one acetate[2] it was necessary to show that these two dibromo compounds were really different. For this purpose, 16,17-dibromopregnan-3(β)-ol-20-one acetate (II) was refluxed with potassium acetate in acetic acid solution. The product isolated was 16-pregnen-3(β)-ol-20-one acetate (I). Similar treatment of 17,21-dibromopregnan-3(β)-ol-20-one acetate has been previously shown[3] to give 21-bromo-16-pregnen-3(β)-ol-20-one acetate. Thus the 16,17-dibromide is readily debrominated to give the olefinic compound, whereas the 17,21-dibromide loses hydrobromic acid under the same conditions to give an unsaturated monobromide. The peculiar reactivity of the 16,17-dibromide is further shown by its action with hydrogen and palladium-barium sulfate catalyst in the presence of dioxane and pyridine to give compound I.

When 16,17-dibromopregnan-3(β)-ol-20-one acetate (II) is treated with a boiling solution of methanolic potassium hydroxide, it gives a mixture of 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid (IV) and the corresponding methyl ester (III). The unsaturated acid agrees in properties and composition with that obtained by similar treatment of 17,21-dibromopregnan-3(β)-ol-20-one acetate. Although the reaction of the latter with alcoholic potash is similar to a reaction reported by Faworskii,[4] who obtained β,β′-dimethylacrylic acid from 3-methyl-1,3-dibromo-2-butanone, we have been unable to find in the literature any analogous rearrangement for α,β-dibromo ketones. Whereas α,β-dibromo ketones are known to hydrolyze to α,β-diketones, it was impossible for our compound to take such a course.

The unsaturated acid (IV) is converted to the unsaturated methyl ester (III) by diazomethane in ether. This methyl ester (III) is identical with the ester isolated in the neutral fraction of this reaction. The ester was not found by us in our previously described rearrangement[2] of the 17,21-dibromo compound, and its isolation here may have an important bearing on any mechanism which might be proposed.

Catalytic hydrogenation of the acid (IV) with Adams catalyst gave a lower melting saturated acid which was identified by composition and physical properties as 3(β)-hydroxypregnan-21-oic acid, previously described by us.[2] Similar hydrogenation of the unsaturated methyl ester (III) followed by alkaline hydrolysis gave the same saturated acid. Both the saturated and the unsaturated (III) methyl esters, acetylated and unacetylated, agree in melting points and properties with the corresponding esters obtained by subsequent treatment of the acid from the rearrangement of the 17,21-dibromide acetate. The saturated methyl ester depresses the melting point of the methyl ester of 3(β)-hydroxy-17-methyl-etiocholanic acid obtained from the reaction of 17-bromopregnan-3(β)-ol-20-one with alcoholic potassium bicarbonate.[5]

In order to furnish additional proof of the identity of this unsaturated acid (IV) it was oxidized by ozonolysis in chloroform to give etio-cholan-3(β)-ol-17-one (V) which was isolated as the semicarbazone. Acid hydrolysis of the latter gives the free hydroxy-ketone (V) which was the same as the compound described before.[2]

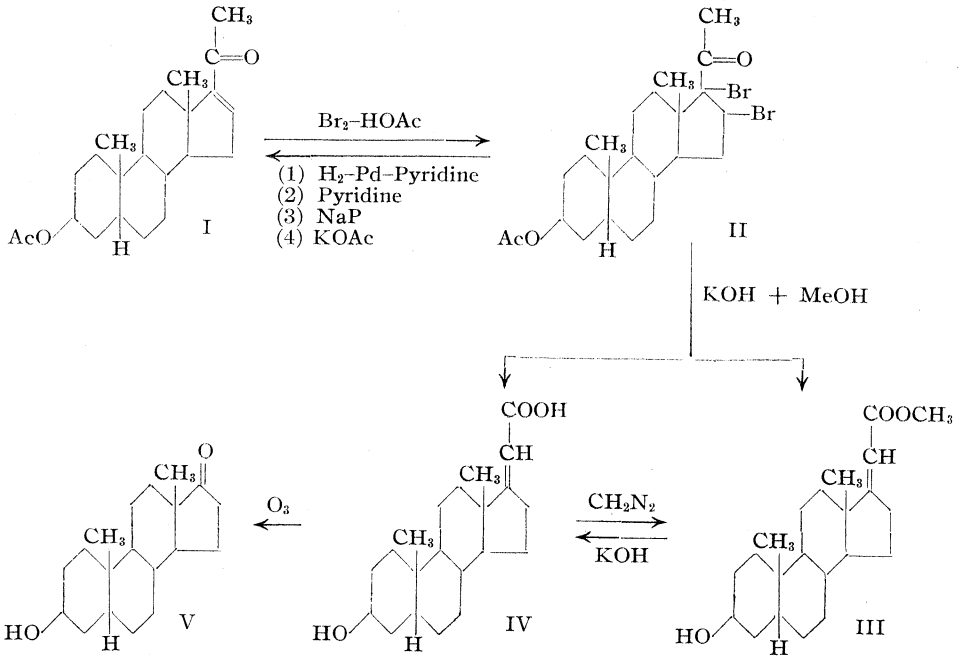
(1) Original manuscript received July 16, 1941.

(2) Marker, Crooks and Wagner, THIS JOURNAL, **64**, 817 (1942).

(3) *Ibid.*, **64**, 213 (1942).

(4) Faworskii, *J. Russ. Phys.-Chem.*, **44**, 1358 (1913); *J. prakt. Chem.*, [2] **88**, 658 (1913).

(5) Marker and Wagner, THIS JOURNAL, **64**, 216 (1942).



The reactions discussed are summarized in the chart.

The easy attainment of 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid by the rearrangement of 17,-21-dibromopregnan-3(β)-ol-20-one[5] has encouraged further studies on this acid. Furthermore, it was desirable to prepare several derivatives which would ensure the identity of the rearrangement products from the 16,17-dibromo compound (II).

While we previously[5] reported the degradation of this unsaturated acid (IV) to *etio*-cholan-3(β)-ol-17-one (V) by the method of ozonolysis or chromic anhydride oxidation, we have now found a much better method for this conversion, namely, alkaline potassium permanganate oxidation. The product (V) is isolated directly in the free state and does not have to be purified in the form of the semicarbazone as previously reported. This modification results in a greater over-all yield and furnishes a good source of the hydroxy-ketone.

In order to obtain the hydroxy-ketone having the *epi*-configuration, the methyl ester of the unsaturated acid (III) was successively oxidized and reduced by the Oppenauer and Meerwein procedures. The methyl ester of 3(α)-hydroxy-Δ^{17-20}-pregnen-21-oic acid was not isolated but was ozonized to give *etio*-cholan-(3)α-ol-17-one isolated as the semicarbazone. Hydrolysis of the semicarbazone gave the free hydroxy-ketone which agreed in properties and composition with the reported values for this compound. It was further identified by mixed melting point with an authentic sample of *etio*-cholan-3(α)-ol-17-one.

The fact that α,β-unsaturated acids are easily reduced by sodium and alcohol was used to advantage when the unsaturated acid (IV) was simultaneously reduced at the 17,20-position and epimerized at C-3 by sodium and amyl alcohol to give 3(α)-hydroxy-pregnan-21-oic acid. Oxidation of 3(β)-hydroxy-pregnan-21-oic acid gave the 3-keto acid which by neutral hydrogenation (Adams catalyst) gave 3(α)-hydroxypregnan-21-oic acid. The methyl esters of these acids were prepared to further characterize them and these were reduced by a Bouveault–Blanc reduction to the corresponding pregnan-3,21-diols.

Experimental Part

16,17-Dibromo-pregnan-3(β)-ol-20-one Acetate (II).—To a solution of 5 g. of 16,17-pregnen-3(β)-ol-20-one acetate (I) in 200 cc. of acetic acid was added 14 cc. of molar bromine in acetic acid solution. The mixture was poured into water and filtered. The dibromide was crystallized twice from methanol, m. p. 137–140°; yield 4.8 g.

Anal. Calcd. for $C_{23}H_{34}O_3Br_2$: C, 53.3; H, 6.6. Found: C, 53.5; H, 6.7.

Debromination of 16,17-Dibromopregnan-3(β)-ol-20-one Acetate (II)—(a) With palladium hydrogen and pyridine: a solution of 1 g. of the dibromide (II) in 125 cc. of dioxane and 3 cc. of pyridine was shaken with hydrogen and 2 g. of palladium–barium sulfate catalyst for two hours at room temperature and three atmospheres. The catalyst was filtered, and the solution was evaporated *in vacuo*. An

ethereal solution of the residue was washed with dilute hydrochloric acid and water, and then evaporated. The residue was crystallized three times from methanol, m. p. and mixed m. p. with 16-pregnen-3(β)-ol-20-one acetate (I), 143–144°; yield 0.5 g.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 77.1; H, 9.7.

(b) **With pyridine:** a solution of 1 g. of the dibromide (II) in 5 cc. of pyridine was refluxed for three hours. Water was added, and the mixture was extracted with ether. The ether layer was washed with water, dilute hydrochloric acid and water, and then evaporated. The residue crystallized from methanol, m. p. and mixed m. p. with 16-pregnen-3(β)-ol-20-one acetate (I), 141–144°; yield 0.1 g.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 77.0; H, 9.7.

(c) **With alcoholic sodium iodide:** a solution of 2.1 g. of the dibromide (II) in 100 cc. of methanol was refluxed with 2.2 g. of sodium iodide for one hour. A solution of sodium bisulfite was added and the mixture extracted with ether. The ether layer was washed with water and evaporated. The residue was recrystallized twice from methanol, m. p. and mixed m. p. with 16-pregnen-3(β)-ol-20-one acetate, 141–144°; yield 1.2 g.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 76.7; H, 9.5.

(d) **With potassium acetate:** a solution of 1 g. of 16,17-dibromo-pregnan-3(β)-ol-20-one acetate (II) in 15 cc. of acetic acid was refluxed with 1.5 g. of fused potassium acetate for one hour. The solution was evaporated *in vacuo* and the residue was extracted with ether. The ether layer was washed and evaporated. The residue was crystallized twice from methanol, m. p. and mixed m. p. with 16-pregnen-3(β)-ol-20-one acetate, 140–143°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 76.9; H, 9.7.

Reaction of Methanolic Potassium Hydroxide with 16,17-Dibromopregnan-3(β)-ol-20-one Acetate (II).—A solution of 5 g. of the dibromide (II) in 1 l. of methanol was refluxed with 25 g. of potassium hydroxide for one hour. Water was added and the mixture was extracted with ether.

Acid Fraction.—The alkaline water layer was acidified with dilute hydrochloric acid and extracted with ether. The ethereal solution was washed with water and evaporated. The crystalline residue was recrystallized from methanol, m. p. and mixed m. p. with 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid, 254–256° dec.; yield 2.0 g.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.8; H, 9.7. Found: C, 76.2; H, 9.7.

(a) **Methyl Ester (III).**—When treated with an ethereal solution of diazomethane, the above unsaturated acid formed a methyl ester, m. p. and mixed m. p. with the methyl ester of 3(β)-hydroxy-$\Delta^{17,20}$-pregnen-21-oic acid, 153–156°.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.2; H, 9.9. Found: C, 76.4; H, 9.8.

(b) **Acetate of (IV).**—The acetate was prepared by the action of pyridine and acetic anhydride on the above unsaturated acid. It was crystallized from dry methanol to give white crystals, m. p. 161–163°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.7; H, 9.2. Found: C, 73.7; H, 9.2.

(c) **Reduction of Unsaturated Acid (IV).**—A mixture of 200 mg. of the above unsaturated acid was hydrogenated with Adams catalyst at room temperature and three atm. for two hours. The product was crystallized from methanol, m. p. and mixed m. p. with 3(β)-hydroxypregnan-21-oic acid, 219–220°.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.4; H, 10.3. Found: C, 75.5; H, 10.2.

(d) **Acetate of the Saturated Acid.**—When the saturated acid from (c) was treated with pyridine–acetic anhydride mixture it gave an acetate which crystallized from methanol, m. p. and mixed m. p. with 3(β)-acetoxypregnan-21-oic acid, 219–221°.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.3; H, 9.6. Found: C, 73.6; H, 9.7.

(e) **Methyl Ester of Saturated Acid.**—An ethereal solution of 200 mg. of the unacetylated saturated acid from (c) was treated with an ethereal solution of diazomethane to give the methyl ester, m. p. and mixed m. p. with the methyl ester of 3(β)-hydroxypregnan-21-oic acid, 141–143°.

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.8; H, 10.4. Found: C, 76.0; H, 10.4.

(f) **Acetate of Saturated Methyl Ester.**—A solution of 100 mg. of the saturated methyl ester from (e) in pyridine–acetic anhydride yielded a product which crystallized from methanol as large white plates, m. p. and mixed m. p. with the methyl ester of 3(β)-acetoxy-pregnan-21-oic acid, 105–106°.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.8; H, 9.8. Found: C, 74.2; H, 9.9.

Neutral Fraction.—The neutral fraction was obtained by evaporating the ether from the alkaline hydrolysis product and crystallizing the residue from methanol, m. p. and mixed m. p. with the methyl ester of the above unacetylated unsaturated acid from (a), 153–156°; yield 0.3 g. This also did not give any depression of melting point when mixed with the methyl ester of 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.2; H, 9.9. Found: C, 76.4; H, 9.8.

(g) **Acetate of the Unsaturated Methyl Ester (III).**—An acetate formed by the pyridine–acetic anhydride procedure crystallized from methanol, m. p. and mixed m. p. with the methyl ester of 3(β)-acetoxy-$\Delta^{17,20}$-pregnen-21-oic acid, 103–105°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.2; H, 9.3. Found: C, 74.1; H, 9.1.

(h) **Reduction of the Acetylated Unsaturated Methyl Ester (III).**—A solution of 150 mg. of the acetate from (g) in acetic acid was hydrogenated with Adams catalyst at room temperature and three atm. for two hours. The product was crystallized from methanol to give fine white needles, m. p. and mixed m. p. with the methyl ester of 3(β)-acetoxy-pregnan-21-oic acid and with the acetylated saturated methyl ester from (f), 102–105°.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.8; H, 9.8. Found: C, 74.1; H, 9.9.

(i) **Hydrolysis of the Saturated Methyl Ester.**—A solution of 100 mg. of the saturated methyl ester from (h) in 20% ethanolic potassium hydroxide was refluxed for sixteen hours, the mixture cooled and diluted with water. The solid suspension was washed with ether, acidified, and ether-extracted. The product crystallized from methanol to give white needles, m. p. and mixed m. p. with (3)-hydroxypregnan-21-oic acid and the saturated acid from (c), 218–220°.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.4; H, 10.3. Found: C, 75.3; H, 10.2.

Ozonolysis of 3(β)-Hydroxy-Δ^{17-20}-pregnen-21-oic Acid (IV) Obtained by Rearrangement of the 16,17-Dibromide (II).—Through a solution of 2.1 g. of the unsaturated acid (IV) in chloroform was bubbled oxygen containing 7% ozone at the rate of 30 l. per hour for ninety minutes. The mixture was decomposed with water and the chloroform steam distilled. The product was extracted with ether and the ethereal solution was washed with 10% potassium hydroxide and evaporated. The residue with an ethanolic solution of semicarbazide acetate yielded a semicarbazone which crystallized from methanol, m. p. and mixed m. p. with the semicarbazone of *etio*-cholan-3(β)-ol-17-one (V), 251–253° dec.; yield 0.8 g.

Anal. Calcd. for $C_{20}H_{33}N_3O_3$: C, 69.1; H, 9.6. Found: C, 69.4; H, 9.6.

A solution of the semicarbazone dissolved in 50 cc. of ethanol containing 5 cc. of concd. sulfuric acid and 10 cc. of water was refluxed for one hour. The product was crystallized from ether–pentane to give long needles, m. p. and mixed m. p. with *etio*-cholan-3(β)-ol-17-one, 150–152°.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4. Found: C, 78.7; H, 10.3.

In the following experiments only 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid from the rearrangement of 17,21-dibromopregnan-3(β)-ol-20-one acetate[2] was used.

Conversion of 3(β)-Hydroxy-Δ^{17-20}-pregnen-21-oic Acid (IV) to etio-Cholan-3(β)-ol-17-one (V).—To 0.5 g. of 3(β)-hydroxy-$^{17-20}$-pregnen-21-oic acid (IV) suspended in 20 cc. of water was added a solution of 0.5 g. of potassium hydroxide in 20 cc. of water. The mixture was stirred at 0° until all of the acid dissolved. To this solution was added 30 cc. of 2% potassium permanganate, which was the amount necessary to give a permanent pink color. The excess permanganate was destroyed with sodium bisulfite and the mixture extracted with ether. The ethereal solution was washed with water and evaporated. The solid residue was crystallized from ether–pentane to give long needles, m. p. and mixed m. p. with *etio*-cholan-3(β)-ol-17-one (V), 150–152°; yield 0.3 g.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4. Found: C, 78.7; H, 10.3.

Methyl Ester of 3(β)-Hydroxy-Δ^{17-20}-pregnen-21-oic Acid.—A solution of 50 mg. of 3(β)-hydroxy-$^{17-20}$ pregnen-21-oic acid (IV) in ether was treated with a cold ethereal solution of diazomethane. The ethereal solution after standing sixteen hours was evaporated and the residue was crystallized from methanol to give white flat plates, m. p. 153–155°.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.2; H, 9.9. Found: C, 76.2; H, 9.9

Conversion of the Methyl Ester of 3(β)-Hydroxy-Δ^{17-20}-pregnen-21-oic Acid to *etio*-Cholan-3(α)-ol-17-one.—To a solution of 4 g. of the methyl ester of 3(α)-hydroxy-$^{17-20}$-pregnen-21-oic acid in 200 cc. of dry toluene was added 25 cc. of dry acetone and 20 g. of aluminum isopropylate. The mixture was refluxed six hours, cooled, and acidified with dilute hydrochloric acid. The product was extracted with ether. After evaporation of the solvent, the residue was again treated with 200 cc. of dry isopropyl alcohol and 20 g. of aluminum isopropylate at reflux temperature for sixteen hours. The solution was slowly distilled over a period of five hours. The residue was acidified with dilute hydrochloric acid and extracted with ether. The product from the removal of the solvent was suspended in water and the volatile oils removed by steam distillation. The water was decanted and the remaining solid was dissolved in methanol and treated with digitonin in the usual manner. The non-digitonin precipitated fraction was dissolved in 200 cc. of chloroform. Through this solution was bubbled oxygen containing 7% ozone for fifteen minutes at the rate of 30 l. per hour. At the end of this time no more ozone was absorbed. The reaction mixture was decomposed with water and the chloroform removed by steam distillation. After cooling, the residue was dissolved in ether and the ethereal solution was washed well with 10% potassium hydroxide. The product from ether was converted to the semicarbazone, which crystallized from ethanol, m. p. 235° dec.; yield 0.5 g.

Anal. Calcd. for $C_{20}H_{33}N_3O_2$: C, 69.1; H, 9.6. Found: C, 68.7; H, 9.6.

The above semicarbazone was dissolved in 25 cc. of ethanol containing 2 cc. of concentrated sulfuric acid and 5 cc. of water. The mixture was refluxed for one hour and then poured into water. The product was crystallized from ether, m. p. and mixed m. p. with *etio*-cholan-3(α)-ol-17-one, 147°.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4. Found: C, 78.5; H, 10.3.

Epimerization and Reduction of 3(β)-Hydroxy-Δ^{17-20}-pregnen-21-oic Acid (IV). (a) With Sodium and Amyl Alcohol.—To a solution of 0.5 g. of the unsaturated acid (IV) in 200 cc. of *n*-amyl alcohol was added 10 g. of sodium. The mixture was heated under reflux for nine hours. The cooled reaction mixture was acidified with dilute hydrochloric acid and extracted with ether. The residue from the ether was warmed with 50 cc. of 10% methanolic potassium hydroxide and the alcohol removed. The remaining oily layer was removed with ether. The aqueous layer was acidified and any volatile acids were removed by steam distillation. The cooled mixture was extracted with ether and the product was crystallized from methanol, m. p. 224–226°; yield 0.2 g. This substance is 3(α)-hydroxy-pregnan-21-oic acid. It depressed the melting point of 3(β)-hydroxy-pregnan-21-oic acid and the starting material (IV).

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.4; H, 10.3. Found: C, 75.1; H,10.2.

The methyl ester was prepared in the usual manner with diazomethane and crystallized from 80% methanol as white needles, m. p. 118–119°.

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.8; H, 10.4. Found: C, 75.6; H, 10.3.

The acetate of the above methyl ester was prepared by the pyridine–acetic anhydride procedure. It was crystallized from aqueous methanol as white platelets, m. p. 85–87°.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.8; H, 9.8. Found: C, 73.7; H, 10.0.

(b) By Catalytic Reduction Followed by Epimerization.—A solution of 0.3 g. of the unsaturated acid in acetic acid was shaken with hydrogen and Adams catalyst for two hours at room temperature and three atm. pressure. This gave 3(β)-hydroxy-pregnan-21-oic acid, previously described.[2] The product was dissolved in 90 cc. of *n*-amyl alcohol and treated with 6 g. of sodium as described in (a). The product was crystallized from methanol, m. p. and mixed m. p. with the material from (a), 224–226°.

3-Keto-pregnan-21-oic Acid.—To a solution of 1 g. of 3(β)-hydroxy-pregnan-21-oic acid in 50 cc. of acetic acid was added a solution of 0.5 g. of chromic anhydride in 50 cc. of 90% acetic acid. After standing one hour at room temperature, the mixture was diluted with water. The precipitated solid was extracted with ether and the ethereal solution was washed thoroughly with water to remove the acetic acid. The solvent was removed and the residue was crystallized from acetone, m. p. 170–172°; yield 0.7 g.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.9; H, 9.7. Found: C, 75.5; H, 9.7.

The methyl ester was prepared as described above and crystallized from aqueous methanol to give white crystals, m. p. 121–123°.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.2; H, 9.9. Found: C, 76.2; H, 10.0.

Reduction of 3-Keto-pregnan-21-oic Acid.—A solution of 200 mg. of the keto acid in dioxane was shaken with hydrogen and Adams catalyst for two hours at room temperature and 3 atm. pressure. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was crystallized from methanol, m. p. and mixed m. p. with the above 3(α)-hydroxypregnan-21-oic acid, 223–226°.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.4; H, 10.3. Found: C, 75.6; H, 10.3.

Methyl Ester of 3(β)-Hydroxypregnan-21-oic Acid.—A solution of 200 mg. of 3(β)-hydroxypregnan-21-oic acid in ether was added to a cold ethereal solution of diazomethane. The product was crystallized from methanol as white plates, m. p. 141–143°.

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.8; H, 10.4. Found: C, 75.8; H, 10.5.

The above mother liquor was evaporated to dryness and the residue was treated with pyridine and acetic anhydride. The product was crystallized from methanol as white crystals, m. p. 102–104°. This is the acetate of the methyl ester of 3(β)-hydroxypregnan-21-oic acid.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.8; H, 9.8. Found: C, 74.2; H, 9.9.

Pregnan-3(β),21-diol.—To a solution of 0.5 g. of the methyl ester of 3(β)-hydroxypregnan-21-oic acid in 100 cc. of absolute ethanol was added 10 g. of sodium metal. After the vigorous reaction had ceased, the mixture was refluxed for thirty minutes. The excess sodium was dissolved with aqueous ethanol and the reaction mixture was acidified with hydrochloric acid. The product was extracted with ether and the ethereal solution was washed with 10% potassium hydroxide. Acidification of the latter aqueous solution gave a small acid fraction. The neutral fraction from the ether was crystallized from aqueous methanol, m. p. 164–166°; yield 0.1 g.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.7; H, 11.3. Found: C, 7.2; H, 11.5.

The diacetate was prepared by the pyridine–acetic anhydride procedure and crystallized from aqueous methanol, m. p. 76–79°.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.4; H, 10.0. Found: C, 74.3; H, 10.0.

Pregnan-3(α),21-diol.—A solution of 0.5 g. of the methyl ester of 3(α)-hydroxypregnan-21-oic acid in 100 cc. of absolute ethanol was treated as described above. The product crystallized from methanol as white platelets, m. p. 205–206°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.7; H, 11.3. Found: C, 78.8; H, 11.3.

Summary

Bromination of 16-pregnen-3(β)-ol-20-one acetate (I) yields 16,17-dibromopregnan-3(β)-ol-20-one acetate (II). Alkali treatment of the latter yields a mixture of 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid (IV) and the corresponding methyl ester (III) by a new rearrangement.

3(β)-Hydroxy-Δ^{17-20}-pregnen-21-oic acid (IV) has been converted to *etio*-cholan-3(β)-ol-17-one (V) by a new method and also to *etio*-cholan-3(α)-ol-17-one. Simultaneous reduction and epimerization of (IV) gave 3(α)-hydroxypregnan-21-oic acid. The latter was also prepared by neutral catalytic hydrogenation of 3-keto-pregnan-21-oic acid and by epimerization of 3(β)-hydroxy-pregnan-21-oic acid. Bouveault–Blanc reduction of the methyl esters of the pregnanoic acid (IV) and its epimer gave the corresponding pregnan-3,21-diols.

STATE COLLEGE, PENNA. RECEIVED JUNE 11, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

The Determination of the Bridge Structure of Dipyrrylmethanes. A New Method for the Estimation of Active Hydrogen[1]

BY ALSOPH H. CORWIN AND RUDOLPH C. ELLINGSON[2]

The preceding paper of this series[3] showed that the imide hydrogens of certain dipyrrylmethanes do not react with molten sodium and potassium. Conceivably, these peculiarities could be due to the absence of imide hydrogens as a result of N–C–N bridges instead of C–C–C bridges as usually formulated. A suitable tool for the investigation of this problem would be a method for the determination of active hydrogens which would permit a demonstration that no rearrangement of the carbon–nitrogen skeleton had taken place during the course of the determination. This could be accomplished by regeneration of the original compound if an active hydrogen reagent could be found which would not alter ester or carbonyl groups.

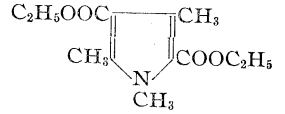
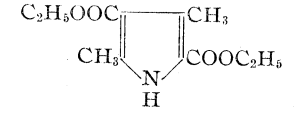
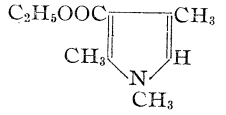
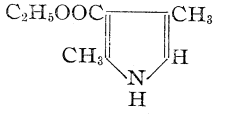
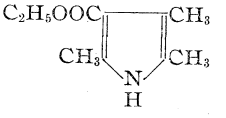
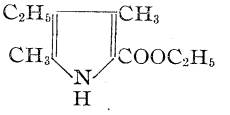
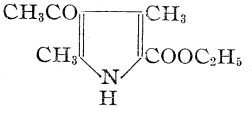
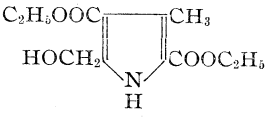
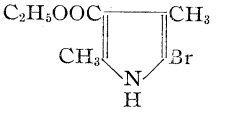
A convenient reagent which has the properties specified above was suggested by the work of Conant and Wheland[4] and that of McEwen.[5] The method involves the titration of a solution of the compound in question with a standardized solution of sodium triphenylmethyl, using the color of the reagent as the end-point indicator. This reagent has the added advantage that it provides a convenient means for the preparation of derivatives, for example, methyl homologs, by reaction with the sodium salt formed during the titration.

To learn whether or not sodium triphenylmethyl is a specific reagent for imide hydrogens, this new method was used on various simple pyrroles. The results of this survey are summarized in Table I.

Perusal of the table establishes the following facts: sodium triphenylmethyl is unreactive toward nuclear methyl groups, carbethoxy groups, bromine or hydrogen on carbon; it is reactive toward imide hydrogens and hydroxyl groups. It is interesting to note that compound V, which is inert to sodium, reacts with this reagent. Compound VII shows more than one active hydrogen and on titration no sharp end-point could be reached. Up to the first mole the color of the reagent disappeared immediately. After that point had been passed, there was a slow fading of the color after each addition of the reagent. McEwen[4] has shown that the pK value of acetophenone is about 19 while that of triphenylmethane is approximately 33. By analogy, the pK value of the eno form of this acetyl pyrrole should be near to that of acetophenone and the

TABLE I

ACTIVE HYDROGEN DETERMINATION ON SIMPLE PYRROLES

Pyrrole		Active H
I		0.0 .0
II		1.13 0.98 .99
III		.0 .0
IV		1.07 1.03 1.17
V		1.00
VI		0.98 .97
VII		> 1.0
VIII		1.94
IX		1.04

(1) Studies in the Pyrrole Series. IX. This paper is from the doctoral dissertation of Rudolph C. Ellingson, The Johns Hopkins University, 1938, and was presented at the Baltimore Meeting of the American Chemical Society, April, 1939.

(2) Present address, Research Laboratory, Mead Johnson and Company, Evansville, Ind.

(3) Corwin, Bailey and Viohl, THIS JOURNAL, **64**, 1267 (1942).

(4) Conant and Wheland, *ibid.*, **54**, 1212 (1932).

(5) McEwen, *ibid.*, **58**, 1124 (1936).

slowly fading color may be ascribed to slow formation of the enol catalyzed by the strong base used.

The sodium salt of pyrrole II, formed during the titration, can be converted to compound I by reaction with dimethyl sulfate. In the same manner, the mono- and di-N-methyl derivatives of 3,5,-3′,5′-tetracarbethoxy-4,4′-dimethyldipyrrylmethane (X, Table II) may be prepared by successive alkylations after the formation of sodium salts by the sodium triphenylmethyl. This duplicates the reaction series described by Corwin, Bailey and Viohl.[3] In every case the sodium salts were hydrolyzed with water and the starting dipyrrylmethanes were recovered unchanged by the reagent.

The final methane in this methylation series, methane XII, Table II, exhibits peculiarities under the conditions of the reaction. On treatment with sodium triphenylmethyl, the end-point color appears as soon as the amount of reagent equivalent to the solvent blank has been added. When one mole of reagent is added, a flocculent orange precipitate settles out. Treatment of this solution with water regenerates the starting dipyrrylmethane. Attempts to methylate the precipitate with dimethyl sulfate failed and in each case starting material and triphenylmethane were isolated. The isolation of triphenylmethane shows that the orange precipitate is not sodium triphenylmethyl because methylation of this substance gives 1,1,1-triphenylethane.

We interpret the peculiarities noted by the assumption that one of the bridge hydrogens of the di-N-methylmethane is sufficiently acidic to react with sodium triphenylmethyl but that the steric relations of the sodium salt formed make methylation difficult.[6] The color obtained upon addition of sodium triphenylmethyl, according to this explanation, would be that of the substituted dipyrrylmethyl ion. From the broadest point of view, such a reaction as this constitutes a limitation to the method which we use. Actually, however, since the N-sodium salts are colorless, the formation of the colored C-sodium salt does not interfere with the determination of active imide hydrogens.

A variety of dipyrrylmethanes was studied with this reagent. The summary of the titrations is given in Table II.

It should be noted that methane XVII, which was inert to sodium,[3] shows two active hydrogens with sodium triphenylmethyl and that the titration values on compound XX confirm the inertness of a pyrryl CH toward this reagent.

The disodium salt of compound XIII, obtained by this titration, methylates nicely at room temperature to give 1,3,5,1′,3′,5′-hexamethyl-4,4′-dicarbethoxydipyrrylmethane (XXI). The compound prepared by this method shows no melting point depression with that obtained by the condensation of 1,2,4-trimethyl-3-carbethoxypyrrole with formaldehyde.[7]

On treating compound XIII with one mole of sodium triphenylmethyl and subsequently methylating, one obtains a mixture of the mono- and di-N-methyldipyrrylmethanes (XIV and XXI) which can be separated by fractional crystallization since the mono-N-methylmethane is the less soluble in alcohol. Methane XIV, after titration, can be methylated in good yield to give methane XXI. In each case the sodium salts were hydrolyzed to the original compound to make certain that no condensation or cleavage was caused by sodium triphenylmethyl.

The possibility that methane XIII might be N–C–N and show active hydrogens due to an active bridge CH group was eliminated by comparing compound XIV with methane XV obtained by the condensation of 2,4-dimethyl-3-carbethoxypyrrole with acetaldehyde.[8] Although these two substances melt only four degrees apart, mixed melting point shows a marked depression.

Mixed melting points of two of the three possible combinations of methanes XIII, XIV and XXI show depressions; the mixture of XIII and XIV shows no definite depression, however. In spite of this, the evidence is overwhelming that compound XIV is one pure compound. Its analysis agrees well with the calculated values and the possibility of its being an equimolar mixture of XIII and XXI was eliminated by comparison with such a mixture prepared artificially: the artificial mixture melts at 148–150° and its mixed melting point with the methane XIV depresses to 141–142°. Finally, such a mixture can be separated into its components by crystallization while repeated recrystallizations of compound XIV fail to effect any separation.

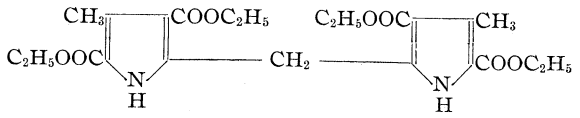
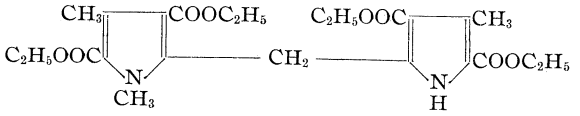
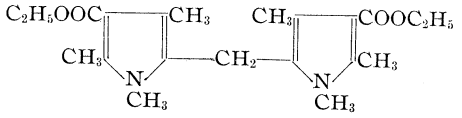
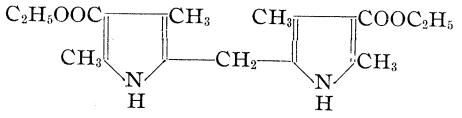
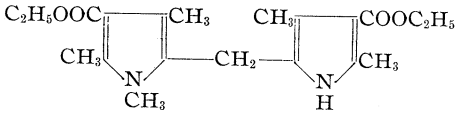
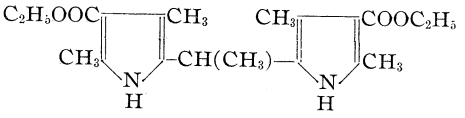
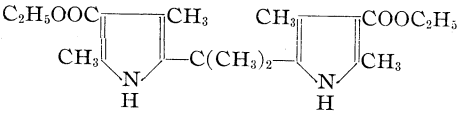
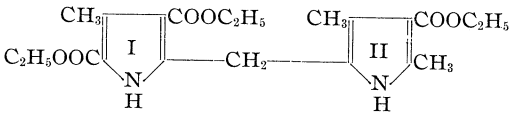
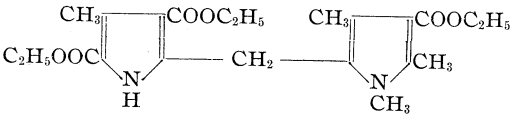
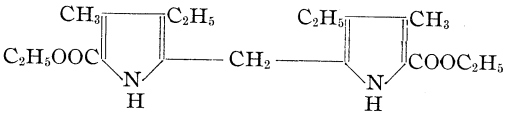
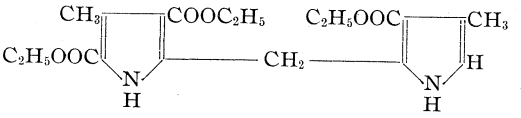
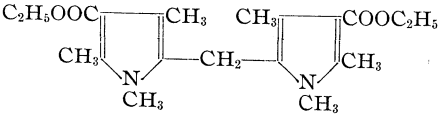
The several lines of evidence summarized above establish the bridge structure of methane XIII and its methyl derivatives as C–C–C and illus-

(6) See Brunings and Corwin, THIS JOURNAL, **64**, 593 (1942).

(7) Corwin and Quattlebaum, *ibid.*, **58**, 1085 (1936).

(8) Fischer and Bartholomäus, *Z. physiol. Chem.*, **87**, 264 (1913).

TABLE II

	Dipyrrylmethane	Solvent	Active H
X		Benzene	1.72, 1.82[a]
XI		Benzene Dioxane	0.96, 0.96, 1.04 1.06, 1.11, 1.13
XII		Benzene	0.0
XIII		Dioxane	2.12, 2.19
XIV		Dioxane	1.01
XV		Dioxane	1.88
XVI		Dioxane	2.10
XVII		Benzene Dioxane	1.95, 1.97 2.08, 2.00, 2.03
XVIII		Dioxane	1.08, 1.09
XIX		Benzene	2.02, 2.08
XX		Dioxane	1.96, 2.10
XXI		Benzene	0.0

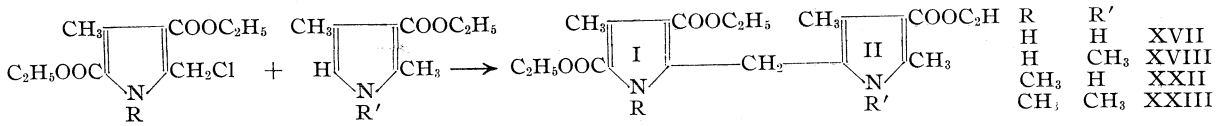
[a] The low values for this compound are undoubtedly due to the use of benzene as a solvent since the mono-sodium salt was later found to precipitate out of the benzene. Our later procedure was to use dioxane as solvent in such cases.

trate the use of the combined titration and methylation technique in a structural investigation.

The study of methane XVII and its methylation products, besides providing proof of its bridge structure, furnishes illustrations of the specificity which may be obtained by the control of reaction conditions and of an unexpected limitation to the method of titration with sodium triphenylmethyl.

Methane XVII was synthesized by application of the following general method

CHART I



in which both R and R′ were H. Its melting point is 158°.

Reaction of this compound with one mole of sodium triphenylmethyl should give a monosodium salt by replacement of the more acidic hydrogen, which, because of the electron-attracting influence of the carbethoxy groups, would be predicted to be that on ring I. Methylation gives a mono-N-methylmethane XXII; m. p. 113°, identical with that prepared by Quattlebaum and Corwin[9] by the method of Chart I in which R is CH_3 and R′ is H. This confirms the prediction as to the relative acidities of rings I and II.

Since the imide hydrogen of ring II is less acidic than that of ring I, its sodium salt will be a stronger base than the sodium salt of ring I, and methylation of the disodium salt should take place most rapidly on ring II as a consequence of the greater availability of electrons at this point. This course of the reaction is that found by experiment. Compound XVIII is formed by monomethylation of the disodium salt. The structure is confirmed by the reaction of Chart I in which R is H and R′ is CH_3. Thus either ring may be selected for specific methylation.

The low solubility of the sodium salt of methane XVIII prevents ready methylation at room temperature. If, however, the disodium salt of XVII is refluxed with two moles of dimethyl sulfate or the monosodium salt of XVIII is refluxed with one mole of dimethyl sulfate, complete N-methylation is accomplished. The structure of the product XXIII melting at 129°, was confirmed by the reaction of Chart I.

When methane XXII was treated in dioxane solution with sodium triphenylmethyl, an intense red-violet color with a blue fluorescence appeared long before one mole of reagent per mole of methane had been added.[3] There was no appreciable precipitate in this solution. Hydrolysis of the solution with water or treatment with dimethyl sulfate gave the same compound in the form of yellow plates melting at 204°. Analysis of the product indicates that a condensation has taken place. The further investigation of the structure of this substance will be the subject of a later communication.

When methane XXII is treated with sodium triphenylmethyl in benzene solution, in which sodium salts are generally much less soluble than in dioxane, a colorless, soap-like precipitate is formed and indications of the condensation reaction appear when nearly one mole of reagent per mole of methane has been added. The violet color and blue fluorescence make it impossible to determine the end-point visually and therefore we cannot titrate accurately for the number of active hydrogens in the molecule. If the solution with its precipitate is immediately treated with water, the sodium salt is hydrolyzed and one obtains an 85% recovery of the starting mono-N-methylmethane XXII. If the solution is treated immediately with dimethyl sulfate, a 60% yield of methane XXIII is obtained.

The anomaly recorded above, while illustrating a limitation of the sodium triphenylmethyl titration, emphasizes one of the advantages of the reagent, namely, that the possibility of regeneration of the starting compound permits a check upon the presence or absence of an undesired side-reaction and thus furnishes a more reliable means for the investigation of structure than the usual active hydrogen determination.

The authors wish to acknowledge their deep indebtedness to Dr. F. Y. Wiselogle for his generous aid and consultation in the manipulation of sodium triphenylmethyl.

Experimental Part

Purification of Nitrogen.—In using standardized solutions of sodium triphenylmethyl, it is necessary to prepare and manipulate the compound under nitrogen that has been freed from carbon dioxide, moisture and oxygen. A convenient purification train is shown in Fig. 1.

Tank nitrogen is passed through a series of six Friedrich's spiral wash bottles. The first two contain 150 cc. each of Fieser's solution.[10] This solution is very effective for removing oxygen. When the first bottle has become exhausted, as evidenced by the change in color, it is refilled with fresh solution and placed in position 2, while bottle 2

(9) Quattlebaum and Corwin, THIS JOURNAL, **64**, 922 (1942).

(10) Fieser, *ibid.*, **46**, 2639 (1924).

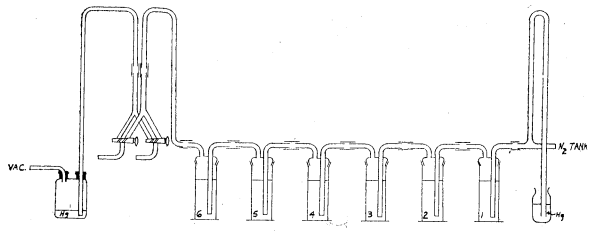


Fig. 1.

is placed in the first position. The third wash bottle contains a saturated lead acetate solution to remove any hydrogen sulfide that may be liberated from the Fieser's solution; in the fourth bottle there is concentrated sulfuric acid to remove water; in the fifth a deep blue toluene solution of the sodium ketyl of benzophenone prepared by dissolving a few grams of benzophenone in dry toluene and adding a small amount of 2% sodium amalgam. This solution removes the last traces of water and oxygen and serves as an indicator for the purity of the nitrogen. The sixth wash bottle contains Nujol in which paraffin has been dissolved to catch the toluene vapors swept from the benzophenone bottle. The train is so constructed that nitrogen can be led to two systems and so arranged that each can be evacuated and filled with nitrogen as many times as necessary, independently of the other. The ground joints of the wash bottles are secured with paraffin during operation.

Preparation of Sodium Triphenylmethyl Solution.—The apparatus in which the sodium triphenylmethyl is prepared consists of a 500-cc. round-bottom flask with a ground joint connection to a filling and sweeping apparatus as shown in Fig. 2. We are indebted to Dr. F. Y. Wiselogle for the design of this apparatus.

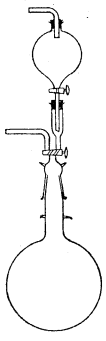


Fig. 2.

The solvents, benzene and ether, are carefully dried over 45% sodium amalgam, distilled and distilled again from 2% sodium amalgam and benzophenone immediately before being used. The blue color of the metal ketyl indicates when the solvents are absolutely dry. The stopcocks and ground joints are lubricated with a lubricant reported by Meloche and Frederick.[11] All parts are baked at 110° for several hours before being used.

In the flask is placed 100 cc. of dry ether and about 20 g. (9–10 cc.) of 45% sodium amalgam is added. In the separatory funnel a solution of 12 g. of pure triphenylmethyl chloride in 100 cc. of dry benzene is placed. The two parts are evacuated and filled with nitrogen three or four times to replace the air. The benzene solution is then run into the flask below. The stopcock is turned so that the lower part is connected to the nitrogen current and the flask shaken for about one-half hour. The flask is left on the nitrogen current to take care of the pressure built up due to vaporization of ether. The stopcock is closed, the separatory funnel removed and the flask placed on a shaking wheel for twelve to fourteen hours.

The sodium triphenylmethyl solution is filtered from sodium chloride and mercury through a 3G4 sintered glass funnel into the storage vessel which is a one liter flask with a delivery tube and inlet neck, each carrying ground glass stopcocks (Fig. 3). On the side arm of the reaction vessel is placed a rubber stopper which fits into the top of the sintered glass funnel and the stem of this has a rubber stopper fitting into the inlet neck of the storage vessel.

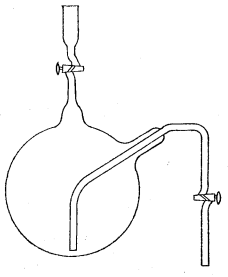


Fig. 3.

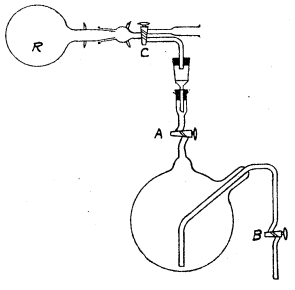


Fig. 4.

The reaction flask and storage vessel are placed in the tilted position (Fig. 4) ready for filtration but are allowed to stand for three or four hours so the finely divided salt, mercury and sodium amalgam have time to settle. This is important or the sintered glass funnel will become stopped up immediately. After the settling, the stopcocks A and B are opened and the vessel evacuated and filled with nitrogen three times; finally stopcock A is closed, the vessel evacuated and the stopcock B is closed. Stopcock C is opened and after the glass funnel has liquid over the bottom, A is opened. The whole apparatus is tilted so liquid always fills the neck of the reaction vessel, R. The filtering proceeds rapidly at first but slows considerably toward the end. After filtering, stopcock A is closed and B opened allowing nitrogen to enter, relieving the vacuum.

The separatory funnel is placed in the neck of the storage vessel and a mixture of 125 cc. of dry ether and 125 cc. of dry benzene is run in. The solution is shaken and is then ready for use. In this way a sodium triphenylmethyl solution of 0.07 to 0.08 molarity is obtained and can be kept for weeks with very little change in strength.

Apparatus for the Titrations.—The apparatus for the titrations is shown in Fig. 5. The storage vessel is mounted high on a ring stand. A tube about four inches long and drawn out at one end is attached to the delivery tube of the vessel by a slip-over rubber seal making the union nearly glass to glass. The narrow end leads into the top of a 10-cc. buret and is also sealed by a slip-over rubber tube. The buret has a side arm about half an inch above the zero mark and is connected to the nitrogen purification train.

The most satisfactory stopcock grease for the buret is graphite and tin amalgam. The two parts of the stopcock are well coated with graphite by rubbing with an extra soft lead pencil and then with a piece of tin that has been dipped in mercury. This lubricant holds the ether–benzene solution very well and will hold a water-pump vacuum quite well. The stopcock does not freeze and may be used several days without relubricating.

The end of the buret carries a rubber stopper that fits into the neck of the reaction flask which is a 50-cc. suction flask to which an "L" side arm has been added. The regular side arm is connected to the purification train while the "L" arm is used for introducing the solvent and the methylating agent.

(11) Meloche and Frederick, THIS JOURNAL, **54**, 3264 (1932).

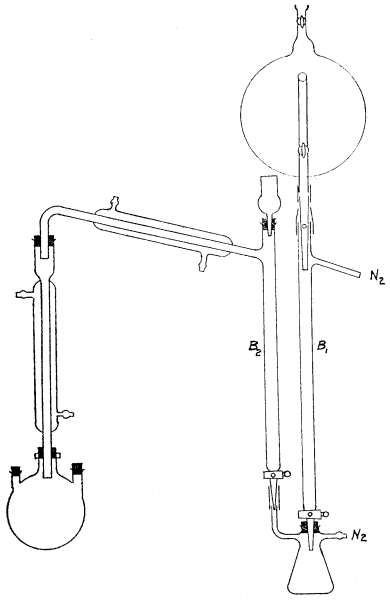


Fig. 5.

The solvent, dioxane or benzene, is refluxed in the flask over 2% sodium amalgam and benzophenone until dry as indicated by the blue color. It is then distilled into the buret, B_2, from which the solvent is measured directly into the reaction vessel. The tip of B_2 fits into the "L" arm of the reaction flask and is sealed with a slip-over rubber tube.

Another reaction vessel was constructed from a 50-cc. suction flask with the "L" side arm and a two-inch glass condenser (Fig. 6). This was used when methylation did not take place at room temperature but required heat. The flask was heated by a small electric furnace.

Directions for Performing a Titration. A. Standardization of Sodium Triphenylmethyl Solution.—The buret is evacuated and filled with nitrogen three times and finally evacuated. Stopcock B of the storage vessel is opened so that a few cc. of solution runs into the buret. B is closed and nitrogen again led into the buret. This amount of reagent is run out and discarded, serving merely to remove any water that may not have been removed on cleaning and drying the buret. The buret is then filled and a definite volume of the solution run into a 50-cc. Erlenmeyer flask containing 20 cc. of distilled water. This flask is heated on a steam-cone to remove the solvents, ether and benzene, cooled and the solution titrated with standard hydrochloric acid using methyl orange as the indicator. Duplicate titrations are run and from these the strength of the reagent solution is calculated.

B. Blanks on the Solvent.—The reaction flasks are dried at 110° to remove all moisture. The empty flask is attached, evacuated and sealed with paraffin at the stopper and rubber slip-over seals while under vacuum. Nitrogen is then allowed to pass in and the evacuation and refilling repeated three times. The flask is evacuated slightly and 5 cc. of solvent measured in from buret B_2 and the stopcock turned to the nitrogen current again. In the meantime the reagent buret has been filled as described earlier. The reagent is then added dropwise, the flask being shaken gently until the permanent orange color appears in the solvent. Duplicates also are performed for this step. For 5 cc. of benzene the blank is 0.22 to 0.26 cc. when the strength of the reagent is 0.07 to 0.08 molar. For 5 cc. of dioxane it is 0.80 to 1.00 cc. for the same strength of reagent. Dioxane that is used as a solvent is purified by storing over calcium chloride for several days, refluxing over sodium for several hours, distilling, and finally distilling from 2% sodium amalgam and benzophenone in the titration apparatus.

C. Titration of the Sample and Methylation.—The pure, dry sample is weighed into the reaction flask and attached to the apparatus. The solvent is introduced as described above for the blank determinations and the reagent buret filled. The reagent is added slowly to the permanent end-point. The number of active hydrogen atoms per molecule of the compound can then be calculated.

If one wishes to hydrolyze the reaction product to see whether or not the starting material will be recovered, the flask is removed, the product treated with water and the material worked up as will be described in the individual experiments.

If one wishes to methylate the reaction product, the solution of dimethyl sulfate is passed into buret B_2, the reaction flask is evacuated slightly and as much of this solution is added as desired. Since the molar quantities used are very small, 1 cc. of dimethyl sulfate is made up to 10 cc. with dry solvent used in the titration to allow a more accurate measurement of the amount of methylating agent. The dimethyl sulfate is also distilled through a small column under vacuum just before being used. For those methylations where heat must be applied the reaction vessel shown in Fig. 6 is used.

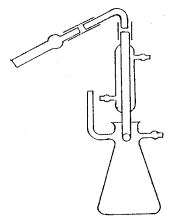


Fig. 6.

Titrations were performed by this method on all the substances listed in Tables I and II with the results shown. In the succeeding section only experiments other than the titrations are described.

1,2,4-Trimethyl-3,5-dicarbethoxypyrrole (I).—2,4-Dimethyl-3,5-dicarbethoxypyrrole (II), (146 mg.) was titrated as described above. The sodium salt formed was methylated by adding 3.5 cc. of dimethyl sulfate. After standing two hours the solution was filtered, the solvent removed and excess dimethyl sulfate destroyed by steam distillation; yield, 110 mg. or 71% of colorless crystals; m. p. 109–111°. The compound gives no melting point depression with a pure sample of the N-methylpyrrole.

Activity of the Reagent toward Nuclear Methyl and Carbethoxy Groups.—To make certain that no reaction had taken place with nuclear methyl and carbethoxy groups, compounds I and III were recovered after the titration by evaporation of the solvent and compound II by hydrolysis of the solution. None showed any depression on mixed melting point with the starting material.

Reactions with 3,5,3′,5′-Tetracarbethoxy-4,4′-dimethyldipyrrylmethane (X). A. Recovery after Titration.—The tetracarbethoxymethane (212 mg.) was titrated in benzene solution. The reaction mixture was shaken with water, the benzene layer separated, dried over sodium sulfate, filtered and evaporated. The residue was extracted with

hexane to remove the triphenylmethane. The crude material (133 mg. or 63%) was crystallized from ethanol; m. p. 134–135°, no depression of m. p. with starting material.

B. Monomethylation.—Two hundred and twenty-eight milligrams of methane X was treated with 11.70 cc. (including 0.40 cc. solvent blank) of 0.0445 molar sodium triphenylmethyl solution. 2.00 cc. of dimethyl sulfate was added and the solution warmed for ninety minutes. The solution was filtered and the solvents removed by steam distillation. The insoluble solid was dried and extracted with 5 cc. of hot hexane to remove the triphenylmethane; yield, 133 mg. or 56%. After recrystallization from alcohol and water the m. p. was 139–140°. There was no depression with compound XI prepared with sodium and dimethyl sulfate but there were marked depressions with methanes X and XII.

C. Dimethylation.—One hundred and ninety-nine milligrams of methane X was treated with 20.19 cc. (including 0.40 cc. solvent blank) of 0.0445 molar sodium triphenylmethyl solution; 3.00 cc. of dimethyl sulfate was added and the solution warmed for ten minutes. The solvents were removed by steam-distillation. The residue was dried and extracted with hexane to remove triphenylmethane; yield, 186 mg. or 91% of the di-N-methylmethane XII.

Reactions with 1,4,4′-Trimethyl-3,5,3′,5′-tetracarbethoxydipyrrylmethane (XI). A. Recovery after Titration.—The procedure was identical with that described for methane X; no depression with starting material.

B. Methylation.—The procedure was identical with that for the monomethylation of compound X with the proper correction for the change in molecular weight; yield, 70–90%. No depression with methane XII.

Reaction with 1,4,1′,4′-Tetramethyl-3,5,3′,5′-tetracarbethoxydipyrrylmethane (XII). A. Treatment with One Mole of Reagent and Hydrolysis.—Three hundred and seven milligrams (0.000635 mole) of the dipyrrylmethane XII in 5 cc. of benzene was treated with enough reagent solution to furnish 0.00064 mole of sodium triphenylmethyl. The permanent end-point appeared as soon as enough solution for the blank had been added. As the addition proceeded a deep red, transient precipitate formed as the drops hit the surface. By the time one mole of reagent had been added there was an orange-yellow substance suspended in the red solution. This solution was treated with water and the product isolated in the usual manner, giving 175 mg. of a colorless solid which after two crystallizations from alcohol melted at 144–145° and did not show a depression with the starting methane.

B. Attempted Methylations.—Two hundred and fifty-six milligrams (0.00053 mole) of methane XII in 5 cc. of benzene was treated with 0.00053 mole of sodium triphenylmethyl; 1 cc. of dimethyl sulfate was added and the solution allowed to stand several hours. It was then shaken with an 8% sodium carbonate solution, washed with water, dried, filtered and evaporated. The residue was extracted with hexane leaving 125 mg. of colorless material which melted at 141–143° and did not depress on mixed m. p. with the starting methane.

The experiment was repeated using 265 mg. of the methane and twice the amount of sodium triphenylmethyl; 85 mg. of material was isolated which proved to be the starting methane.

Two hundred and nineteen milligrams (0.00045 mole) of the dipyrrylmethane in 5 cc. of benzene was treated with 0.00045 mole of sodium triphenylmethyl and 0.0011 mole of dimethyl sulfate and allowed to stand for twelve hours. The solution was filtered and evaporated in vacuum. The residue was boiled with hexane, filtered, and 42 mg. of a pink solid that melted at 92–96° was isolated. The hexane filtrate was evaporated down leaving 200 mg. of residue which was crystallized from alcohol and water; m. p. 87–90°. It showed no depression on mixed melt with triphenylmethane but gave a 30° depression with 1,1,1-triphenylethane. This demonstrated that sodium triphenylmethyl was not present in the solution after treatment with methane XII.

Reactions with 3,5,3′,5′-Tetramethyl-4,4′-dicarbethoxydipyrrylmethane (XIII). A. Recovery after Titration.—The procedure was identical with preceding recoveries; 53 mg. was obtained from 98 mg. and was identical with the starting material.

B. Monomethylation.—Four hundred and thirteen milligrams (0.0012 mole) of methane XIII was dissolved in 10 cc. of dioxane and treated with 0.0012 mole of sodium triphenylmethyl; 1.0 cc. of dimethyl sulfate was added and the sodium salt went into solution rapidly leaving a small amount of sodium methyl sulfate suspended. The solution was washed with water, the benzene–ether layer separated, dried over sodium sulfate, filtered, evaporated and the residue extracted with hexane, leaving 450 mg. of a tan powder. The powder was boiled with 30 cc. of 2:1 alcohol–water and filtered, leaving 290 mg. of undissolved material melting at 150–160°. This was crystallized several times from alcohol and water; m. p. 176° with decomposition. The compound crystallized in colorless plates and depressed with di-N-methylmethane XXI. Mixed m. p. with the starting material (XIII), m. p. 229°, was 178–179° thus showing no definite depression. The filtrate from the first crystallization gave, on cooling, 85 mg. of impure di-N-methylmethane XXI.

Anal. Calcd. for $C_{20}H_{22}N_2O_4$ (methane XIV): C, 66.65; H, 7.83. Found: C, 66.58; H, 7.79.

C. Dimethylation.—Three hundred and fifty milligrams (0.00101 mole) of methane XIII in 10 cc. of dioxane was treated with 0.0020 mole of sodium triphenylmethyl; 1.0 cc. of dimethyl sulfate was added and the solution allowed to stand for several hours. It was then treated in the same manner as for the monomethylation; 255 mg. or 67% of crude di-N-methyl methane XXI was isolated. After five recrystallizations from alcohol and water its melting point rose to 150–152° and showed no depression on mixed melt with a sample prepared by the method of Corwin and Quattlebaum.[7]

Methylation of 1,3,5,3′,5′-Pentamethyl-4,4′-dicarbethoxydipyrrylmethane (XIV).—After titration in 5 cc. of dioxane, the sodium salt from 123 mg. of methane XIV was treated with 0.0007 mole of dimethyl sulfate and warmed gently. After standing for several hours the solution was shaken with water, the benzene–ether layer separated, dried over sodium sulfate, filtered and evaporated in a vacuum. The residue was extracted with 5 cc. of warm hexane; yield, 78 mg. or 61%; m. p. 153°. The melting

point was raised to 157–158° by repeated recrystallizations from alcohol and water. No depression with methane XXI, m. p. 153°, prepared by the method of Corwin and Quattlebaum.[7]

Comparison of Methane XIV with XV.—The bridge methylated methane XV was prepared by the method of Fischer and Bartholomäus.[8] After recrystallization from alcohol and water the melting point was 170°. The melting point of methane XIV was 176°; mixed m. p. 153°.

Reactions of 3,5,4′-Trimethyl-4,3′,5′-tricarbethoxydipyrrylmethane (XVII). A. Recovery after Titration.—The solution obtained by titrating 174 mg. of methane XVII was poured into 50 cc. of water, heated on the steam-cone to remove the ether and benzene, cooled and the solid filtered off. This solid was boiled with hexane, the solution cooled and filtered; recovery, 163 mg. or 94% of crude starting material. After one crystallization from alcohol and water the compound melted at 156–158° and gave no depression with starting material, m. p. 158–159°.

B. Monomethylation of XVII on Ring I.—Two hundred and four milligrams (0.000505 mole) of methane XVII was dissolved in 5 cc. of dioxane and treated with 0.00051 mole of sodium triphenylmethyl. To the clear solution, 0.9 cc. of a 10% solution by volume of dimethyl sulfate and benzene was added and the reaction mixture allowed to stand overnight; 50 cc. of water was added and the mixture heated on the steam-cone to remove the ether and benzene, cooled, the solid removed and dried. The solid was extracted with cold hexane; yield, 153 mg. (72%) of a colorless powder; m. p. 105°. After two crystallizations from water and alcohol, m. p. 110°; mixed m. p. with methane XXII prepared by the method of Quattlebaum and Corwin,[9] no depression.

C. Monomethylation of XVII on Ring II.—Two hundred and two milligrams of methane XVII (0.00050 mole) was dissolved in 5 cc. of dioxane and 0.00104 mole of sodium triphenylmethyl beyond the solvent blank was added. The sodium salt came out as a gelatinous mass; 1.8 cc. of dimethyl sulfate solution (1 cc. in 9 cc. of dioxane) was added. Within two minutes the solution had become apparently clear and within the next few seconds a large amount of a white precipitate separated—much more than the sodium methyl sulfate could account for. The flask was allowed to stand attached to the apparatus overnight; 40 cc. of water was added, the mixture heated on the steam-cone to remove the solvents, cooled and the solid separated and dried. The solid was boiled with 3.0 cc. of hexane, the solution cooled, filtered and the residue washed with cold hexane; yield, 145 mg. or 68%; m. p., after one crystallization from alcohol and water, 96°. Repeated crystallizations raised this to 97°; no depression with methane XVIII prepared by the method given below.

D. Synthesis of 1,3,5,4′-Tetramethyl-4,3′,5′-tricarbethoxydipyrrylmethane (XVIII) by Condensation.—Two and seventy-three hundredths grams of 2-chloromethyl-3,5-dicarbethoxy-4-methylpyrrole was dissolved in 10 cc. of methanol and 1.81 g. of 1,2,4-trimethyl-3-carbethoxypyrrole in 5 cc. of methanol. The solutions were combined and refluxed two hours. The reaction mixture was cooled until crystallization was complete and the solid filtered off; yield, 2.60 g. or 62%; m. p. 92–94°. No attempt was made to recover the product in the mother liquors from the condensation; m. p., after one crystallization from water and alcohol, 96–97°. For analysis, crystallized twice from hexane; m. p. 97°.

Anal. Calcd. for $C_{22}H_{30}N_2O_6$: C, 63.14; H, 7.22. Found: C, 63.08; H, 7.26.

E. Dimethylation of Methane XVII.—One hundred and five milligrams (0.00026 mole) of methane XVII in 5.0 cc. of benzene was treated with 0.000556 mole of sodium triphenylmethyl; 3.0 cc. of dimethyl sulfate solution (1 cc. in 9 cc. benzene) was added and the solution refluxed for forty minutes. The sodium salt dissolved and deposited sodium methyl sulfate; 50 cc. of water was added, the solution heated to remove the benzene and ether, cooled and filtered. The solid was extracted with hexane; yield, 85 mg. or 75%; m. p. 125°; after crystallizing from hexane, m. p. 128–129°; no depression with methane XXIII prepared by the condensation below.

F. Synthesis of 1,3,5,1′,4′-Pentamethyl-4,3′,5′-tricarbethoxydipyrrylmethane (XXIII) by Condensation.—Two and eighty-seven hundredths grams of 1,4-dimethyl-2-chloromethyl-3,5-dicarbethoxypyrrole and 1.81 g. of 1,2,4-trimethyl-3-carbethoxypyrrole were each dissolved in 5 cc. of methanol. The solutions were combined and refluxed for two hours. On cooling the dipyrrylmethane crystallized out; yield 3.85 g. or 89%; m. p. 128–129°. The analytical sample was crystallized twice from alcohol and water and once from hexane; m. p. 129°.

Anal. Calcd. for $C_{23}H_{32}N_2O_6$: C, 63.87; H, 7.46. Found: C, 63.88, 63.80; H, 7.46, 7.38.

Reactions for Methane XVIII. A. Recovery after Titration.—The recovery was performed as for methane XVII; 166 mg. or 79% was recovered from 211 mg. One recrystallization brought the m. p. to 96°; mixed m. p. with XVIII, no depression.

B. Methylation.—The sodium salt obtained by titrating 202 mg. of methane XVIII in benzene was treated with 3.0 cc. of dimethyl sulfate solution and the mixture refluxed for two hours. The product was treated as described under the dimethylation of XVII; yield, 180 mg. or 86%. After two recrystallizations from hexane, m. p. 125–127°; no depression with methane XXIII, m. p. 129°.

Reactions of 3,5,1′,4′-Tetramethyl-4,3′,5′-tricarbethoxydipyrrylmethane (XXII). A. In Benzene; Attempted Titration.—One hundred and ninety-nine milligrams (0.000475 mole) of methane XXII was dissolved in 5 cc. of benzene and treated with 0.00047 mole of sodium triphenylmethyl. As the addition was made, the colorless sodium salt settled out as a soapy mass and as time passed the solution took on a blue fluorescence and violet color indicating that condensation had taken place to some extent.[3] On adding water to the solution, the violet color disappeared. The mixture was warmed to remove the benzene and ether, cooled and filtered. The solid was extracted with a small amount of hexane leaving 170 mg. of a yellow powder melting at 95–105°; after two crystallizations from alcohol and water, m. p. 110°; no depression with starting material.

B. Methylation.—Two hundred and twenty-eight milligrams (0.000545 mole) of methane XXII in 5.0 cc. of benzene was treated with 0.0005 mole of sodium triphenylmethyl and 1.0 cc. of dimethyl sulfate solution was added

immediately. Within a few minutes the sodium salt of the dipyrrylmethane had dissolved. The flask was allowed to stand overnight and the product isolated in the usual manner; yield, 210 mg. of crude material which after two crystallizations from hexane melted at 125°; no depression with methane XXIII, m. p. 129°.

C. Condensation Reaction in Dioxane.[3]—Five hundred and fifteen milligrams (0.00123 mole) of methane XXII was dissolved in 10 cc. of dioxane and treated with 0.00123 mole of sodium triphenylmethyl. After the first drop of reagent had been added, the blue fluorescence noted above appeared. As the addition progressed the solution became cherry-red and finally deep violet. No precipitate was deposited. After ten minutes the flask was removed and the contents poured into water. The violet color disappeared leaving a yellow ether–benzene layer with a blue fluorescence. The mixture was warmed to remove the ether and benzene, cooled, filtered and the yellow solid extracted with hexane, leaving 430 mg. of a yellow powder which melted at 150–192°. After crystallizing twice from ethanol the compound melted at 203–204°; yield, 300–400 mg.

Anal. Calcd. for $C_{20}H_{24}N_2O_5$: C, 64.50; H, 6.49; mol. wt., 372. Found: C, 64.46, 64.44; H, 6.40, 6.43; mol. wt., 388, 369, 379 (b. p. elevation in chloroform).

When the violet solution was treated with dimethyl sulfate, the deep color disappeared immediately but the compound isolated from the reaction was identical with that prepared above. Evidently this material shows a resistance to methylation similar to that of methane XII.

Summary

1. It is shown that a standardized solution of sodium triphenylmethyl may be used to titrate for active hydrogens.

2. This reagent is inert to ester groups, C–Br links and most CH groups.

3. The >CH–CO– linkage is active to sodium triphenylmethyl.

4. The reagent permits a check upon possible condensations by regeneration of the starting material.

5. A dipyrrylmethane with a bridge hydrogen acidic to sodium triphenylmethyl has been discovered.

6. Titration followed by methylation has been used to confirm the structures of a number of dipyrrylmethanes.

7. A method for specific, selective methylation of bifunctional weak acids is presented.

8. A new pyrrole condensation is recorded.

BALTIMORE, MARYLAND RECEIVED MAY 28, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Rearrangements of Pyrrole Rings in the Oxidation of Dipyrrylmethanes[1]

BY ALSOPH H. CORWIN AND KARL J. BRUNINGS[2]

Previous papers of this series[3] have developed the fact that certain pyrrole-carbon single bonds which can cleave to give stable resonating systems are rapidly split by acid at room temperature and below. Brunings and Corwin[4] extended this study with the observation that, under even milder conditions, it is possible to cleave a pyrryl-carbon bond belonging to the resonating system of a pyrrole pigment. This observation provides a starting point for the systematic study of pyrrole pigments which may be of significance with respect to the catabolic processes which these substances undergo in biological systems. The conversion of hemoglobin to bile pigments and the problem of the reactions causing varying sequences of substituents on naturally occurring porphyrins are examples of fundamental biological processes which may be elucidated by studies upon the stability of variously substituted pigments. This paper reports a study of an even readier cleavage of a pyrrole pigment system than that previously discussed.

Our earlier papers show that attempts to prepare mono-N-methyldipyrrylmethenes by the condensation of pyrryl aldehydes with α-free pyrroles yield either symmetrical N-free methenes or products which have not been identified. That this peculiarity is not due to the impossibility of preparing an N-methyl methene was demonstrated by the preparation of 1,3,5,1′,3′,5′-hexamethyl-4,4′-dicarbethoxydipyrrylmethene salts (I).[4] Among the reactions generally used in dipyrrylmethene synthesis, the oxidation of dipyrrylmethanes would appear to be the most reliable for preparing and establishing the structures of

(1) Studies in the Pyrrole Series, X. Paper IX, Corwin and Ellingson, THIS JOURNAL, **64**, 2098 (1942).

(2) A portion of this paper is taken from the doctoral dissertation of Karl J. Brunings, The Johns Hopkins University, 1939, and was presented at the Baltimore Meeting of the American Chemical Society in April, 1939.

(3) Corwin and Andrews, THIS JOURNAL, **58**, 1086 (1936); Andrews and Corwin, *ibid.*, **59**, 1973 (1937); Paden, Corwin and Bailey, *ibid.*, **62**, 418 (1940).

(4) Brunings and Corwin, *ibid.*, **64**, 593 (1942).

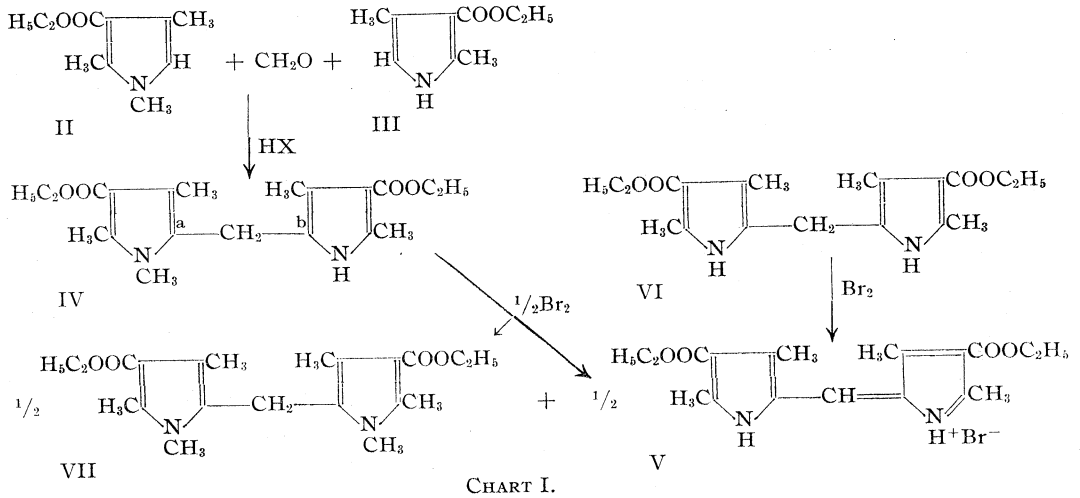


CHART I.

these pigments. This method was successful in the preparation of methene I.

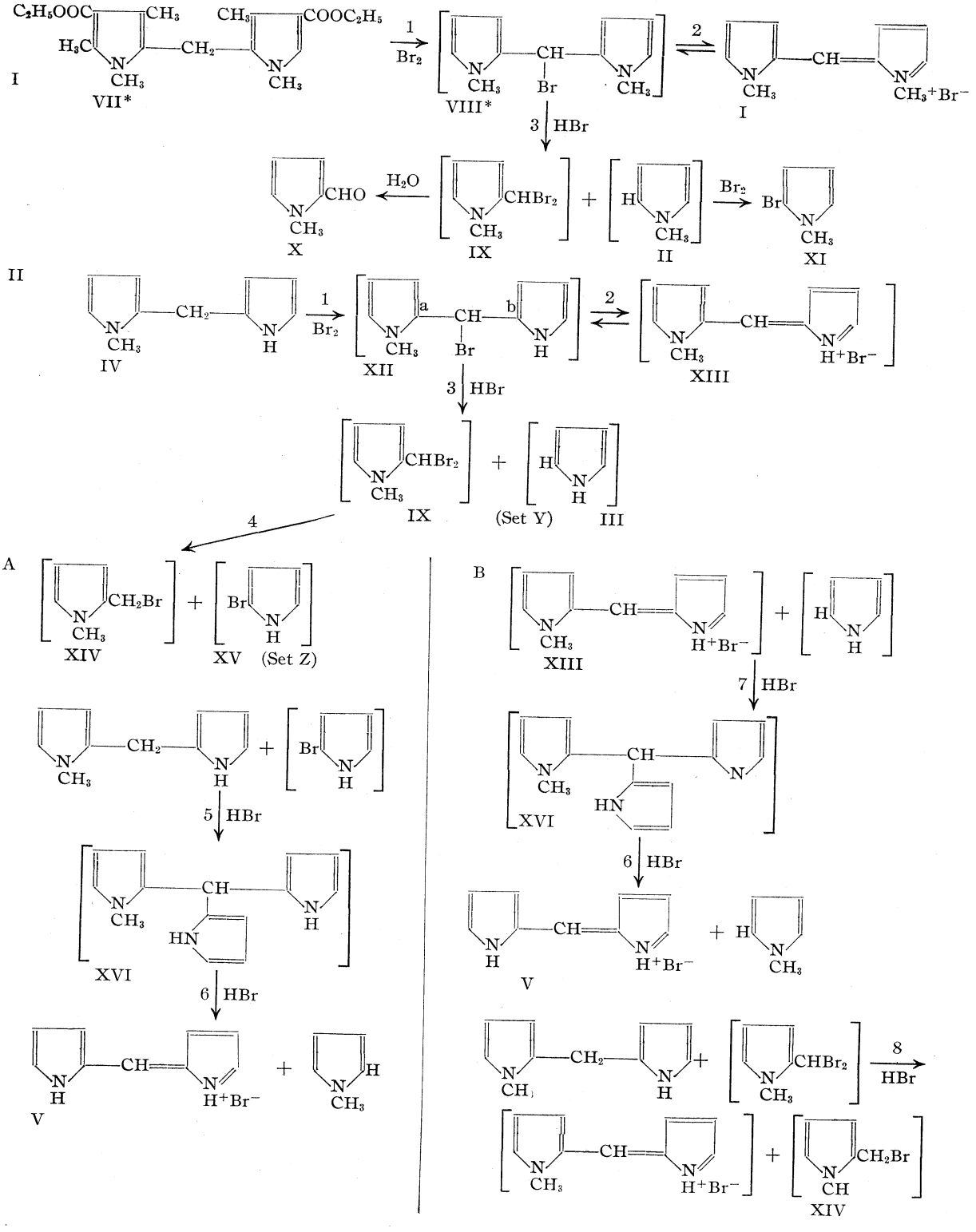
To study mono-N-methylmethane bromination on a comparable system, 1,3,5,3′,5′-pentamethyl-4,4′-dicarbethoxydipyrrylmethane (IV, Chart I) was prepared by the unsymmetrical condensation of the N-methylated and NH α-free pyrroles II and III (Chart I) with formaldehyde. The methane was then brominated under the conditions that had successfully produced the di-N-methyl methene (I). Instead of the expected mono-N-methylmethene (XIII, Chart II) the symmetrical di-NH-methene (V) was obtained in about 60% yield based on the amount of NH-pyrrole ring in the starting methane (IV). Investigation of the mother liquor showed that 1,3,5-trimethyl-2-bromo-4-carbethoxypyrrole (XI, Chart II) was a by-product of the reaction. It was then found that by using only one-half mole of bromine with one mole of methane a practically quantitative yield of pure crystalline di-NH-methene (V) was obtained. Di-N-methyl dipyrrylmethane (VII) was isolated from the mother liquor. The di-NH-methene (V) obtained by this anomalous reaction may be prepared in quantitative yield by the bromination of the corresponding di-NH-methene (VI). These reactions are given in Chart I.

The possibility that the dipyrrylmethane (IV) might be a mixture of the unmethylated and di-N-methylated methanes (VI and VII) was excluded by bromination of actual mixtures of the two symmetrical methanes and by a thorough investigation of the structure of this compound.[1] Any explanation based on the removal of the methyl groups from the nitrogens is excluded by the isolation of the di-N-methyl methane (VII) and N-methyl-α-bromopyrrole (XI) as by-products of the half-molar and molar brominations, respectively, and by the quantitative yield based on the amount of NH-pyrrole in the starting methane.

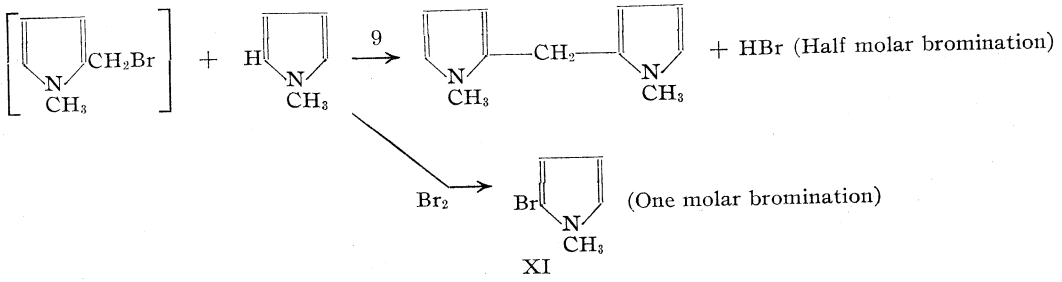
Assured then of the structure of the starting dipyrrylmethane and the stability of the methyl groups on the nitrogens, it is apparent that a cleavage of the C–C bond (IV, a or b) takes place. The motivating force of the reaction is supplied by the hydrobromic acid. Realizing the possibility of acid cleavage, a score of oxidation reactions in neutral and basic medium were tried in an effort to obtain the mono-N-methylmethene. In every case either no reaction occurred or the methane was degraded to products no longer identifiable as pyrrole derivatives. On the other hand, acidic oxidizing agents of low activity, *e. g.*, formic acid or oxygen and mineral acid, are capable of giving the reaction. The rate and completeness of the reaction depend both on the oxidizing agent and the strength of the acid. For example, air in the presence of hydrobromic acid gives a low yield of the methene (V) at a slow rate, while the bromination gives a 75% yield in less than five minutes. The rate of bromine consumption is too fast to measure with accuracy by ordinary techniques. Chlorination results in a rather complete and very rapid reaction but the rate of appearance of the methene is slow.

Cleavage of a dipyrrylmethene system to pyrrole fragments has been shown to take place as a by-reaction in the bromination of the di-N-methylmethane (VII) to the corresponding methene (I) in paper VI of this series. Evidence was presented there to show that the steric interference

of the methyl groups on the nitrogens reduces the stability of the methene system. Although the steric interference between the methyl group and the hydrogen in the mono-N-methylmethene would be considerably less, the lack of symmetry in the Kekulé resonance forms would also lead to a decrease in the stability of the dipyrrylmethene system. Finally, the possibility of the pyrrole



A and B



XI

CHART II.

* The substituents present in the 3, 4 and 5 positions of compound VII are understood to be present on all the remaining pyrrole rings of the chart.

fragments forming insoluble crystalline end-products might be expected to bring about complete cleavage by disturbance of the equilibria.

Fischer and Riedl[5] have demonstrated acid cleavage of two unsymmetrical dipyrrylmethanes under non-oxidizing conditions, and thus the possibility of cleavage of the methane by hydrobromic acid produced in the early stages of the reaction must also be considered in formulating a mechanism for the anomalous bromination of mono-N-methyldipyrrylmethane IV. This alternative may be shown to be untenable by tests on the stability of the methane in the presence of hydrobromic acid under conditions considerably more drastic than those of the bromination. In order to test for cleavage products the methane dissolved in alcohol was boiled with formaldehyde in the presence of both hydrochloric and hydrobromic acids. If the bonds *a* or *b* were broken under this treatment, α-free pyrrole II or III would result. Since both the NH- and N-methylpyrroles condense with formaldehyde to produce dipyrrylmethanes, the mono-N-methylmethane would disproportionate to the di-NH- (VI) and the di-N-methyl- (VII) methanes. Such a disproportionation was not observed.

The di-NH-methene and N-methylpyrrole fragments are also obtained when the mono-N-methylmethane is treated with formic acid in the presence of hydrobromic acid. This reaction might be formulated as resulting from a condensation of formic acid with the α-free pyrrole produced by acid cleavage, a standard methene condensation. However, it can be shown that this explanation is not valid, since formic acid will not condense with the α-free NH-pyrrole under the conditions of the reaction. These experiments show that the cleavage does not occur on the methane and thus oxidation of the methane must be the initial reaction of the bromination.

The extremely fast rate of the reaction and the failure of all methods intended to stop the reaction after the initial bromination make isolation of NH-intermediates in the formation of the di-NH-methene (V) impossible. However, in the case of the bromination of the di-N-methylmethane (VII), previously referred to,[4] the pyrrole fragments resulting from cleavage are actually isolated in addition to the expected di-N-methylmethene from the normal oxidation. Moreover, this reaction lends itself to careful study and evidence has been presented[4] to show that the cleavage does not occur on the methene salt but on an intermediate in the bromination. The chemical and physical properties of the sterically hindered methene suggested that the covalent dipyrrylmethyl bromide (VIII, Chart II) is the intermediate in the reaction. The steps involved in the cleavage of the di-N-methylmethane are given in the first series of reactions in Chart II.

If one assumes that the cleavage of the mono-N-methylmethane proceeds analogously to that of the di-N-methyl system, the problem of setting up a mechanism becomes one of finding established reactions involving the pyrrole derivatives which may be present in the bromination solution and which will produce the di-NH-methene (V) and the N-methylated by-products. Two alternative mechanisms, A and B, are described in the second series of reactions in Chart II. Reactions 1, 2 and 3 of this series are identical with those of the di-N-methyl system in the first series. Cleavage of the dipyrrylmethyl bromide (XII) is postulated to occur at bond b to give the α-dibromomethyl pyrrole (IX) and the α-free pyrrole (III) (Set Y), since cleavage at bond a would yield pyrrole fragments which cannot condense according to known

(5) Fischer and Riedl, *Z. physiol. Chem.*, **207**, 200 (1932).

reactions to produce the products obtained in the bromination.

One mole of bromine cleaves two moles of the methane in the over-all reaction, and, therefore, one of the cleavage products must react with the starting methane (IV). In mechanism A this reaction is preceded by a disproportionation of the primary cleavage products (Reaction 4) to yield α-bromomethylpyrrole (XIV) and the α-bromopyrrole (XV) (Set Z). Reactions of this type have not been studied as yet in the pyrrole series since dihalomethyl derivatives are very difficult to prepare. However, it is reasonable to assume that the intermediate bromopyrrole would be a very good brominating agent and it can be shown that the α-free pyrrole brominates with extreme rapidity. The reaction between the mono-N-methylmethane (IV) and the α-bromopyrrole (XV) (Reaction 5) can be carried out under the conditions of the bromination to give a quantitative yield of the di-NH-methene (V) with a rate which is compatible with that of the bromination. In analogy to similar reactions in the pyrrole series it is reasonable that this reaction should have tripyrrylmethane (XVI) as an intermediate. The cleavage of this tripyrrylmethane with hydrogen bromide (Reaction 6) has also been carried out under comparable conditions[3] to give the expected methene (V) with both the rate and the yield in agreement with those of the bromination. The N-methyl α-free pyrrole (II) has been isolated from both reactions.

The fundamental reaction of the alternative mechanism B is the condensation of the primary cleavage product, the α-free pyrrole (III) and the mono-N-methyldipyrrylmethene (XIII) (Reaction 7) to yield the di-NH-methene (V) through the tripyrrylmethane (XVI). Since the methene (XIII) has not been isolated, this reaction could not be imitated. However, the condensation has well-established analogies in the pyrrole series and its mechanism has been thoroughly worked out.[3] As described above, Reaction 6 may be carried out under conditions of the bromination. The reactions thus far account for only one-half of the yield of the di-NH-methene and, therefore, another oxidation of the starting methane must occur. The dibromomethylpyrrole (IX) is the only oxidizing agent remaining and thus Reaction 8 is postulated to provide an additional mole of mono-N-methylmethene which then reacts according to the preceding scheme, leading to a chain mechanism. This reaction is without analogy in the pyrrole series for the reasons mentioned above. However, the oxidizing action of this type of dihalomethyl derivative can be demonstrated by the reaction between 2-dichloromethyl-3,5-dicarbethoxy-4-methylpyrrole and the mono-N-methylmethane (IV) which again yields the anomalous di-NH-methene. This reaction is very slow and incomplete, a behavior which might be predicted on the basis of the effect of the carbethoxy groups on the pyrrole ring.

Common to both mechanisms (A and B) is the final reaction 9 which accounts for the isolation of the di-N-methylmethane (VII) from the bromination reaction. The isolation of the α-free pyrrole from the formic acid oxidation and the incomplete yield of the di-N-methyl methane from the bromination are in agreement with the generally slow rate of this methane condensation.

Essentially, the question as to which of these two proposed mechanisms is the correct one becomes a problem of determining whether the α-free pyrrole (III) or the starting methane (IV) reacts more rapidly with the dibromomethylpyrrole (IX). Lacking the dibromomethylpyrrole, a selection between the two mechanisms can only be made on indirect evidence. No difference in bromination rate of the pyrrole and methane could be found by the techniques at our disposal, both reactions going to completion in less than five seconds. It is significant, however, that in the cleavage of the di-N-methyl system, α-free pyrrole is never isolated. This is easily interpreted by assuming that the rate of bromination (k_4) of the pyrrole is faster than that of the methane (k_1). It must be pointed out, however, that the comparative rates of bromination may depend upon the type of brominating agent in question and thus might be reversed in going from bromine to α-dibromomethylpyrrole.

Strong positive support is given mechanism A by the low yields obtained when one mole of bromine per mole of methane is employed. In mechanism A the formation of methene depends on the presence of unoxidized starting methane (Reaction 5), while in mechanism B the methene is formed from the oxidation intermediate (XIII) and one of its cleavage products (Reaction 7). Therefore the use of an extra half mole of bromine should either give no methene or at least a greatly diminished yield if mechanism A is valid. According to mechanism B, however, one molar bromina-

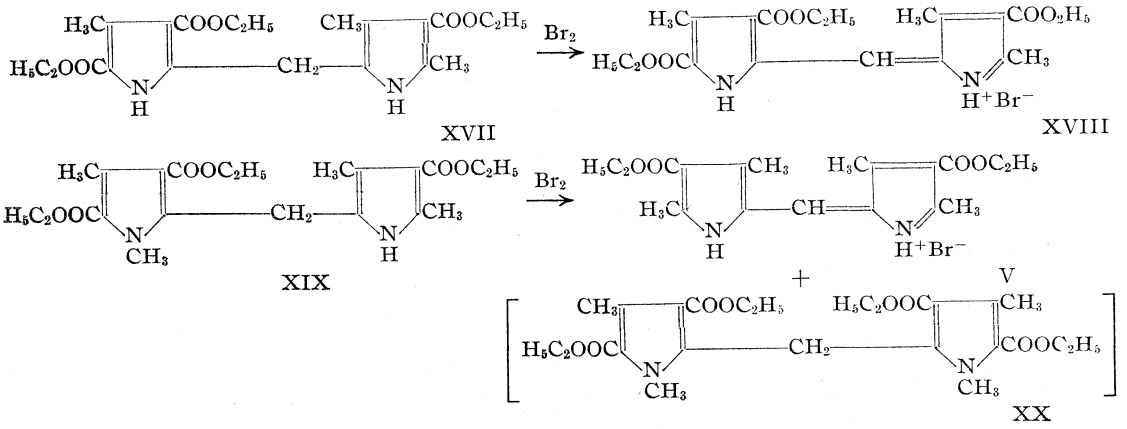


CHART III.

tion should not affect the yield of methene but rather the state of oxidation of the pyrrole fragments. Actually, the yield is depressed almost a half and a considerable amount of unidentifiable by-product is obtained. The fact that a 60% yield of the methene is obtained instead of one mole of α-bromomethylpyrrole (XIV) and one mole of the α-bromopyrrole (XV) may be accounted for by the rapidity with which the bromopyrrole–dipyrrylmethane condensation (Reaction 5) takes place.

Until the mono-N-methylmethene can be prepared and its properties studied, the validity of either one of these mechanisms cannot be uniquely established. It is possible, of course, that both mechanisms operate, the importance of each depending on the conditions under which the bromination is carried out. As indicated above, dibromomethylpyrrole derivatives are unknown and a study of their properties would do much toward elucidating the present unusual reaction.

The anomalous course of the bromination of the mono-N-methylmethane must destroy our confidence in the absolute reliability of this synthetic method as a proof of the structure of dipyrrylmethenes. In order to determine whether this anomalous reaction is in any way general for unsymmetrical methanes, a series of dipyrrylmethanes[6] was subjected to bromination. Of those tried, one other example, the 1,4,3′,5′-tetramethyl-3,5,4′-tricarbethoxydipyrrylmethane (XIX, Chart III) was observed to give the symmetrical methene (V). Bromination of the di-NH-methene (XVII) of the corresponding configuration gave a normal result, while the methane having a methyl group on the other pyrrole ring yielded unidentifiable products. The reactions are given in Chart III.

The oxidation of unsymmetrical dipyrrylmethanes has not been extensively employed as a method of preparing dipyrrylmethenes. However, in a few cases the method has been applied[7,8] successfully to give normal results. On the basis of the studies made on the mono-N-methyl and the di-N-methyl systems,[4] it may be stated that an anomalous course of the methane bromination may be looked for whenever there is reason to believe that the corresponding methene will be unstable. Unfortunately, no reliable criteria exist for predicting the stability of dipyrrylmethenes. The three examples which have been shown to be subject to acid cleavage all contain methyl groups on the nitrogens and it has been shown that the steric interference of these groups gives rise to a reduction in the stability of the dipyrryl systems. Lack of symmetry and the electrical effect of groups on the pyrrole rings are other factors which must be considered in predicting the stability of dipyrrylmethenes but their use must await an orderly correlation of the physical and chemical properties of the many dipyrryl systems now available.

The authors wish to express their appreciation to the Rockefeller Foundation which has supported a portion of this investigation.

The junior author also wishes to acknowledge a grant-in-aid from the Hynson, Westcott and Dunning Fund.

Experimental Section

Preparation of 1,3,5,3′,5′-Pentamethyl-4,4′-dicarbethoxydipyrrylmethane (IV).—A solution of 20 g. of 1,2,4-

(6) Corwin and Quattlebaum, THIS JOURNAL, **64**, 922 (1942).

(7) Fischer and Adler, *Z. physiol. Chem.*, **200**, 220 (1931).

(8) Fischer and Baumler, *Ann.*, **468**, 74 (1929).

trimethyl-3-carbethoxypyrrole (II) in 100 cc. of alcohol and a solution of 20 g. of 2,4-dimethyl-3-carbethoxypyrrole (III) in 100 cc. of alcohol are mixed in a 500-cc. Erlenmeyer flask and 28 cc. of formalin added. After the temperature has been raised to 45°, 10 cc. of concentrated hydrochloric acid is run in. The temperature is kept below 60° by cooling the flask from time to time in running water. After standing in the cold for several hours, 40 g. of crude product is filtered from the mixture and washed with cold 50% alcohol–water. The material is then refluxed in 50% alcohol–water for one hour and again filtered. Recrystallization of the precipitate from alcohol yields 30 g. of large crystalline plates, melting irreversibly at 178–179°; yield, 75%. Mixed melt with mono-N-methyldipyrrylmethane prepared by Dr. R. C. Ellingson by a different method,[1] 178–179°.

One Molar Bromination of Mono-N-methyldipyrrylmethane (IV).—A solution of 100 mg. of the mono-N-methylmethane (IV) in 10 cc. of dry carbon tetrachloride is placed in a 25-cc. Erlenmeyer flask; 0.05 g. of bromine dissolved in 0.5 cc. of carbon tetrachloride is added quickly while the flask is vigorously twirled. The mixture is allowed to stand several hours in the cold to ensure complete precipitation and then filtered; 35 mg. (58% of the theoretical) of yellow methene-like needles is obtained. This material on treatment with concentrated ammonia and subsequent recrystallization from hexane–benzene yields long red needles, melting with decomposition at 189–190°. Mixed melt with 3,5,3′,5′-tetramethyl-5,5′-dicarbethoxydipyrrylmethene (V), 189–190° with decomposition. Reduction of the original product with palladium–hydrogen gives the dipyrrylmethane corresponding to the configuration of di-NH-methene V.

Isolation of 1,3,5-Trimethyl-2-bromo-4-carbethoxypyrrole (XI) from the One Molar Bromination of Mono-N-methyldipyrrylmethane IV.—The mono-N-methylmethane (1.5 g.) is dissolved in 150 cc. of dry carbon tetrachloride and placed in a 250-cc. Erlenmeyer flask; 200 cc. of water containing 20 g. of potassium carbonate is placed in a separatory funnel and 0.61 g. of bromine dissolved in 6.1 cc. of carbon tetrachloride is then run into the methane solution quickly and the flask shaken for thirty seconds. The mixture is poured immediately into the separatory funnel containing the potassium carbonate solution and shaken vigorously for several minutes. The carbon tetrachloride layer, which is highly colored, is drawn off and dried with anhydrous potassium carbonate. A chromatograph is then prepared using a six-inch column of activated alumina (150–200 mesh) as adsorbent. The solution is passed through the chromatograph developing a bright yellow band of di-NH-methene V on the alumina. In addition to the yellow band of the di-NH-methene another red band develops indicating an additional methene as by-product. After 200 cc. has been collected, a new receiver is used and additional carbon tetrachloride is passed through until a second fraction of 200 cc. is collected. The first fraction is evaporated to dryness and leaves 125 mg. of fine white needles which melt at 54–55°, decompose with gas evolution at 145–150° and give no depression with N-methyl-α-bromopyrrole (XI).[4] The second fraction gives a larger amount of solid with a yellow tinge. On warming to about 60° the whole mass turns blood red. If the mixture is not warmed but recrystallized more α-bromopyrrole may be isolated. This behavior is indicative of the presence of another compound. Since the two pyrroles must be equivalent in state of oxidation to a dipyrrylmethene, the accompanying compound is assumed to be the α-bromomethylpyrrole (XIV, see Chart II). A highly colored third fraction gives a resinous solid which has not been identified.

Half-Molar Bromination of Mono-N-methyldipyrrylmethane IV.—The methane (1.5 g.) is dissolved in 300 cc. of dry carbon tetrachloride and brominated according to the directions given above using 0.37 g. of bromine in 3.7 cc. of carbon tetrachloride; 850 mg. of fine orange-yellow needles is obtained. When submitted to the tests described in the one molar bromination the product is shown to be di-NH-dipyrrylmethene V. The yield is 96% of the theoretical based on the amount of NH-pyrrole in the starting methane.

Isolation of 1,3,5,1′,3′,5′-Hexamethyl-4,4′-dicarbethoxydipyrrylmethane (VII) from the Half Molar Bromination.—The mother liquor of the above reaction is evaporated in a suction flask at room temperature. The resinous residue is taken up in about 25 cc. of dry hexane, decolorized with Norite A and allowed to crystallize. On repeated recrystallization a colorless compound is obtained; m. p. 156–157°. Mixed melt with 1,3,5,1′,3′,5′-hexamethyl-4,4′-dicarbethoxydipyrrylmethane 156–157°.

Oxidation of Mono-N-methyldipyrrylmethane IV with Formic Acid and Hydrobromic Acid.—A solution of 500 mg. of mono-N-methylmethane IV in 100 cc. of carbon tetrachloride is placed in a 250-cc. glass-stoppered Erlenmeyer flask. After the solution has cooled to room temperature 0.2 cc. of formic acid and 5 cc. of aqueous (45%) hydrobromic acid is run in. The flask is then stoppered, wired and placed on a rotary shaker for four hours. At the end of this time the precipitate of red needles is filtered; yield, 200 mg. The precipitate is ground in a mortar with concentrated ammonia. The free base thus formed is recrystallized from hexane–benzene; m. p. (dec.) 190°; mixed melt with di-NH-dipyrrylmethene (V) (free base) 190° (dec.).

Reaction of Formic Acid with 2,4-Dimethyl-3-carbethoxypyrrole (III).—The α-free pyrrole (III) (230 mg.) is dissolved in 100 cc. of carbon tetrachloride and placed in a 250-cc. Erlenmeyer flask; 0.1 cc. of formic acid and 5 cc. of aqueous hydrobromic acid (45%) are run in as above. After four hours of shaking, no crystals are noted and the color of the solution remains light yellow. On heating to 40° and shaking, the reaction mixture does not change color. If the solution is heated to 65° the solution turns deep red, and on cooling a crop of fine red needles is obtained. The product is the expected di-NH-methene (V).

Isolation of 1,2,4-Trimethyl-3-carbethoxypyrrole (II) from Formic Acid Oxidation of Mono-N-methyldipyrrylmethane IV.—The mono-N-methyl methane (500 mg.) is treated with formic acid and hydrobromic acid in the manner described above. After the methene is filtered off, the carbon tetrachloride solution is shaken with saturated sodium bicarbonate solution, separated and filtered. The filtrate is then evaporated to dryness in a filter flask at room temperature. When the residue appears dry, the

filter flask is fitted with a cold finger and the suction continued while the filter flask is warmed to 60–70° on a water-bath. A heavy coating of N-methyl-α-free pyrrole (II) sublimes onto the cold finger; m. p. 61–62°; mixed melt with N-methyl-α-free pyrrole (II), 61–62°.

Chlorination of Mono-N-methyldipyrrylmethane IV.—A solution of chlorine in carbon tetrachloride is prepared by bubbling chlorine slowly through dry carbon tetrachloride. The resulting stock solution is stored over calcium chloride in a glass-stoppered Erlenmeyer flask. Just before using, the solution is standardized using excess potassium iodide and titrating with 0.1 *N* thiosulfate solution. The solution used in the present experiment is 0.56 *N*.

A solution of 100 mg. of dipyrrylmethane IV dissolved in 10 cc. of dry carbon tetrachloride is placed in a 25-cc. Erlenmeyer flask and 1.1 cc. of 0.56 *N* chlorine–carbon tetrachloride (1 mole plus 10%) is added quickly. The solution turns red immediately and then gradually a deep brown. After fifteen minutes fine yellow needles begin to separate; precipitation is complete after standing four hours in the cold. Yield of the di-NH-dipyrrylmethene (V) hydrochloride is 35 mg. or 70% of the theoretical.

Rate of Bromine and Chlorine Consumption in the Bromination and Chlorination of Mono-N-methyldipyrrylmethane IV.—The following standard solutions were prepared: (1) 0.0055 *M* mono-N-methylmethane IV in carbon tetrachloride; (2) 0.0284 *N* bromine in carbon tetrachloride; (3) 0.028 *N* chlorine in carbon tetrachloride; (4) 0.0300 *N* thiosulfate solution.

Approximately 1 g. of potassium iodide was dissolved in 20 cc. of concentrated acetic acid in a 50-cc. glass-stoppered Erlenmeyer flask; 10 cc. of the 0.0055 *M* mono-N-methylmethane solution was pipetted into a 50-cc. glass-stoppered Erlenmeyer flask. To this solution 3.9 cc. of the 0.0284 *N* bromine solution (1 mole) was added quickly, the flask shaken vigorously for five seconds and the potassium iodide solution added immediately. The flask was shaken again and the resulting solution titrated with 0.0300 *N* thiosulfate solution, using starch as an indicator; 3.0% of the bromine remained, indicating 97% consumption in five seconds. A series of experiments gave values ranging from 96–100% consumption of bromine in five seconds.

A similar experiment was run using 11.7 cc. of the standard bromine solution (3 moles). The reaction was terminated after five seconds as described above. Titration with standard thiosulfate solution showed that 92% of 2 moles of bromine had been consumed.

Identical rate measurements were made on the di-N-methyldipyrrylmethane (VII) and the corresponding di-NH-methane (VI). No difference could be observed between the rates of bromine consumption of the di-N-methyl and the mono-N-methyldipyrrylmethanes. A slightly slower rate was observed in the case of the di-NH-methane. An accurate difference could not be ascertained with the methods at our disposal but the difference could be qualitatively reproduced in a series of experiments.

The rate of chlorine consumption by the mono-N-methylmethane was studied in an analogous manner. Titration for chlorine after five seconds reaction time gave a blank in a series of experiments. The rate was thus too fast to measure by this technique.

The rate of bromination of the α-free pyrrole (III) has been measured by other workers[9] in this Laboratory and found to be similar to that of the mono-N-methylmethane.

Behavior of Mono-N-methylmethane IV with Respect to Neutral and Alkaline Oxidation.—As mentioned in the theoretical part of this paper, many attempts were made to carry out the oxidation of the mono-N-methylmethane IV in neutral or basic medium using different reagents under different conditions. In order to test the applicability of the methods to general methene synthesis, every reaction was run on 3,5,3′,5′-tetramethyl-4,4′-dicarbethoxydipyrrylmethane (VI). All results on the mono-N-methylmethane (IV) were negative. The most interesting of the reagents tried was neutral permanganate which, when applied to the di-NH-methane, gives a good yield of very pure dipyrrylmethene in the form of its free base. This method appears to be the best so far developed for preparing the free base of the di-NH-methene V in a high state of purity.

Oxidation of 3,5,3′,5′-Tetramethyl-4,4′-dicarbethoxydipyrrylmethane (VI) by Means of Potassium Permanganate.—The methane (150 mg.) was dissolved in 50 cc. of pure acetone in a 100-cc. Erlenmeyer flask fitted with a reflux condenser. (The acetone used in this reaction was obtained by refluxing commercial acetone for four hours over potassium permanganate.) 100 mg. of C. P. potassium permanganate was dissolved in the smallest amount of distilled water possible. The acetone solution was brought to a boil, the potassium permanganate solution added, and the mixture refluxed for five minutes. The reddish purple solution containing manganese dioxide was then filtered through asbestos; 125 mg. of the di-NH-methene (V) free base was obtained from the highly colored solution by rapid evaporation of the acetone. This material may then be recrystallized by dissolving in very little acetone, adding a small amount of water and allowing to stand overnight. It may also be recrystallized in the usual manner from hexane–benzene; m. p. (dec.) 190°.

The amount of potassium permanganate used in the above experiment was fixed by trial. The use of smaller amounts resulted in an impure product containing starting material; the use of larger amounts lowered the yield considerably. By following the *p*H of the reaction by means of a *p*H meter it was found that the *p*H rose rapidly to 13 and beyond when the methane solution and permanganate were mixed. By passing a stream of carbon dioxide through the reaction mixture, the *p*H could be maintained between 8 and 9. The reaction proceeded in this case much more slowly and considerably less permanganate was necessary. The product was of high purity but the yields were not so satisfactory as in the reaction just described. By using large excesses of permanganate and extending the reflux time, the methane was entirely converted to water soluble, colorless products.

When this technique was applied to the mono-N-methylmethane (IV) a white, crystalline product which was coated by a yellowish oil was obtained. On purification this product was found to consist largely of starting material.

Although many trials were made, no modification could be found whereby the expected methene could be prepared. Starting material was always obtained in decreasing

(9) Corwin and co-workers, unpublished work.

amounts with the use of large excesses of potassium permanganate. On the basis of work by Sackur and Taegener[10] it was hoped that the use of a calculated amount of potassium permanganate in slightly alkaline solution would provide the methene. The results were disappointing since no reaction took place with increasing sodium hydroxide until a point was reached where the solvent itself was oxidized. In such cases the methane was completely destroyed.

Attempted Basic Bromination of Mono-N-methyldipyrrylmethane (IV).—A solution of 2.5 g. of potassium hydroxide dissolved in 100 cc. of methyl alcohol was cooled to −10°; 2 g. of mono-N-methylmethane (IV) was dissolved in 200 cc. of carbon tetrachloride and placed in a 500-cc. three-necked flask equipped with a stirrer and dropping funnel. The methene solution was then cooled in a salt–ice mixture and stirring begun. The potassium hydroxide solution was poured into the flask and 0.9 g. of bromine dissolved in 25 cc. of carbon tetrachloride was added by means of the dropping funnel. After all the bromine solution had been added the stirring was continued for two hours. At the end of this time the solution had a bright yellow tinge. The solvent was evaporated off and water added to dissolve the potassium hydroxide. The yellowish residue after one crystallization proved to be the starting material; 2.25 g. was recovered. Warming the solution had no effect.

Formaldehyde Test on the Cleavage of the Mono-N-methyldipyrrylmethane in the Presence of Hydrobromic Acid.—The methane (500 mg.) was dissolved in 30 cc. of alcohol. To the solution 0.7 cc. of formaldehyde and 2 cc. of 45% hydrobromic acid were added. The solution was refluxed for one hour and the flask set aside to cool. The methane was precipitated by pouring the solution into cold water and filtering. The precipitate was dried and then refluxed with 66% alcohol. The mixture was filtered and the residue recrystallized from alcohol; yield, 425 mg. of beautifully white crystals; m. p. 178–179° (irreversible); mixed melt with starting methane, 178–179°. The filtrate (66%) alcohol was evaporated down and a small precipitate obtained (50 mg.) which melted at 161–162°; mixed melt with starting methane 170–174° (irreversible).

The same treatment was carried out in boiling carbon tetrachloride solution with the same results. It was assumed, therefore, that an appreciable cleavage of the methane under the influence of acid in boiling solvent does not take place.

Bromination of an Equimolar Mixture of the Di-NH-dipyrrylmethane (VI) and Di-N-methyldipyrrylmethane (VII).—The di-NH methane (VI) (250 mg.) is dissolved in 500 cc. of dry carbon tetrachloride by refluxing until the solution becomes clear. 275 mg. (1 mole) of di-N-methylmethane (VII) is then added. After the methane has completely dissolved, the solution is allowed to cool to room temperature and 0.16 g. of bromine dissolved in 1.6 cc. of dry carbon tetrachloride is run from a 10-cc. buret. The flask is then placed in an icebox overnight. The solution on filtering yields 380 mg. of red crystals covered with an appreciable amount of red oil. The crystals are treated with water which dissolves out the red oil (di-N-methylmethene). Weight of the dried crystals is 370 mg. or 85.4% of the theoretical based on one molar bromination of the di-NH-methene. The free base of the methene melts at 190° (dec.).

At the same dilution the yield of the di-NH-methene on half molar bromination of mono-N-methylmethane is 96%. The experiment shows that formation of these two methanes by cleavage of mono-N-methylmethane and recombination of the cleavage products to give a mixture of the two symmetrical methanes cannot account for the anomalous bromination of mono-N-methylmethane.

The apparent contradiction between the results of this experiment and those obtained from the preliminary rate studies, indicating a more rapid bromine consumption by the di-N-methylmethane than by the di-NH-methene may be explained by the greater stability and insolubility of the di-NH-methene. These factors tend to shift the equilibrium of the dipyrrylmethenes and their cleavage products in favor of the di-NH-methene.

Condensation of Mono-N-methyldipyrrylmethane (IV) with 2-Bromo-3,5-dimethyl-4-carbethoxypyrrole (XV) (Reaction 5 Chart II).—The mono-N-methyldipyrrylmethane (360 mg.) is dissolved in 100 cc. of carbon tetrachloride. After cooling the solution to room temperature gaseous hydrogen bromide is passed in for one-half minute. A solution of α-bromopyrrole (XV) in carbon tetrachloride (250 mg. in 25 cc. of carbon tetrachloride) is run into the methane solution. After standing in the cold four hours, the solution on filtering yields 400 mg. of red crystals. The free base melts at 190° (dec.) and gives no depression with di-NH-methene (V); yield, 95%. Evaporation of the mother liquor yields N-methyl-α-free pyrrole.

Comparative Rates of Methene Formation in Mono-N-methyldipyrrylmethane-α-Bromopyrrole Condensation (Reaction 5) and Dipyrrylmethane Bromination.—A solution of 180 mg. of methane (IV) dissolved in 20 cc. of dry carbon tetrachloride (A) and a solution of 100 mg. of the methane (IV) in 15 cc. of dry carbon tetrachloride (B) were prepared in separate 50-cc. Erlenmeyer flasks. Dry, gaseous hydrogen bromide was then passed through each for thirty seconds. To solution A, 45 mg. of bromine dissolved in 0.5 cc. of carbon tetrachloride was added and the flask stoppered; 123 mg. of α-bromopyrrole (XV) in 5 cc. of carbon tetrachloride was then added to solution B. Each solution was allowed to stand for five minutes and then filtered. Solution A gave 70 mg. of the di-NH-methene (V) or 65% of the theoretical. Solution B yielded 165 mg. of methene (V) or 77% of the theoretical. Thus it could be shown that the condensation was a feasible reaction in the bromination.

Cleavage of 1,3,5,3′,5′,3″,5″-Heptamethyl-4,4′,4″-tricarbethoxytripyrrylmethane (XVI) by Hydrogen Bromide under the Conditions of the Bromination of the Mono-N-methyldipyrrylmethane (IV) (Reaction 6).—A solution of 100 mg. of the tripyrrylmethane (XIV) is prepared in a 50-cc. Erlenmeyer flask. Dry, gaseous hydrogen bromide is then passed through the solution for thirty seconds. After five minutes the solution is filtered; 75 mg. or 90% of the theoretical yield is obtained. Evaporation of the mother liquor yields N-methyl-α-free pyrrole (II).

Oxidation of Mono-N-methyldipyrrylmethane (IV) by 2-Dichloromethyl-4-methyl-3,5-dicarbethoxypyrrole.—A solution of 180 mg. of the methane (IV) in 5 cc. of rectified

(10) Sackur and Taegener, *Z. Elektrochem.*, **18**, 718 (1912).

dioxane is prepared in a 25-cc. Erlenmeyer flask. To this solution is added 160 mg. of the dichloromethylpyrrole dissolved in 5 cc. of rectified dioxane. Dry gaseous hydrogen chloride is then passed in until the solution is saturated and the stoppered flask allowed to stand in the cold for several days; 35 mg. of deep red needles is obtained. Tests described above show the product to be the di-NH-methene (V); m. p. (dec.) of the free base 190°.

Bromination of 3,5,4′-Trimethyl-4,3′,5′-tricarbethoxydipyrrylmethane (XVII).—The dipyrrylmethane (XVII) (500 mg.) is dissolved in 500 cc. of dry carbon tetrachloride; 0.2 g. of bromine dissolved in 5 cc. of carbon tetrachloride is added to this solution at room temperature. After standing for several hours 500 mg. of fine red needles is filtered from the mixture. On conversion to the free base, by treatment of the solid methene salt with dilute ammonium hydroxide, this compound is shown to be identical with the unsymmetrical 3,5,4′-trimethyl-4,3′,5′-tricarbethoxydipyrrylmethene (XVIII), synthesized by independent methods; m. p. of free base 125° (dec.); yield 83%.

Bromination of 1,4,3′,5′-Tetramethyl-3,5,4′-tricarbethoxydipyrrylmethane (XIX).—The mono-N-methylmethane (XIX) (0.5 g.) is dissolved in 500 cc. of dry carbon tetrachloride; 0.2 g. of bromine dissolved in 5 cc. of carbon tetrachloride is added quickly to this solution with stirring. The dark red solution is allowed to stand in the cold overnight. On filtration 100 mg. of fine yellow-red needles is obtained. In addition, a large amount of red oil is found on the walls of the flask. No identifiable products have been obtained from this residue. Tests described above showed the red crystals to be the symmetrical di-NH-methene (V).

Summary

1. The oxidation of the leuco base of an unsymmetrical pyrrole pigment to a symmetrical pyrrole pigment having the sequence of substituents which corresponds to one of the pyrrole rings in the base has been observed.

2. This anomalous reaction has been shown to result from a reshuffling of intact pyrrole rings rather than by attack on the pyrrole substituents.

3. The application of this reaction to the study of the regrouping of pyrrole rings in naturally occurring pyrrole pigments is suggested by the mild conditions under which the reaction takes place.

4. The transformation has been shown to involve a cleavage of a carbon–carbon bond in the aromatic system of an intermediate in the reaction.

5. Two similar mechanisms have been proposed and supported by experimental evidence.

6. The oxidation of a number of unsymmetrical dipyrrylmethanes has been studied to test the generality of the anomalous reaction. Another example has been found.

BALTIMORE, MARYLAND RECEIVED MAY 28, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Preparation and Dehydration of 6-Methoxy-*i*-norcholenyldiphenylcarbinol

BY BYRON RIEGEL, MELVIN F. W. DUNKER[1] AND MCCALIP J. THOMAS[2]

For the systematic degradation of the side chain of methyl 3-hydroxy-5-cholenate (I), an investigation involving the use of the so-called *i*-methyl ether, primarily to protect the hydroxyl group and the double bond, has been made. The dehydration of the carbinol, resulting from the reaction with the Grignard reagent, proved to be a critical reaction provided the *i*-ether structure is retained. Hence, this reaction was studied.

Methyl 3-*p*-toluenesulfonoxy-5-cholenate (II)[3] was converted to methyl 6(α)-methoxy-*i*-cholenate (III) by the usual method, namely, by heating a methanol solution containing anhydrous potassium acetate. The reaction of this *i*-methyl ether methyl ester (III) with phenylmagnesium bromide gave the desired 6(α)-methoxy-*i*-norcholenyldiphenylcarbinol (IV) which melted at 139.0–140.2° and gave a specific rotation of +43.9°. Carbinol (IV) could not be dehydrated in a solution of boiling glacial acetic acid without changing the *i*-methyl ether structure to the normal acetate, thus giving 3-acetoxy-24,24-diphenyl-5,23-choladiene (VII). Even heating a glacial acetic acid solution of carbinol (IV) for a short time caused dehydration with a simultaneous loss of the *i*-ether configuration. Because of the lability of the *i*-steroid structure, particularly toward acidic reagents, many dehydrating agents cannot be used if this structure is to be retained. Although Heilbron, Beynon and Spring[4] had dem-

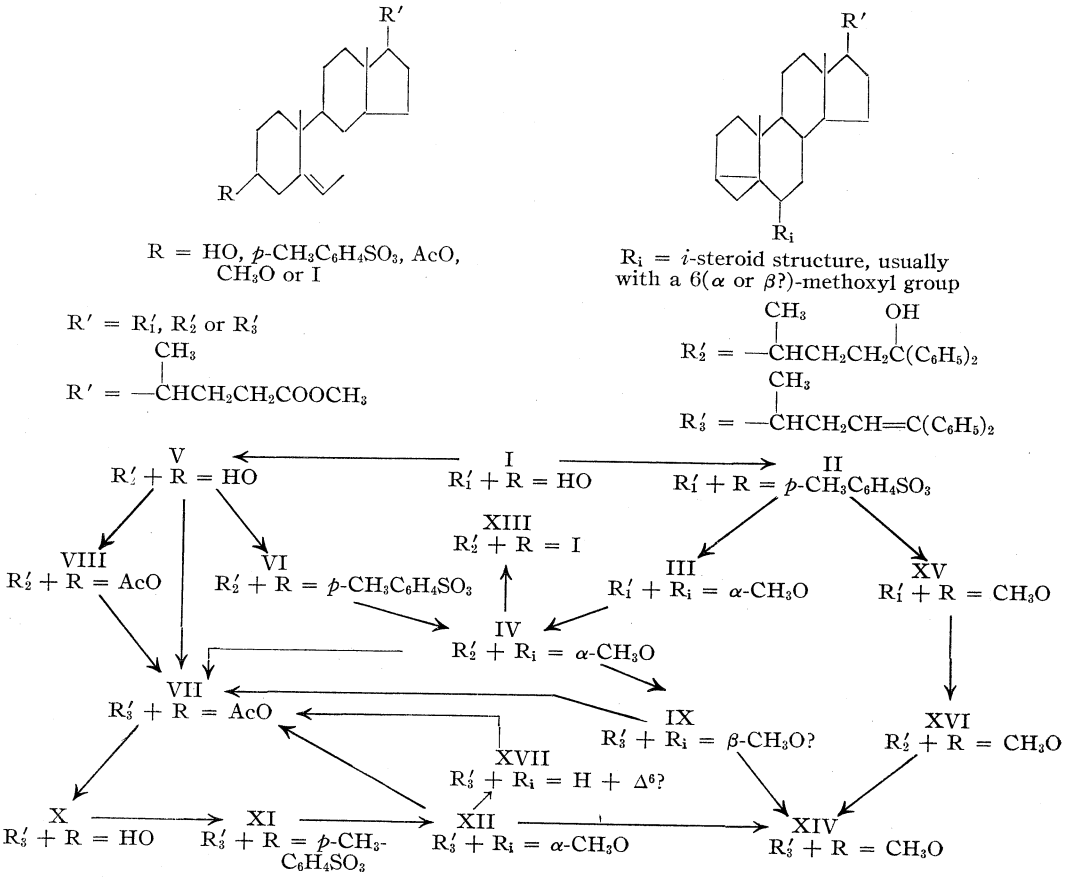
(1) Rockefeller Foundation Research Associate, 1940–1941. Present address: School of Pharmacy, University of Wisconsin.

(2) Abbott–Glidden–Upjohn Research Associate, 1941–1942.

(3) B. Riegel, J. A. Vanderpool and M. F. W. Dunker, THIS JOURNAL, **63**, 1630 (1941).

(4) I. Heilbron, J. H. Beynon and F. S. Spring, *J. Chem. Soc.*, 907 (1936); 406, 1459 (1937).

CHART I



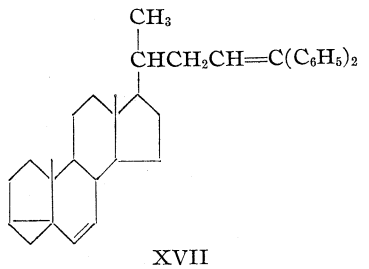
onstrated that bromine destroys the *i*-steroid structure an iodine-catalyzed dehydration of carbinol (IV) in boiling xylene was attempted. Both the analysis of the resulting product and method of preparation suggest that this substance is 3-iodo-5-norcholenyldiphenylcarbinol (XIII). Refluxing a xylene solution of the carbinol containing activated alumina did cause dehydration, but as will be indicated later also produced an isomerization. The product recovered from this treatment melted at 161.8–163° and gave a specific rotation of −39°. Previously all *i*-ether structures have given positive rotations, but as will be pointed out, structure (IX) seems to best explain our experimental data. The carbinol (IV) could not be dehydrated by the following methods and was recovered in each case unchanged; vacuum sublimation, slow distillation of benzene, toluene or xylene solutions and heating to 215° for three hours with anhydrous potassium bisulfate under nitrogen.

To help elucidate the isomerization caused by the aluminum oxide, each important intermediate was synthesized by an independent method as outlined in Chart I, thus substantiating their assigned structures. 3-Hydroxy-5-norcholenyldiphenylcarbinol (V) was produced by treating methyl 3-hydroxy-5-cholenate[3] with phenylmagnesium bromide. Carbinol (V) was converted to 3-*p*-toluenesulfonoxy-5-norcholenyldiphenylcarbinol (VI) which in turn was converted to the *i*-methyl ether carbinol (IV). This substance was identical with that obtained from III as previously described where the *i*-ether configuration was introduced before the Grignard reaction. When carbinol (V) was acetylated at room temperature 3-acetoxy-5-norcholenyldiphenylcarbinol (VIII) was obtained and subsequently converted to the acetoxy-diene (VII) upon refluxing in glacial acetic acid. The latter compound could also be obtained in one step from carbinol (V) merely by refluxing its acetic acid–acetic anhydride solution. The readily available acetoxy-diene (VII) was saponified and the resulting 3-hydroxy-24,24-diphenyl-5,23-choladiene (X) was converted to the *p*-toluenesulfonate (XI).

Heating an anhydrous methanol solution of compound (XI), containing fused potassium acetate, gave 1,1-diphenyl-2[6(α)-methoxy-*i*-bisnorcholenyl]-ethylene (XII). It melted at 109.1–110.1° and gave a specific rotation of +67.8°. The fact that compounds (IX) and (XII) were not identical stimulated further study of their structures.

One characteristic of *i*-methyl ethers is the ease with which they may be rearranged to the normal methyl ethers. Both compounds (IX) and (XII), on refluxing their anhydrous methanol solutions containing a few drops of sulfuric acid, gave 3-methoxy-24,24-diphenyl-5,23-choladiene (XIV), m. p. 114.5–115.3°, rotation −11.55°. The normal methyl ether (XIV) was independently prepared from compound (II) by the following reactions. On heating the *p*-toluenesulfonate (II) in anhydrous methanol, methyl 3-methoxy-5-cholenate (XV) was obtained which on reacting with phenylmagnesium bromide gave 3-methoxy-5-norcholenyldiphenylcarbinol (XVI). This carbinol was dehydrated in the usual manner to give the normal methyl ether (XIV) which was identical with that made by the rearrangement of compounds (IX) and (XII). Another characteristic reaction of *i*-ethers is their smooth conversion to normal acetates by heating their glacial acetic acid solutions. Both compounds (IX) and (XII) were converted by this treatment into the acetoxydiene (VII); however the conversion was effected with greater ease with XII than with IX.

The methods of preparation, analyses and reactions of compounds (IX) and (XII) strongly indicate that they contain the reactive configuration where one carbon atom is common to three rings, one of which is a cyclopropane ring. Steroidal compounds possessing this peculiar structure, first suggested by Wallis, Fernholz and Gephart,[5] are called *i*-steroids. Compound (IX) seems to be an *i*-steroid but contrary to all others possesses a negative rotation. Further study will be necessary to determine the structural changes produced by the alumina. A tentative explanation might be the epimerization of the 6-methoxyl group. We have indicated steroids of this structure with β and the ordinary *i*-steroids (dextrorotatory) with α. Consequently, an attempt was made to isomerize compound (XII) to (IX) by treatment with alumina in xylene; however, a hydrocarbon (XVII) resulted. It melted at 162.0–163.0°, gave a specific rotation of −18.5° and analysis for $C_{36}H_{44}$. We suggest as a provisional structure for this hydrocarbon (XVII)



XVII

The β-form of the *i*-methyl ether appears to be more stable than the α-form, and this may explain why it does not give the hydrocarbon on treatment with alumina. As previously stated, heating glacial acetic acid solutions of *i*-steroids usually destroys the *i*-structure, hence, the hydrocarbon (XVII) was subjected to this treatment and curiously enough gave the well-known 3-acetoxy-24,24-diphenyl-5,23-choladiene (VII). It is interesting and unusual that an acetate should be formed by the uncatalyzed addition of acetic acid to a hydrocarbon. The hydrocarbon (XVII) may represent a type of conjugated system where a carbon–carbon double bond is conjugated with the potentially unsaturated cyclopropane ring. Thus, a possible mechanism for this reaction would be the 1,4 (or 1,5)-addition of acetic acid across this system.

The authors wish to thank the Abbott Laboratories, the Glidden Company, the Rockefeller Foundation, and the Upjohn Company for research grants which made this work possible.

Experimental[6]

Methyl 6(α)-Methoxy-*i*-cholenate (III).—A solution of 3.85 g. of methyl 3-*p*-toluenesulfonoxy-5-cholenate[3] and 3.85 g. of fused potassium acetate in 175 ml. of anhydrous methanol was refluxed for eight hours. After most of the solvent was removed, water and ether were added. The aqueous layer was extracted two more times with ether and the combined ether extracts were washed with water, a solution of sodium bicarbonate and finally with water. On drying the ether solution with anhydrous sodium sulfate and removing the ether, 2.77 g. of light yellow sirup remained. The yield varies from 97–100%. The sirup was dissolved in hexane and shaken with finely powdered activated alumina. This seemed to remove some of the color. After filtering off the alumina and removing the hexane under reduced pressure, an almost colorless sirup remained. All attempts to crystallize it failed, $[\alpha]^{21}D$

(5) E. S. Wallis, E. Fernholz and F. T. Gephart, THIS JOURNAL, **59**, 137 (1937).

(6) All melting points are corrected. Microanalyses are by Dr. T. S. Ma, University of Chicago.

+44.1° (79 mg. in 2.42 ml. of chloroform α_D +1.44°; *l*, 1 dm.).

Anal. Calcd. for $C_{26}H_{42}O_3$: C, 77.56; H, 10.52. Found: C, 77.66; H, 10.20.

6(α)-Methoxy-*i*-norcholenyldiphenylcarbinol (IV) from Compound (III).—An ether solution of 2.69 g. of the preceding compound was slowly added to an ether solution of phenylmagnesium bromide prepared from 11 g. of bromobenzene and 1.68 g. of magnesium. The mixture was refluxed for one and one-half hours and then decomposed with ice and a solution of ammonium chloride. The aqueous layer was extracted with ether and the combined ether extracts washed with water, dilute alkali and with water. The ether solution was dried with anhydrous sodium sulfate. Removal of the ether left 4 g. of a yellow sirup. From acetone–petroleum ether 1.972 g. (57%) of crystalline material was obtained. In subsequent runs the yields were above 80%. Crystallization of crude material from acetone–methanol gave white crystals melting at 139.0–140.2°, $[\alpha]^{27}D$ +43.9° (38 mg. in 2.42 ml. of chloroform α_D +0.69°, *l*, 1 dm.).

Anal. Calcd. for $C_{37}H_{50}O_2$: C, 84.36; H, 9.57. Found: C, 84.17; H, 9.55.

3-Hydroxy-5-norcholenyldiphenylcarbinol (V).—On treating 5.5 g. of methyl 3-hydroxy-5-cholenate[3] (I) with an excess of phenylmagnesium bromide as described above, a viscous sirup was obtained. All volatile material was removed by steam distillation; the residue was extracted with ether, dried and the solvent removed. There remained 8.3 g. of sirup from which 3.4 g. of crystalline material was isolated using acetone and methanol as the solvent. Several crystallizations gave white platelets with a peculiar and characteristic m. p. behavior which may be due to the dehydration of the carbinol. The crystals soften at 95°, melt with effervescence, resolidify at 108° and remelt at 169.4–172.2°.

Anal. Calcd. for $C_{36}H_{48}O_2$: C, 84.32; H, 9.44. Found: C, 83.82; H, 9.16.

3-*p*-Toluenesulfonoxy-5-norcholenyldiphenylcarbinol (VI).—A mixture of 1.4 g. of the previously described carbinol (V), 1.08 g. of *p*-toluenesulfonyl chloride and 3 ml. of dry pyridine was warmed slightly to effect solution and allowed to stand at room temperature for twenty-four hours. Water and ether were added to the crystalline mass and the ether layer extracted with water, dilute hydrochloric acid, water, dilute alkali and water. After drying and removing the ether an almost colorless sirup remained. From acetone–petroleum ether 1.47 g. (81%) of crystals, m. p. 143.2–144.0°, were obtained. Several crystallizations again gave material with a peculiar m. p. behavior probably due to the loss of water. It melts at 62°, resolidifies and remelts at 136–137°.

Anal. Calcd. for $C_{43}H_{54}O_4S$: C, 77.44; H, 8.16. Found: C, 77.73; H, 8.33.

6(α)-Methoxy-*i*-norcholenyldiphenylcarbinol (IV) from Compound (VI).—A mixture of 622 mg. of the above *p*-toluenesulfonate (VI), 625 mg. of fused potassium acetate and 100 ml. of anhydrous methanol was refluxed for four hours. The reaction mixture was worked up in the usual manner to give 369 mg. (75%) of white crystals identical with those prepared as described above.

3-Acetoxy-5-norcholenyldiphenylcarbinol (VIII).[7]—A 1.32-g. portion of the crude 3-hydroxy-5-norcholenyldiphenylcarbinol (V) was dissolved in 6 ml. of acetic anhydride and 10 ml. of dry pyridine and allowed to stand at room temperature overnight. The solvent was removed under reduced pressure. The residue was dissolved in acetone and gave 1.17 g. (82%) of crystalline material on standing in the refrigerator. Recrystallization from acetone gave large, clear, flat plates, m. p. 163.2–165.5°. Hattori and Nakamura prepared this compound by a similar method and gave its m. p. as 172–172.5°.

Anal. Calcd. for $C_{38}H_{50}O_3$: C, 82.26; H, 9.08. Found: C, 82.49; H, 9.00.

3-Acetoxy-24,24-diphenyl-5,23-choladiene (VII).—(a) By dehydration of carbinol (VIII): A solution of 1.1 g. of the above carbinol (VIII) in 7 ml. of glacial acetic acid was refluxed for three hours. The acetic acid was removed *in vacuo* and the residue dissolved in acetone from which 1.01 g. (95%) of crystalline material was obtained. Recrystallization from acetone gave brilliantly sparkling, small cubes, m. p. 166.6–167.4°.

Anal. Calcd. for $C_{38}H_{48}O_2$: C, 85.02; H, 9.01. Found: C, 85.18; H, 9.05.

(b) By dehydration and acetylation of carbinol (V): The crude carbinol (V) made from 5.5 g. of methyl 3-hydroxy-5-cholenate,[3] as described above, was dissolved in 40 ml. of glacial acetic acid and 60 ml. of acetic anhydride and refluxed for two hours. The excess acetic anhydride was decomposed by the careful addition of alcohol and heating continued for fifteen minutes, after which the solvent was removed *in vacuo*. The residue crystallized from acetone giving 6.66 g. (88%) of material sufficiently pure, m. p. 165°, for further reactions.

(c) By dehydration, acetolysis and rearrangement of carbinol (IV): When 1.2 g. of carbinol (IV) was dissolved in 15 ml. of glacial acetic acid, refluxed for two hours and worked up in the usual manner, 959 mg. (80%) of the acetoxy-diene was obtained. It gave no melting point depression when mixed with samples prepared by other methods.

3-Hydroxy-24,24-diphenyl-5,23-choladiene (X).—One gram of sodium was dissolved in 150 ml. of 1-propanol to which was added 3.7 g. of the previously described acetoxy-diene (VII). The solution was diluted with water after refluxing two hours. Most of the alcohol was removed under reduced pressure and the product extracted with ether. The ether extract was washed with water, dried and concentrated. On cooling a crystalline mass formed which was separated by filtration and washed with a small quantity of cold acetone. The product weighed 3.01 g. (89%) and melted at 172.2–173°.

Anal. Calcd. for $C_{36}H_{46}O$: C, 87.39; H, 9.37. Found: C, 87.37; H, 9.13.

To 254 mg. of the acetoxy-diene (VII) in 53 ml. of xylene 6 g. of powdered activated alumina was added and the mixture was refluxed for three hours. The alumina was separated by filtration and washed with acetone and ether. The filtrates were combined and the solvents completely removed *in vacuo*. The sirupy residue was dissolved in

(7) J. Hattori and K. Nakamura, *J. Pharm. Soc.* (Japan), **60**, 126 (1940).

acetone–methanol from which several crops of crystals were obtained. The first crop weighed 71 mg. and on recrystallization gave white crystals melting at 173–174°. They gave no melting point depression when mixed with those made by alcoholic saponification.

Anal. Calcd. for $C_{36}H_{46}O$: C, 87.39; H, 9.37. Found: C, 87.20; H, 9.24.

3-*p*-Toluenesulfonoxy-24,24-diphenyl-5,23-choladiene (XI).—A mixture of 3 g. of the well-dried hydroxy-diene (X), 3.01 g. of *p*-toluenesulfonyl chloride and 6 ml. of pyridine was treated as described for the preparation of the *p*-toluenesulfonate (VI) above. The viscous oil, left after the removal of the ether, was dissolved in acetone and cooled, which caused the formation of fine white crystals. They were removed by filtration and washed with petroleum ether; yield 3.35 g. (85%), m. p. 130.6–131.5°.

Anal. Calcd. for $C_{43}H_{52}O_3S$: C, 79.59; H, 8.08. Found: C, 79.31; H, 7.80.

1,1-Diphenyl-2-[6(α)-methoxy-*i*-bisnorcholenyl]-ethylene (XII).—A solution of 1 g. of the *p*-toluenesulfonate (XI), 1 g. of fused potassium acetate in 100 ml. of anhydrous methanol was refluxed for nine hours. The reaction mixture was worked up as described for the preparation of the *i*-methyl ether (III). Removal of the ether gave 878 mg. (100%) of an almost colorless sirup which crystallized from methanol–acetone to give 638 mg. (82%) of large thick needles, m. p. 106–108°. Recrystallization of the needles raised the m. p. to 109.1–110.1°; $[\alpha]^{23}D$ +67.8° (33.2 mg. in 5 ml. of chloroform α_D +0.45°, *l*, 1 dm.).

Anal. Calcd. for $C_{37}H_{48}O$: C, 87.35; H, 9.51. Found: C, 87.65; H, 9.46.

This *i*-methyl ether (XII) was quantitatively converted into the acetoxy-diene (VII) by refluxing in a glacial acetic acid–acetic anhydride solution.

3-Iodo-5-norcholenyldiphenylcarbinol? (XIII).—In an attempt to dehydrate the *i*-methyl ether carbinol (IV) a solution of 100 mg. in 60 ml. of dry xylene containing a few crystals of iodine was refluxed for about two hours. After cooling, the solution was extracted with an aqueous solution of sodium thiosulfate. The xylene solution was dried and the xylene completely removed *in vacuo*. The residue crystallized from acetone giving 60 mg. of shiny prisms, m. p. 168.2–169.4°. Since the compound gave a qualitative test for halogen and the C–H analysis showed only one atom of halogen could be present, we suggest the above structure.

Anal. Calcd. for $C_{36}H_{47}IO$: C, 69.44; H, 7.61. Found: C, 69.28; H, 7.59.

1,1-Diphenyl-2-[6(β)-methoxy-*i*-bisnorcholenyl]-ethylene? (IX).—A solution of 678 mg. of the *i*-methyl ether carbinol (IV) in 125 ml. of dry xylene was concentrated by slowly distilling about 15 ml. of xylene. The solution was then refluxed for three hours after adding 10 g. of powdered activated alumina. A calcium chloride tube was attached to the top of the condenser during the heating. The alumina was separated by filtration and washed with ether. The solvents were removed *in vacuo* and the residue was crystallized from an acetone–methanol mixture. The first crop weighed 304 mg., m. p. 156–158°, but was not homogeneous. Several crystallizations were required before pure material was obtained melting at 161.8–163°, $[\alpha]^{25}D$ −38.6 ± 2° (55.7 mg. in 5 ml. of chloroform, α_D −0.43 ± 0.02°, *l*, 1 dm.).

Anal. Calcd. for $C_{37}H_{48}O$: C, 87.35; H, 9.51. Found: C, 87.72, 87.70; H, 9.06, 9.46.

A solution of 46 mg. of the above compound in 15 ml. of glacial acetic acid and 5 ml. of acetic anhydride was refluxed for two and one-half hours and the reaction mixture worked up in the usual manner. This gave 32 mg. of material melting at 160–165°. Recrystallization from acetone–methanol gave large prisms melting at 165–167° and giving no melting point depression when mixed with an authentic sample of compound (VII). It required more strenuous conditions for this conversion than with compound (XII).

Methyl 3-Methoxy-5-cholenate (XV).—A solution of 5.46 g. of *p*-toluenesulfonate[3] (II) in 150 ml. of anhydrous methanol was refluxed for seven hours. On cooling, crystals formed which weighed 3.79 g. (93.5%) and melted at 108.5–109°. The filtrate was concentrated, diluted with water and extracted with ether. The ether extract was washed with water, dilute alkali and dried. The residue, after removing the ether, gave additional crystalline material from methanol sufficient to make the crude yield practically quantitative. Further crystallization from methanol raised the m. p. to 109.2–109.6°, $[\alpha]^{22}D$ −44.6° (70.5 mg. in 2.42 ml. of chloroform α_D −1.30°, *l*, 1 dm.).

Anal. Calcd. for $C_{26}H_{42}O_3$: C, 77.56; H, 10.52. Found: C, 77.60; H, 10.60.

3-Methoxy-5-norcholenyldiphenylcarbinol (XVI).—Two grams of the above ester (XV) was treated with an excess of phenylmagnesium bromide and the reaction mixture was worked up as described for the preparation of compound (V). The residue left after removing the ether was crystallized from acetone–chloroform giving 2.26 g. (96%) of product melting at 164.8–165.9°.

Anal. Calcd. for $C_{37}H_{50}O_2$: C, 84.36; H, 9.57. Found: C, 84.38; H, 9.58.

3-Methoxy-24,24-diphenyl-5,23-choladiene (XIV).—(a) By dehydration of carbinol (XVI): The previously described carbinol (XVI) was quantitatively dehydrated by refluxing a glacial acetic acid solution for two and one-half hours. The product was crystallized from an acetone–methanol mixture, m. p. 114.5–115.3°, $[\alpha]^{24}D$ −11.55 ± 0.66° (62.8 mg. in 5 ml. of chloroform α_D −0.145°, *l*, 1 dm.).

Anal. Calcd. for $C_{37}H_{48}O$: C, 87.35; H, 9.51. Found: C, 87.14; H, 9.25.

(b) By rearranging the *i*-methyl ether (XII): The *i*-methyl ether ethylene (XII) was smoothly and quantitatively rearranged by refluxing a methanol solution containing a few drops of sulfuric acid. This was confirmed by a melting point and mixed m. p.

(c) By rearranging the *i*-methyl ether (IX): By exactly the same procedure as described in (b) the *i*-methyl ether ethylene (IX) was smoothly and quantitatively rearranged to the normal methyl ether. This was again confirmed by a melting point and a mixed m. p.

Hydrocarbon $C_{36}H_{44}$ (XVII).—In an attempt to rearrange the synthetic *i*-methyl ether ethylene (XII) to

that obtained by the alumina dehydration of carbinol (IV) a hydrocarbon was obtained instead. Ten ml. of solvent was slowly distilled from a solution of 500 mg. of the *i*-methyl ether (XII) in 100 ml. of xylene. To the remaining solution was added 8 g. of powdered activated alumina and the mixture was refluxed for three hours. The alumina was separated by filtration and washed with acetone. The acetone–xylene filtrates were concentrated *in vacuo* and the residue was dissolved in an acetone–methanol mixture from which there was obtained 320 mg. of crystalline material. Several crystallizations gave thick needles melting at 162.0–163.0°, $[\alpha]^{25}D$ −18.5° (51.3 mg. in 5 ml. of chloroform α_D −0.19°, *l*, 1 dm.). The needles fluoresced in ultraviolet light.

Anal. Calcd. for $C_{36}H_{44}$: C, 90.70; H, 9.30. Found: C, 90.35; H, 9.33.

A solution of 48 mg. of the above hydrocarbon (XVII) in 15 ml. of glacial acetic acid was refluxed for four hours. The solvent was removed under reduced pressure and the colorless sirup crystallized from acetone–methanol to give 35 mg. of brilliant cubes, m. p. 165–166.5°. From the mother liquors a second crop of 8 mg. was obtained. There was no melting point depression when the substance was mixed with the acetoxy-diene (VII).

Summary

1. 6(α)-Methoxy-*i*-norcholenyldiphenylcarbinol (IV) was prepared by two different methods.

2. The dehydration product of the carbinol (IV) by treatment with activated alumina in boiling xylene was considerably different from compound (XII) where the unsaturated side chain (R_3') was prepared by conventional methods before introducing the *i*-methyl ether configuration. We have tentatively suggested that this may be due to the epimerization of the 6-methoxyl group.

3. In an attempt to epimerize the synthetic product (XII), by alumina in boiling xylene, an interesting hydrocarbon (XVII) was obtained.

4. Heating the hydrocarbon (XVII) in acetic acid caused the addition of acetic acid forming a normal acetate. A mechanism for this reaction has been proposed.

5. Several intermediates and conversion products have been described.

EVANSTON, ILLINOIS RECEIVED MAY 18, 1942

[COMMUNICATION NO. 854 FROM THE KODAK RESEARCH LABORATORIES]

The Action of Alkaline Reagents on the Bimolecular Product Formed by the Action of Acidic Dehydrating Agents on Anhydracetonebenzil

BY C. F. H. ALLEN AND J. W. GATES, JR.

The bimolecular product I that results from the action of acidic dehydrating agents on anhydracetonebenzil is a very reactive substance, having many points of attack for reagents. In this paper are described the results secured by the use of alkaline reagents.

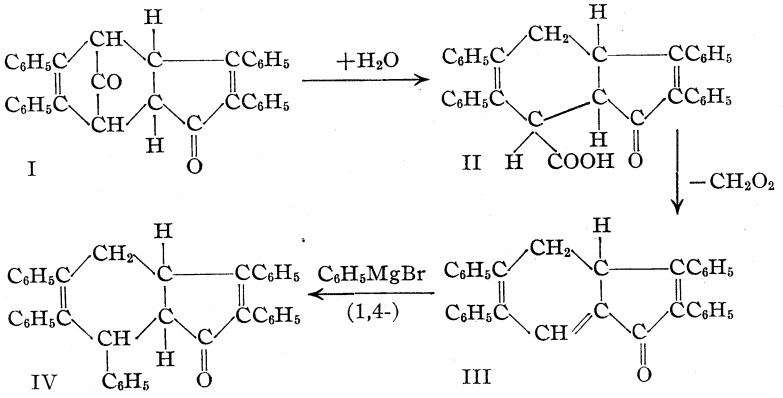
It had previously been observed[1] that Japp's chloride was converted to the bimolecular product by a short (ten-minute) treatment with alcoholic potash, whereas a longer time resulted in a viscous product.[2] It has now been found that this material, also obtainable directly from the bimolecular product itself, will crystallize in time, or at once, if seeded, and that it is mainly a carboxylic acid. The use of sodium methylate or ethylate gives the corresponding methyl and ethyl esters in a few minutes; the ethyl ester has been hydrolyzed to the acid, and the latter re-esterified by diazomethane and also converted to an anilide.

(1) Allen and Spanagel, THIS JOURNAL, **55**, 3773 (1933).
(2) Allen and Rudoff, *Can. J. Res.*, **B15**, 327 (1937).

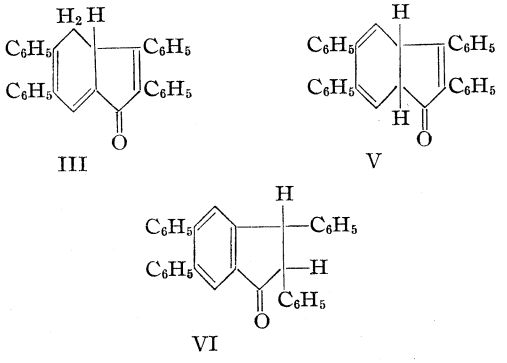
Analyses show that the only change is the addition of one molecule of water (or alcohol, depending upon the reagent); hence the carboxyl group must comprise one of the two carbonyl groups present originally. Since the acid does not lose carbon monoxide when heated, it is the carbonyl bridge that has been cleaved. The bimolecular product and the esters are not attacked by permanganate in acetone, perhaps because of their insolubility, but the sodium salt of the acid is easily oxidized. During the reaction the carboxyl group disappears, and a dienone is formed; this new dienone is an isomer of the one (V) previously obtained by heating the bimolecular product, when the carbonyl bridge is lost as carbon monoxide.[1] Analyses show that the loss, in the case of the acid, is CH_2O_2.

The new dienone is an α,β-unsaturated ketone (III), for it gives both 1,4- and 1,2-addition with the Grignard reagent; this establishes the location of one double bond. Although there is, to be sure, another α,β-unsaturated system involving the

indene ring, the possibility of 1,4-addition of the Grignard reagent to this is excluded by the observation that other indenones containing the same system give only carbinols, formed by 1,2-addition. Taken in conjunction with the disappearance of the carbonyl bridge by alkali, the structure of the acid II follows. The oxidation results are accounted for by a retrograde Michael reaction, in which formic acid (CH_2O_2) is split off, and destroyed by the permanganate.

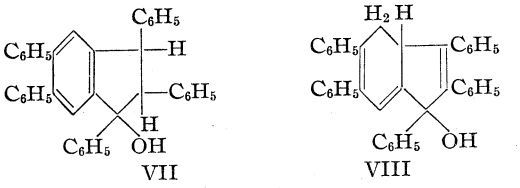


The new dienone III, in contrast to the isomer previously described,[2] does not add maleic anhydride, but, like it, is isomerized by heating to the known indanone VI. The only difference is in the position of the extra hydrogen atoms and double bonds; that is, these are allylic systems, in which rearrangements occur with the greatest of ease; the most stable form is that of the indanone VI, owing to its aromatic structure. The mobility of



the systems makes it almost impossible to state positively which structure goes with which substance, but the available evidence seems to be in best agreement with the structures as assigned.

Even as gentle a reagent as phenylmagnesium bromide is not useful. For example, the carbinol VIII, formed by 1,2-addition and mentioned above, is isomeric with one (VII) easily obtained from the indanone VI, whereas the dienone V



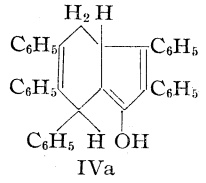
forms a glasslike product with phenylmagnesium bromide.[3] All give the same hydrocarbon on removal of water, that is, there must have been a rearrangement in two of the dehydrations. These reactions will form the subject of a later paper.

When attempts were made to repeat the earlier preparation of the dienone (V), the results were erratic; sometimes it was readily isolated after decarbonylation of the bimolecular product, but at others, under what appeared to be identical conditions, only the rearrangement product, the indanone VI, could be obtained. This difficulty was traced finally to small amounts of sulfuric acid in the bimolecular product (the latter was always formed in the presence of that acid). The mineral acid was thereafter eliminated by adding potassium acetate to the solution from which crystallization took place.

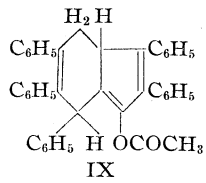
This result influenced us to examine the effect of acid alone upon the dienone V; it was found that mineral acids brought about an isomerization to a different dienone—which proved to be identical with III, described above. Both these, on heating, gave the indanone VI. This is an additional instance of the mobility of the allylic systems present in this series.

The 1,4-addition product IV probably exists largely in the enolic modification IVa, for it evolves 0.7 equivalent of methane when treated with methylmagnesium iodide, and gives an enol acetate IX with acetyl chloride. The latter consumes two equivalents of methylmagnesium iodide, and regenerates the enol; this is the usual behavior of an enol acetate. It is readily brominated, forming a monobromo ketone X, which is unaffected by acetyl chloride. The bromine is in the *alpha* position, since it is removed by methylmagnesium iodide, with regeneration of the starting material.

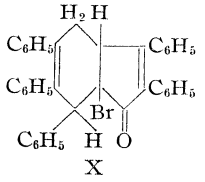
(3) The absence of mineral acid was ensured by decomposition of the complex with ammonium chloride; otherwise, dehydration occurs and the carbinol cannot be isolated.



IVa



IX



X

Experimental

I. The Acid, 3a,4,7,7a-Tetrahydro-2,3,5,6-tetraphenyl-7-carboxyindenone-1 (II) and Related Substances.—The bimolecular product I, 3a,4,7,7a-tetrahydro-2,3,5,6-tetraphenyl-4,7-methanoinden-1,8-dione, was prepared in the usual way,[1] but the benzene solution was refluxed for half an hour, after the addition of anhydrous sodium or potassium acetate, filtered hot and diluted with twice the volume of alcohol or petroleum ether. The average yield of several preparations was 90%.

The acid II was secured as follows. To an alcoholic solution of potassium hydroxide (23 g. in 300 cc.) was added 46.4 g. of the bimolecular product, and the mixture refluxed for four hours; at the end of this time all the solid had dissolved. The solution was poured into 2 l. of water, 70 cc. of concentrated hydrochloric acid added, and the mixture extracted with three 100-cc. portions of chloroform. After drying the extract, distilling two-thirds of the solvent, and diluting with an equal volume of benzene and two volumes of petroleum ether, the acid separates in a yield of 38 g. (79%). After purification from benzene–ligroin, it forms prisms which melt at 275–276°. It is practically insoluble in absolute ethanol.

Anal. Calcd. for $C_{34}H_{26}O_3$: C, 84.7; H, 5.4. Found: C, 84.3; H, 5.3.

The methyl ester, prepared by use of sodium methylate, separated when the solution was chilled after three hours; the yield was 76%, and it forms prisms that melt at 193°. It also resulted when the acid was esterified by diazomethane.

Anal. Calcd. for $C_{35}H_{28}O_3$: C, 84.6; H, 5.4. Found: C, 84.3; H, 5.7.

The ethyl ester was secured in a similar manner but only ten minutes of refluxing was required. Some acid was formed during the manipulation; this was removed by triturating the oil with absolute ethanol. The ethyl ester crystallizes in prisms from alcohol–petroleum ether; m. p. 159–160°.

Anal. Calcd. for $C_{36}H_{30}O_3$: C, 84.7; H, 5.9. Found: C, 84.9; H, 5.9.

The anilide was prepared from the acid chloride in the usual manner; it forms prisms from benzene–petroleum ether; m. p. 269°.

Anal. Calcd. for $C_{40}H_{31}O_2N$: N, 2.5. Found: N, 2.5.

II. The Dienone III, 3a,4-Dihydro-2,3,5,6-tetraphenylinden-1-one.—Twenty-four grams of the acid was dissolved in 2 l. of 3% potassium carbonate, and, while stirring at 85–95°, 350–370 cc. of 6% aqueous potassium permanganate was added dropwise; a yellow precipitate was formed. The cooled suspension was extracted with three 150-cc. portions of chloroform, the solvent removed, and the residue recrystallized from xylene or acetic acid. It forms lemon-yellow prisms that melt at 239–240°. The yield was 12 g. (56%).

Anal. Calcd. for $C_{33}H_{24}O$: C, 90.8; H, 5.5. Found: C, 90.7; H, 5.5.

The isomeric dienone V, reported previously as being obtained by a carefully controlled pyrolysis, resulted in a 70–75% yield by heating the purified bimolecular product for only five to six minutes at 220–225°. When 10 g. of this dienone (m. p. 167°) was suspended in 50 cc. of glacial acetic acid and treated with 5 cc. of 32% hydrogen bromide in acetic acid, the solution became dark red; after warming for half an hour on the steam-bath, the dienone III crystallized quantitatively. A dilute solution of sulfuric acid in acetic acid brought about the isomerization equally well.

The new dienone does not add maleic anhydride. In the Grignard machine it shows one addition without evolution of gas. It isomerized to the indanone VI by heating for half an hour at 300°.

1,2,3,5,6-Pentaphenylindanol-1, VII, was obtained by the action of phenylmagnesium bromide upon the indanone VI in ether in the usual way, decomposing the complex with ammonium chloride. It crystallizes in prisms from benzene–petroleum ether; m. p. 228–229° with dec.

Anal. Calcd. for $C_{39}H_{30}O$: C, 91.0; H, 5.8. Found: C, 90.5; H, 5.7.

This carbinol gave the hydrocarbon, m. p. 222°, described below, when treated with an acetic acid solution of sulfuric acid. The dienone V gave a glasslike carbinol, which formed the same hydrocarbon upon dehydration.

III. The Grignard Reaction.—To a solution of phenylmagnesium bromide (4.8 g. of magnesium, 31.5 g. of bromobenzene, 200 cc. of ether) at room temperature was added a suspension of 25 g. of the dienone III in 50 cc. of ether. After stirring for one hour, the mixture was decomposed by ammonium chloride, and the oily product worked up by an appropriate manipulation; it was found advantageous to inoculate the dried and concentrated solution with some of the carbinol VIII from a previous preparation, and remove it first. The second product was the ketone IV. When the Grignard mixture was decomposed by mineral acid, the hydrocarbon was obtained instead of the carbinol, being isolated after the ketone.

The carbinol, 3a,4-dihydro-1,2,3,5,6-pentaphenylinden-1-ol (VIII) was obtained in a yield of 25%; it separates from benzene–ligroin in needles, m. p. 233°.

Anal. Calcd. for $C_{39}H_{30}O$: C, 91.0; H, 5.8. Found: C, 91.0; H, 6.0.

The hydrocarbon crystallizes in bunches of prisms from benzene–ligroin; m. p. 222°.

Anal. Calcd. for $C_{39}H_{28}$: C, 94.4; H, 5.7. Found: C, 94.1; H, 5.6.

This hydrocarbon does not add maleic anhydride, nor is it affected by hydrogen bromide in acetic acid.

The ketone, 3a,4,7,7a-tetrahydro-2,3,5,6,7-pentaphenyl-

inden-1-one (IV, IVa), forms prisms on crystallization from benzene–petroleum ether. The melting point is usually 178–179°, but occasionally a low-melting form is obtained; this melts at 145–146°, but on admixture with the higher melting form, the observed melting point is 178–179°.[4] The yield was 60%.

Anal. Calcd. for $C_{39}H_{30}O$: C, 91.1; H, 5.9. Found: C, 90.9; H, 6.1.

This ketone does not react with maleic anhydride nor form an oxime. In the Grignard machine it evolves 0.67 mole of methane, indicating that it is enolized to a considerable extent. An acetate is secured in a 70% yield by refluxing an acetyl chloride solution for half an hour; it separates from benzene–ligroin in prisms that melt at 115°.

Anal. Calcd. for $C_{41}H_{32}O_2$: C, 88.5; H, 5.8. Found: C, 88.1; H, 6.0.

When treated quantitatively with methylmagnesium iodide, the acetate consumes two equivalents of reagent without evolution of gas; upon acidification the ketone IV is obtained.

The bromoketone, 3a,4,7,7a-tetrahydro-7a-bromo-2,3,5,6,7-pentaphenylinden-1-one (X) was secured by bromination in chloroform in the usual manner; it crystallized from chloroform–alcohol solution in pale yellow rods; m. p. 218–219°. It separated from benzene solutions in pointed rods with solvent of crystallization; the solid softened at about 144°, finally melting at 234°.

Anal. Calcd. for (A) $C_{39}H_{29}OBr$: Br, 13.5; for (B) $C_{39}H_{29}OBr \cdot C_6H_6$: C, 80.5; H, 5.2; Br, 11.9. Found: (A) Br, 13.8, 13.2; (B) C, 80.4, 80.2; H, 5.1, 5.1; Br, 11.9, 12.0.

In the Grignard machine both forms consume one mole of reagent without evolution of gas, and regenerate the parent ketone IV.

The bromine is not removed by pyridine or potassium acetate (*e. g.*, there is no adjacent hydrogen atom in the *alpha* position to the carbonyl group) but alcoholic potash gave an intractable black oil. It is unaffected by hydrogen bromide, by acetyl chloride, or by excess bromine.

(4) Drs. Jelley and Titus of these Laboratories report that examination of these substances failed to show any significant differences of readily determinable optical properties.

Summary

The bimolecular product, resulting from the action of acidic dehydrating agents upon anhydracetonebenzil, is transformed into a carboxylic acid by the action of alkaline reagents. The carbonyl bridge disappears in the process, being converted into the carboxyl group.

The acid is decarboxylated and dehydrogenated to give a new dienone, isomeric with one previously known.

The new dienone is also obtained by the action of mineral acids on the one described earlier, and both are isomerized to the same known indanone by acids or heat.

The new dienone gives products with phenylmagnesium bromide formed by both 1,2- and 1,4-addition. The 1,4-addition product is an easily enolizable ketone.

The 1,2-addition product is a carbinol, isomeric with one obtained from the closely related indanone. Both are dehydrated to the same hydrocarbon, which is also formed from the isomeric dienone.

ROCHESTER, NEW YORK RECEIVED MAY 5, 1942

[COMMUNICATION NO. 855 FROM THE KODAK RESEARCH LABORATORIES]

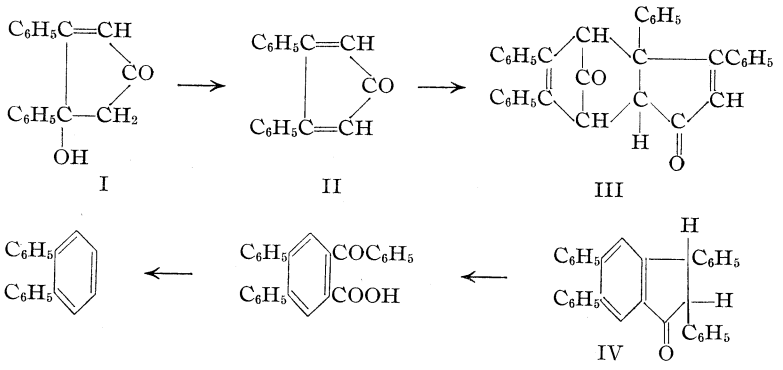
The Structure of the Bimolecular Product Formed by the Action of Acidic Dehydrating Agents on Anhydracetonebenzil

BY C. F. H. ALLEN AND J. W. GATES, JR.

Several years ago[1] from an examination of the substance obtained by degrading the bimolecular product, formed by the action of acidic dehydrating agents upon anhydracetonebenzil I, a structure, III, which seemed in best accord with the available evidence, was suggested for this substance and a mechanism proposed to account for its formation. Others interested in this field[2,3] appear to have accepted these conclusions. The salient features were the dehydration of anhydracetonebenzil to diphenylcyclopentadienone II, which then underwent a diene synthesis with itself, forming the bimolecular product III. The latter lost carbon monoxide on heating, to give an indenone that was rearranged to an isomeric indanone IV, which was then degraded, stepwise, by unambiguous reactions to *o*-terphenyl. Later on[4] several of the intermediate degradation products were synthesized, so that the position of the various groups around the benzene ring was established. Only the pertinent formulas are given below.

The two novel features were the presence of a phenyl group on a carbon atom common to two

(1) Allen and Spanagel, THIS JOURNAL, **55**, 3773 (1933).
(2) Dilthey, private communication.
(3) Burton and Shoppee, *J. Chem. Soc.*, 201 (1934).
(4) Allen, Bell, Bell and VanAllan, THIS JOURNAL, **62**, 656 (1940).

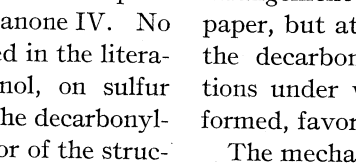


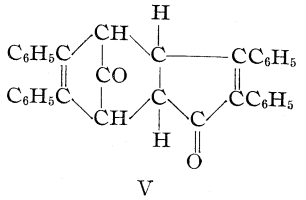
I II III

IV

rings in III, and its apparent 1,3-shift to the position in which it is found in the indanone IV. No similar instances have been recorded in the literature. The formation of thiophenol, on sulfur fusion of the dienone formed after the decarbonylation of III, was interpreted in favor of the structure having the phenyl group on the bond common to the two rings, by analogy with the behavior under similar conditions of Ruzicka's alkyl decalins.[5] Further work was accordingly undertaken, with the view of clearing up the uncertainty.

As a result[6] isomeric indenones were discovered and the prevalence of allylic rearrangements in the series was noted. It was found that sulfur dehydrogenation (a high temperature reaction) gave varying amounts of thiophenol in instances where there was no reasonable doubt as to the absence of an angular phenyl group, so this argument lost its force. Furthermore, had the phenyl group been in this position, there should have been more isomers than were found experimentally. Finally, it has been possible[6] to open one ring to form a monocarboxylic acid, which, on oxidation with permanganate, in alkaline solution, gave one of the dienones—all the reactions taking place below 100° under conditions too mild to bring about such a drastic change as a migration of a phenyl group. It has, thus, seemed necessary to abandon both concepts, and to conclude that the phenyl group is in the position where it is found in the indanone, *alpha* to the carbonyl; the new structure is written in formula V.

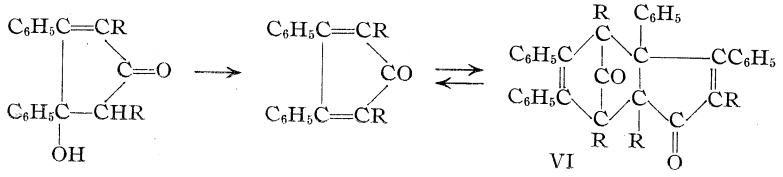




V

It differs from the older one first proposed[1] only in an interchange of the angular phenyl group and one hydrogen atom. This was accounted for by assuming a 1,3-shift of a phenyl group. Such a rearrangement was, indeed, proposed in the first paper, but at a different point, namely, following the decarbonylation. The experimental conditions under which the bimolecular products are formed, favor such allylic rearrangements.

The mechanism of the reaction is, as previously outlined, a diene synthesis. Alternative interpretations have had to be excluded, because of the various experimental conditions under which the bimolecular product can be formed, and the fact that substituted anhydracetonebenzils can partake only if there is at least one hydrogen atom left to be removed as water with the hydroxyl group (this is, of course, essential to the production of the intermediate cyclopentadienone).



VI

Now, when in the bimolecular product, R = H, it will exchange (an allylic rearrangement) with the angular phenyl group, giving a substance of type V, but if both R's = CH_3, there will be no further change—in fact, it has been shown that this type, VI, dissociates into its components in most reactions.[7] Any open-chain structure for the bimolecular product is also excluded because such a structure would be impossible with the dimethyl homolog (both R's = CH_3).

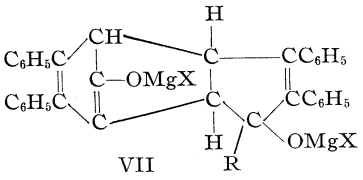
The behavior of the bimolecular product with the Grignard reagent is unusual; in the Grignard machine it shows one active hydrogen and one addition. Previous work[6] has shown that in indenones the carbonyl group always gives carbinols, and that a carbonyl bridge does likewise in the absence of adjacent *alpha* hydrogen atoms.[7] Since the product is always a monocarbinol, that

(5) Ruzicka, *Helv. Chim. Acta*, **5**, 349 (1922).

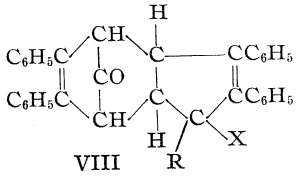
(6) Allen and Gates, THIS JOURNAL, **64**, 2120 (1942).

(7) Allen and VanAllan, *ibid.*, **64**, 1260 (1942).

loses carbon monoxide on heating, it is the keto group on the indene ring that has been attacked, *i. e.*, the one addition has occurred here. But, since no exposed carbonyl group could persist unchanged, the carbonyl bridge must have been protected in some way from the action of the excess reagent. The obvious explanation is that it forms an enolate, VII, thus accounting for the one active hydrogen observed; acidification then regenerates the original carbonyl group.



VII

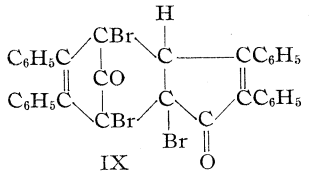


VIII

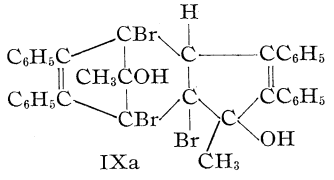
Carbinols, VIII (X = OH), have been prepared in which R = CH_3, C_6H_5, α-$C_{10}H_7$. All carbinols lost carbon monoxide and water, when heated, and gave hydrocarbons. The carbinols were studied in more detail; in the Grignard machine they showed two active hydrogens (one due to enolate and one to carbinol). The hydroxyl was replaced by halogens on treatment with acid halides; they gave isomeric acetates with acetic anhydride and acetyl chloride. The acetates (VIII: R = CH_3, X = $OCOCH_3$) showed one active hydrogen and two additions in the Grignard machine, and regenerated the carbinol, as would be expected.

The bimolecular product was previously reported[1] to give two stereoisomeric dioximes. Both of these have now been hydrolyzed, with production of the bimolecular product; this excludes the possibility that the starting material was a mixture.

The bimolecular product was brominated to form a tribromoketone IX, gave a monochloroketone with phosphorus pentachloride, did not condense with aromatic aldehydes, and was destroyed by concentrated sulfuric acid. The tribromoketone is the result of complete replacement of all the available hydrogen atoms in the *alpha* positions to both carbonyl groups. Its formation excludes any of the open-chained isomeric structures that might be written, confirming the conclusion already mentioned above, concerning the formation of bimolecular products from substituted anhydracetonebenzils. In the Grignard machine it consumes two moles of reagent without evolution of gas. The product is a di-carbinol IXa, for it evolves two equivalents of gas when treated with excess methylmagnesium iodide. These reactions afford confirmation of the assumption previously made in regard to the bimolecular product, that the production of gas is connected with the presence of an enolizable hydrogen; in the tribromoketone there is no *alpha* hydrogen, and the two carbonyl groups behave normally, giving two additions.



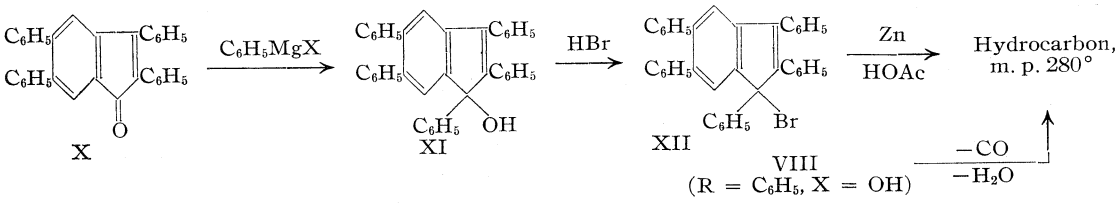
IX



IXa

The monochloroketone is isomeric with one described as a result of chlorination of 3,4-diphenylcyclopenten-3-one-1.[8]

It was mentioned earlier that hydrocarbons were formed by loss of water during decarbonylation. From the phenyl carbinol (VIII: R = C_6H_5, X = OH) the hydrocarbon obtained was identical with one secured from 2,3,5,6-tetraphenylindenone X by the following sequence of reactions

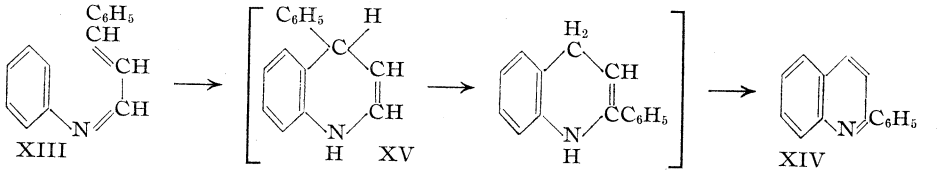


X XI XII VIII (R = C_6H_5, X = OH)

It is obvious from inspection of the formulas that in one instance there has been a rearrangement. The substance in question is also isomeric with a closely related hydrocarbon described previously[6]; a discussion of these and other related compounds will be considered separately.

(8) Burton and Shoppee, *J. Chem. Soc.*, 205 (1934).

One other instance, best explained as a 1,3-shift of a phenyl group, has been found in the literature. When cinnamalaniline XIII is heated in acid solution, it forms 2-phenylquinoline XIV.[9] It must be assumed *either* that a 1,3-shift of a phenyl group is involved, *or* that the anil is hydrolyzed in part to its components, the aniline so formed then adding to a molecule of unchanged anil, with subsequent ring closure and dehydrogenation. In considering the first alternative, it should be noted that *before* dehydrogenation the substance XV has an allylic system, in which rearrangements are facile and common.



XIII XV XIV

The explanation involving a 1,3-shift of a phenyl group seems preferable in this case, for Peine showed that cinnamalaniline showed a remarkable stability to acids, there being but a very slight hydrolysis to the components. It is much simpler than the necessary series of consecutive reactions required by the second alternative. We have found that cinnamalaniline is monomolecular, thus excluding interpretations involving polymeric forms.

Experimental

The bimolecular compound V and its two dioximes were prepared as reported previously.[1] Both dioximes (m. p. 176 and 229°) were hydrolyzed by refluxing a suspension of 4 g. of the dioxime in 100 cc. of alcohol containing 25 cc. of concentrated hydrochloric acid for twenty-four hours; after cooling, the precipitate was filtered. The yield was 2.5 g.; the melting point, 202–204°, was not lowered when mixed with the pure bimolecular product.

Bromination: 3a,4,7,7a-Tetrahydro-2,3,5,6-tetraphenyl-4,7,7a-tribromo-4,7-methanoinden-1,8-dione, IX; a mixture of 100 cc. of glacial acetic acid and 5 g. each of bromine and the bimolecular product was heated on the steam-bath for seventy-two hours; after the usual manipulative procedures, 1.5 g. of tribromoketone was obtained. It crystallizes from benzene–ligroin in prisms, m. p. 229–230°.

Anal. Calcd. for $C_{34}H_{21}O_2Br_3$: Br, 34.2. Found: Br, 33.6.

2,3,5,6-Tetraphenyl-1,8-dimethyl-4,7,7a-tribromo-1,8-dihydroxy-3a,4,7,7a-tetrahydro-4,7-methanoindene, IXa, was formed when the diketone IX reacted with methylmagnesium iodide. It crystallizes from benzene–ligroin in rods, m. p. 278°.

Anal. Calcd. for $C_{36}H_{29}O_2Br_3$: C, 58.9; H, 4.0; Br, 32.7. Found: C, 59.2; H, 3.7; Br, 33.0.

It evolved two equivalents of methane in the Grignard machine, consuming 2.7 moles of reagent. Upon acidification, most of the starting material was recovered unchanged.

Chlorination: The monochloroketone was secured by refluxing for one-half hour a benzene solution of 4.6 g. of the bimolecular product and 6.2 g. of phosphorus pentachloride. It separates in prisms from benzene, m. p. 215°.

Anal. Calcd. for $C_{34}H_{23}O_2Cl$: Cl, 7.1. Found: Cl, 6.6.

The Grignard reaction products (carbinols, VIII) were prepared in the usual manner with yields of 75–85%. There was nothing new in the experimental procedures employed when they were treated with acetyl chloride, acetic anhydride and a trace of sulfuric acid, thionyl chloride, hydrogen bromide in glacial acetic acid or phosphorus pentachloride. The properties of the various compounds are given in Table I.

TABLE I

PROPERTIES OF SUBSTANCES RELATED TO THE CARBINOLS

Formula VIII R	X	Yield, %	M. p., °C.	Analyses, % Calcd. C	H	Found C	H
CH_3	OH	80[a]	262	87.5[e]	5.8	87.6	5.8
CH_3	$OCOCH_3$	75[b,f]	202	85.1[h]	5.7	85.3	5.8
CH_3	$OCOCH_3$	75[b,g]	180	85.1[h]	5.7	84.9	5.9
CH_3	Cl[i]	50[d]	219	(Cl 7.1)		(Cl 7.3)	
CH_3	Br[j]	60[b]	191	(Br 14.7)		(Br 14.3)	
C_6H_5	OH	81[a]	226	88.6[e]	5.5	88.6	5.5
C_6H_5	$OCOCH_3$	30[c,g]	235	86.3[h]	5.5	86.6	5.6
C_6H_5	Cl	50[b,k]	216	(Cl 6.3)		(Cl 6.4)	
α-$C_{10}H_7$	OH	80[a]	295	89.2[e]	5.4	89.1	5.5
α-$C_{10}H_7$	Br[j]	85[b]	233	(Br 12.2)		(Br 12.2)	

[a] Prisms, from xylene. [b] Prisms, from benzene–petroleum ether. [c] Rods, from benzene–petroleum ether. [d] Needles, from benzene–petroleum ether. [e] Two active hydrogens, no addition in Grignard machine. [f] Action of acetyl chloride. [g] Action of acetic anhydride and one drop of concentrated sulfuric acid. [h] One active hydrogen, two additions in Grignard machine and recover carbinol. [i] Action of phosphorus pentachloride. [j] Action of 32% hydrogen bromide in acetic acid. [k] Action of thionyl chloride.

2,3,5,6-Tetraphenylindenone X was obtained in a 20% yield from the indenone, m. p. 167°,[1] or in a 70% yield from its isomer, m. p. 240°,[6] by heating at 220–280° for fifteen minutes with sulfur; there is a strong odor of thiophenol in each instance.

1,2,3,5,6-Pentaphenylindenol-1, XI, was obtained in a yield of 87% from 2,3,5,6-tetraphenylindenone and phenylmagnesium bromide in the usual manner. It separates from benzene–petroleum ether in prisms, m. p. 220°.

Anal. Calcd. for $C_{39}H_{28}O$: C, 91.4; H, 5.5. Found: C, 91.2; H, 5.5.

(9) Peine, *Ber.*, **17**, 2117 (1884).

1,2,3,5,6-Pentaphenyl-1-bromoindene, XII, resulted on warming an acetic acid solution of hydrogen bromide (30–32%) with one-fourth its weight of the above carbinol for one hour; it was then cooled and diluted with an equal volume of acetic acid; the yield was 89%. It forms prisms, m. p. 203°.

Anal. Calcd. for $C_{39}H_{27}Br$: Br, 13.9. Found: Br, 13.6.

The hydrocarbon, m. p. 280°, was isolated, after refluxing a mixture of 4 g. of the bromoindene, 10 g. of zinc dust, and 50 cc. of acetic acid for three hours, by pouring into 200 cc. of water. The hydrocarbon crystallized on chilling the chloroform extract of the aqueous mixture. It separates in prisms.

The same hydrocarbon was formed by heating the phenyl carbinol (m. p. 226°) of the bimolecular product at 290–310° for one hour; steam and carbon monoxide were evolved. The residue was crystallized from chlorobenzene.

The α-naphthyl homolog was prepared in a similar manner; it forms tiny prisms, m. p. 298°.

Anal. Calcd. for (280°) $C_{39}H_{28}$: C, 94.4; H, 5.7; for (298°) $C_{43}H_{30}$: C, 94.5; H, 5.5. Found: (280°) C, 93.9; H, 5.6; (298°) C, 94.3; H, 5.5.

Cinnamalaniline[10] is monomolecular in boiling alcohol, the calculated value being 187, whereas 194 was found.

Acknowledgment.—We are greatly indebted to Dr. Bell of this Laboratory for the many quantitative examinations, in the Grignard machine, of the substances described in this and related papers.

Summary

A new structure, differing only in the position of a phenyl group and a hydrogen atom, has been proposed for the bimolecular product resulting from the action of acidic dehydrating agents upon anhydracetonebenzil. The new structure is in better accord with the chemical behavior of the substance.

The nature of the Grignard reaction products and related substances is described. A tribromo substitution product has been obtained.

(10) Doebner and Miller, *Ber.*, **16**, 1665 (1883). We are indebted to Mr. VanAllan for the preparation of this substance.

ROCHESTER, N. Y. RECEIVED MAY 26, 1942

[COMMUNICATION NO. 856 FROM THE KODAK RESEARCH LABORATORIES]

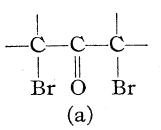
The Structures of Certain Highly Arylated Indenones and their Behavior with Bromine

BY C. F. H. ALLEN AND J. W. GATES, JR.

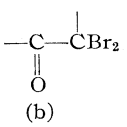
Some time ago[1] it was shown that decarbonylation of the bimolecular product that resulted from the dehydration of anhydracetonebenzil gave a dienone that was rearranged by gentle heating to an isomeric indanone I. On account of the peculiar features of this rearrangement, it was considered desirable to examine the behavior of these substances with other reagents. The action of bromine upon these and closely related substances is described in this paper, and the pertinent structures are discussed. Owing to the reactivity of the system and to the many possible structures, it usually takes a sequence of reactions to enable one to draw significant conclusions.

With one equivalent of bromine, the indanone I gives a monobromoketone, which, with an excess of the reagent, forms a dibromo compound; hydrogen bromide is evolved in both reactions. When the dibromo compound is treated with the Grignard reagent,[2] the monobromoketone is reformed, and a subsequent treatment of this with more Grignard reagent removes the remaining bromine atom and furnishes a fourth, isomeric dienone. The new indenone is very sensitive to heat reverting to its isomer I below its melting point. For this reason, its reactions appear to be those of the indanone, *e. g.*, both give the same dibromo substitution product, and the same phenyl carbinol. Neither of the bromoketones appears to add maleic anhydride.

The replacement of the bromine atoms, stepwise, by the Grignard reagent with the formation of a ketone, shows that they must be in positions *alpha* to the carbonyl group,[3] *i. e.*, either (a) or (b)



(a)



(b)

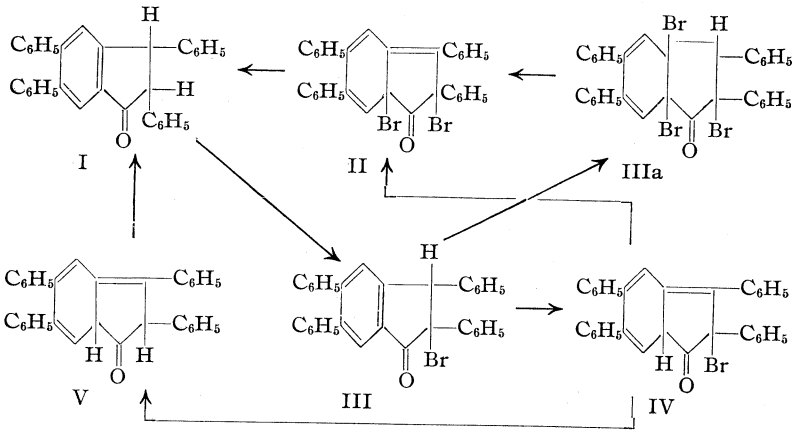
Dibromoketones of type (b), having both bromine atoms on the same carbon atom, however, are very easily hydrolyzed to α-diketones; this property is not exhibited by the dibromoketone

(1) Allen and Spanagel, THIS JOURNAL, **55**, 3773 (1933).

(2) It is of interest to note that in the Grignard machine [Kohler and Richtmyer, *ibid.*, **52**, 3736 (1930)] α-bromoketones show no immediate evolution of gas and use up one mole of reagent (usually interpreted as addition).

(3) Kohler and Tishler, *ibid.*, **54**, 1594 (1932).

in question, consequently, it is best represented by Formula II.



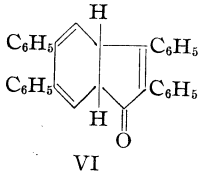
The formation of the dibromoketone II from the indanone I probably takes the following course; the hydrogen atom *alpha* to the carbonyl group is first replaced in the usual manner, giving a monobromoketone III. This can be considered to contain an allylic system, involving the double bond common to both rings, which is isomerized to IV under the influence of the hydrogen bromide present. The resulting ketone now contains a hydrogen atom *alpha* to the carbonyl group and is brominated in the usual way to form II.

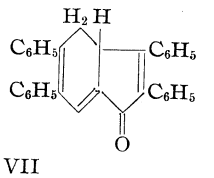
An alternative mechanism which avoids the rearrangement suggested is possible for the second step. If the monobromoketone had the structure III, a molecule of bromine could add to the double bond to give IIIa, which would then lose hydrogen bromide. Since this involves an aromatic double bond of the benzene ring, it seems less likely, although the *ortho*-phenyl groups may have a sufficient activating effect to permit of such an addition. Furthermore, the hydrogen atoms, not being *alpha* to a carbonyl group, will be much less active, and have less tendency to be eliminated as hydrogen bromide.

The position of the hydrogen atom in the monobromoketone is less certain. Since this substance was obtained by a reduction of the dibromide by the Grignard reagent, it would seem that it should have the structure IV; in confirmation, the monobromoketone, though secured from the indanone, is unaffected by hydrogen bromide, yet it brominates easily to give the dibromoketone II. Easy bromination is characteristic of only those ketones that have a hydrogen atom in the *alpha* position. Reduction of the dibromide with zinc and acetic acid also replaces the bromine by hydrogen; zinc in acetone or ethyl acetate has no effect—that is, in the dibromide the two bromine atoms are not on adjacent carbon atoms.

The dienone secured by reduction with the Grignard reagent, from its method of preparation and behavior on bromination, most probably is represented correctly by the structure V. In this, it will be noted that the hydrogen atom on the carbon atom common to the two rings is between three double bonds, and would be expected to be unusually likely to isomerize to a more stable system; by virtue of its aromatic structure, the most stable system is the indanone I. This dienone does form the indanone when warmed in solutions below its melting point; the change is very rapid in boiling acetic acid. For this reason, its reaction products, always formed in hot solutions, are identical with those of the indanone.

The dienone VI found earlier[1] was assigned its structure because it added maleic anhydride, gave some thiophenol when heated with sulfur, and was easily rearranged to the indanone I, showing it had the same skeletal structure. In view of the facile migration of hydrogen in this series, the production of thiophenol loses some of its significance—it is noticeable in all the sulfur melts. Its occurrence was interpreted[1] to indicate the presence of an angular phenyl group on the top carbon atom common to the two rings; this phenyl was then assumed to undergo a 1,3-shift in forming the indanone I. Such a shift was at that time without analogy, whereas 1,3-shifts of hydrogen in allylic systems are common. We are now[4] of the opinion that the phenyl group is already in the position where it is found in the indanone and that this dienone has the structure VI; this is in better accord with its chemical behavior.


VI

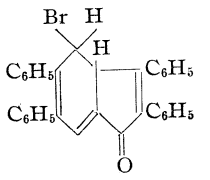

VII

Of these four isomers, the indanone I seems to be the most stable, for the three dienones are con-

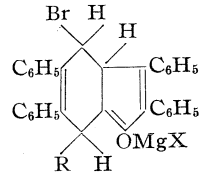
(4) Allen and Gates, THIS JOURNAL, **64**, 2123 (1942).

verted to it by heating.[5] The indanone I is white, whereas the three isomers are various shades of yellow, and it does not add maleic anhydride. On heating with sulfur, hydrogen sulfide is evolved and a red indenone results; this substance has already been degraded stepwise[1] by unambiguous reactions to compounds of known structure.[6] The formula I seems in best accord with these properties. Although the dienone VII gave both 1,2- and 1,4-addition with phenylmagnesium bromide,[7] it was pointed out that this reagent was of no value in determining structures in this series, owing to the prevalance of allylic rearrangements.

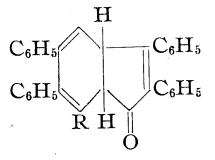
The isomeric dienones VI and VII give the same monobromoketone VIII upon bromination, with evolution of hydrogen bromide. This result would be expected in view of the known ease of the rearrangement of VI to VII.[7] Excess bromine dehydrogenates the monobromoketone. Examination of this ketone VIII in the Grignard machine[2] revealed little.[8] Both methylmagnesium iodide and phenylmagnesium bromide gave mixtures, from which were isolated bromine-free ketones, *different* from the original dienones. The 1,4-addition reaction, resulting in the formation of the ketones, which differ from the original by having an additional phenyl or methyl group, involves the carbonyl group. Thus, this group is not available for other purposes, and the elimination of the bromine must have been a side reaction. The following mechanism seems a plausible interpretation of the facts, and enables one to assign structure VIII to the bromoketone with a considerable degree of assurance. The magnesium enolate formed by the 1,4-addition of the Grignard reagent is shown in IX; upon acidification the enol XI ketonizes, but at some stage, there is a transannular elimination of hydrogen bromide, for the resulting ketone X contains no bromine. This probably occurs in the enol XI, for the requisite hydrogen atom in the 7-position is then activated by its position between the unsaturated linkages.[9,10]



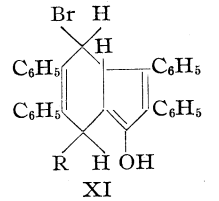
VIII



IX

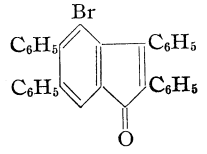


X

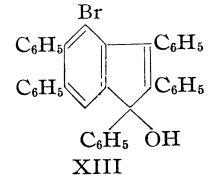


XI

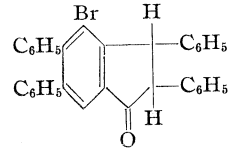
The aromatic ketone that results from the action of excess bromine upon the bromoketone VIII is probably 4-bromo-2,3,5,6-tetraphenylindenone XII. The bromine atom is inactive, phenylmagnesium bromide giving a carbinol XIII. The indenone is reduced to an indanone XIV by zinc and acetic acid, thus paralleling the behavior of the unbrominated indenone.



XII



XIII



XIV

Experimental

2,3,5,6-Tetraphenyl-2,7a-dibromo-2,7a-dihydroindenone-1 II.—This compound was obtained by bromination of the indanone I in the usual manner, using two equivalents of bromine and acetic acid as the solvent. It was also formed by a further bromination of the monobromoketone IV. The latter was secured by a similar procedure, but using one equivalent of bromine and chloroform as a solvent. The properties of these substances are given in Table I.

Both bromoketones were unaffected by hydrogen bromide in acetic acid, and did not add maleic anhydride. The dibromoketone was reduced to the monobromoketone

(5) Examination of the formulas of the isomeric ketones reveals that all the indenones have hydrogen atoms activated by adjacence to two or more double bonds, which are part of an allylic system. They would, therefore, be expected to rearrange to the more stable indanone I system.

(6) Allen, Bell, Bell and VanAllan, THIS JOURNAL, **62,** 656 (1940).

(7) Allen and Gates, *ibid.*, **64,** 2120 (1942).

(8) It should be emphasized that abnormal results from the Grignard machine have little significance, other than to indicate that several reactions are taking place simultaneously. It is always necessary to isolate and determine the nature of the reaction products before drawing useful conclusions. If there is no immediate evolution of gas, it indicates the absence of an active hydrogen atom.

(9) In one fortuitous instance, with methylmagnesium iodide, a bromoketone was isolated; immediate analysis showed 85% of the calculated amount of bromine, all of which was lost on recrystallization.

(10) A direct replacement of bromine in VIII by double decomposition with the Grignard reagent is an admitted possibility, and reaction products of this type may be present in the residual oils which comprise about one-half the reaction product.

TABLE I

PROPERTIES OF NEW SUBSTANCES

Substance	Yield, %	M. p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. Br	Found C	Found H	Found Br
II	75	270d.[a,d]	$C_{33}H_{22}OBr_2$			26.9			26.5
III	84	241d.[b,e]	$C_{33}H_{23}OBr$			15.5			15.2
V	50	125[a,e]	$C_{33}H_{24}O$	90.8	5.5		90.7	5.4	
VIII	84	196[a,f]	$C_{33}H_{23}OBr$	76.9	4.5	15.5	76.8	4.4	15.3
X, R = CH_3	33	170[a,e]	$C_{34}H_{26}O$	90.9	5.6		90.9	5.6	
X, R = C_6H_5	27	246[a,e]	$C_{39}H_{28}O$	91.4	5.5		90.9	5.4	
Xa	10	217[a,e]	$C_{34}H_{26}O$	90.9	5.6		89.5	6.0	
XII	90	235[c,f]	$C_{33}H_{21}OBr$	77.2	4.1	15.6	77.2	4.0	15.4
XIII	52	249[b,e]	$C_{39}H_{27}OBr$			13.5			13.2
XIV	57	175[a,f]	$C_{33}H_{23}OBr$			15.5			15.0
XV	69	240[a,e]	$C_{45}H_{34}O$	91.5	5.8		91.3	5.8	
XVI	50	194[c,e]	$C_{39}H_{27}Br$	81.4	4.7	13.9	81.6	4.8	13.8
XVII	20	229d.[b,e]	$C_{78}H_{57}O_2Br$	84.7[g]	5.2	7.2	85.2	4.9	6.8, 6.5
XVIII	80	239[a,e]	$C_{34}H_{25}OBr$	77.3	4.5		77.1	4.6	

[a] Prisms. [b] Needles. [c] Rods. [d] From xylene. [e] From benzene–petroleum ether. [f] From benzene–alcohol. [g] Calcd. mol. wt. 1105; found, mol. wt. (in benzene) 522, 519. The explanation of this discrepancy is unknown.

by reduction with potassium iodide in acetic acid, alcoholic potash, and the Grignard reagent, and to the parent indanone with zinc and acetic acid, by the customary procedures.

2,3,5,6-Tetraphenyl-2,7a-dihydroindenone-1 V.—To a 0.1 mole of phenylmagnesium bromide in 100 cc. of ether was added 6 g. of the monobromoketone III. After it had been stirred for an hour, the mixture was decomposed by ammonium chloride, and the organic material crystallized from benzene–petroleum ether; the yield was 3 g. Heated in the ordinary way, in a capillary tube, it melts at 95°, then solidifies and remelts at 164–166°; if the tube and sample are plunged into a heated bath, the melting point is found to be 125°. By repeated recrystallizations, it isomerizes, most rapidly in acetic acid, to the indanone II, m. p. 176°.

2,3,5,6-Tetraphenyl-3a,4-dihydro-4-bromoindenone-1 VIII resulted when either indenone VI or VII in chloroform solution was brominated in the usual way. It crystallized from benzene–alcohol in lemon-yellow prisms, m. p. 196°d. It does not add maleic anhydride and is unaffected by hydrogen bromide. In the Grignard machine it shows 0.5 active hydrogen and 1.5 addition. Upon treatment with bromine in chloroform, hydrogen bromide is evolved, and an orange indenone (2,3,5,6-tetraphenyl-4-bromoindenone-1 XII, m. p. 234–235°) is isolated from the residue by evaporating to dryness on a water-bath.

This last substance is reduced by zinc and acetic acid (without removal of the bromine) to an indenone XIV in exactly the same way as the unbrominated analog, 2,3,5,6-tetraphenylindenone[1] gave the indanone I, m. p. 176°. It gave a phenyl carbinol XIII with phenylmagnesium bromide.

Reaction Products from the Bromoindenone VIII.—(a) Phenylmagnesium bromide gave a complex mixture, from which the ketone X, (R = C_6H_5) and a bimolecular product were isolated in this order. In the Grignard machine the ketone consumed one equivalent of reagent and evolved a half equivalent of gas (possibly indicating 50% enolization). When treated with phenylmagnesium bromide it gave a new carbinol, 1,2,3,5,6,7-hexaphenyl-3a,7a-dihydroindenol-1 XV, which did not dehydrate with a 2% solution of sulfuric acid in acetic acid.

The ketone behaved in a puzzling manner with hydrogen bromide, the oxygen being lost and a bromine atom introduced. Possibly the acid is added to the carbonyl group and then water is split off. The product XVI is a bromohydrocarbon.

The bimolecular product XVII was assumed to be such because of the bromine analyses; the minimum molecular weight, if one bromine atom is present, is 1100–1200. The substance was secured from two different preparations, and was unchanged on recrystallization from two different solvents. It consumed 2.7 equivalents of reagent (on the basis of this molecular weight), showing two active hydrogens. Upon acidification, about half the starting material was recovered from the black oil. It was not investigated further.

(b) Methylmagnesium iodide likewise gave a complex mixture, from which was isolated the ketone, 2,3,5,6-tetraphenyl-7-methyl-3a,7a-dihydroindenone-1 (X, R = CH_3). In the Grignard machine it consumed one equivalent of reagent and evolved 0.3 equivalent of gas. It was unaffected by hydrogen bromide and did not add maleic anhydride. It readily substituted with bromine; the α-bromoketone, 2,3,5,6-tetraphenyl-7-methyl-3a,7a-dihydro-7a-bromoindenone-1 XVIII, was reduced back to the starting material by methylmagnesium iodide. In one instance a very small amount of an isomeric ketone Xa was obtained.

Summary

The behavior of several closely related isomeric polyphenylated indenones with bromine has been determined. Structures have been assigned the various substances, in accord with the experimental evidence obtained from a series of reactions. The occurrence of allylic rearrangements has again been noted.

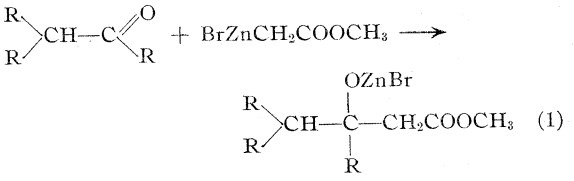
ROCHESTER, N. Y. RECEIVED MAY 29, 1942

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

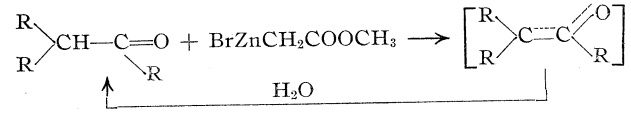
Enolization in the Reformatsky Reaction

BY MELVIN S. NEWMAN

In the Reformatsky reaction it is generally thought that zinc reacts with a bromoester to form an organozinc intermediate which then adds to the ketone or aldehyde to yield a bromozinc derivative of a β-hydroxyester, as follows



The recovery of ketone from the products of such a reaction would seem to indicate incomplete reaction. However, it was found to be a fact that practically all of the theoretical amount of zinc was consumed in experiments where considerable amounts of ketone were recovered. This finding suggested that the ketone reacted in some way with the organozinc intermediate so that on hydrolysis the ketone was regenerated. Bearing in mind the probability that the Reformatsky reaction involves an organozinc intermediate which would be expected to behave like other organometallic compounds, it seemed likely that the recovered ketone was tied up as an enolate during the reaction,[1] as follows



Acetomesitylene was chosen as an excellent test for this hypothesis because it has been shown to react by the enolization mechanism with Grignard reagents[2] and with organolithium[3] and organosodium[3] compounds. It was found that acetomesitylene reacted vigorously with zinc and methyl bromoacetate. After hydrolysis of the reaction mixture 90% of acetomesitylene was recovered and in addition approximately 50% of the theoretical amount of methyl acetate was isolated.

When 23.3 g. of acetomesitylene, 23.0 g. of methyl bromoacetate and 5 g. of freshly sandpapered zinc foil[4] were brought together in 100 cc. of dry sulfur-free benzene, an extremely vigorous reaction ensued. Approximately the theoretical amount of zinc was consumed in a short time. After hydrolysis with dilute hydrochloric acid the benzene layer was distilled. On fractionation of the low boiling fraction, 5.3 g. (50%) of methyl acetate was obtained. This was identified by boiling point, 57–58° uncor., odor and hydrolysis to yield acetic acid, identified as its *p*-bromophenacyl ester[5], m. p. and mixed m. p. 83–84° cor. More methyl acetate was present as judged by the boiling point and odor of intermediate fractions. From the higher boiling fraction there was isolated 20.9 g. (90%) of acetomesitylene, b. p. 124–125° uncor., at 20–21 mm. This was identified further by conversion in 64% yield to 3,5-dinitro-2,4,6-trimethylacetophenone,[6] m. p. and mixed m. p. 139–140° cor.

In a similar experiment it was shown that methyl acetate could be distilled from the reaction mixture before hydrolysis, thereby proving that the methyl acetate formed did not arise from a reaction of any bromozinc intermediate with water. It should be emphasized that the formation of methyl acetate in a Reformatsky reaction is entirely analogous to the formation of methane in a Zerewitinoff determination. In order to rule out the possibility that the methyl acetate might have arisen from some other side reaction, zinc and methyl bromoacetate were refluxed in benzene for a day. Considerable reaction occurred but at no time was a positive organometallic color test with Michler ketone[7] obtained. A small amount of methyl acetate was produced but not nearly enough to account for the methyl acetate resulting when acetomesitylene was present. Therefore, on the basis of the above facts, it is concluded that in the Reformatsky reaction acetomesitylene reacts mainly by the enolization mechanism.

(1) Newman, THIS JOURNAL, **62**, 870 (1940).

(2) Kohler and Baltzly, *ibid.*, **54**, 4015 (1932).

(3) Gilman and Jones, *ibid.*, **63**, 1162 (1941). In this paper it is pointed out that enolization of a ketone prior to reaction with an organometallic compound does not necessarily have to occur. It may be that the initially formed complex between the carbonyl oxygen and the organometallic reagent react so that the products characteristic of an enolization reaction are formed. See also Arnold, Bank and Liggett, *ibid.*, **63**, 3444 (1941).

(4) Natelson and Gottfried, *ibid.*, **61**, 970 (1939). The zinc foil was obtained from the J. T. Baker Co., Phillipsburg, N. J.

(5) Judefind and Reid, *ibid.*, **42**, 1043 (1920).

(6) Fuson and Walker, *ibid.*, **52**, 3269 (1930). Under the same conditions the pure known compound yielded 66% of the derivative.

(7) Gilman and Schulze, *ibid.*, **47**, 2002 (1925). To allow for the possibly lesser reactivity of an organozinc compound, the test solution was heated for one to five hours before hydrolysis, at the suggestion of the Referee. However, the success or failure in obtaining a color test does not affect the argument in favor of enolization, for no appreciable amount of methyl acetate is formed unless acetomesitylene is added.

A solution of 67.5 g. of methyl bromoacetate in 350 cc. of dry sulfur-free benzene and a few crystals of iodine was refluxed over 32 g. of zinc[4] for twenty hours. Shortly after the refluxing commenced the solution turned yellow-green. A test[7] with Michler ketone at this stage was negative. After about thirty minutes of refluxing an orange-yellow viscous complex was seen to adhere to the active spots on the zinc. Some of this complex was removed on a glass rod when it first appeared, but this also gave a negative color test. After twenty hours of refluxing the decanted solution was distilled through a 10–15 plate column. With a reflux ratio of over 80 to 1 about 3 g. of a fraction, b. p. 57–64°, was collected. Methyl acetate was present in this as judged by boiling point, odor, and identification of acetic acid on hydrolysis as the *p*-bromophenacyl ester.[5] On weighing the zinc it was found that 19.5 g. had reacted. This amounts to 68% of that required to react with the bromoester used.

The isolation of ketone from the products of Reformatsky reactions does not necessarily mean that the ketone was tied up as an enolate during the reaction, but, if the theoretical amount of zinc was consumed in a short time during the reaction and if no insoluble complex coated out on the zinc to hinder complete reaction, it seems most likely that enolization offers the best explanation for the recovery of unchanged ketone. In the past few years the author has carried out many such reactions in which, although ample excesses of zinc and bromoesters were present, and approximately the theoretical quantity of zinc was rapidly consumed, considerable amounts of starting ketone were recovered. At the time when most of these reactions were run, the possibility of enolization as a factor in Reformatsky reactions was not under consideration. Accordingly, a thorough study of the factors which influence the enolization of ketones in this reaction cannot be reported. However, it is possible to point out a few observations which seem to be substantiated by the experimental results.

The ketones studied were 1-keto-2-phenyl-1,2,-3,4-tetrahydronaphthalene,[1] I, 1-keto-2-*o*-tolyl-3-methyl-1,2,3,4-tetrahydronaphthalene,[8] II, and 4-keto-1,2,3,4-tetrahydrophenanthrene,[9] III.

Preparation of Keto ne

Ketones I and II were prepared as previously reported. Ketone III was prepared as follows. The acid chloride prepared in benzene solution from 199 g. of γ-2-naphthylbutyric acid and phosphorus pentachloride was dissolved in 500 cc. of sulfur-free dry benzene, and 127 g. of aluminum chloride[10] was added in portions with stirring. Very little hydrogen chloride was evolved and the color of the complex first formed was still a pale yellow-green when 90% of the aluminum chloride had been added. Also there had been considerable evolution of heat. When the last portions of aluminum chloride were added the color deepened rapidly to a red-brown, the temperature started to rise rapidly (cooling required), and much hydrogen chloride was evolved. After regulation of the internal temperature at 35–40° for one hour, the temperature was raised to 60° for an hour and to 65° for one-half hour. The mixture was then cooled and worked up in the usual manner. On rapid vacuum distillation at 2 mm. a pale yellow viscous oil, 170 g. (93%), was obtained. By crystallization from 400 cc. of alcohol, two crops of crystals totalling 157 g. (86%), m. p. 66.0–67.4° cor., were obtained. About 3 to 5% of starting acid was recovered from alkaline extracts of the reaction mixture.

General Description of Procedure

A solution of the pure ketone (usually 0.1 to 0.2 mole) and bromoester (in 15–20% excess) in dry sulfur-free benzene (80–100 cc. per 0.1 mole) was placed in a round-bottom flask fitted to a ground-in condenser which could be changed from refluxing to distilling by turning a stopcock. This solution was distilled for a short while to render completely anhydrous. An excess of freshly sandpapered zinc foil was added while the solution was still hot, and, when desired, a few crystals of iodine were allowed to fall on the foil. In most cases a vigorous exothermic reaction set in as soon as the solution was heated to boiling. Refluxing then continued spontaneously until the reaction was virtually complete. This took about ten to twenty minutes. After further refluxing with added heat for not more than thirty minutes the reaction mixture was cooled and decomposed with dilute hydrochloric acid. The organic material was separated by ether extraction and the unreacted zinc collected and weighed.[11] After thorough washing with dilute acid and water, the solvent was removed from the benzene layer and the residue was heated for a short while in the neighborhood of 200° to effect dehydration. When iodine was used in starting the reaction it was generally unnecessary to add more iodine for dehydration. The residue was vacuum distilled, the distillate refluxed with dilute aqueous-alcoholic potassium hydroxide, and the hydrolyzate separated into acidic and neutral fractions. The original ketone was recovered from the neutral fraction by vacuum distillation, crystallization, or a combination of the two, and the yields of ketone reported represent practically pure ketone. The acid fractions were crystallized from benzene. In some cases all of the acid crystallized. The amounts of non-crystalline acid were determined by evaporating the solvent from the mother liquors to constant weight of residue, and these values were checked by esterification and vacuum distillation of the ester.

Discussion of Results

From a consideration of the experiments cited

(8) Newman, THIS JOURNAL, **62**, 2295 (1940).

(9) Compare Haworth, *J. Chem. Soc.*, 1125 (1932), and Bachmann and Edgerton, THIS JOURNAL, **62**, 2219 (1940).

(10) Calco Chemical Co., Standard grade, anhydrous.

(11) If dilute hydrochloric acid is used, it is possible to separate the zinc rapidly before any appreciable amount of it reacts with the acid. It is surprising how slowly the unreacted zinc is attacked by dilute acids. Washing with acetone hastens the cleaning of the zinc prior to drying and weighing.

below the following conclusions seem justified.[12]

1. The use of a small amount of iodine to initiate the reaction decreases enolization.[13] In two experiments with ketone I and ethyl α-bromopropionate, 38% of acid[14] and 27% of ketone I were obtained when iodine was used. Without iodine the yields were 23% of acid[14] and 42% of ketone. In other experiments with ketone III and ethyl bromoacetate, when iodine was used 87% of acid and 6% of ketone III were isolated. Without iodine the yields were 77% of acid and 17% of ketone.

2. The use of dioxane as a solvent promotes enolization. In experiments with ketone I and ethyl bromoacetate, 68% of acid[14] and a small but undetermined amount of ketone were obtained in benzene as solvent. In pure dioxane the reaction took place more vigorously than in benzene but the yields were 29% of acid[14] and a large but undetermined amount of ketone I. No iodine was used. In other experiments with methyl bromoacetate and ketone II, when iodine was used in benzene, 52% of acid and 41% of ketone II were isolated. In dioxane and with no iodine the reaction was much more vigorous than in benzene but only 10% of acid and 70% of ketone were obtained.

3. The tendency to cause ketones to react by enolization increases in the following esters: ethyl bromoacetate <ethyl α-bromopropionate <ethyl α-bromobutyrate. In experiments with ketone I using no iodine, ethyl bromoacetate yielded 68% of acid[14] and a small amount of ketone, whereas ethyl α-bromopropionate yielded 23% of acid and 42% of ketone. In experiments with ketone I using iodine, ethyl α-bromopropionate yielded 38% of acid[14] and 27% of ketone I, whereas ethyl α-bromobutyrate yielded 28% of acid[14] and 48% of ketone I. In experiments with ketone III using no iodine, ethyl bromoacetate yielded 77% of acid and 17% of ketone III, whereas ethyl α-bromopropionate yielded 55% of acid and 39% of ketone III.

(12) It should be emphasized that the experiments cited were not isolated cases but those in which the results had been duplicated to within a few per cent. In all of these cases the zinc reacted approached the theoretical and in all cases the reactions had proceeded for a maximum of ninety minutes.

(13) The amount of enolization is probably more accurately estimated by the amount of ketone recovered than by the amount of acid isolated. Those cases where the total amount of products accounted for is less than 85% were from earlier work, where the technique was not as good as in later work.

(14) The percentages indicated in these cases represent pure crystalline acid only; additional non-crystalline acid was present but was not accounted for.

Summary

Evidence is presented that the recovery of starting ketone from the products of a Reformatsky reaction may be due to enolization of the ketone during reaction. In the case of acetomesitylene, 90% of the ketone is recovered after reaction. A few factors influencing the enolization of ketones in the Reformatsky reaction are discussed.

COLUMBUS, OHIO RECEIVED APRIL 24, 1942

[COMMUNICATION NO. 863 FROM THE KODAK RESEARCH LABORATORIES]

Investigation of Pyrazole Compounds. I. The Reaction Product of Phenylhydrazine and Ethyl Cyanoacetate

BY A. WEISSBERGER AND H. D. PORTER

Conrad and Zart[1] treated ethyl cyanoacetate with phenylhydrazine, using sodium alcoholate as a condensing agent, and obtained a colorless compound of the composition $C_9H_9N_3O$ and the m. p. 219°. This, they assumed to be 1-phenyl-3-hydroxy-5-pyrazolone-imide, I. However, the reaction between ethyl cyanoacetate and phenylhydrazine could also lead to the isomeric 1-phenyl-3-amino-5-pyrazolone, II. The intermediate in the formation of I might be the β-cyanoacetylphenylhydrazine, III, while the formation of β-imino-β-(β-phenylhydrazino)-propionic ester, IV, as the primary product would lead to II.

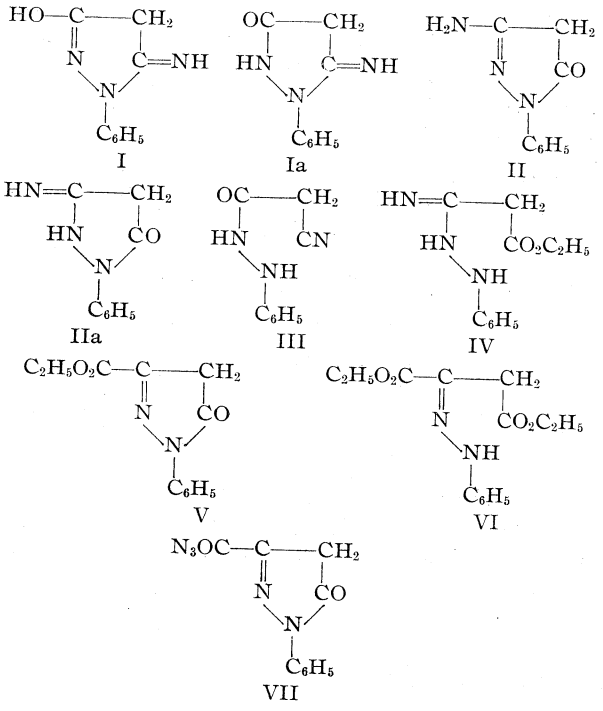
The compound synthesized by Conrad and Zart is of importance in color photography,[2] and it appeared desirable to get definite information about its structure. In order to decide between I and II, I was synthesized in an unambiguous way, starting with 1-phenyl-3-carbethoxy-5-pyrazolone, V.[3] This compound can be prepared by ring closure from the well-characterized ethyl

(1) Conrad and Zart, *Ber.*, **39**, 2282 (1906).

(2) British Patent 478,990.

(3) Wislicenus, *Ann.*, **246**, 319 (1888).

oxalacetate phenylhydrazone,[3] VI. V was transformed to the hydrazide and azide, VII, and the latter subjected to a Curtius degradation. The compound obtained is identical with that prepared according to Conrad and Zart. Hence, *the formulation of this compound as I is erroneous and has to be replaced by II.* The identity of the compound made from V with that prepared according to Conrad and Zart was proved by m. p. and mixed m. p., and by the identical behavior of the two substances in the reactions leading to and the m. p.'s and mixed m. p.'s of the monobenzoyl derivative, the monocarbethoxy derivative and



the reaction product with aniline described below. Both I and II are capable of forming by prototropic shift, equilibria with tautomeric forms, *e. g.*, I with Ia, and II with IIa, and the same applies to the derivatives described below. However, the family of I differs from that of II by the position of the phenyl group, and the two families are not subject to tautomeric interchange. In the following, all compounds which by prototropic shift could form derivatives of pyrazolone will be named as such.

Treatment of II with one mole of benzoyl chloride yields a monobenzoyl derivative which is soluble in aqueous sodium carbonate. A monocarbethoxy derivative of similar behavior is obtained by treatment of II with ethyl chlorocarbonate. The same compound is formed by decomposition of the azide VII in boiling ethanol, which shows that it is 1-phenyl-3-carbethoxyamino-5-pyrazolone. By analogy, the monobenzoyl derivative is 1-phenyl-3-benzoylamino-5-pyrazolone. With phenyl isocyanate II forms a compound of the composition $C_{16}H_{14}N_4O_2$ which is soluble in aqueous sodium carbonate, and, in analogy to the two derivatives just mentioned, is formulated as 1-phenyl-3-phenylcarbamylamino-5-pyrazolone. Treatment of II with one mole of acetyl chloride yields a monoacetyl derivative, behaving like the other monoacyl derivatives. The compound, therefore, is formulated as 1-phenyl-3-acetylamino-5-pyrazolone, IX. Acetylation with excess acetic anhydride gives a diacetyl derivative which is insoluble in carbonate. The second acetyl group is very easily split off by caustic alkali forming IX, and the diacetyl derivative, therefore, is most likely the 1-phenyl-3-acetamino-5-acetoxy-pyrazole. On heating II with aniline, ammonia is split off and C_6H_5NH is introduced. The compound so obtained is soluble in aqueous sodium carbonate. It is, most likely, the 1-phenyl-3-phenylamino-5-pyrazolone.

Experimental

1-Phenyl-3-amino-5-pyrazolone (Method of Conrad and Zart[1]).—To a solution of sodium ethylate prepared from 4.6 g. of sodium and 80 ml. of absolute ethanol, was added 11.3 g. of ethyl cyanoacetate and 10.8 g. of phenylhydrazine. The mixture was heated under reflux in an oil-bath of 120° for sixteen hours. After removal of the alcohol under vacuum, the residue was dissolved in 100 ml. of water and extracted with 50 ml. of ether. The aqueous layer, on acidification with 10 ml. of acetic acid, deposited 8.3 g. of a tan powder, sintering at 208° and melting at 213–215° dec. The product was purified by boiling with 50 ml. of 95% ethanol, cooling, filtering and washing with 10 ml. of ethanol; 7.6 g. (43%), m. p. 216–218° dec. This material is sufficiently pure for the preparation of derivatives. It can be recrystallized from 10 parts of ethanol–dioxane (2:1). After three recrystallizations, including treatment with Norite, small white prisms were obtained, m. p. 218–220°.

At least two equivalents of sodium ethylate are necessary for the reaction, but larger amounts do not improve the yields, which are the highest, if equal moles of phenylhydrazine and ethyl cyanoacetate are employed.[4]

1-Phenyl-3-amino-5-pyrazolone from 1-Phenyl-3-carbethoxy-5-pyrazolone

1-Phenyl-3-carbethoxy-5-pyrazolone was synthesized following, in principle, the method of Wislicenus.[3] A solution of 60 g. of ethyl oxalacetate phenylhydrazone[3] in

(4) These results were obtained in a series of experiments by E. C. Armstrong of these Laboratories. The authors wish to thank Mr. Armstrong for his assistance.

250 ml. of benzene and 10 ml. of glacial acetic acid was heated under reflux for three hours. The product obtained after cooling was washed on the filter with 25 ml. of benzene; 40 g. (80%) of white, feathery needles, m. p. 185–186°.

In the absence of acetic acid no 1-phenyl-3-carbethoxy-5-pyrazolone was formed even though the heating time was doubled, while refluxing in xylene for three hours in the absence of acid gave a yield of 28%. When phenylhydrazine was added gradually to a boiling solution of ethyl oxalacetate in xylene, and water and alcohol were distilled off as they formed, yields of only about 40% were obtained. A yield of 54% was obtained when the phenylhydrazone was heated in about 10 parts of water.

1-Phenyl-5-pyrazolone-3-carboxamide.—Twenty grams of 1-phenyl-3-carbethoxy-5-pyrazolone was stirred in 200 ml. of concentrated ammonium hydroxide (28%) until a clear solution was formed and then left standing for ninety-six hours at room temperature. The solution was acidified with 30% acetic acid to give 15 g. (86%) of almost white crystals which darkened at 215° and melted at 228° dec., recrystallized from 200 ml. of 95% ethanol; 10 g. (57%) of white crystals, m. p. 233–235° dec.

Anal. Calcd. for $C_{10}H_9N_3O_2$: N, 20.7. Found: N, 20.14.

1-Phenyl-5-pyrazolone-3-carboxhydrazide.—A mixture of 34 g. of 1-phenyl-3-carbethoxy-5-pyrazolone and 100 ml. of 42% hydrazine hydrate solution was stirred at room temperature. The solution warmed spontaneously to *ca.* 40° and became clear. After standing for four hours an equal volume of water was added. On acidification with acetic acid, 27.5 g. (86%) of fine, cream colored needles separated, m. p. 235–237° dec. The melting point was not changed by recrystallization from ethanol.

Anal. Calcd. for $C_{10}H_{10}N_4O_2$: N, 25.65. Found: N, 25.19.

1-Phenyl-5-pyrazolone-3-carboxazide.—To a solution of 10 g. of 1-phenyl-5-pyrazolone-3-carboxhydrazide in 200 ml. of 70% ethanol containing 6 ml. of concentrated hydrochloric acid, was added dropwise with stirring 2.3 g. of sodium nitrite in 10 ml. of water, while keeping the temperature below 5°. Stirring was continued at this temperature for one hour. The product was filtered and washed with water; 6.5 g. (62%) of granular orange powder, deflagrating at 140°.

1-Phenyl-3-carbethoxyamino-5-pyrazolone.—A solution of 3 g. of 1-phenyl-5-pyrazolone-3-carboxazide in 30 ml. of absolute ethanol was refluxed for three hours, cooled and filtered; .2 g. (63%) of yellowish crystals, m. p. 197–199°, recrystallized from 70 cc. of 95% ethanol (Norite); white needles, m. p. 198–199°. A mixed m. p. with the 1-phenyl-3-carbethoxyamino-5-pyrazolone described below showed no depression.

1-Phenyl-3-amino-5-pyrazolone.—A solution of 2.5 g. of 1-phenyl-3-carbethoxyamino-5-pyrazolone in 12.5 ml. of 10% sodium hydroxide was heated on the steam-bath for half an hour, then cooled and acidified with acetic acid; 1.4 g. (m. p. 215–216° dec.) of tan crystals, recrystallized from 95% ethanol, small, white prisms; m. p. 218–220° dec. A mixed m. p. with the compound prepared by the method of Conrad and Zart, showed no depression.

Other reactions attempted in the preparation of 1-phenyl-3-amino-5-pyrazolone were given up after the success of the Curtius degradation. The conventional Hofmann degradation of 1-phenyl-5-pyrazolone-3-carboxamide gave uninviting brominated products. When the sodium salt of 1-phenyl-3-chloro-5-pyrazolone[5] was treated with potassium phthalimide in boiling alcohol for twenty hours, or with sodium amide in liquid ammonia at −33° for forty hours, the unchanged starting material was recovered. Treatment with sodium amide in ammonia at 100° under pressure for twenty hours gave no water-insoluble product. The starting material was recovered after treatment of 1-phenyl-5-pyrazolone-3-carboxylic acid with hydrazoic acid in the presence of sulfuric acid following the method of von Braun.[6]

Derivatives of 1-Phenyl-3-amino-5-pyrazolone

1-Phenyl-3-benzoylamino-5-pyrazolone.—A mixture of 5 g. of 1-phenyl-3-amino-5-pyrazolone[7] and 4 g. of benzoyl chloride in 20 ml. of dioxane was stirred and heated on the steam-bath for eighteen hours. The product which crystallized after addition of 5 ml. of water, was purified by slurrying with 15 ml. of methanol; 5 g. (64%) of fine, cream colored needles, m. p. 218–220°, recrystallized from 15 parts of dioxane, m. p. 220–221°.

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: N, 15.06. Found: N, 14.95.

The compound is soluble in 3% sodium carbonate or 2% sodium hydroxide. It is recovered unchanged on acidification with acetic acid.

1-Phenyl-3-carbethoxyamino-5-pyrazolone.—A mixture of 8.75 g. of 1-phenyl-3-amino-5-pyrazolone and 5.4 g. of ethyl chlorocarbonate in 35 ml. of dioxane was stirred and heated on the steam-bath for three and one-half hours. On addition of 5 ml. of water and cooling, 1.5 g. of tan crystals separated, recrystallized from 50 ml. of 95% ethanol; 1 g. of fine white needles, m. p. 198–199°.

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: N, 17.00. Found: N, 16.97.

When the filtrate was diluted with an equal volume of water, 4.6 g. of a tan crystalline product separated which, after recrystallization from 15 ml. of 95% ethanol gave 3 g. of tan crystals, m. p. 106–108°. This product, probably a dicarbethoxy derivative, on heating under reflux in 65 ml. of absolute alcohol with 1 ml. of piperidine for one-half hour yielded 1.2 g. of the 1-phenyl-3-carbethoxy-amino-5-pyrazolone, m. p. 198–199°.

1-Phenyl-3-acetylamino-5-pyrazolone.[4]—To a suspension of 8.75 g. of 1-phenyl-3-amino-5-pyrazolone in 50 ml. of dioxane was added all at once while stirring 5.5 g. of acetyl chloride. The solution formed was warmed in a water-bath at 40° for one hour, cooled, the product collected on the filter and recrystallized from 30 ml. of 95% ethanol; 4.5 g. (43%) of short, white needles, m. p. 218–220°. The m. p. is the same as that of the starting material; however, a mixed m. p. was depressed by about 30–40°.

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: N, 19.35. Found: N, 19.44.

(5) Michaelis and Röhmer, *Ber.*, **31**, 3003 (1898).

(6) von Braun, *Ann.*, **490**, 125 (1931).

(7) Prepared by either method given above.

Toward carbonate and hydroxide solutions the compound behaves like the 1-phenyl-3-benzoylamino-5-pyrazolone.

1-Phenyl-3-acetylamino-5-acetoxypyrazole.[4]—A solution of 8.75 g. of 1-phenyl-3-amino-5-pyrazolone in 50 ml. of acetic anhydride was refluxed for half an hour. After decomposing the mixture in 250 ml. of water, the product was filtered off and recrystallized from 90 ml. of toluene; 8 g. (62%) of fine, cream colored crystals; m. p. 144–145°.

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: N, 16.22. Found: N, 16.12.

The compound is insoluble in 3% sodium carbonate. It dissolves in cold 2% sodium hydroxide with saponification of one acetyl group; on acidification with acetic acid 1-phenyl-3-acetylamino-5-pyrazolone is obtained; m. p. and mixed m. p. 218–220°.

1-Phenyl-3-phenylcarbamylamino-5-pyrazolone.—To a hot solution of 5 g. of 1-phenyl-3-amino-5-pyrazolone in 20 ml. of dioxane was added 3.4 g. of phenyl isocyanate and the mixture heated for two hours on the steam-bath. The product which crystallized on cooling was purified by stirring with 25 ml. of ethanol; 2.3 g. (28%) of pure white microcrystals, m. p. 235–236°.

Anal. Calcd. for $C_{16}H_{14}N_4O_2$: N, 19.0. Found: N, 19.00.

Toward carbonate and hydroxide solutions the compound behaves like the 1-phenyl-3-benzoylamino-5-pyrazolone.

1 Phenyl-3-anilino-5-pyrazolone.—A mixture of 20 g. of 1-phenyl-3-amino-5-pyrazolone[7] and 50 ml. of aniline was refluxed gently over a flame for one and one-half hour, *i. e.*, until the evolution of ammonia slacked off. After some cooling, 100 ml. of chloroform was added and the solution cooled in an ice-bath. The product (14.6 g.) was recrystallized from 300 ml. of 95% ethanol, filtering hot from a small amount of insoluble yellow material; 12 g. (43%) of white, feathery needles, m. p. 219–221°.

Anal. Calcd. for $C_{15}H_{13}N_3O$: N, 16.70. Found: N, 16.77.

The compound is sparingly soluble in cold 3% sodium carbonate, but soluble in cold 2% sodium hydroxide, from which it separates unchanged on acidification.

Summary

1. 1-Phenyl-3-amino-5-pyrazolone was prepared, starting with the ethyl ester of 1-phenyl-3-carboxy-5-pyrazolone, by way of the corresponding hydrazide and azide and Curtius degradation of the latter.

2. The reaction product is identical with the compound prepared by Conrad and Zart[1] from ethyl cyanoacetate and phenylhydrazine and formulated as 1-phenyl-3-hydroxy-5-pyrazolone imide.

3. The compound prepared by Conrad and Zart is, therefore, 1-phenyl-3-amino-5-pyrazolone.

4. A number of derivatives of 1-phenyl-3-amino-5-pyrazolone were prepared.

ROCHESTER, N. Y. RECEIVED JUNE 24, 1942

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

The Reaction of Methyl Furoate with Benzene and Chlorobenzene

BY CHARLES C. PRICE AND C. F. HUBER

The aluminum chloride-catalyzed reaction of furoic acid with benzene has been found to yield, in addition to α-naphthoic acid,[1] a large amount of an amorphous mixture of acids of higher molecular weight.[2] Although some suggestions as to the nature of certain components of this material were advanced on the basis of degradation products of the crude mixture, the isolation of any pure acids has proved extremely difficult. Since attempts at fractional crystallization or precipitation of the acids or of various derivatives were so generally unsuccessful, the condensation reaction has been investigated employing methyl furoate in place of furoic acid, with the aim of separating by distillation the esters so formed.

(1) Gilman, McCorkle and Calloway, THIS JOURNAL, **56**, 745 (1934).

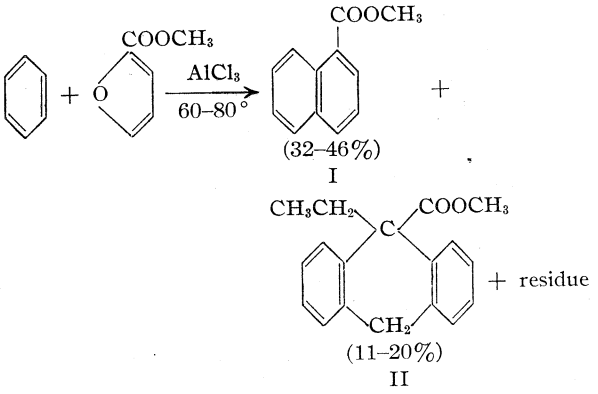
(2) Price, Chapin, Goldman, Krebs and Shafer, *ibid.*, **63**, 1857 (1941).

McCorkle and Turck[3] were able to isolate a 56% yield of methyl α-naphthoate from the aluminum chloride-catalyzed reaction of methyl furoate with benzene, and Calloway[4] reported that a considerable residue remained after distillation of the naphthoate. We have obtained the same results, isolating methyl α-naphthoate in 32–46% yield accompanied by a residue of higher-boiling products.

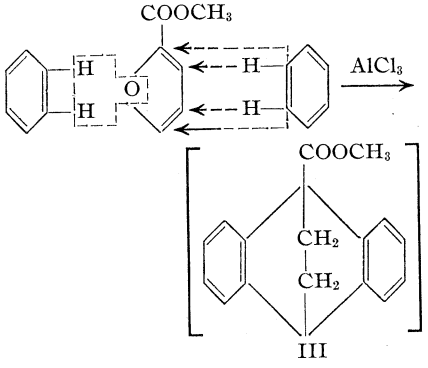
Fractional distillation of this residue under the vacuum of a mercury vapor pump yielded a pale yellow, viscous oil, boiling at 144–145° (0.04 mm.), which crystallized after standing for seven months, m. p. 52–54°. The yield of this substance, which proved to be methyl 9-ethyl-9,10-dihydro-9-anthroate (II), corresponded to 11–20% of the theoretical amount.

(3) McCorkle and Turck, *Proc. Iowa Acad. Sci.*, **43**, 205 (1936).

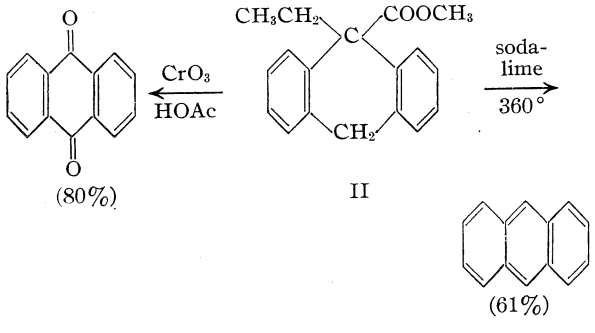
(4) Calloway, *Chem. Rev.*, **17**, 343 (1935).



A product of this nature, containing an anthracene nucleus, had been expected on the basis of the previously reported isolation of anthraquinone from the permanganate oxidation of the crude high-molecular-weight acids from the benzene–furoic acid reaction.[2] We had anticipated, however, that its structure would be that of methyl 9,10-*endo*-ethano-9,10-dihydro-9-anthroate (III). Such a compound could be pictured as having been formed by the addition of an *o*-phenylene group across the two double bonds originally present in the furoic acid ring.

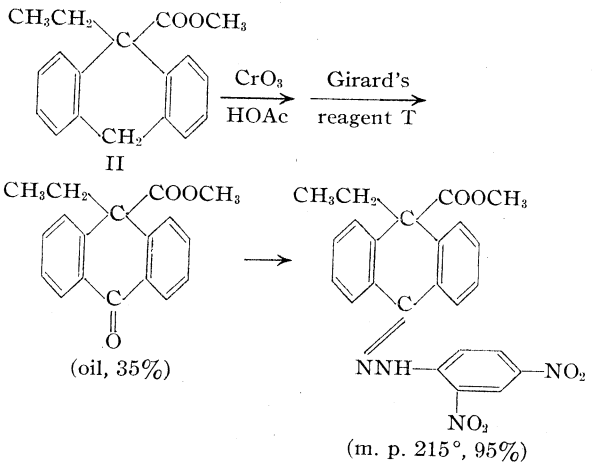


The crystalline ester (II) actually isolated, however, analyzed consistently for a substance with a molecular formula containing two more hydrogen atoms than the expected *endo*-ethano anthroate, III. If III actually is formed as an intermediate, its anthracene nucleus is not destroyed by the addition of these two hydrogen atoms, however, since II could be converted to anthraquinone in 80% yield by chromic acid oxidation and to anthracene in 61% yield by soda-lime distillation.



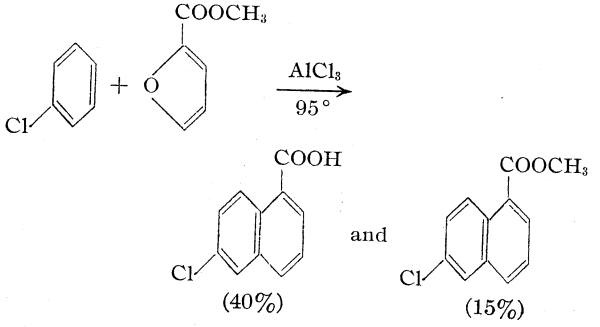
The apparent scission of the *endo*-ethano ring of III to give II is closely analogous to some experiments recorded by Huston and Friedeman.[5] These authors found that treatment of α-phenylethyl or α-phenylpropyl alcohols with benzene and aluminum chloride led principally to the expected product, the 1,1-diphenylalkane.

$$C_6H_5CHR + C_6H_6 \xrightarrow[10^\circ]{AlCl_3} (C_6H_5)_2CHR$$
$$\quad\quad\quad



ester (II) toward hydrolysis: even saponification in boiling diethylene glycol failed. Of the three possible modes of cleavage of the *endo*-ethano ring, that forming the 9-ethyl derivative would yield the compound with a maximum of steric hindrance to reactions of the ester group.

When the reaction of methyl furoate with chlorobenzene was carried out by exactly the same procedure as that employed for the reaction with benzene, with the exception that the condensation was carried out at 95° rather than 70°, a 40% yield of 6-chloro-1-naphthoic acid was isolated by acidification of the sodium bicarbonate wash liquor. Only a small amount of neutral product remained in the chlorobenzene layer; this consisted principally of methyl 6-chloro-1-naphthoate (15%). The reaction thus differed in two essentials from that with benzene: (1) the ester group was largely cleaved to a carboxyl group and (2) no significant amount of higher molecular weight material was formed. In this latter respect the reaction corresponds to that of furoic acid with chlorobenzene. The yield of chloronaphthoic acid from methyl furoate was nearly three times that from furoic acid.



Thus, for both benzene and chlorobenzene, condensation to form a naphthalene nucleus seems to be far more satisfactory with methyl furoate than with furoic acid.

Experimental

Methyl Furoate plus Benzene.—Methyl furoate (125 g., 1.1 mole) and 625 cc. of dry benzene (thiophene-free and dried over sodium) were cooled in an ice-bath and treated with anhydrous aluminum chloride (267 g., 2.0 moles) at 0°. After the reaction mixture had been stirred at room temperature for two hours, it was heated in an oil-bath at 70° for thirty hours. The dark red-black mixture was poured into ice and hydrochloric acid and stirred for two hours at room temperature to ensure hydrolysis of the aluminum chloride complex. The layers were separated, and the benzene solution was washed once with dilute hydrochloric acid, twice with saturated sodium bicarbonate solution and finally with water. The solution was dried over anhydrous magnesium sulfate, the benzene was removed by distillation, and 250 cc. of a dark oil was obtained. This oil was distilled under reduced pressure and two fractions were obtained: I, methyl α-naphthoate (80 g., 43%) b. p. 100–102° (0.04 mm.), $n^{20}D$ 1.6068, d^{20}_4 1.129; and II, methyl 9-ethyl-9,10-dihydro-9-anthroate, a pale yellow viscous oil (53 g., 20%) b. p. 144–145° (0.04 mm.), $n^{20}D$ 1.5931; after standing for seven months this oil finally crystallized, m. p. 52–54°.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.80; mol. wt., 266. Found: C, 81.18; H, 6.72; mol. wt., 264, 268.

The residue could not be distilled and when the temperature of the heating bath was raised above 275° it began to decompose, making it impossible to maintain the diminished pressure.

The methyl α-naphthoate was characterized by saponification; 20 g. (0.11 mole) and 150 cc. of 25% potassium hydroxide were placed in a flask and refluxed overnight (twenty hours). The mixture was then cooled, diluted with an equal amount of water and neutralized with dilute hydrochloric acid. Seventeen and one-half grams (95%) of α-naphthoic acid was obtained, which was crystallized from 95% ethanol, m. p. 160–161°. The α-naphthoic acid was further characterized by conversion to the amide by treatment with thionyl chloride followed by ice-cold aqueous ammonia, m. p. 204–205°.

Reaction of II with Soda Lime.—Eight grams (0.03 mole) of II was placed in a distilling flask with 15 g. of soda lime. The flask was heated to slightly above 360° for three-quarters of an hour. It was then set for distillation *in vacuo* and the pressure reduced to 2 mm. An oil distilled which immediately crystallized, yielding 3.3 g. (61%) of anthracene, m. p. 211–212°. Mixed with an authentic sample of anthracene melting at 212–213° it gave a melting point of 211–212°. The hydrocarbon was further characterized by the formation of its picrate, m. p. 136–137°.

Oxidation of II to Anthraquinone.—Five grams (0.019 mole) of II was dissolved in 60 cc. of glacial acetic acid. The solution was stirred while chromic anhydride (12.5 g., 0.125 mole) dissolved in 15 cc. of water and 25 cc. of acetic acid was added slowly from a dropping funnel. It was stirred for three hours longer at room temperature and then poured into 400 cc. of ice-water. A precipitate of anthraquinone (3.2 g., 80%) was obtained. This was crystal-

lized from ethanol, m. p. 268–269°. Mixed with an authentic sample, m. p. 272–273°, it melted at 270–271°. The quinone was further characterized by preparing the derivative with phenylhydrazine, m. p. 180–181°.

Oxidation of II to the Ketone.—Six grams (0.023 mole) of II was dissolved in 75 cc. of glacial acetic acid and cooled to about 10°. The solution was stirred vigorously while 3 g. (0.031 mole) of chromic anhydride, dissolved in 10 cc. of water and 10 cc. of acetic acid, was added slowly. The cooling-bath was then removed and the reaction mixture stirred at room temperature for three-quarters of an hour. It was poured into ice-water (200 cc.) yielding an oil which was extracted with benzene. The benzene solution was washed with sodium bicarbonate solution followed by water. The solvent was evaporated leaving an oil (5.6 g., 90%). This crude ketone was purified by the use of betainehydrazide hydrochloride (Girard's reagent T). The oil was dissolved in 125 cc. of absolute ethanol, to which was added 8.4 g. (0.05 mole) of Girard's reagent T and 12 cc. of glacial acetic acid. The mixture was refluxed for one hour, cooled and poured into 900 cc. of ice-water containing enough sodium hydroxide to neutralize nine-tenths of the acetic acid. The solution was then acid to brom thymol blue indicator. The water solution was extracted three times with 125-cc. portions of benzene, then acidified with enough concentrated hydrochloric acid to make the entire solution 0.5 normal, and allowed to stand overnight. It was again extracted with benzene (250 cc. in three portions). The benzene solution was washed with sodium bicarbonate, followed by water. The benzene was evaporated, yielding 2 g. (35%) of pale, viscous oily ketone. From this material a 2,4-dinitrophenylhydrazone was prepared by refluxing in alcohol solution. Crystals began to separate in a few minutes; yield, 3.1 g. (95%). After crystallization from alcohol and ethyl acetate, the bright red crystals melted sharply at 215°.

Anal. Calcd. for $C_{24}H_{20}O_6N_4$: C, 62.60; H, 4.35; N, 12.18. Found: C, 62.72; H, 4.34; N, 12.32.

Reaction of Methyl Furoate and Chlorobenzene.—Seventy-five grams (0.6 mole) of methyl furoate dissolved in 500 cc. of chlorobenzene was cooled to 0° in an ice-bath. The solution was stirred and 162 g. (1.2 mole) of anhydrous aluminum chloride was added over a period of thirty minutes. The stirring was continued for thirty minutes at 0°, for one and one-half hours at room temperature and finally for twenty-eight hours at 90–100°. The reaction mixture was then poured into a mixture of ice and hydrochloric acid and stirred for three hours at room temperature. The mixture emulsified badly and one liter of ether was added to facilitate the separation. The ether layer was washed with dilute hydrochloric acid, with water, three times with saturated sodium bicarbonate, and finally with water. It was then dried over anhydrous magnesium sulfate and the ether removed by evaporation. The residue was placed in a modified Claisen flask and distilled; 20 g. (15%) of methyl 6-chloro-1-naphthoate was obtained, b. p. 165–170° (2 mm.).

The sodium bicarbonate extract was acidified with hydrochloric acid and 53 g. (44%) of crude 6-chloro-1-naphthoic acid was obtained. This was recrystallized once from 95% ethanol and once from benzene, yielding 46 g. (39%) of 6-chloro-1-naphthoic acid, m. p. 188–189°.

Summary

The aluminum chloride-catalyzed reaction of methyl furoate with benzene has been found to yield methyl α-naphthoate in 32–46% yield while chlorobenzene was converted to 6-chloro-1-naphthoic acid in good yield. Esterification of furoic acid thus appears to favor this condensation to a naphthalene derivative.

In addition to methyl α-naphthoate, the reaction with benzene yielded a higher boiling product in 11–20% yield. Evidence has been presented indicating that this compound is methyl 9-ethyl-9,10-dihydro-9-anthroate.

URBANA, ILLINOIS RECEIVED APRIL 14, 1942

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

A Study of the Products Obtained from Starch by the Action of the Amylase of *Bacillus macerans*

BY W. S. MCCLENAHAN, EVELYN B. TILDEN AND C. S. HUDSON

Preliminary experiments on the conversion of potato starch to the crystalline Schardinger dextrins by *Bacillus macerans* showed that the action was produced by a new type of amylase present in bacteria-free filtrates of the cultures.[1] In this paper we wish to report precise data on the nature and extent of the changes in optical rotation,[2] viscosity and reducing action occurring during digestion of various starch samples by purified concentrates[3] of the *macerans* amylase, and to record the yields of alpha and beta dextrins obtainable. Also, the crystalline alpha and beta dextrins have been purified, their constants determined, and their stability toward *macerans* amylase studied.

When *macerans* amylase was allowed to act for one month upon a 2% suspension of potato

(1) (a) Tilden and Hudson, THIS JOURNAL, **61**, 2900 (1939); (b) Tilden and Hudson, *J. Bact.*, **43**, 527 (1942).

(2) In the preliminary publication it was reported that there was no significant change in rotation during digestion, but we now find under more exact test that the change is of considerable magnitude, as shown in Fig. 3.

(3) Tilden, Adams and Hudson, THIS JOURNAL, **64**, 1432 (1942).

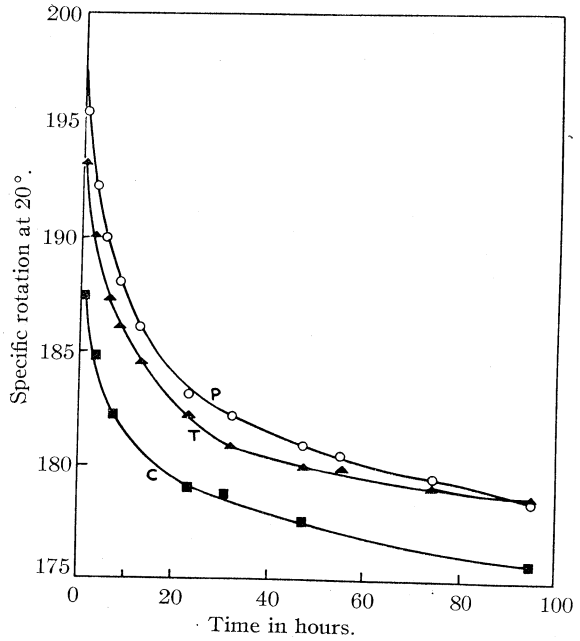


Fig. 1.—Rotatory changes in buffered digests at 20°; *p*H 6.2–6.5; enzyme concentration 10 units per gram of starch in 2% solution: P, potato starch; T, tapioca starch; C, oxidized cornstarch (hypochlorite).

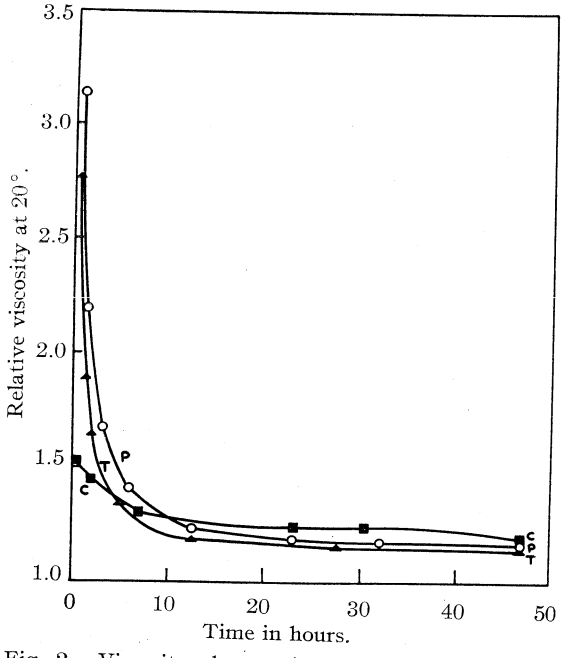


Fig. 2.—Viscosity changes in buffered digests at 20°; *p*H 6.2–6.5; enzyme concentration 10 units per gram of starch in 2% solution: P, potato starch; T, tapioca starch; C, oxidized cornstarch (hypochlorite).

starch, the reducing power[4] was only 1.6%, calculated as the percentage of the total amount of glucose available by complete acid hydrolysis of the starch; this result confirms the earlier work[1a] in showing that the *macerans* enzyme does not produce reducing sugars. Correspondingly low values for reducing power were obtained with digests of tapioca starch and with a commercial thin boiling cornstarch which had been made by the hypochlorite process.

The changes in viscosity and rotation that were observed were very similar for digests of the three starches, as shown in Figs. 1 and 2. Unoxidized defatted cornstarch has been found to give similar results.

The data obtained from digestion of several lots of potato starch, on which the enzyme was allowed to act for periods varying from eight hours to fifty days, are shown in Table I. The presence of the dextrins was demonstrated by the iodine test[1] and confirmed by precipitation of the crystalline products with trichloroethylene. Under the conditions employed the beta dextrin appeared to be formed more gradually than the alpha dextrin, the yield of which appeared to reach a maximum of 20% in the early stages of the conversion. Longer digestion resulted in a higher total yield of dextrins, but there seemed to be a decrease in yield of the crude alpha compound and a definite increase in its rotation, indicating a possible secondary action of the enzyme. This hypothesis was confirmed by experiments in which the enzyme was added to sterile solutions of pure alpha dextrin; the rotation gradually rose from +150.5°[5] to about +169°, while a slight reducing action became evident (Fig. 3 and Table II). No beta dextrin could be detected in the solution at the end of these experiments, and the new dextrin or mixture of dextrins behaved in the iodine test in a manner similar to that of the alpha compound. No effect of the enzyme on sterile solutions of pure β-dextrin was detected.

In an attempt (Digest 4, Table I) to increase the yield of crystalline dextrins, the products were continuously precipitated from solution by adding trichloroethylene soon after the addition of the enzyme, and by allowing the digest to stand for several weeks. Surprisingly, the yield of beta dextrin was thereby increased from 22 to 54%,[6]

(4) Values for reducing power were determined by the Shaffer–Hartmann micro-technique (*J. Biol. Chem.*, **45**, 365 (1921)).

(5) All rotations here reported are specific rotations at 20° for sodium light; *c* is the concentration in grams per 100 ml. of solution, and *l* is the tube length in decimeters. The crystalline dextrins contain water of crystallization, but the rotations are expressed on the anhydrous basis corresponding to their general formula $(C_6H_{10}O_5)_x$.

(6) Beta dextrin has been obtained in a yield of 46% from the action of whole cultures of *Bacillus macerans*.

TABLE I

PREPARATION OF CRYSTALLINE DEXTRINS FROM POTATO STARCH AT 20°[a]

Digest	Time, days	$[\alpha]^{20}D$	Relative viscosity	Reducing power,[b] %	Yield of dextrin, % crude	beta	alpha[c]	$[\alpha]^{20}D$ crude alpha dextrin
1	0.67	+189.8	1.49	0.05	33	9	19	+152
2	3	180.5	1.16	0.25	45	12	20	156
3A	20	177.4	1.09	1.35	50	22	17	160
3B	32	177.4	1.09	1.64	50	22	16	161
4[d]	50	...	..	..	61	54[e]	1	...

[a] The starch concentration was 2%, and 8 units of enzyme was used for each gram of starch. No buffer was added; the *p*H was 6.5. [b] Percentage of the theoretical quantity of glucose available. [c] Includes all material of apparently crystalline nature from aqueous methanol solution. [d] Trichloroethylene was present during the digestion. [e] Crude material rotated +164°.

TABLE II

ACTION OF *macerans* ENZYME UPON STERILIZED 2% SOLUTIONS OF THE SCHARDINGER DEXTRINS AT 20°

Dextrin	Time, days	Units of enzyme per gram of dry dextrin	$[\alpha]^{20}D$	Reducing power,[a] %
alpha	23	0	+150.6	0.0
alpha	10[c]	8	166.4	0.8
alpha	24[c]	8	169.7	1.2
alpha	9	16	169.2	1.4
alpha	10	16	167.3[b]	1.4
alpha	13	16	168.6[b]	1.6
beta	6	0	162.0	...
beta	6[d]	8	162.0	...
beta	14	16	163.2	0.0

[a] As percentage of the theoretical quantity of glucose. [b] Rotation determined after diluting solution to 1%. [c] Not sterile at time of observation. [d] Beta dextrin recovered quantitatively.

while the yield of alpha dextrin was reduced to 1%.[7] No increase in yield resulted from the addition of fresh enzyme to the mother liquor, hence the limit of the conversion of whole starch appears to be about 55%. No explanation can be advanced as yet for the difference in the relative proportions of the two dextrins obtained under different conditions.

The preparations of beta dextrin, obtained from starch by the action of *macerans* enzyme, were readily purified to constant rotation by recrystallization from water. The specific rotation was always +162.5 ± 0.5° instead of +158°, the value which has previously been accepted.[8] After acetylation and careful purification of the crystalline acetate, deacetylation was found to give rise to beta dextrin of the same high rotation. This was the case irrespective of whether pyridine or zinc chloride was used as the acetylation catalyst. We conclude, therefore, that the higher value is the correct one. In other respects (appearance, solubility, decomposition point, formation of orange-brown needles or prisms with iodine solution, and content of water of hydration) the dextrin was identical with preparations previously described. Alpha dextrin rotated +150.5 ± 0.5°, which is somewhat higher than the value (+148°) recorded by other workers.[9]

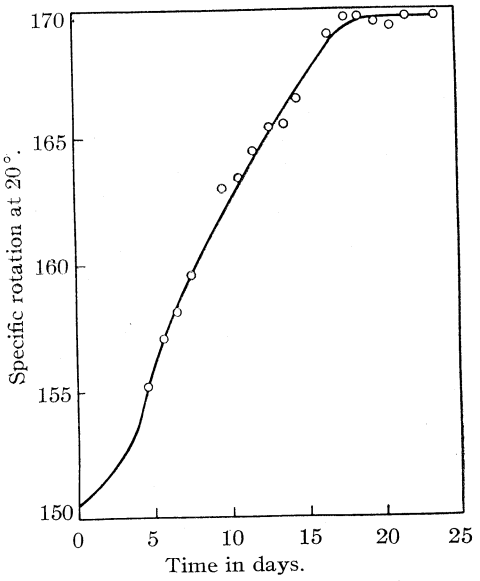


Fig. 3.—Rotatory change in a 2% solution of alpha dextrin at 20°: enzyme concentration 8 units per gram of dextrin (dry basis).

Beta dextrin acetate rotated +125.5° (chloroform); the values given by earlier workers are +121°[8h] and +142°.[9a] Its melting point was 196–196.5° (cor.), and it appears that this constant is a far better criterion of purity than is its rotation, since on several occasions a crystalline

(7) Dr. R. E. Rundle of Iowa State College has reported to us similar results, obtained through the precipitating action of benzene or toluene when used in the digests as preservatives.

(8) (a) Schardinger, *Zentr. Bakt. Parasitenk.*, Abt. II, **22**, 98 (1908); **29**, 188 (1911); (b) Pringsheim and Langhans, *Ber.*, **45**, 2533 (1912); (c) Pringsheim and Eissler, *ibid.*, **47**, 2565 (1914); (d) Pringsheim and Dernikos, *ibid.*, **55**, 1433 (1922); (e) Karrer and Bürklin, *Helv. Chim. Acta*, **5**, 181 (1922); (f) Leibowitz and Silmann, *Ber.*, **58**, 1889 (1925); (g) Pringsheim, Weidinger and Ohlmeyer, *ibid.*, **64**, 2125 (1931); (h) Freudenberg and Jacobi, *Ann.*, **518**, 102 (1935).

(9) (a) Pringsheim, Weidinger and Sallentien, *Ber.*, **64**, 2117 (1931); (b) Miekeley, *ibid.*, **63**, 1957 (1930).

product with approximately the correct rotation had a low acetyl content and softened at 140 to 150°. According to Pringsheim and his co-workers,[10] the use of zinc chloride as an acetylation catalyst brings about the depolymerization of both alpha and beta dextrins. This finding has not been confirmed by other investigators,[8e,8h,9b] and we have found no evidence of such behavior in studying beta dextrin and its acetate.[11] Our rotatory data also suggest that many of the conflicting observations with regard to the nature and behavior of these compounds may have been the result of insufficiently purified (though crystalline) materials.[12]

Experimental Part

Purification of the Enzyme.—The enzyme solution which was used had been concentrated and purified by precipitation with acetone, as previously described.[3] It contained one unit of enzyme in 0.05 ml. (1 unit = amount required to convert 30 mg. of starch in thirty minutes at 40°, as indicated by the iodine test).[1b] It had no rotation or reducing power and was free from maltase, as shown by its failure to influence the rotation of a maltose solution.

Comparative Digestions of Potato, Tapioca and Oxidized Cornstarches (Figs. 1 and 2).—The quantity of starch (commercial grade) equivalent to 2.00 g. of dry material was placed in a 100-ml. volumetric flask, and 50 ml. of water and 1 ml. of 0.2 *M* Sørensen phosphate buffer of *p*H 6.2 was added. A smooth paste was produced by swirling the flask in a boiling water-bath; the wall of the flask was then washed down with a little hot water, and the heating continued for thirty minutes. A layer of hot water was allowed to flow over the surface of the starch paste, after which the flask was plugged with cotton and the solution autoclaved for one hour at 125° (the glass stopper was sterilized at the same time). The solution was diluted with hot sterile water, and cooled to 20° overnight. There was then added sufficient enzyme (1 ml. or 20 units) to convert the starch to the brown-violet stage with iodine in about seven hours at 20°, and after dilution to 100 ml. the flask was closed with the sterile stopper and the contents thoroughly mixed. Viscosity measurements were made as described previously.[1b] Part of the digest was centrifuged to remove any traces of material which might clog the viscosity pipet; the centrifuged material was also used for measurements of rotation, while tests for reducing power[4] were made on 5-ml. aliquots. The entire experiment was carried out at 20–21°.

Preparation of Crystalline Dextrins from Potato Starch. (See Table I.)—Substrates containing 20.0 g. (dry basis) of potato starch were prepared in one-liter volumetric flasks in the above manner, except that the buffer solution was omitted. Eighty units (4 ml.) of enzyme was added to Digest 1 and 160 units to each of the others. The changes at 20° in rotation, viscosity, reducing power and appearance with iodine solution were similar to those obtained in the case of the smaller buffered digests. After sixteen hours and three days, respectively, Digests 1 and 2 were boiled for a few minutes to inactivate the enzyme, and the dextrins were precipitated with trichloroethylene. After Digest 3 had stood overnight, half of it was filtered through a Berkefeld *N* filter into a sterile flask and left undisturbed for thirty-two days. The remainder was kept in the stoppered volumetric flask, and after twenty days a portion of the clear solution gave no evidence of contamination when tested on glucose agar. The details of Digest 4 are given in the next section.

About 15 ml. of trichloroethylene was found sufficient to precipitate the crystalline dextrins in these experiments. The mixture was kept for a day at room temperature and was occasionally shaken; the precipitate was filtered on a Büchner funnel, washed with a little water, and suction applied until the precipitate was almost dry.[13] The aqueous layer of the filtrate was then concentrated *in vacuo* to about 100 ml. and treated again with trichloroethylene. A second precipitate was allowed to form at room temperature, and a third was obtained by stirring the mixture in an ice-bath and filtering after it had stood for a day in the refrigerator. Small quantities of dextrin continued to separate over a period of several weeks. The moisture content of the combined products from each experiment was determined by drying at 100° and 12 mm. to constant weight over calcium chloride. The air-dried material was then dissolved in two parts of water and the solution boiled to remove the trichloroethylene. A very small quantity of difficultly soluble material (Schardinger's "Schlamm") was removed by filtering the hot solution through carbon; crystalline beta dextrin separated on cooling the filtrate. A second crop was obtained by concentrating the mother liquor to a thin sirup, seeding, and allowing it to stand several days in the refrigerator.

The filtrate contained the more soluble alpha dextrin, together with a considerable amount of amorphous material. Methanol was added to the concentrated solution at room temperature until turbidity developed. The solution was clarified by filtering with carbon, and crystallization induced by scratching or seeding. By adding more methanol, filtering and allowing to stand, first at room temperature and then in the refrigerator, the yield could be increased; however, in order to obtain the maximum quantity of crude alpha dextrin, it was usually necessary to concentrate the mother liquor to a sirup, add methanol in the manner described, and repeat the process several times. Whenever considerable amorphous material separated, it was removed by filtration with carbon; it was then dissolved in water and the solution tested for the presence of alpha dextrin with iodine. The yields of crude dextrins are given in Table I.

(10) Pringsheim, "Chemistry of the Monosaccharides and of the Polysaccharides," McGraw-Hill Book Co., Inc., New York, N. Y., 1932, p. 280.

(11) The depolymerization theory was based to a great extent upon cryoscopic molecular weight determinations. This method has been shown in a number of instances to lead to erroneous conceptions of the molecular size of polysaccharides and their derivatives [Hanes, *New Phytologist*, **36**, 101 (1937); Klages, *Ann.*, **520**, 71 (1935); Haworth, Hirst and Ant-Wuorinen, *J. Chem. Soc.*, 2368 (1932); Freudenberg and Bruch, *Ber.*, **63**, 535 (1930); Kratky and Mark, *Fortschr. Chem. org. Naturstoffe*, **1**, 255 (1938)].

(12) Samples of alpha and beta dextrin prepared by Dr. Thomas J. Schoch of the Corn Products Refining Company showed the same rotations as our preparations.

(13) When bulky precipitates are obtained in large scale work, it is advantageous to remove the trichloroethylene by washing the filter cake with small portions of methanol.

Precipitation with Trichloroethylene during Digestion (Digest 4, Table I).—After an hour's digestion at 20°, Digest 4 was filtered through filtercel; 50 ml. of trichloroethylene was added to the filtrate, and the digestion was allowed to continue at 20°. The crystalline dextrins were removed by filtration after two, three, five and six weeks, the final crop being obtained after concentrating at low temperature to 100 ml. Three milliliters of enzyme was added to the mother liquor, but no further precipitation occurred after the solution had stood at 20° for several weeks.

Purification of the Dextrins.—The beta dextrin was recrystallized four times from four parts of water. The air-dried product rotated +139.4° (*c*, 1.0; *l*, 4). Its weight became constant after drying at 66° and 12 mm. for ninety minutes over calcium chloride; loss, 14.13%. The specific rotation was therefore +162.4°; other samples showed +163.0° and +162.8°.

Crude alpha dextrin, which contained some amorphous material, was recrystallized by adding methanol to its concentrated aqueous solution, according to the procedure given in the preceding section. Further recrystallizations were made from 70% methanol by dissolving the dextrin in one part of hot water and adding the alcohol to the warm solution. After two such recrystallizations the air-dried material rotated +136.5° (*c*, 1.1; *l*, 4). Its weight became constant after drying five hours at 100° and 12 mm.; loss, which may have been partly methanol, 9.48%. The specific rotation was therefore +150.8°; after two further recrystallizations it rotated +150.4° and +150.3°, respectively, while an entirely different preparation showed +150.8°.

Acetylation of Beta Dextrin.—Five grams of pure, anhydrous, powdered beta dextrin was dissolved in 15 ml. of pyridine, the solution becoming slightly warm. Since cooling the solution caused it to set to a gel, 15 ml. of acetic anhydride was added while it was still warm. The stoppered flask was then shaken and cooled occasionally, its contents becoming homogeneous after half an hour. After standing at room temperature for three days, the solution was poured into 400 ml. of ice water, and the product crystallized immediately in nearly theoretical yield. The acetate was recrystallized four times from seven parts of methanol, from which it separated in the form of elongated, hexagonal plates. It could not be recrystallized satisfactorily from absolute ethyl alcohol, possibly because a partial deacetylation occurred. It melted at 196–196.5° (cor.). The rotation and analytical data were obtained from a portion which had been dried *in vacuo* to remove the methanol and then allowed to stand overnight in the air. This sample rotated +122.3° (*c*, 1.0, chloroform; *l*, 4); its loss in weight after forty-five minutes at 66° and 12 mm. was 2.20%, and hence the specific rotation was +125.0°. A second preparation rotated +125.4°. The dry acetate was extremely hygroscopic, and in order to determine its moisture content accurately it was necessary to employ a modified Abderhalden drying apparatus.[14]

Anal. Calcd. for $(C_{12}H_{16}O_8)_x$: C, 49.99; H, 5.60; CH_3CO, 44.79. Found: C, 50.04; H, 5.86; CH_3CO, 45.85.

(14) Milner and Sherman, *Ind. Eng. Chem., Anal. Ed.*, **8**, 427 (1936).

Four grams of the acetate in 50 ml. of methanol was deacetylated in the cold with 4 g. of potassium hydroxide dissolved in 25 ml. of methanol. The resulting precipitate was dissolved in water, and, after neutralization of the solution with dilute acetic acid, the beta dextrin began to crystallize. The recovery was 92% of the theoretical amount. After two recrystallizations from water, the dextrin rotated +162.9°.

Four grams of dry powdered beta dextrin and 0.5 g. of pulverized zinc chloride were added to 20 ml. of acetic anhydride, and the mixture was heated on the steam-bath for one hour. The hot, faintly yellow solution was poured into a liter of ice-water, and the acetate began to solidify after a few minutes of stirring. The acid was neutralized with sodium bicarbonate, and the product obtained in nearly theoretical yield. After recrystallization the acetate melted at 196–196.5° (cor.). The air-dried sample contained 2.06% moisture and rotated +123.8° (*c*, 1.0; *l*, 4), or +126.3° calculated to the dry basis.

Anal. Calcd. for $(C_{12}H_{16}O_8)_x$: C, 49.99; H, 5.60; CH_3CO, 44.79. Found: C, 50.10; H, 5.96; CH_3CO, 45.62.

A three-gram portion of the acetate was deacetylated. The dextrin was recovered quantitatively, and after two recrystallizations from water it rotated +163.0°.

Action of *macerans* Enzyme on the Crystalline Dextrins.—One-gram samples of the pure, air-dried dextrins were dissolved in hot water in 50 or 100 ml. volumetric flasks. Alpha dextrin solutions were heated fifteen minutes on the steam-bath to remove possible traces of methanol before autoclaving for thirty minutes at 124°; beta dextrin solutions were autoclaved directly. After the flasks had been cooled to 20°, the enzyme was added, and the solutions were diluted to 50 ml. with sterile water. The small amount of beta dextrin which separated after a few days was redissolved by warming to 40° before the flasks were opened. Sterility tests were made on glucose agar at the conclusion of each experiment. The data obtained in several experiments with both dextrins are presented in Table II, while the changes in rotation observed in one non-sterile experiment are shown in Fig. 3.

During the conversion of alpha dextrin the solutions gave iodine tests similar to that of the original substance. The product could be precipitated with trichloroethylene, but no beta dextrin was obtained when the solution was concentrated *in vacuo* to a sirup. Addition of methanol to the solution caused it to cloud, and a mixture of amorphous and crystalline material gradually separated. Methods for fractionating the mixture are being investigated.

The authors wish to express their appreciation to Dr. Thomas J. Schoch of the Corn Products Refining Company for samples of oxidized starch and Schardinger dextrins, and to Dr. E. Justin Wilson, Jr., of this Laboratory for helpful assistance.

Summary

The action of the purified enzyme of *Bacillus macerans* on starch substrates proceeds with a

rapid decrease in viscosity and a gradual decrease in optical rotation. Unlike other amylases, the *macerans* amylase does not increase the reducing power of whole starch to any noteworthy extent.

The Schardinger dextrins have been prepared from potato starch by means of the *macerans* amylase in a maximum yield of 55%. The relative proportions of alpha and beta dextrins in the product have been shown to vary greatly with different digestion conditions; the factors involved in this behavior are receiving further study. Beta dextrin is stable toward *macerans* amylase at 20°, whereas the alpha dextrin is converted, at least in part, to higher rotating material which exhibits slight reducing properties and contains no beta dextrin.

The rotations of carefully purified alpha and beta dextrins have been found to be +150.5 ± 0.5° and +162.5 ± 0.5°, respectively, instead of +148° and +158°, as previously reported. The new value for beta dextrin was confirmed by preparing its acetate (rotation +125.5° in chloroform; m. p. 196–196.5° (cor.)), from which the original high rotating beta dextrin was regenerated. The same beta dextrin acetate was produced when either pyridine or zinc chloride was used as the acetylation catalyst.

BETHESDA, MARYLAND RECEIVED MAY 28, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE CITY COLLEGE OF THE COLLEGE OF THE CITY OF NEW YORK]

The Nature of the Fatty Acids Associated with Starch. The Adsorption of Palmitic Acid by Potato and Defatted Corn and Rice Starches

BY LEO LEHRMAN

It is well known that starches, with the exception of potato, have associated with them small amounts of fatty material which is not extracted by the usual fat solvents, such as ether or carbon tetrachloride.[1] Acid hydrolysis is usually employed to liberate this fatty material, which is therefore termed "fat by hydrolysis" to distinguish it from the fatty material which can be extracted by ether or carbon tetrachloride. The fatty material that can be extracted from raw starches by ether or carbon tetrachloride is usually referred to as extraneous extractable fatty matter. Recently Schoch reported that fat solvents having hydrophilic groups, particularly methanol, the cellosolves and 80% dioxane, extract practically all the fatty acids in three cereal starches.[2] He further reported that the defatted starches retain a number of the usual properties of the original starches. In addition, fatty acid can be introduced into the defatted starches and cannot be removed by extraction with the usual fat solvents, such as ether or carbon tetrachloride. On the basis of these results, Schoch concluded that free fatty acid is present in starch as an extraneous impurity.

This author submitted a comment which stated his reasons for disagreeing with this conclusion and suggested the possibility of the fatty acids being adsorbed by starch.[3] Lately, it has been shown that the amount of fatty material extracted by methanol from corn starch ground in a rod mill is the same as that extracted from the unground corn starch. From this observation the conclusion has been drawn that the fatty acids are not present extraneously.[4] Adsorption has been mentioned in connection with the occurrence of fatty acids in starch but the evidence is meager.[5]

Potato starch has been shown not to contain any "fat by hydrolysis"[6] and, therefore, could be used like a defatted starch. Oleic acid was introduced into potato starch, though only in a small percentage, by refluxing with a methanol solution of the fatty acid.[7] In order to determine how a fatty acid combines with starch, varying concentrations of palmitic acid in a hydrophilic solvent (methanol) were refluxed with potato starch. Palmitic acid was chosen because it occurs in the "fat by hydrolysis" of all starches; it is saturated and, therefore, no special precautions are neces-

(1) (a) Sostegni, *Gazz. chim. ital.*, **15**, 376 (1885); (b) Taylor and Nelson, THIS JOURNAL, **42**, 1726 1920); (c) Taylor and Lehrman, *ibid.*, **48**, 1739 (1926); (d) Lehrman, *ibid.*, **51**, 2185 (1929); **52**, 808 (1930); **54**, 2527 (1932); **55**, 850 (1933); **59**, 1050 (1937).

(2) Schoch, *ibid.*, **60**, 2824 (1938).

(3) Lehrman, *ibid.*, **61**, 212 (1939).

(4) Evans and Briggs, *Cereal Chem.*, **18**, 447 (1941).

(5) (a) Schoch, *ibid.*, **18**, 124 (1941); (b) ref. 4, p. 453; (c) Evans and Briggs, *ibid.*, **18**, 467 (1941).

(6) Lehrman and Kabat, THIS JOURNAL, **55**, 850 (1933).

(7) Schoch, private communication.

sary to prevent oxidation; and finally, it is taken up by corn starch in preference to unsaturated fatty acids.[8] After removing the excess palmitic acid by extraction with carbon tetrachloride, the "fat by hydrolysis" was determined.

A graph of the results of these experiments is a typical Freundlich isotherm indicating that the palmitic acid was probably adsorbed by the potato starch. The experimental work was carried out with defatted corn and rice starches to determine whether a similar Freundlich isotherm would be obtained.

Experimental

Preparation of Defatted Corn and Rice Starch.—Corn and rice starch[9] having negligible extraneous fatty material and 0.65 and 0.69% "fat by hydrolysis," respectively, were extracted in a Soxhlet extractor with methanol for two weeks. Though the "fat by hydrolysis" in each starch had decreased to 0.03%, further extraction had no effect. This result agrees with that found by others.[10] That the methanol extraction of the fat from the starches cannot be due to hydrolysis has already been shown.[11]

Introduction of Palmitic Acid into the Fat-Free Starches.—Ten-gram samples of potato (negligible extraneous fat) and defatted corn and rice starches separately, were refluxed while stirring with 1–20 g. of pure palmitic acid dissolved in 50 ml. of pure methanol for five hours. It was found that longer heating did not increase the amount of palmitic acid taken up by the starches. The mixtures were filtered, the residues washed with carbon tetrachloride and allowed to dry. The residues then were extracted for three hours with hot carbon tetrachloride in a rubber extractor and allowed to dry. The dry starch products were hydrolyzed with dilute hydrochloric acid, cooled, filtered through petroleum ether extracted filter papers, the papers and fatty acids washed several times with distilled water and allowed to dry. The filter papers and fatty acids then were extracted with petroleum ether, the extracts allowed to evaporate in weighed beakers and the residues weighed. Figure 1 is the graph obtained by plotting these values.

Discussion

The fact that the palmitic acid taken up by the starches follows a typical Freundlich isotherm indicates either adsorption or solid solution. While X-ray diffraction patterns would be necessary to decide which phenomenon took place, from the generally accepted amorphous state of starch, adsorption is the more probable. It has already been noted that defatted starches have a number

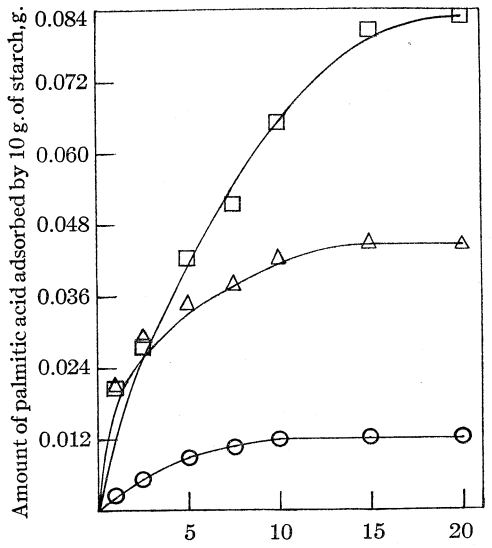


Fig. 1.—Adsorption isotherms of palmitic acid with potato and defatted corn and rice starches; O , potato starch; △, defatted corn starch; □, defatted rice starch.

of the usual physical properties of the original starches. This is to be expected if the fatty acids are adsorbed on the starch. The fact that a starch component is electrically charged only when it contains fatty acid (fat by hydrolysis)[12] can be accounted for on the basis of an adsorption of the fatty acid. There would be no electrical charge if the fatty acid were chemically combined with carbohydrate (such as by esterification or etherification). It is interesting to note that potato starch, which has no fatty acid associated with it, has practically no charged component.[13]

The amount of fatty acid taken up by each starch gives additional weight to the case for adsorption. Thus, potato starch, known to have no fatty acid, adsorbs only a very small amount of palmitic acid compared with defatted corn and rice starches. Furthermore, defatted rice starch, which in its original condition has a higher percentage of "fat by hydrolysis" than corn starch, adsorbs more palmitic acid than defatted corn starch.

It has already been shown that corn starch takes up (adsorbs) saturated fatty acid in preference to unsaturated fatty acid.[8] It is difficult to explain on this basis, however, why defatted corn starch adsorbs less than its original fatty acid content, while defatted rice starch adsorbs more, or that potato even adsorbs any. It does show that these

(8) Ref. 4, p. 454; ref. 5c.

(9) The author wishes to thank Stein, Hall and Co., Inc., New York City, for their kindness in supplying these starches.

(10) (a) Schoch, private communication; (b) ref. 4, pp. 447, 448.

(11) (a) Ref. 10a. In this communication Schoch states that from his experimental data none of the fatty acids in corn, wheat or rice starch is esterified with carbohydrate; (b) ref. 4, p. 451.

(12) Taylor and Werntz, THIS JOURNAL, **49**, 1584 (1927).

(13) Taylor and Iddles, *Ind. Eng. Chem.*, **18**, 713 (1926).

three starches are different in their surface effects.

All these data are consistent with the conclusion that the fatty acids associated with starch are adsorbed.

Summary

1. Potato and defatted corn and rice starches take up palmitic acid from a methanol solution probably by adsorption.

2. A discussion of known facts leads to the conclusion that fatty acids associated with starch are probably adsorbed.

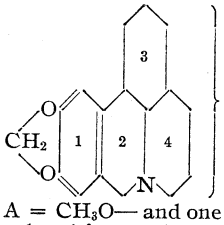
NEW YORK, N. Y. RECEIVED JUNE 1, 1942

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

Erythrina Alkaloids. XIII. Studies on the Constitution of Erythraline, Erythramine, and Erythratine

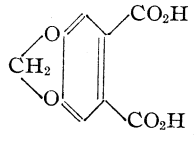
BY KARL FOLKERS, FRANK KONIUSZY AND JOHN SHAVEL, JR.

Studies[1] on the constitution of erythramine and erythraline led to the formulation of the partial structure I with the comment that the presence of one five-atom nucleus was not excluded. The initial studies[2] showed that erythramine, $C_{18}H_{21}NO_3$, contains a methylenedioxy group, a methoxyl group, a tertiary nitrogen atom probably common to two nuclei, and an ethylenic double bond, besides one aromatic nucleus. It consists apparently of four nuclei (exclusive of the methylenedioxy bridge), three being partially or completely saturated and one aromatic. Erythraline, $C_{18}H_{19}NO_3$, differs only in having one more ethylenic double bond since dihydroerythramine and tetrahydroerythraline were found to be identical when the free bases and hydriodides were compared. Ring 1 of the partial structure was established by the formation of hydrastic acid (II) by oxidation of erythraline methohydroxide; and rings 1 and 2 were strongly indicated by the very close similarity between the ultraviolet absorption spectra of dihydroerythramine and 6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline hydrobromides. The hydroindole formulation (III) which might be anticipated because of the accompanying hypaphorine, which is so widely distributed in seeds of species of *Erythrina*, was excluded by the formation of hydrastic acid. Rings 3 and 4 were indicated tentatively because of the tertiary nitrogen atom. It was of interest that these two alkaloids and lycorine and tazettine, of the *Lycoris* alkaloids, possess methoxyl and hydroxyl groups on hydroaromatic nuclei of structures identical for rings 1 and 2.

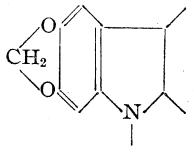


A = CH_3O— and one double bond for erythramine
A = CH_3O— and two double bonds for erythraline

I

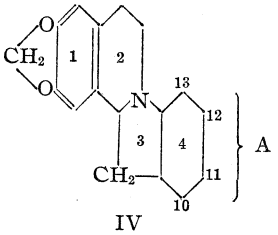


II

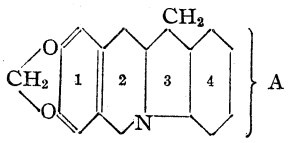


III

Recently,[3] new structural studies were presented including experiments performed on β-erythroidine, which led to the isolation of indole from the products of potassium hydroxide fusion. Although β-erythroidine appears to differ considerably from erythraline and erythratine in functional groups and nuclear formulation, it was of interest to examine the products from the fusion of erythraline with potassium hydroxide for the presence of indole. By a modified procedure which involved adding erythraline hydriodide in portions to the molten alkali, pure indole picrate, identical with an authentic specimen, was obtained by appropriate technique. Interpretation of the indole formation suggests erythraline and erythramine actually do



IV



V

A = CH_3O— and >C=C< for erythramine
A = CH_3O— and 2 >C=C< for erythraline
A = CH_3O— and HO— and >C=C< for erythratine

(1) Folkers and Koniuszy, THIS JOURNAL, **62**, 1673 (1940).
(2) Folkers and Koniuszy, *ibid.*, **61**, 3053 (1939).
(3) Folkers, Koniuszy and Shavel, Jr., Abstracts of Papers, meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1941, Division of Organic Chemistry, page 30.

contain one five-atom nucleus, and rings 3 and 4 may be written now as in the C_{16} four-ring structures, IV or V.

Erythratine,[4] $C_{18}H_{21}NO_4$, has now been found to possess one methylenedioxy group, one methoxyl group and one non-phenolic hydroxyl group. It does not contain $CH_3C\equiv$ or $CH_3N\equiv$ groups. The presence of the non-phenolic hydroxyl group was shown by active hydrogen determination, insolubility in sodium hydroxide solution, and formation of benzoyl and acetyl derivatives. Erythratine is a tertiary base, as evidenced by the formation of a methiodide and methohydroxide of expected properties. Erythratine absorbed one mole of hydrogen over a platinum catalyst at atmospheric pressure to give a dihydroerythratine.

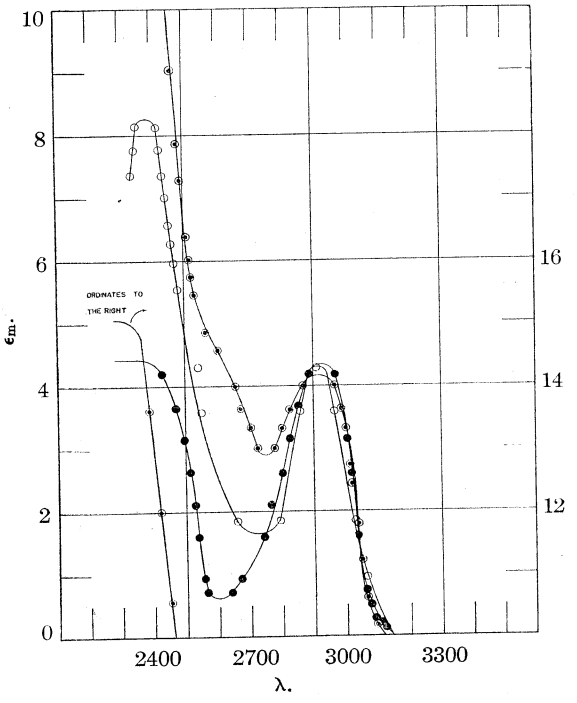
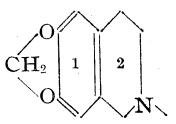
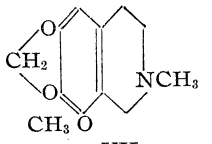


Fig. 1.—Absorption spectra in ethanol for: ●, erythratine; ○, erythramine; ◉, erythraline (note for erythraline that the ordinates are indicated on the right for ϵ_m 10–16). Absorptions are represented in terms of the extinction coefficient computed on the basis of one millimole per liter; wave lengths, in Ångström units.

It is seen from the ultraviolet absorption spectra data[5] in Figs. 1 and 2 that erythratine and dihydroerythratine hydrobromide exhibit a maximum at *ca.* 2930 Å. and ϵ_m 4.3 to 4.8, as is also exhibited by erythramine, erythraline, dihydroerythramine hydrobromide and 6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline hydrobromide. It has been assumed that this band is characteristic of the partial nucleus VI, and it differs considerably from the corresponding band of the spectrum of hydrocotarnine (VII), shown in Fig. 2, which has



VI



VII

a methoxyl group in addition to the methylenedioxy group on the benzenoid nucleus. The spectra as shown in Fig. 1 for erythratine, erythraline and erythramine differ at wave lengths below *ca.* 2900 Å. probably chiefly in accord with the different double bonds and oxygen groups in rings 3 and 4 for the three alkaloids. The absorption of dihydroerythramine and dihydroerythratine parallels that of the known methylenedioxy-tetrahydroisoquinoline derivative as shown in Fig. 2.

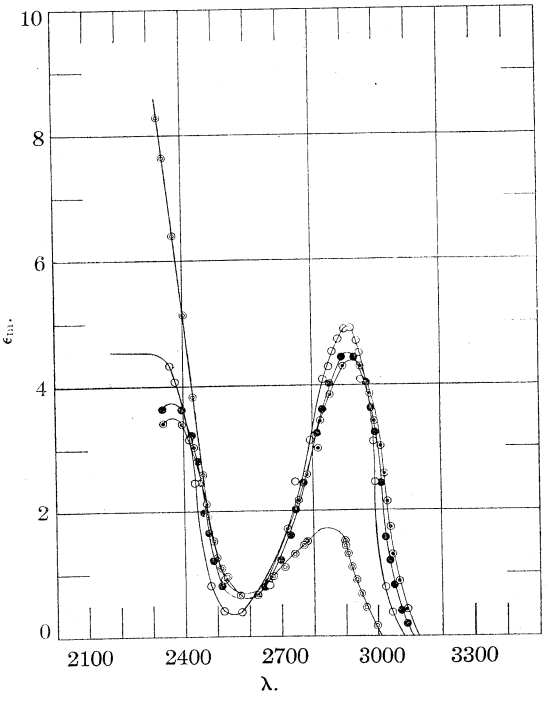
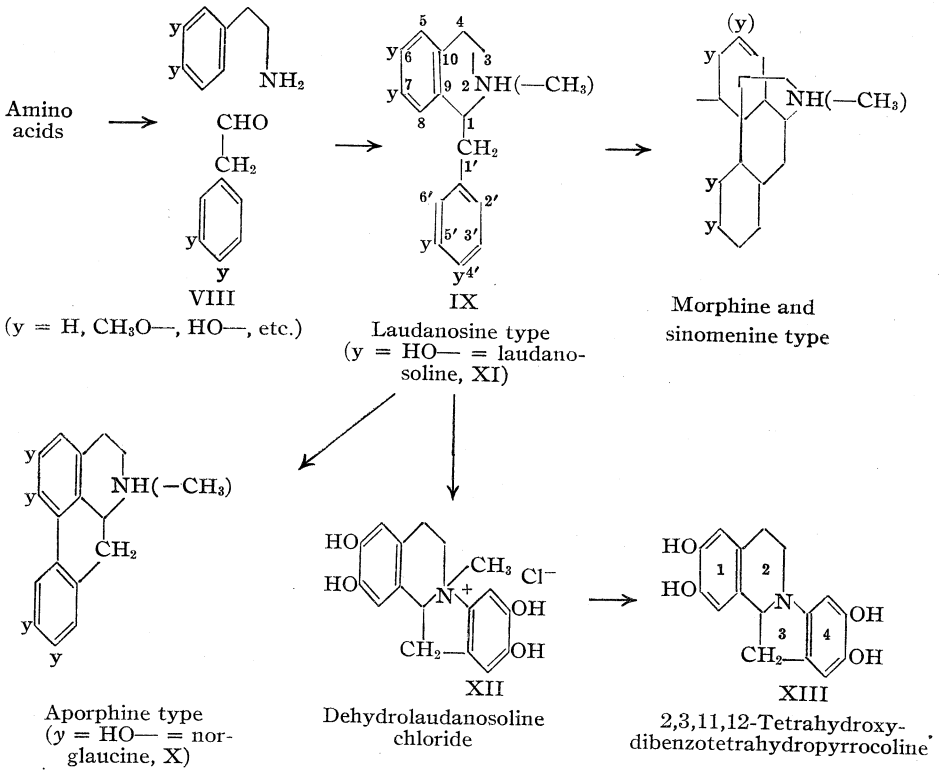


Fig. 2.—Absorption spectra in ethanol for: ○, dihydroerythratine hydrobromide; ●, dihydroerythramine hydrobromide; ◉, 6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline hydrobromide; hydrocotarnine represented by curve with concentric circles.

This behavior indicates that the remainder of the alkaloidal structures is not influencing the absorption spectrum of these compounds to any pronounced degree. Thus, erythratine also appears

(4) Folkers and Koniuszy, THIS JOURNAL, **62**, 436 (1940).

(5) Acknowledgment is hereby made to Mr. W. A. Bastedo, Jr., of this Laboratory for the measurements of the absorption spectra.



to contain the methylenedioxy-tetrahydroisoquinoline nucleus (VI) and the methoxyl and hydroxyl groups elsewhere. Taking into account the benzenoid nucleus, one ethylenic double bond, and the functional groups in erythratine, the molecule consists apparently of four fused nuclei (exclusive of the methylenedioxy bridge), three being partially or completely saturated and one being aromatic.

When erythratine was degraded by fusion with potassium hydroxide, and after purification chromatographically of the solvent fraction bases over aluminum oxide, indole was isolated and identified as such and as its picrate. When all these related facts on erythramine, erythraline and erythratine are considered, it appears that erythratine is also represented by structure IV or V when A signifies a methoxyl and hydroxyl group and one carbon–carbon double bond.

Structure IV, rather than V, would be preferred for these alkaloids on the basis of several biogenetical relationships. The nuclei 1, 2 and 4 of IV are inherently a benzyl-tetrahydroisoquinoline derivative dehydrogenated between nuclei 2 and 4 to give the fourth nucleus 3, as may be seen from the following relationships. The generally accepted origin of benzyl-tetrahydroisoquinoline alkaloids (IX) from substituted phenylethyl amines and phenylacetaldehydes (VIII) both *via* amino acids, proposed from the studies of Winterstein and Trier, Barger,[6] and Robinson[7] is shown in the scheme according to VIII → IX. Dehydrogenation with ring closure between atoms 8 and 2′ of IX leads to the aporphine type of alkaloid. Dehydrogenation with ring closure between atoms 10 and 6′ leads to the morphine and simomenine type of alkaloid. Although this formal relationship between the benzylisoquinoline type and the aporphine and morphine types has not been achieved experimentally as yet by oxidative or dehydrogenative reagents, such studies have been made.[8] Of particular interest to these three *Erythrina* alkaloids are the experiments of both Robinson[9] and Schöpf[10] to convert laudanosoline (XI) into norglaucine (X) or to convert directly a benzylisoquinoline type into an aporphine type. The product of several reagents (chloranil, potassium ferricyanide, air, and oxygen over platinum) on XI was dehydrolaudanosoline chloride (XII) which is a quaternary dihydroindole deriva-

(6) Barger, *IX Congreso Internacional de Quimica, Conferencias de Introduccion*, Madrid, 1934, p. 97.
(7) Robinson, *ibid.*, p. 168; *J. Chem. Soc.*, 1079 (1936).
(8) For protosinomenine, Robinson, *J. Chem. Soc.*, 1079 (1936).
(9) Robinson and Sugasawa, *ibid.*, 789 (1932).
(10) Schöpf and Thierfelder, *Ann.*, **497**, 22 (1932).

tive. Instead of effecting ring closure between atoms 8 and 2′, the closure took place between atoms 2 and 2′. Reaction in boiling acetic anhydride converted XII into the tetraacetyl derivative of the pyrrocoline derivative, XIII. Proof of structure XII was established through Hofmann and Emde degradations.

If structure IV represents these three *Erythrina* alkaloids, then Robinson and Schöpf, failing to convert a benzylisoquinoline type directly into an aporphine type, have achieved its conversion into an *Erythrina* type *before* natural alkaloids of this hydropyrrocoline class were recognized!

The methoxyl group of erythramine and erythraline is probably at position 12, on the basis of tyrosine as the precursor.[6] Similarly, the methoxyl and hydroxyl groups of erythratine are probably at positions 11 and 12, as in XIII, although positions 12 and 13 are possible.[6] The ethylenic double bonds in structure IV appear to be in ring 4 and not 3, because the pure alkaloids do not show the Ehrlich color test for indole derivatives. Of course, the pyrrocoline derivative, XIII, and these *Erythrina* alkaloids, if so related, would show some different properties because the natural products are partially saturated in ring 4. Nevertheless, the tetramethyl ether of XIII gave a weak blue color with Ehrlich's reagent, whereas its dehydro (ring 3) derivative gave an intense indole reaction, and an aged specimen of erythratine (better for comparison because it has two oxygen atoms on ring 4 to enhance reactivity) gave a blue color at 25° and a strong royal blue color at 90°. A new specimen of erythratine gave only a slight positive test; presumably, the aged specimen had undergone slight atmospheric oxidation in ring 3. A solution of erythraline with Ehrlich's reagent slowly developed a deep pink color.

Whereas the threshold dose of erythratine hydrobromide for curare-like paralyzation of frogs was 75 mg./kg. injected intralymphatically,[11] the threshold dose of erythratine methiodide was found by Dr. Klaus Unna of the Merck Institute for Therapeutic Research to be 100 mg./kg. frog. As for erythramine and erythraline and their respective methiodides,[1,2] the conversion of the tertiary base, erythratine, into its quaternary methiodide did not enhance its curare-like physiological activity. The threshold dose of dihydroerythratine hydrobromide was 300 mg./kg., but the frogs did not recover.

(11) Folkers and Koniuszy, THIS JOURNAL, **62**, 436 (1940).

Experimental Part

Indole from the Fusion of Erythraline with Potassium Hydroxide.—When 1.07 g. of erythraline hydriodide was ground with 25 g. of potassium hydroxide and fused, only 9 mg. of residue was obtained from the solvent extraction. It gave the color test for indole. It appeared by this procedure[12] that partially decomposed alkaloid floated as a film on the molten alkali during the fusion and the degradation was not satisfactory. After a second similar fusion, on 1.2 g. of erythraline base, only a few mg. of an impure picrate was obtained. Successful characterization of indole was accomplished only after fusion of larger quantities by the following modified procedure.

When 4.28 g. of pure erythraline hydriodide (from *E. glauca* Willd.) was added slowly to 30 g. of well-stirred molten potassium hydroxide, a vigorous reaction ensued with each addition of alkaloid. After all of it had been added, the homogeneous melt was heated for another ten minutes to insure complete reaction. The melt was then carefully poured on 200 g. of ice, and the resulting solution extracted continuously with ether for ten hours.

The ether extract was concentrated carefully to a volume of about 5 ml. by distillation through a Widmer column. The residual ether solution was then concentrated to a moist residue by distillation at 10° at a somewhat reduced pressure. The residue had an indole odor and gave the pink color test with *p*-dimethylaminobenzaldehyde. The picrate (23 mg.) made from this residue showed the m. p. 166.5–168°. After two recrystallizations from benzene in a centrifuge cone, 12 mg. of red indole picrate, m. p. 172–172.5°, was obtained. A mixed melting point with freshly prepared authentic indole picrate, m. p. 172–172.5°, showed no depression of the melting point.

Extraction of the acidified aqueous solution by ether and chloroform yielded residues too small for the isolation of other degradation products.

Indole from the Fusion of Erythratine with Potassium Hydroxide.—A quantity of 8.27 g. of erythratine (newly isolated from *E. glauca* Willd.) was slowly added to 50 g. of well-stirred molten potassium hydroxide. The reaction was quite vigorous, and the melt was heated for another ten minutes, in which time it started to froth considerably. The melt was then carefully poured on 300 g. of ice, and the resulting alkaline solution was extracted continuously with ether for ten hours.

The ether extract was concentrated to a small volume by careful distillation through a Widmer column to minimize the loss of the volatile indole. The residual ether solution was concentrated to a gummy moist residue at 10° at a somewhat reduced pressure.

The residue was dissolved in 5 ml. of ethyl ether and passed over a 1 × 3 cm. column of aluminum oxide Merck (Brockmann). A 2-mm. band of brown decomposition products appeared at the top, while the solution passing through was colorless. The column was developed further with 25 ml. of ether.

To the eluate was added 5 ml. of petroleum ether and after partial concentration on the steam-bath, 163 mg. of crystals of m. p. 52° was obtained. Besides the identity of the melting point with that of indole, they gave with *p*-

(12) Barger and Scholz, *Helv. Chim. Acta*, **16**, 1352 (1933).

dimethylaminobenzaldehyde the pink color reaction characteristic for indole.

Anal. Calcd. for C_8H_7N: C, 82.04; H, 6.02. Found: C, 81.83, 81.86; H, 6.08, 6.09.

On converting a portion of the crystals to the picrate, red needle-like crystals were obtained, m. p. 172–173°. These crystals were mixed with freshly prepared indole picrate (m. p. 172–172.5°) and there was no melting point depression.

Further extractions with ether and chloroform of the original aqueous solution, after acidification, yielded very small residues, which did not satisfactorily permit the isolation of other degradation products.

The Oxygen Atoms of Erythratine.—A Friedrich determination on the hydriodide showed 6.78% —OCH_3 group and no =NCH_3 group; calcd. for one —OCH_3 group, 6.98%. When compared with erythramine and hydrastine, erythratine gave a positive result when tested for the presence of a methylenedioxy group.[13] Erythratine was insoluble in 10% sodium hydroxide solution at 25°. A 117.2 mg. quantity of the base was dissolved in 4 ml. of ethanol, treated with 10 ml. of 10% sodium hydroxide solution, and the mixture was refluxed four hours. Crystals separated on cooling and, by chloroform extraction, a total of 94% of the erythratine was recovered. An active hydrogen determination gave 1.23 to 1.35 active hydrogen atoms for the erythratine hemihydrate base. It is apparent that the fourth oxygen atom exists as a non-phenolic hydroxyl group.

Erythratine does not contain a $CH_3C\equiv$ group as shown by a Kuhn–Roth determination.

O-Benzoyl-erythratine Dihydrate.—To 10 ml. of dry pyridine was added 90 mg. of erythratine and 4 drops of redistilled benzoyl chloride. The solution was refluxed for five minutes and the straw-colored liquid was then poured into 100 ml. of ice and water. A white precipitate and a few oil globules appeared. The oil globules disappeared on the addition of 250 mg. of sodium bicarbonate, but most of the precipitate remained, even after vigorous shaking. Extraction of the mixture by six 25-ml. portions of chloroform dissolved all of the precipitate and concentration of the extracts to dryness *in vacuo* left 104 mg. of transparent gum. The addition of 3 ml. of water caused a partial transformation into a white amorphous solid. A total of 50 ml. of a mixture of ethyl ether and acetone was required to dissolve the solid and gum. The solvent solution was concentrated to 4 ml. which caused immediate crystallization of brown colored needles. They were filtered and washed once with 2 ml. of absolute ethanol; the brown crystals immediately dissolved, leaving 63 mg. of brilliant white needles of m. p. 247–249° (decomp.). These crystals were recrystallized twice from hot absolute ethanol (not very soluble) but the melting point remained at 248–249° (decomp.). A sample was dried for one hour at 100° *in vacuo*, then analyzed. The melting point did not change. The O-benzoyl-erythratine was a dihydrate.

Anal. Calcd. for $C_{25}H_{25}NO_5$: C, 71.65; H, 6.01; N, 3.33. Calcd. for $C_{25}H_{25}NO_5 \cdot 2H_2O$: C, 65.98; H, 6.42; N, 3.07. Found: C, 65.66; H, 6.30; N, 3.22.

O-Acetyl-erythratine.—A 500-mg. quantity of erythratine base was dissolved in 5 ml. of acetic anhydride. After the solution was refluxed ten minutes, it was poured into 100 ml. of ice and water. The solution was made alkaline with sodium bicarbonate and extracted ten times with chloroform, etc. A yield of 503 mg. of pale yellow gum was obtained which was quite soluble in ether and did not crystallize. It was sublimed at 125° and 10^{-4} mm. The sublimate was a white brittle solid which softened at 43 and melted at 55°. In another experiment, the sublimate was resublimed to give a crystalline product melting at 128°. Since the analyses on these products were not entirely satisfactory, the reaction was repeated on larger scale for better purification of the product.

A solution of 2 g. of erythratine in 25 ml. of acetic anhydride was refluxed for twenty minutes, cooled, and poured into 250 ml. of ice and water. Shaking of this mixture caused disappearance of the excess acetic anhydride, and after making the solution alkaline with sodium bicarbonate, it was extracted with ten 25-ml. portions of chloroform. Distillation of the solvent and pumping *in vacuo* left 2.1 g. of acetylated erythratine as a clear gum. Although this erythratine problem was suspended for two years, the acetylated product remained unchanged in physical appearance. It was then sublimed twice at 10^{-4} mm. and 130°. The sublimate was crystalline, m. p. 128–129°.

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 65.88; H, 6.35; N, 3.92; CH_3CO—, 11.80. Found: C, 66.04; H, 6.35; N, 3.88; CH_3CO—, 12.08 (alkaline hydrolysis), 11.79 (Kuhn–Roth $CH_3C\equiv$ determination).

The check acetyl determination by the Kuhn–Roth method for $CH_3C\equiv$ groups was done to be sure that the product was not an N-acetyl-O-acetyl-erythratine. An N-acetyl group would be expected to be more resistant to hydrolysis, if the formation of one had resulted from a nitrogen ring cleavage in boiling acetic anhydride, as has been observed for the conversion of chelidonine into N-acetyl-anhydrochelidonine.[14,15]

Hydrolysis of O-Acetyl-erythratine.—The following hydrolysis of the O-acetyl derivative to erythratine confirms the absence of nuclear change in the acetylation reaction. A solution of 25 mg. of O-acetyl-erythratine in 4 ml. of 95% ethanol and 10 ml. of 4% hydrochloric acid was refluxed four hours. After diluting to 50 ml. with water, extracting with six 20-ml. portions of chloroform, and the solvent removal, 9.3 mg. of gum was obtained. Addition of one drop of ether caused crystallization; m. p. 170–171°, $(\alpha)_D$ +145°. Addition of sodium bicarbonate and chloroform extraction eventually yielded 12.8 mg. of gum, which crystallized on adding a drop of ether; m. p. 169–170°, $(\alpha)_D$ +145°. Thus, erythratine was recovered, and its extraction from an acid solution is indicative of its low basicity.

Erythratine Methiodide.—A 50-mg. quantity of erythratine ($(\alpha)^{25}_D$ +146.0) was dissolved in 25 ml. of anhydrous ethyl ether and treated with 0.5 ml. of redistilled methyl iodide. The clear liquid became progressively turbid, but no crystals were immediately apparent. The turbid solution was allowed to stand overnight at 25°. This resulted in tiny white crystals that appeared somewhat amorphous; m. p. 121–125°, $(\alpha)^{25}_D$ +109.7, C, 0.164, water.

(13) Gadamer and Winterfeld, *Arch. pharm.*, **262**, 601 (1924).

(14) Gadamer, *ibid.*, **262**, 265 (1924).

(15) Späth and Kuffner, *Ber.*, **64**, 375 (1931).

Anal. Calcd. for $C_{18}H_{21}NO_4 \cdot CH_3I \cdot {}^1/_2H_2O$: C, 48.96; H, 5.40. Found: C, 48.85; H, 5.36.

After drying for two hours at 100° *in vacuo*, the methiodide was fairly well dehydrated; m. p. 135–136°, $(\alpha)_D$ +110.4.

Anal. Calcd. for $C_{18}H_{21}NO_4 \cdot CH_3I$: C, 49.94; H, 5.29. Found: C, 49.56; H, 5.39.

Further drying with heat initiated slight decomposition.

N-Methyl-erythratine Methine.—A solution of 174 mg. of erythratine methiodide in 20 ml. of water was treated with 500 mg. of silver oxide and the mixture was shaken for three hours at 25°, then filtered. The filtrate gave a negative halogen test, and yielded only 1.8 mg. of chloroform-soluble material when extracted five times. The aqueous erythratine methohydroxide solution was concentrated to dryness at 35° and 20 mm. *in vacuo*, then dried for two hours at 35° and 2 mm. The yield of quaternary base was 135 mg. On heating *in vacuo* in an oil-bath at 150°, rapid effervescence occurred. The bubbling stopped after two minutes, but the heating was continued for another two minutes. The methine was shaken with 25 ml. of water for fifteen minutes, but nothing apparently dissolved. When 5 ml. of chloroform was added, all the methine went into the chloroform layer. Concentration of the chloroform solution to dryness yielded 103.2 mg. of methine that could not be crystallized. Sublimation at 2.5×10^{-4} mm. vacuum and a temperature of 110–125° gave a transparent brittle sublimate.

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.29; H, 7.03. Found: C, 68.96; H, 6.75.

Zn Dust Distillation of N-Methyl-erythraline Methine.—A distillation at 500–560° of 400 mg. N-methyl-erythraline-methine mixed with 40 g. of zinc dust yielded a yellow oil. It was completely soluble in 10% hydrochloric acid solution, and concentration of this solution yielded 91 mg. of gummy hydrochloride which could not be crystallized. From this material, 69 mg. of free base was obtained as a yellow gum which likewise could not be crystallized.

Dihydroerythratine Hydrobromide.—A quantity of 494 mg. of pure erythratine hemihydrate was dissolved in 25 ml. of water containing 1 ml. of 40% hydrobromic acid solution. The hydrogenation was performed over 75 mg. of Adams platinum catalyst and at atmospheric pressure. After two hours, one mole of hydrogen was absorbed. The filtrate was concentrated to dryness at 30° and 18 mm. The residue was dissolved in 5 ml. of absolute ethanol and brought to the crystallization point with 5 ml. of ether. After fifteen hours at 10°, 291.1 mg. of pinkish crystals was obtained. Recrystallization did not alter the melting point of 249°. A sample was dried at 100° and 2 mm. for one hour before analysis.

Anal. Calcd. for $C_{18}H_{23}NO_4 \cdot HBr$: C, 54.31; H, 6.07. Found: C, 54.10; H, 6.06.

After standing at 25° for two to three days, decomposition had taken place.

Acknowledgment.—We wish to express our appreciation to Messrs. Hayman, Reiss, Clark and Boos for the microanalyses.

Summary

Erythraline ($C_{18}H_{19}NO_3$), erythramine ($C_{18}H_{21}NO_3$), and erythratine ($C_{18}H_{21}NO_4$) contain a methylenedioxy group, a methoxyl group, a tertiary nitrogen atom common to two nuclei, and two, one and one ethylenic double bonds, respectively. Erythratine contains an additional nonphenolic hydroxyl group. These alkaloids appear to contain four fused nuclei (exclusive of the methylenedioxy bridge), three being partially or completely saturated and one aromatic. Three of the fused nuclei appear to be identical for each alkaloid, the fourth differing in unsaturation and oxygen groups.

Indole was isolated from the fusion of erythraline and erythratine with potassium hydroxide.

They are structurally formulated as hydropyrrocoline derivatives on the basis of present facts. If this formulation be correct, Robinson and Schöpf, failing to convert directly a benzylisoquinoline type of alkaloid into an aporphine type, have achieved its conversion into an *Erythrina* type, before natural alkaloids of this hydropyrrocoline type were known.

RAHWAY, N. J. RECEIVED JULY 1, 1942

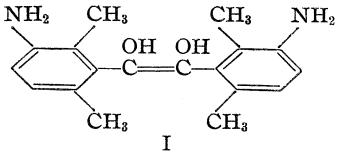
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Enediols. X.[1] An Amino Stilbenediol

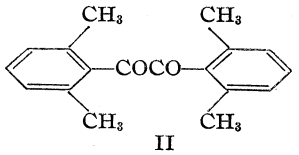
BY REYNOLD C. FUSON AND S. L. SCOTT

The study of the effect of nuclear substituents on the properties of stilbenediols is limited to groups, the presence of which is tolerated by the sensitive enediol group. The most interesting are those that have a profound influence on the character of the benzene ring such as the amino group. The present paper reports the preparation of an enediol which contains this group.

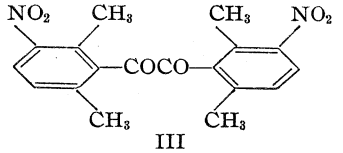
The amino compound selected for study was 1,2-di-(3-amino-2,6-xylyl)-acetylene glycol (I). It was made from 2,6-xylil (II) by nitration followed by catalytic hydrogenation of the dinitro diketone, 3,3′-dinitro-2,6-xylil (III).



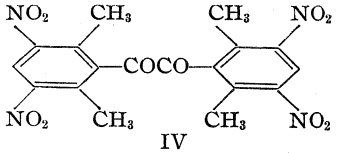
I



II



III



IV

The nitration of 2,6-xylil yielded small amounts of two by-products one of which was identified as the tetranitro derivative, 3,3′,5,5′-tetranitro-2,6-xylil (IV). A procedure was developed, however, which afforded very high yields of the desired dinitro compound (III).

It is extremely interesting that the dinitro diketone failed to form an oxime. That it might do so seemed possible in view of the report that 3-nitromesitonitrile and 3,5-dinitromesitonitrile undergo hydrolysis more readily than does mesitonitrile.[2] Similarly 3,5-dinitromesitaldehyde undergoes the Perkin condensation at a normal rate whereas mesitaldehyde itself reacts very slowly.[3] Thus it would appear that the nitro-groups counteract the hindering effect of the *ortho* methyl groups of the mesityl radical. The result of the present work indicates that one nitro group is insufficient to nullify the hindrance afforded by the 2,6-xylyl group.

Although the diaminostilbenediol (I) was actually obtained, it was always contaminated with its oxidation product, the diaminol xylil. The great ease with which it was oxidized to the diketone coupled with the low solubility of both compounds in ordinary solvents made purification extraordinarily difficult. Moreover, the insolubility of the diamino xylil caused the hydrogenation to proceed very slowly and did not afford definite evidence of the existence of the two geometrical isomers that were expected. This was equally true for 3,3′-diacetamino-2,6-xylil.

Tests made on the diaminostilbenediol are reliable, however, since the contaminating diketone offers no interference. The stability of the enediol to air is of the same order as that of 1,2-di-(2,6-xylyl)-acetylene glycol. In other words, the amino groups do not alter greatly this property of the enediol.

Experimental

Nitration of 2,6-Xylil.—Two and three-tenths grams of finely powdered 2,6-xylil was added slowly, with shaking, to 40 cc. of red fuming nitric acid (sp. gr. 1.59–1.60) at 0°. Each portion of the diketone immediately produced a deep red color, which gradually faded to yellow. When the addition was complete the mixture was allowed to stand overnight in a stoppered container. The product was obtained by pouring the mixture on 100 g. of cracked ice. The solid was collected on a filter, washed and dried. The dinitro compound was extracted with acetone from which it crystallized in glistening yellow prisms; m. p. 211–212° (cor.); yield 92%.

Anal. Calcd. for $C_{18}H_{16}O_6N_2$: C, 60.65; H, 4.53; N, 7.86. Found: C, 60.80; H, 4.64; N, 8.11.

A second product, difficultly soluble in acetone, melted at 241–243° (cor.), with decomposition. It was not identified.

The tetranitroxylil (IV) was insoluble in acetone but could be crystallized from glacial acetic acid; m. p. 273–275° (uncor.), with decomposition; yield 1%.

(1) For the ninth paper in this series see Fuson, McKeever and Behr, THIS JOURNAL, **63**, 2648 (1941).

(2) Küster and Stallberg, *Ann.*, **278**, 207 (1894).

(3) Lock and Bayer, *Ber.*, **72**, 1064 (1939).

Anal. Calcd. for $C_{18}H_{14}O_{10}N_4$: C, 48.42; H, 3.14. Found: C, 48.58; H, 3.16.

In subsequent experiments the nitration mixture was allowed to stand only fifteen minutes after the diketone had been added. At the end of this time the product had crystallized and was removed by filtration. The yield of crude product from 7.5 g. of 2,6-xylil and 121 cc. of fuming nitric acid was 10 g.

The dinitroxylil was treated for long periods with hydroxylamine and also with phenylhydrazine. In each experiment it was recovered unchanged.

Preparation of 3,3′-Diamino-2,6-xylil

(a) **By Catalytic Hydrogenation.**—A mixture of 2.5 g. of the dinitro diketone, 50 cc. of glacial acetic acid and 0.2 g. of platinum oxide was subjected to hydrogenation over a period of eighteen hours. The milky solution was poured into 50 cc. of water, and concentrated hydrochloric acid was added gradually until the solution became clear. The catalyst was removed by filtration and the filtrate made alkaline with ammonium hydroxide. The flocculent white precipitate was collected on a filter, sucked as dry as possible and allowed to stand in a vacuum desiccator over sulfuric acid. The diamino enediol developed a yellow color during the drying process. The yield was 95%. It decolorized a solution of 2,6-dichlorobenzeneoneindophenol. An attempt to recrystallize it from *n*-butyl alcohol converted it to the diamino diketone. The diketone melted at 201–202°.

Anal. Calcd. for $C_{18}H_{20}O_2N_2$: C, 72.93; H, 6.81. Found: C, 73.12; H, 7.06.

When the clear filtrate, obtained from the original hydrogenation mixture, was evaporated nearly to dryness in a nitrogen atmosphere, a mass of white crystals was obtained. These were undoubtedly the hydrochloride of the enediol. They immediately decolorized a basic solution of the indophenol. A silver nitrate test caused the precipitation of metallic silver.

The hydrochloride was very stable when dry but turned yellow when crystallized from alcohol. Washing with dilute sodium hydroxide to free the base produced an orange-colored compound that melted at 229–230° (cor.), with decomposition.

(b) **By Stannous Chloride.**—A mixture of 5 g. of the dinitro diketone, 20 g. of stannous chloride, 25 cc. of concentrated hydrochloric acid and 250 cc. of absolute alcohol was heated under reflux for about eight hours. The diketone had dissolved completely at the end of six hours. By distillation of the solvent the volume was reduced to about 75 cc. The solution was poured into 500 cc. of water and made alkaline to litmus with 10% sodium hydroxide solution. The orange solid that separated was collected on a filter, sucked as dry as possible and recrystallized from *n*-butyl alcohol. The bright red 3,3′-diamino-2,6-xylil melted at 201–202° (cor.); yield 2.45 g.

The diamino compound (1 g.) was converted to 3,3′-diacetamido-2,6-xylil, by heating under reflux for three hours with 20 cc. of acetic anhydride. It separated from methanol or glacial acetic acid in yellow crystals; m. p. 296–297° (uncor.); yield 94%.

Anal. Calcd. for $C_{22}H_{24}O_4N_2$: C, 69.44; H, 6.36. Found: C, 69.51; H, 6.23.

Attempts to hydrogenate the acetylated xylil by the Adams method failed; the diketone was recovered unchanged.

1,2-Di-(3-diacetamido-2,6-xylyl)-acetylene Glycol Diacetate.—A mixture of 0.2 g. of the diamino enediol and 25 cc. of acetic anhydride was heated under reflux for three hours, cooled and poured into water. The hexaacetate separated from methanol in glistening white crystals; m. p. 241–242° (cor.).

Anal. Calcd. for $C_{30}H_{34}O_8N_2$: C, 65.42; H, 6.23; N, 5.09. Found: C, 65.31, 65.57; H, 6.18, 5.97; N, 5.39.

The hexaacetate was also made by treating the enediol hydrochloride with acetic anhydride and pyridine.

Both of the acetylation experiments yielded a yellow by-product, melting at 296–297° (uncor.), which is believed to be 3,3′-diacetamido-2,6-xylil.

Summary

Nitration of 2,6-xylil with fuming nitric acid produces the 3,3′-dinitro derivative in high yields. Reduction of the dinitro compound yields 1,2-di-(3-amino-2,6-xylyl)-acetylene glycol. Its stability to air is comparable with that of the parent enediol, 1,2-di-(2,6-xylyl)-acetylene glycol.

URBANA, ILLINOIS RECEIVED JUNE 29, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF NEW HAMPSHIRE]

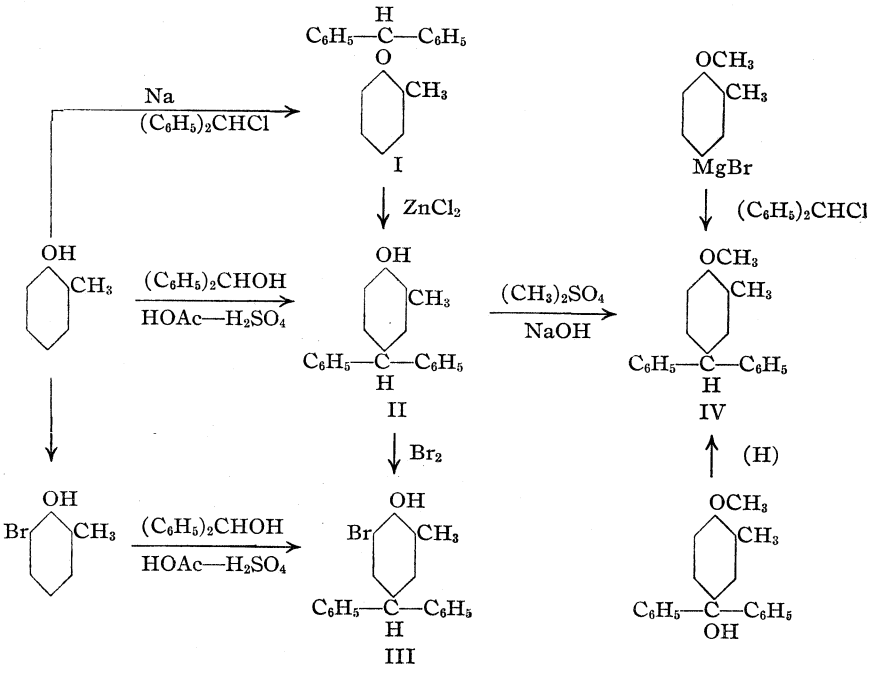
Formation and Rearrangement of the Diphenylmethyl Ether of *o*-Cresol

BY H. A. IDDLES, D. H. CHADWICK, J. W. CLAPP AND R. T. HART

To aid in interpreting the rearrangement of the triphenylmethyl ether of *o*-cresol, or the direct introduction of the triphenylmethyl radical into the *o*-cresol nucleus, the methyl ether of the postulated product, 3-methyl-4-hydroxyphenyltriphenylmethane was synthesized.[1] The complete agreement between rearranged and synthetic products showed that the triphenylmethyl radical had migrated to the para position of the *o*-cresol nucleus.

In similar alkylation studies, earlier investigators[2,3,4,5] have used the less highly substituted diphenylmethyl radical and have recorded the conditions which favor the formation of the diphenylmethyl ether of phenol or lead to the introduction of one, two or three diphenylmethyl radicals into the nucleus. In one experiment, Schorigin[3] treated *o*-cresol with diphenylcarbinol in acid medium and postulated the introduction of one diphenylmethyl radical ortho to the hydroxyl which seemed to be in agreement with his analytical data. Since this interpretation differed from the observed para migration of the triphenylmethyl radical[1] or the isopropyl group,[6] and was not substantiated in any way, a further detailed study of this reaction is presented in this paper.

The direct preparation of the diphenylmethyl ether of *o*-cresol I was accomplished by treating sodium *o*-cresylate in ether solution with diphenylchloromethane. Besides the ether, some free phenolic product II was formed. This could be prepared also by direct rearrangement of the ether with zinc chloride or through the reaction at room temperature of *o*-cresol with diphenylcarbinol in acid medium. The orientation of groups in structure II was established in the first instance by its monobromination and comparison with the diphenylmethyl derivative formed from 6-bromo-*o*-cresol and also by two direct syntheses focusing on structure IV. Thus the rearrangement of I or the direct introduction of one diphenylmethyl radical involves the para position of the *o*-cresol, as was shown in the case of the triphenylmethyl radical.

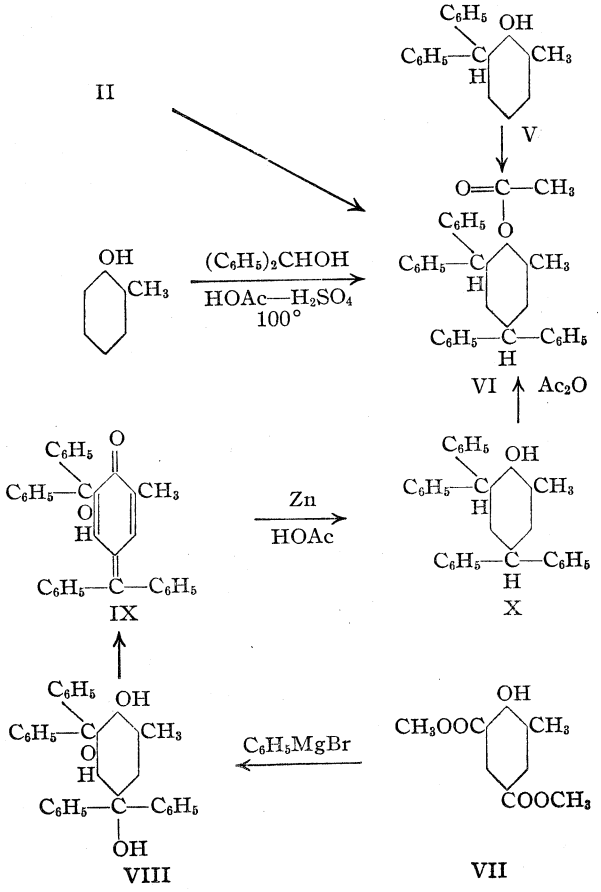


In addition it was necessary to characterize Schorigin's product, m. p. 139°, which could be prepared by heating *o*-cresol and diphenylcarbinol in an acetic–sulfuric acid medium.[3] As a direct approach, Schorigin's suggested structure V was synthesized by the action of the Grignard reagent on methyl *o*-cresotinate followed by reduction of the resulting carbinol. This synthetic material was further characterized by bromination and comparison with a product formed by condensing 4-bromo-*o*-cresol with diphenylcar-

(1) Iddles and Minckler, THIS JOURNAL, **62**, 2757 (1940).
(2) Claisen, *Ann.*, **442**, 210 (1924).
(3) Schorigin, *Ber.*, **59**, 2502 (1926); **61**, 2516 (1928).
(4) Van Alphen, *Rec. trav. chim.*, **46**, 799 (1927).
(5) Busch and Knoll, *Ber.*, **60**, 2243 (1927).
(6) Niederl and Natelson, THIS JOURNAL, **53**, 1928 (1931).

binol. However, the synthetic material of structure V melted at 76–78°, which demonstrated its non-identity with Schorigin's material, m. p. 139°.

When it was determined that Schorigin's material could not be brominated or methylated and that structures II and V would both yield Schorigin's product when heated with diphenylcarbinol in acetic–sulfuric acid medium, then structure VI was suggested in which two diphenylmethyl groups had been introduced and the acetate formed. To establish this postulate, structure VI was synthesized by the action of phenylmagnesium bromide on the dimethyl ester of 6-hydroxyuvitinic acid VII, which passed through a di-carbinol structure VIII to form an orange-colored substance postulated to be IX. In the succeeding steps, this material was reduced by zinc and acetic acid producing a colorless phenol X and treatment with acetic anhydride gave the acetate VI of m. p. 139° which was identical with Schorigin's rearranged product.



Experimental

o-Tolyldiphenylmethyl Ether.—*o*-Cresol (120 g.) in absolute ether (500 ml.) was treated with metallic sodium (10 g.) and, after complete reaction, diphenylchloromethane (66 g.) was introduced slowly. The mixture was refluxed for sixteen hours and for three hours after evaporation of the ether. The reaction mixture was poured into water, extracted with ether and the ether layer was washed with 10% sodium hydroxide and then dried. Upon evaporating the ether, the resulting oil was taken up in ligroin (90–110°) and extracted with Claisen's solution. From the ligroin layer, 10 g. of the desired ether distilled between 175–178° at 4 mm. It was a viscous, yellowish-green oil. The Claisen's extract, upon acidification, produced a rearranged product (25 g.) which was first purified by distillation at 3 mm. pressure and 205–215°, followed by crystallization from ligroin, m. p. 99–100°.

Preparation of Rearranged Compound.—To carry out a direct rearrangement, 5 g. of the *o*-tolyldiphenylmethyl ether was heated with 3 g. of zinc chloride for five hours at 150°. The material was then dissolved in ligroin, washed with water and extracted several times with Claisen's solution. Upon acidification, 3 g. of oil was obtained which was distilled at 213–220° and 3–5 mm. and recrystallized from ligroin yielding a colorless product, m. p. 99°.

The same product was obtained when 20 g. of diphenylcarbinol[7] and 24 g. of *o*-cresol were dissolved in 300 ml. of glacial acetic acid, and 60 g. of concd. sulfuric acid was added over a period of one hour. After standing for 7–8 days, the product was obtained by pouring the reaction mixture into water, extracting with ether, washing with 10% sodium hydroxide, water, and drying the ether extract. Upon evaporation of the ether, the residue was vacuum distilled at 180–185° and 2 mm. and twice recrystallized from ligroin yielding 15 g. of final product, m. p. 101°.

Anal. Calcd. for $C_{20}H_{18}O$: C, 87.5; H, 6.62. Found: C, 87.4; H, 6.62.

Bromination of 3-Methyl-4-hydroxyphenyldiphenylmethane.—Five grams of the rearranged compound, m. p. 101°, was dissolved in 200 ml. of carbon tetrachloride, and to the cooled solution 3 g. of bromine in 20 ml. of carbon tetrachloride was added. After an hour, excess bromine was removed with bisulfite solution and the product recovered. Recrystallization from alcohol gave 4 g. or a yield of 62% of light yellow product, m. p. 117–118°.

Direct Condensation of 6-Bromo-*o*-cresol and Diphenylcarbinol.—Five grams of diphenylcarbinol and 15 g. of 6-bromo-*o*-cresol[8] were dissolved in 100 ml. of glacial acetic acid, and 20 ml. of concd. sulfuric acid was added slowly while cooling. During the addition an oil began to separate and soon solidified. After standing two days, the solid product was filtered off, washed with glacial acetic acid and recrystallized from alcohol with a yield of 7 g. or 70%, m. p. 117–117.5°. A mixed melting point with the above brominated product was 117°.

Anal. Calcd. for $C_{20}H_{17}OBr$: Br, 22.6. Found: Br, 22.4.

Methylation of Compound II.—Three grams of the rearranged compound II, suspended in 200 ml. of 2 *N* sodium hydroxide, was warmed to 40°, and 15 g. of dimethyl sulfate was added over a period of two hours. After destroying excess dimethyl sulfate, the solution was

(7) "Organic Syntheses," Collective Vol. I, 1941, p. 90.
(8) Huston and Neeley, THIS JOURNAL, 57, 2176 (1935).

neutralized with hydrochloric acid and the insoluble organic material separated. The product was taken up in a mixture of 1 part diethyl ether and 9 parts petroleum ether, washed with Claisen's solution and water, and finally recrystallized from alcohol with a yield of 2.11 g. or 67%, m. p. 74–76°.

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.5; H, 6.98. Found: C, 87.5, 87.8; H, 7.05, 7.63.

Direct Synthesis of Compound IV. Procedure I.—A Grignard solution, prepared from 7 g. of 3-bromo-6-methoxytoluene[1] and 3 g. of magnesium turnings in 100 ml. of dry ether, was coupled by adding 7 g. of diphenylchloromethane dissolved in 100 ml. of dry ether during a period of forty minutes. After refluxing for two hours, the ethereal solution was successively washed with dilute hydrochloric acid, 10% sodium carbonate, and water and then dried. Subsequent evaporation of the ether left an oil which was recrystallized from ligroin, yielding 4.3 g. or 43%, m. p. 74–75°.

Procedure II.—Seven grams of 3-methyl-4-methoxytriphenylcarbinol[1] was dissolved in 200 ml. of glacial acetic acid and reduced by adding zinc dust[9] and refluxing for an hour. The zinc dust was allowed to settle and the clear solution decanted into 500 ml. of water. The precipitate was dissolved in hot alcohol, treated with Norite, and yielded 5 g. or 75%, m. p. 75.5°. A mixed melting point using each of the synthetic products with the methylated rearranged product gave no depression.

Reaction of *o*-Cresol and Diphenylcarbinol at 100°.—According to Schorigin's procedure[3] a solution of *o*-cresol (13.5 g.) and diphenylcarbinol (39 g.) in glacial acetic acid (300 ml.) was treated with concd. sulfuric acid (20 ml.) while refluxing on the steam-bath. Purification of the product from alcohol gave 8 g. of colorless material, m. p. 139–140°.

Anal. Calcd. for $C_{35}H_{30}O_2$: C, 87.1; H, 6.27. Found: C, 86.7; H, 6.42.

Preparation of Compound V.—Ten grams of 2-methyl-6-diphenylhydroxymethylphenol, prepared by the reaction of phenylmagnesium bromide on methyl-*o*-cresotinate,[10,11] was reduced with zinc and glacial acetic acid as previously described.[9] Recrystallization from alcohol produced colorless crystals in a yield of 6.5 g. or 70%, m. p. 76–78°.

Anal. Calcd. for $C_{20}H_{18}O$: C, 87.5; H, 6.61. Found: C, 87.1; H, 6.59.

Preparation of 2-Methyl-4-bromo-6-diphenylmethylphenol.—To characterize compound V, 2 g. was treated with 2.2 g. of bromine in carbon tetrachloride and the product recovered and crystallized from dilute alcohol, yielding 1.3 g. or 45%, m. p. 97–100°.

Further, 60 g. of 4-bromo-*o*-cresol[12] and 30 g. of diphenylcarbinol, dissolved in 400 ml. of glacial acetic acid, were heated on the steam-bath while 5 ml. of sulfuric acid was added gradually. Recovery of the condensation product in the usual way gave 17 g. of product, m. p. 100–103°. A mixed melting point of the two bromo derivatives gave no depression and either bromo derivative could be acetylated to give an acetyl derivative, m. p. 157–158°.

Anal. Calcd. for $C_{20}H_{17}OBr$: Br, 22.6. Found: Br, 22.4.

Preparation of the Dimethyl Ester of 6-Hydroxyuvitinic Acid.—The dried potassium salt from 154 ml. of *o*-cresol was placed in the glass liner of a pressure bomb and carbon dioxide forced into the bomb under ninety pounds pressure.[13] The bomb was heated in an electric furnace to 210°, and the pressure of carbon dioxide was increased to two hundred pounds. These conditions were maintained for fifty hours or until absorption of carbon dioxide was complete, as evidenced by no pressure drop. For purification, the solid reaction product was suspended in 700 ml. of hot water, and sodium bicarbonate added until the solution was complete, then treated with Norite, filtered and reprecipitated with dilute hydrochloric acid. After three such treatments, a yield of 105 g. or 36% of a faintly pink product was obtained, m. p. 290–295°.

The methyl ester was then prepared by refluxing 15 g. of the above acid in 200 ml. of absolute methanol and 22 ml. of concd. sulfuric acid.[14] Upon cooling, the ester crystallized from the methanol in a yield of 10 g. or 60%, m. p. 129–130°.

Preparation of Compound IX.—A Grignard solution prepared from 125 g. of bromobenzene and 19.4 g. of magnesium turnings in one liter of dry ether was refluxed while adding 18 g. of compound VII dissolved in 800 ml. of ether. After refluxing for six hours, the reaction product was poured into water containing enough hydrochloric acid for complete solution. The ether layer was separated, washed with water, 10% sodium carbonate and again with water. The ether was evaporated and the residue steam distilled to remove biphenyl. On cooling, an orange solid formed and this was recrystallized from acetic acid in a yield of 27 g. or 75%, m. p. 206–208°. The color and analysis agreed with the aurin structure assigned.

Anal. Calcd. for $C_{33}H_{26}O_2$: C, 87.2; H, 5.76. Found: C, 87.3, 87.1; H, 5.80, 5.92.

Preparation of Compound X.—Ten grams of the aurin-type compound IX was dissolved in 250 ml. of hot glacial acetic acid in a three-necked flask fitted with a stirrer and reflux condenser. Zinc dust (35 g.) was added slowly and refluxing continued for eight hours. After filtering off excess of zinc dust, the reaction mixture was poured into 1000 ml. of ice water yielding a crude product of 9.6 g. No suitable solvent for recrystallization was found, but a vacuum sublimation produced an amorphous product, m. p. 50–60°, which changed to a dark gum upon standing.

Anal. Calcd. for $C_{33}H_{28}O$: C, 89.9; H, 6.41. Found: C, 89.1; H, 6.52.

Since the product could not be crystallized, it was characterized as the 3,5-dinitrobenzoate which was obtained as a colorless crystalline material from dilute acetone, m. p. 206–207°.

Anal. Calcd. for $C_{40}H_{30}O_6N_2$: N, 4.42. Found: N, 4.48.

Preparation of 2-Methyl-4,6-di-(diphenylmethyl) Phenylacetate VI.—Two grams of the phenol X was treated with 7–8 ml. of acetic anhydride and 1 ml. of concd. sulfuric acid. When the reaction mixture had cooled,

(9) Sachs and Thonet, *Ber.*, **37**, 3333 (1904).
(10) Guillaumin, *Bull. soc. chim.*, **7**, 374 (1910).
(11) Berlitzer, *Monatsh.*, **36**, 200 (1915).
(12) Goldschmidt, Schulz and Bernard, *Ann.*, **478**, 14 (1930).
(13) Chem. Fabr. v. Heyden, German Patent 65,316, *Frdl.*, **3**, 829.
(14) Anschütz and Robitsek, *Ann.*, **346**, 358 (1906).

water was added and the gummy product recrystallized from alcohol yielding 1.3 g. (60%), m. p. 139–141°. A mixed melting point of this synthetic material with Schorigin's compound showed no depression.

Anal. Calcd. for $C_{35}H_{30}O_2$: C, 87.1; H, 6.27. Found: C, 86.8; H, 6.30.

Summary

1. The rearrangement of the diphenylmethyl ether of *o*-cresol or the direct introduction of the diphenylmethyl group under mild conditions involves the para position of the *o*-cresol.

2. 2-Methyl-4,6-di-(diphenylmethyl) phenylacetate has been synthesized and found to be identical with Schorigin's product obtained by heating diphenylcarbinol and *o*-cresol in an acetic–sulfuric acid medium.

DURHAM, NEW HAMPSHIRE RECEIVED JUNE 27, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES AND HARVARD UNIVERSITY]

Allylic Rearrangements. XIII. Kinetics and Mechanisms of the Conversion of Crotyl and Methylvinylcarbinyl Chlorides to Acetates and Ethyl Ethers[1]

BY JOHN D. ROBERTS, WM. G. YOUNG AND S. WINSTEIN[2]

Many investigators, notably Hughes, Ingold and collaborators,[3] have demonstrated that the mechanisms of nucleophilic replacement reactions at a saturated carbon atom may be classified into three general types. One mechanism, designated as S_N2 is the familiar[4] bimolecular, usually second-order, substitution of an electron-donor such as hydroxide ion, alkoxide ion or acetate ion for the halide or a similar group as in equation (1), the replacement resulting in a complete Walden inversion.

$$Y^- + RX \longrightarrow YR + X^- \qquad (1)$$

Another mechanism, designated as S_Ni, involves the internal rearrangement of an intermediate compound to give the final product with retention of configuration. An illustration of this mechanism is furnished in equation (2) by the rearrangement of the intermediate from an alcohol and thionyl chloride to produce a chloride and sulfur dioxide.

$$ROSOCl \longrightarrow RCl + SO_2 \qquad (2)$$

The third mechanism, designated as S_N1, is comprised of an electrophilic attack of solvent on halogen or similar groups to yield an unfree[3,5] carbonium ion which subsequently reacts rapidly with an electron donor to yield the final product. Equation (3) represents the sequence of these reactions.

$$\begin{gathered} RX \longrightarrow R^+X^- \longrightarrow R^+ + X^- \\ R^+ + YH \longrightarrow RY + H^+ \text{ or} \\ R^+ + Y^- \longrightarrow RY \end{gathered} \qquad (3)$$

A variation of the S_N1 type of reaction involves the electrophilic attack of such a reagent as silver ion on a halogen group to produce the unfree carbonium ion intermediate.[3,6]

The application of the foregoing types of mechanisms to the replacement reactions of allylic systems[7] has been of great value in explaining the phenomenon of the allylic rearrangement.[7d] The recognition of the possibility of the simultaneous operation of both S_N1 and S_N2 processes, according to equations (4) and (5), has been used to correlate various results with the assumption that the

$$Y^- + -\overset{|}{C}=\overset{|}{C}-\overset{|}{C}-X \longrightarrow -\overset{|}{C}=\overset{|}{C}-\overset{|}{C}-Y + X^- \qquad (4)$$

S_N2 reaction is normal and the S_N1 reaction yields a mixture, the same mixture resulting from either starting allylic isomer.

For example, the formation of similar but not identical bromide mixtures from the action of hydrogen bromide on crotyl alcohol and methylvinylcarbinol has been explained in this way.[7a]

(1) Most of the material of this paper was presented before the Organic Division at the St. Louis and Atlantic City meetings of the American Chemical Society, April and September, 1941.

(2) National Research Fellow at Harvard University, 1939–1940.

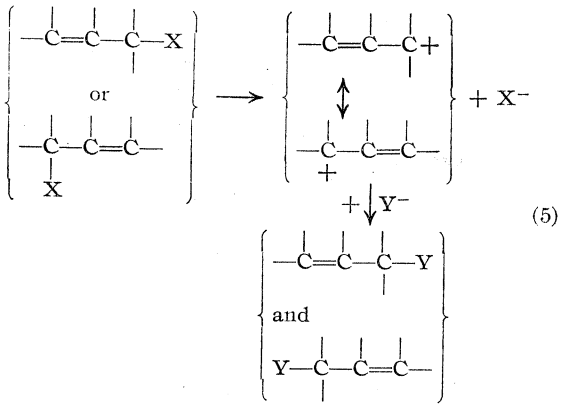
(3) (a) Cowdrey, Hughes, Ingold, Masterman and Scott, *J. Chem. Soc.*, 1252 (1937); (b) Bateman, Church, Hughes, Ingold and Taher, *ibid.*, 979 (1940).

(4) (a) Olson, *J. Chem. Phys.*, **1**, 418 (1933); (b) Bergmann, Polanyi and Szabo, *Z. physik. Chem.*, **20**, 161 (1933).

(5) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 172.

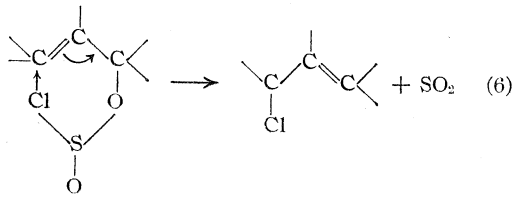
(6) Ref. 5, p. 138.

(7) (a) Young and Lane, THIS JOURNAL, **60**, 847 (1938); (b) Arcus and Kenyon, *J. Chem. Soc.*, 1912 (1938); (c) Ref. 5, p. 315; (d) After the completion of this manuscript, the paper by Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941), appeared, which reports unpublished work in similar directions to the experiments we report in this article. The conclusions drawn by Hughes are in substantial agreement with our own.



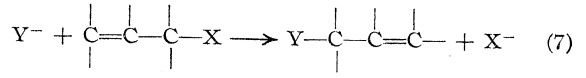
(5)

A special form of the S_Ni mechanism would account for the results obtained by Meisenheimer and Link[8] on the reactions of the α- and γ-ethylallyl alcohols with thionyl chloride. It was reported that the primary isomer gave principally secondary chloride and from the secondary isomer mostly primary chloride was obtained. These reactions may be explained by a rearrangement involving addition of the halogen to the γ-carbon atom, simultaneous shift of the double bond and elimination of sulfur dioxide as shown in equation (6).



(6)

This indicated special form of the S_Ni mechanism suggests a possible abnormal S_N2 reaction,[9] illustrated in equation (7), involving an attack by an electron donor at the γ-carbon atom, a shift of the double bond and elimination of a group, all occurring simultaneously.[10]



(7)

Indeed, the work of Meisenheimer and Beutter[11] on the reactions of cinnamyl chloride with potassium acetate in acetic acid seems to verify that such an abnormal S_N2 reaction does occur.

These investigators found that in solutions of low concentration of potassium acetate, the kinetics of the reaction with cinnamyl chloride in acetic acid were between first- and second-order. At high concentrations of potassium acetate there was obtained a mixture of esters containing a considerable fraction of phenylvinylcarbinyl acetate and, in fact, this fraction of abnormal ester did not decrease with increasing acetate concentration as would be expected if it were produced only by a first-order reaction. Using rate constants which Meisenheimer and Beutter found to fit their data, it is possible to calculate that only 7% of the reaction proceeds by the first-order path at 50° if one starts with an acetic acid solution which is 1 N in cinnamyl chloride and 1.5 N in potassium acetate, whereas 35% of abnormal product was actually isolated. Hence, even if the S_N1 reaction produced only abnormal product, the experimentally found composition seemingly cannot be explained unless an abnormal S_N2 reaction is assumed. However, in the work of Meisenheimer and Beutter,[11] there was no consideration of ionic strength and specific salt effects, so that the large bimolecular contribution to the kinetics may have been only apparent. It is possible that a reinvestigation of this situation would disclose that the conversion of cinnamyl chloride to ester in acetic acid is almost exclusively solvolytic in character. Evidence in favor of this possibility is that cinnamyl chloride gives only cinnamyl acetate on treatment with potassium acetate in acetic anhydride, a solvent sure to be unfavorable[3] for the operation of an S_N1 mechanism.

We have begun investigations designed to show the relative tendencies for S_N1 and S_N2 mechanisms in typical allylic cases and to formulate generalizations as to the products to be expected from the reactions by these mechanisms. In this paper we present the results so far obtained on the conversion of crotyl and methylvinylcarbinyl chlorides to ethyl ethers and acetates with special attention being given to any possible abnormal S_N2 reaction.

Simultaneous First- and Second-Order Reactions.—If, in a conversion of a halide to ether or acetate, both second-order and first-order reactions are proceeding, an apparent bimolecular constant, K_2, calculated by equation (8) where a is the original concentration of halide, b the original concentration of alkoxide or acetate salt, x the concentration of inorganic halide produced at time, t, will show a drift in a rate run. So

$$K_2 = \frac{1}{t(a-b)} \ln [b(a-x)]/[a(b-x)] \qquad (8)$$

(8) Meisenheimer and Link, *Ann.*, **479**, 211 (1930).

(9) (a) Winstein, Dissertation, California Institute of Technology, 1938; (b) Hughes, *Trans. Faraday Soc.*, **34**, 185 (1938).

(10) A mechanism leading to the same result but requiring preliminary addition of a nucleophilic reagent to one of the ethylenic carbons has been proposed by Ogg, THIS JOURNAL, **61**, 1946 (1939).

(11) Meisenheimer and Beutter, *Ann.*, **508**, 58 (1933).

also will K_1 calculated on the basis of a reaction first-order with respect to organic halide. If only a second-order reaction according to equation (1) is proceeding, then K_2 equals k_2 the specific second-order rate constant. Similarly, if only a first-order reaction is proceeding, K_1 will equal k_1 the specific first-order rate constant. If both first- and second-order contributions are important, equation (9) is useful.

$$\frac{dx}{dt} = k_1(a - x) + k_2(a - x)(b - x) \qquad (9)$$

The fraction of reaction F_1 which has proceeded by a first-order reaction at any fraction conversion can be shown to be given by equation (10).

$$F_1 = k_1/(k_2x) \ln (k_1 + k_2b)/[k_1 + k_2(b - x)] \qquad (10)$$

Rate Work on the Conversion of Crotyl Chloride to Crotyl Ethyl Ether.—The reaction of crotyl chloride with sodium ethoxide in absolute ethanol displayed second-order kinetics, the first-order reaction which gives rise to hydrogen chloride in the absence of sodium ethoxide being slow enough to enable very good isolation of the second-order reaction. One main source of crotyl chloride was employed and no large rate trends were noticed.[12] Table I summarizes a typical run. Table II summarizes the rate constants obtained at 25.00°, using various original concentrations without attempt to keep ionic strength constant. There is some trend in K_2 with original concentrations, as is usually found in work of this kind.[13] The change of K_2 with the water content of the alcohol from pure alcohol to 10% water, is not very extensive and has about the magnitude of the change of K_2 with concentrations of sodium ethoxide from 0.6 to 0.06 M.

Crotyl chloride in alcohol at 25.00° slowly produces hydrogen chloride and the rate of this solvolytic process was followed. Also, the effect on the solvolytic reaction of adding water was noted. Table IV summarizes the measurements on the solvolytic reaction while Table III presents a typical run.

The usual increase[3,14] in the rate of solvolysis of a halide with increase in the water content of the alcohol solvent is noticed with crotyl chlorides. What fraction of the first-order reaction observed in the absence of sodium ethoxide is due to an S_N1 process (equation 3) and what fraction is due to an S_N2 process (equation 1), involving

TABLE I

THE REACTION OF NaOEt WITH CROTYL CHLORIDE IN ABSOLUTE ALCOHOL

a, 1.008 *N*; *b*, 1.218 *N*

t, hr.	NaOEt, ml. HCl	Crotyl chloride, ml. HCl	K_2
0	61.32	50.79	
0.47	56.91	46.38	0.165
1.23	51.39	40.86	.159
2.02	46.30	35.77	.165
3.12	41.25	30.72	.163
4.37	36.96	26.43	.161
6.75	31.30	20.77	.157
9.33	27.16	16.63	.155

Mean 0.161 ± 0.003

TABLE II

SUMMARY OF RATE CONSTANTS FOR THE REACTION OF CROTYL CHLORIDE WITH SODIUM ETHOXIDE

Run	*a*	*b*	H_2O moles/liter	K_2
1	1.01	1.22	0	0.161
2	0.50	0.61	0	.171
3	.50	.24	0	.199
4	.20	.24	0	.189
5	.48	.12	0	.222
6	.09	.11	0	.214
7	.09	.06	0	.231
2	.50	.61	0	.171
8	.50	.60	0.55	.178
9	.48	.58	2.67	.209
10	.41	.50	5.62	.229

TABLE III

THE SOLVOLYTIC REACTION AT 25.00° OF 0.487 *M* CROTYL CHLORIDE IN H_2O–ALCOHOL (9.99 ML. H_2O IN 103.3 ML. SOLUTION)

t, hr.	Ml. NaOH (38.07 ml. for completion)	$K_1 \times 10^3$
3.9	0.20	(1.35)
20.5	0.96	1.25
29.4	1.34	1.22
45.9	2.08	1.22
73.5	3.24	1.21
140.8	6.10	1.24

Mean 1.23 ± 0.01

TABLE IV

VARIATION OF RATE OF ALCOHOLYSIS OF CROTYL CHLORIDE AT 25.00° WITH WATER CONTENT OF THE ALCOHOL

H_2O, mole/liter	$K_1 \times 10^4$
0	1.84
0.55	2.66
3.74	8.1
5.35	12.3

(12) Mr. L. Andrews has found in preliminary work that crotyl chlorides prepared in various ways give somewhat variable rate constants. It seems likely that some preparations contain *cis*-crotyl chloride and that an increase in rate is associated with these.

(13) (a) Hecht, Conrad and Brückner, *Z. physik. Chem.*, **4**, 273 (1889); (b) Segaller, *J. Chem. Soc.*, **103**, 1154 (1913), **103**, 1421 (1913), **105**, 106 (1914); (c) Quayle and Royals, THIS JOURNAL, **64**, 226 (1942).

(14) (a) Farinacci and Hammett, *ibid.*, **59**, 2542 (1937); (b) Olson and Halford, *ibid.*, **59**, 2644 (1937); (c) Hughes, *J. Chem. Soc.*, 255 (1935).

alcohol or water molecules as the attacking reagents, remains to be seen.[15]

From the constants given in Tables II and IV, it is clear that in the reaction of crotyl chloride with aqueous–alcoholic solutions of sodium ethoxide or sodium hydroxide it is necessary to use low concentrations of base and considerable water in the solvent to attain serious proportions of first-order reaction.

Isolation of Products of Reaction of Crotyl and Methylvinylcarbinyl Chlorides with Sodium Ethoxide in Absolute Ethanol.—Crotyl chloride was converted to ether by treatment with sodium ethoxide in absolute ethanol under conditions where essentially second-order kinetics prevailed. When the original crotyl chloride concentration was approximately 0.7 *M* and the NaOEt was approximately 0.9 *M*, ether which was at least 99% crotyl ethyl ether with a maximum of 1% methylvinylcarbinyl ethyl ether was isolated.

No kinetic investigations on the reaction of methylvinylcarbinyl chloride with sodium ethoxide were carried out, but the product of the reaction under conditions favoring a bimolecular reaction was isolated. As shown in Table V the ether produced was at least 96% methylvinylcarbinyl ethyl ether with a maximum of 4% crotyl ethyl ether under the conditions used.

TABLE V

THE PRODUCTS OF REACTION OF ALLYLIC HALIDES WITH ABSOLUTE ALCOHOLIC NaOEt

Halide	Orig. NaOEt Concn. mole/l.	Orig. halide Concn. mole/l.	% Normal product	% Abnormal product
Crotyl chloride	0.9	0.7	100	0
3-Chloro-1-butene	1.8	1.3	>96	<4

It would certainly seem that the bimolecular reaction of sodium ethoxide with the primary and secondary 4-carbon chlorides proceeds without allylic rearrangement.

Product of Reaction of Silver Acetate with the Butenyl Chlorides.—The study of the kinetics of the reactions of the butenyl chlorides with acetate ion in acetic acid showed that it was impossible to isolate the bimolecular replacement reaction free of the solvolytic one, which in the case of an acetic acid solvent, will be more exclusively S_N1 than in absolute alcohol because of the large difference in basicity between acetic acid and ethyl alcohol molecules. In order to determine whether the products of such reactions could be accounted for quantitatively by a normal bimolecular reaction and a partially abnormal solvolytic one, it was necessary to have an estimate of the composition of the product arising from the S_N1 solvolytic reaction. Since there are many indications that reactions of halides with silver salts proceed similarly to S_N1 reactions in that an unfree carbonium ion is produced as an intermediate, the products of reaction of silver acetate with the butenyl chlorides were isolated and taken as an indication of what might be expected from the solvolytic mechanism.

Table VI contains along with other results the composition of the acetates produced from the two chlorides on treatment with silver acetate in acetic acid at 25°. A mixture of acetates is produced from either chloride as expected from a carbonium ion intermediate, but the mixtures are not quite identical. Thus, the primary chloride gives an acetate mixture which is about 63% primary and the secondary chloride gives a mixture which is only 56% primary. This spread seems to be real and Meisenheimer and Link[8] report a similar but somewhat smaller spread in the results from pentenyl chlorides.

TABLE VI

THE COMPOSITION OF BUTENYL ACETATES FROM THE REACTIONS OF CROTYL AND METHYLVINYLCARBINYL CHLORIDES WITH VARIOUS ACETATES

Experimental method	Chloride used	Time of reaction, hr.	Composition of product % primary acetate	% secondary acetate	Yield,[a] %
1 *M* Potassium acetate in acetic acid at 78.6°	primary	138	84	16	87
	secondary	48	51	49	31
	secondary	72	50	50	52
1 *M* Diphenylguanidinium acetate in acetic acid at 78.6°	primary	50	88	12	68
	secondary	45	51	49	66
Potassium acetate in acetic anhydride at 100°	primary	192	100	0	63
Tetraethylammonium acetate acetone at 58°	secondary	194	0	100	53
Silver acetate in acetic acid at 25°	primary	190	65	35	42
	primary	120	60	40	61
	secondary	120	56	44	59

[a] Yield based on the butenyl chloride, assuming reaction goes to completion.

This difference is an interesting one and will be considered more fully in later work. It may be due either to a second-order process in which acetate ion replaces chloride normally, or a termolecular process in which silver ion removes the chloride ion and acetate ion, or an acetic acid molecule simultaneously forms a bond to the carbon atom

(15) Preliminary work has shown that the solvolytic reaction of crotyl chloride in dry alcohol is considerably faster than the reaction of methylvinylcarbinyl chloride.

TABLE VII

RESULTS OF KINETIC EXPERIMENTS WITH POTASSIUM ACETATE IN ACETIC ACID

Run I (CrCl) = 1.017 (KOAc) = 0.973			Run II (CrCl) = 1.017 (KOAc) = 0.238				Run III (M.V.C.Cl) = 0.993 (KOAc) = 0.974				Run IV (M.V.C.Cl) = 0.993 (KOAc) = 0.226		
Time, hr.	x	K_2	Time, hr.	x	K_2	(dx/dt)	Time, hr.	x	K_2	(dx/dt)	Time, hr.	x	K_2
3	0.174	0.0709	2	0.032	0.0731	0.0150	2	0.061	0.0339	0.0294	2	0.022	0.0525
4	.219	.0710	4	.060	.0734	.0139	4	.117	.0342	.0274	4	.044	.0554
6	.299	.0720	6	.086	.0766	.0121	6	.169	.0351	.0241	6	.064	.0572
10	.415	.0720	10	.132	.0860	.0093	8	.216	.0357	.0220	8	.084	.0616
14	.497	.0718	14	.164	.0910	.0077	10	.260	.0364	.0218	10	.101	.0636
19	.572	.0720	18	.190	.0992	.0048	12	.298	.0368	.0185	12	.118	.0681
25	.630	.0695	24	.201	.1041	.00083							
48	.764	.0828											

losing the chloride ion. The possibility of a normal bimolecular substitution of acetate ion for chloride competing with the predominant process when silver acetate is being used, seems unlikely in view of the very low concentration of acetate ion and the relatively rapid action of silver acetate. Whether a third-order process ever contributes in reactions of silver salts is not yet clear. Still another likely explanation is that the inequality in the compositions of the acetate mixtures from the two halides is another indication of the lack of freedom of the carbonium ion being formed.[16]

Kinetics of Reaction of Butenyl Chlorides with Potassium and Diphenylguanidinium Acetates. —The kinetic data on the reaction of potassium acetate with the butenyl chlorides in acetic acid at 78.6 ± 0.1° are summarized in Table VII. The apparent second-order rate constant drifts upward in all the runs except in the one employing crotyl chloride with a high concentration of potassium acetate. This drift indicates a considerable amount of first-order reaction.

High concentrations of materials were employed in these rate measurements because it was desired to isolate reaction products using comparable conditions. Under these conditions potassium chloride precipitates, changing the ionic strength in the course of the reactions. Ionic strength effects and also specific salt effects are so serious in acetic acid that we were unable to treat the data of Table VII so as to obtain first- and second-order rate constants and to decide how much of the reaction proceeded by each of the two paths.

From the work of Steigman and Hammett[17] on the acetolysis of α-phenylethyl choride it appeared to us that diphenylguanidinium acetate was an ideal salt to use in place of potassium acetate since diphenylguanidinium chloride is soluble in acetic acid. Also, diphenylguanidinium chloride and acetate seem to have about the same salt effect, unlike some other salt pairs. Thus, rate measurements on the reaction of diphenylguanidinium acetate with the butenyl chlorides should be relatively free of trends due to change of ionic strength and change of the nature of the salt making up the ionic strength.

The rate measurements using diphenylguanidinium acetate are summarized in Table VIII. Run V is similar to Run I, K_2 now being higher and drifting upward. The drift is small enough to indicate that crotyl chloride reacts predominantly by a second-order path. Run VI using methylvinylcarbinyl chloride and 0.9 M diphenylguanidinium acetate displays a K_2 which drifts upward and a K_1 which is constant.[18] Run VII using a lower concentration of acetate yields a K_2 which drifts upward badly and a K_1 with only a slight downward drift. Clearly methylvinylcarbinyl chloride undergoes a first-order reaction almost exclusively under conditions where crotyl chloride reacts predominantly by a second-order reaction. Runs VI and VII show the large trend in the first-order constant with ionic strength.

From Run V the rate constants for the first- and second-order reactions of crotyl chloride were estimated. By plotting x against t, dx/dt at any time was obtained. A plot of $dx/dt/(a-x)$ against $(b-x)$ gives a straight line according to equation

(16) One might suppose that shielding by the chloride ion being extracted might favor the abnormal product but apparently this effect is overshadowed by the tendency for the cationic charge to favor the carbon atom losing the chloride ion while the chloride ion is still in the immediate vicinity.

(17) Steigman and Hammett, THIS JOURNAL, **59**, 2536 (1937).

(18) It would appear that no very serious amount of reaction of chloride ion with the unfree carbonium ion intermediate occurs nor is there much rearrangement of the halides. In either case drifts in the first-order constant for the secondary isomer would be found, unless some cancellation of effects accidentally takes place. Actually, from the work of Hughes and Ingold and co-workers,[3b] the intervention of chloride ion is less likely to occur in our system than with more complex ones. The intervention of chloride ion may be quite serious in the cinnamyl chloride work of Meisenheimer and Beutter,[11] however.

TABLE VIII

DATA ON THE RATE OF REACTION OF DIPHENYLGUANIDINIUM ACETATE WITH BUTENYL CHLORIDES IN ACETIC ACID

Run V (CrCl) = 1.020 (D.P.G.OAc) = 0.921					Run VI (M.V.C.Cl) = 0.987 (D.P.G.OAc) = 0.925				Run VII (M.V.C.Cl) = 0.987 (D.P.G.OAc) = 0.222			
Time, hr.	x	K_2	(dx/dt) obs.	(dx/dt) calcd.	Time, hr.	x	K_1	K_2	Time, hr.	x	K_1	K_2
4	0.279	0.1040	0.0476	0.0478	4	0.138	0.0376	0.0439	2	0.032	0.0165	0.0795
8	.441	.1079	.0308	.0304	8	.253	.0370	.0474	4	.062	.0163	.0859
12	.541	.1090	.0206	.0215	12	.354	.0370	.0515	6	.090	.0160	.0929
16	.614	.1120	.0161	.0161	16	.437	.0365	.0554	8	.116	.0156	.0999
20	.672	.1176	.0128	.0123	20	.518	.0372	.0622	13	.173	.0148	.1325

(9). The intercept and slope give k_1 and k_2, respectively: k_1 is 0.017 and k_2 is 0.074. Table VIII shows a comparison between dx/dt calculated for these constants and dx/dt obtained from the plot of the actual data. Clearly the values chosen for k_1 and k_2 reproduce the data well. Table IX summarizes the rate constants for the reactions of the butenyl chlorides.

TABLE IX

RATE CONSTANTS FOR REACTION OF BUTENYL CHLORIDES WITH DIPHENYLGUANIDINIUM ACETATE IN ACETIC ACID AT 78.6°

Halide	Concn. OAc^-, M	k_1	k_2
Secondary	0.925	0.037	...
Secondary	.222	.016	...
Primary	.921	.017	0.074

Products of Reaction of Butenyl Chlorides with Potassium and Diphenylguanidinium Acetates in Acetic Acid.—Using conditions that had been explored kinetically, the products of the reactions in acetic acid were isolated and analyzed. Table VI includes the analyses of the products obtained from the reactions with initial concentrations of approximately 1 M. The two salts give about the same products.

The product of reaction of crotyl chloride with diphenylguanidinium acetate was the result of a reaction, 36% of which was first-order, calculated by the use of equation (10) with $b = 0.92$ and x at the time the reaction was interrupted equal to 0.85 (estimated by analogy with Run V, Table VIII). With the information we have so far, the best approximation to the product to be expected from the first-order reaction of crotyl chloride in acetic acid containing diphenylguanidinium acetate, is the same mixture crotyl chloride gives with silver acetate (38% secondary acetate) in spite of some differences in the two reactions. The reaction employing silver acetate proceeds at a lower temperature and is heterogeneous. The unfree crotyl ion may coördinate for the most part with different reagents (acetic acid or acetate ion) in the two reactions.

If one assumes the second-order reaction gives only normal product, then a reaction which is 36% first-order should give 36(0.38) or 14% secondary ester. Actually 12% is obtained.

With potassium acetate 16% of secondary ester is obtained from crotyl chloride. However, the reaction was allowed to proceed more nearly to completion. This is expected to increase the fraction of the reaction proceeding by a first-order path and thus the per cent. of secondary ester obtained from crotyl chloride. Hence there is no evidence for an abnormal second-order reaction of crotyl chloride with acetate ion, the data being entirely compatible with a normal second-order reaction and a first-order reaction yielding a mixture.[19]

Methylvinylcarbinyl chloride gives with either diphenylguanidinium or potassium acetate a mixture of acetates which is 51% crotyl acetate and only 49% secondary acetate. A completely first-order reaction might be expected as a first approximation to yield 56% crotyl acetate by analogy with the silver acetate reaction. Part of the difference between 51 and 56% may be due to a small contribution of a normal second-order reaction to the total reaction of the secondary chloride.

Products of Reaction of Butenyl Chlorides with Acetates in Other Solvents.—If, as it appears, the second-order reactions of the butenyl chlorides are completely normal and a reaction

(19) The failure to find the abnormal bimolecular mechanism seems to be in line with the usual inability of the isolated ethylenic linkage to be susceptible to attack by nucleophilic reagents. However, suitable variation in the structure of the allylic molecule may produce this mechanism.

After this article was submitted for publication we noticed that, in a general article on configurational changes in reactions at a saturated and unsaturated carbon atom, Bergmann [Bergmann, *Helv. Chim. Acta*, **20**, 590 (1937)] claims that this abnormal bimolecular mechanism operates in the reaction of sodium malonic ester and sodium diphenylmethide with active 2-chloropentene-3. It is still possible, however, that some other reason exists for the racemization observed by Bergmann and further confirmation of the mechanism would be desirable.

proceeds partly abnormally only when part of the reaction is S_N1 in character, the proper choice of solvent should enable one to force certain replacement reactions to proceed entirely normally. Non-hydroxylic solvents are known to be unfavorable[3,17] for the solvolytic first-order reactions so that reactions in these solvents might be expected to be normal and quite useful synthetically.

As was expected, the reaction of methylvinylcarbinyl chloride with tetraethylammonium acetate in acetone gave an acetate with no detectable amount of crotyl acetate. Also, crotyl chloride and potassium acetate in acetic anhydride yielded an acetate with no detectable amount of secondary ester. These results are shown in Table VI.

Experimental Part

Crotyl and Methylvinylcarbinyl Chlorides.—Mixtures of chlorides from Shell Development Corporation or prepared from the alcohols with concentrated hydrochloric acid were dried over calcium chloride or potassium carbonate, distilled once and then fractionated through a six-foot column of glass helices. The secondary chloride could be obtained at atmospheric or reduced pressure. For the primary chloride reduced pressure was employed. The pure chlorides: secondary b. p. 24.2–24.6° (178 mm.), 63.5° (750 mm.), $n^{20}D$ 1.4150; primary b. p. 43.7–44.0° (177 mm.), 45.6–45.7° (191 mm.), $n^{20}D$ 1.4351, were used in this work. One pair of chloride samples were kept in a cold room several months with no appreciable change in refractive index. After a year at room temperature, this pair of chlorides showed an increase of 0.0004 and 0.0013 in the refractive index for the primary and secondary chlorides, respectively. This change was largely due to other factors than isomerization for distillation at reduced pressure nearly restored the refractive indices to the old values.

Rate of Conversion of Crotyl Chloride to Ether.—Proper volumes of stock solutions of crotyl chloride and sodium ethoxide in absolute ethanol (Commercial Solvents Gold Shield), water, and absolute ethanol, all previously brought to temperature, were mixed in glass-stoppered Erlenmeyer flasks and kept at 25.00°. The volumes of the alcohol solutions were considered additive. When water was added, an approximate correction on the final volumes was estimated.[20] Aliquot portions of the reaction mixture were withdrawn from time to time and titrated with alcoholic hydrogen chloride or aqueous sodium hydroxide with phenolphthalein as the indicator.

The sodium ethoxide stock solution was freshly made up by dissolving cleaned sodium rinsed with absolute alcohol in absolute alcohol with protection against moisture and carbon dioxide. The solution was standardized before use.

Preparation of Crotyl Ethyl Ether.—A mixture of 92.5 g. of crotyl chloride in 800 ml. of ethanol and 700 ml. of approximately 2 *N* sodium ethoxide was kept ten days at 25° and then diluted with water to six times the volume. The mixture was then extracted with 1000 ml., then 500 ml., and then 250 ml. of pure ether. The ether extracts were washed with a little water and dried over potassium carbonate. Some of the ether was distilled off at 34.1–34.4° through a Weston[21] type column using a good reflux ratio. The residue was distilled through a four-foot modified Podbielniak column. The fractions other than pure diethyl ether collected at 762 mm. were

Fr. 1	1.0 g.	34.1–65.0°	
Fr. 2	3.0 g.	65.0–77.1°	
Fr. 3	34.5 g.	77.1–77.6°	$n^{21}D$ 1.3751
Fr. 4	3.0 g.	77.6–100.8°	
Fr. 5	68.5 g.	100.8–100.9°	$n^{21}D$ 1.4038
Holdup	3.0 g.		

Fraction 3 was a constant-boiling mixture of alcohol and crotyl ethyl ether,[22] so fractions 1, 2, 3 and 4 were poured into 200 ml. of water and the ether separated with the aid of 100 ml. of pure carbon disulfide. The carbon disulfide layer was dried over potassium carbonate and distilled through the four-foot Podbielniak column. The fractions collected other than pure carbon disulfide were as follows at 765 mm.

Fr. 1	2.3 g.	46.7–100.7°	
Fr. 2	9.5 g.	100.7–100.9°	$n^{23}D$ 1.4030
Holdup	2.0 g.		

There was no indication of methylvinylcarbinyl ethyl ether. A generous estimate of the amount of this ether would be one-third of Fraction 1. This places the proportion of secondary ether as less than 1% of the total. The yield of ether was 82%.

Preparation of Methylvinylcarbinyl Ethyl Ether.—A mixture of 63 g. of methylvinylcarbinyl chloride and 500 ml. of approximately 2 *N* sodium ethoxide in absolute ethanol was left two weeks at 25° and four days at 35°. The mixture was poured into 2.5 liters of water and the ether separated with the aid of 200 ml. of pure carbon disulfide and two 100-ml. portions more. The extracts were dried briefly over potassium carbonate and distilled through the four-foot Podbielniak column. The fractions collected at 760 mm. which contained other than water, alcohol and carbon disulfide were

Fr. 1	5.0 g.	46.9–76.4°	
Fr. 2	32.5 g.	76.4–76.8°	$n^{23}D$ 1.3882
Holdup	3.5 g.		

The holdup was distilled through a short Vigreux column, 2.7 g. distilling 77–96° and having $n^{23}D$ 1.3960. This indicated a maximum of 1.4 g. of crotyl ethyl ether out of a total of approximately 37.2 g. (53% yield) considering 2.0 g. of Fraction I as ether.

Kinetic Experiments in Acetic Acid.—The procedure used for the rate determinations was the same as that of Steigman and Hammett[17] except that the excess acetate ion was titrated with a solution of perchloric acid in acetic acid. The acetic acid solvent was purified by treatment with potassium permanganate and then triacetyl borate,[23] material, m. p. 16.6° being obtained. The potassium acetate was dried at 110–120° for three hours and the diphenylguanidine was Eastman Kodak Co. material.

(20) Data used are listed in Lewis and Randall, "Thermodynamics," McGraw-Hill Book Co., Inc., New York, N. Y., 1923, p. 40.

(21) Weston, *Ind. Eng. Chem., Anal. Ed.*, **5**, 179 (1933).

(22) Lepingle, *Bull. soc. chim.*, **39**, 864 (1926).

(23) Eichelberger and La Mer, THIS JOURNAL, **55**, 3633 (1933).

Analysis of Reaction Products in the Ester Preparations.—In order to determine the composition of the esters produced in various conversions of the butenyl chlorides to acetates, runs were made using in each case, unless otherwise specified, 250 ml. of solution approximately 1 *N* in chloride and acetate. Final analysis of the esters with an accuracy of 2 or 3% was accomplished by distillation through a three-foot Podbielniak type column. The results are summarized in Table VI.

Reaction of Potassium and Diphenylguanidinium Acetates with the Butenyl Chlorides in Acetic Acid.—The reaction mixtures of dry base, dry acetic acid and butenyl chloride were held at 78.6° for the desired interval and then poured into ice-water. The acid was carefully neutralized with concentrated sodium hydroxide and the ester was extracted with ether. After being dried over potassium carbonate, the extracts were distilled. A blank experiment was carried out on methylvinylcarbinyl acetate which showed that the ester remained unchanged under the conditions of the experiment.

Reaction of Crotyl Chloride with Potassium Acetate in Acetic Anhydride.—A mixture of 25 ml. of crotyl chloride and 28 g. of dry potassium acetate and 300 ml. of fractionated acetic anhydride (b. p. 139.0–139.1°) was heated on a water-bath under reflux with efficient stirring. After the heating period, the mixture was quite dark. The volatile material was distilled (25–40°) at reduced pressure, the distillate was poured onto crushed ice and the mixture was allowed to stand for an hour to hydrolyze the anhydride. The resulting solution was neutralized and treated as in the previous case. On distillation of the ester, there was no evidence of secondary acetate.

Reaction of Methylvinylcarbinyl Chloride with Tetraethylammonium Acetate in Acetone.—A mixture of 41 g. of tetraethylammonium acetate prepared from the directions of Steigman and Hammett,[17] 20 ml. of the butenyl chloride and 200 ml. of dried and fractionated Merck C. P. acetone was boiled under reflux. After heating, the volatile material was distilled from salts at reduced pressure, the receiver being cooled with a dry-ice-bath. The distillate was then fractionated. There was no evidence of any crotyl acetate in the product.

Reaction of Silver Acetate with the Butenyl Chlorides in Acetic Acid.—A mixture of 45 g. of silver acetate which had been recrystallized from water and dried over sulfuric acid for three days, 25 ml. of butenyl halide and 250 ml. of dry acetic acid was stirred at room temperature. At the end of the reaction period, excess sodium chloride was added, the mixture was filtered and the filtrate was treated as in the case of the runs with potassium acetate in acetic acid.

Summary

The kinetics of conversion of crotyl and methylvinylcarbinyl chlorides to ethyl ethers and acetates and the compositions of the products of the conversions have been studied. The compositions of the products can be well accounted for on the basis that bimolecular replacement of the chloride group by an ethoxide or acetate ion gives rise only to normal product while solvolytic or S_N1 type reaction gives rise to a mixture of allylic isomers.

By choosing conditions unfavorable for the S_N1 type of reaction, it is possible to convert the butenyl halides to the corresponding pure acetates or ethyl ethers.

LOS ANGELES, CALIFORNIA RECEIVED MARCH 24, 1942

[CONTRIBUTION FROM BELL TELEPHONE LABORATORIES, INC.]

The Relation of Dielectric Properties to Structure of Crystalline Polymers. I. Polyesters

BY W. A. YAGER AND W. O. BAKER

The interpretation of dielectric properties in terms of molecular structure[1,2] may be attempted for assembles of macromolecules when knowledge of polymer constitution and structure permits recognition of polar groups and of their relative disposition. The following factors have been considered in the succeeding report of the dielectric behavior of linear polyesters.

The most probable source of orientation polarization in solids containing long chain molecules with polar linkages has been attributed to the rotational–vibrational (liberational) motion of atomic groups rather than to the unified displacement of a given molecule.[3,4] Of course, potentials inhibiting rotation around most single bonds, especially the carbon–carbon bond,[5] prevent complete independence of the motion of polar groups from the size and form of their attached chains.

Also, in polymers, the loss component, ϵ'', of the dielectric constant generally deviates from the value it should have at an absorption maximum on the Debye theory for a single relaxation time.[6,7]

(1) P. Debye, "Polar Molecules," Chemical Catalog Co., New York, N. Y., 1929.

(2) C. P. Smyth, "Dielectric Constant and Molecular Structure," Chemical Catalog Co., New York, N. Y., 1931.

(3) W. A. Yager, *Trans. Electrochem. Soc.*, **74**, 113 (1938).

(4) W. O. Baker and C. P. Smyth, THIS JOURNAL, **60**, 1229 (1938).

(5) See C. Gorin, J. Walter and H. J. Eyring, *ibid.*, **61**, 1876 (1939), and references therein.

(6) W. A. Yager, *Physics*, **7**, 434 (1936).

(7) R. M. Fuoss and J. G. Kirkwood, THIS JOURNAL, **63**, 385 (1941).

In polymer chains, the dipoles do not exhibit Brownian motion along three axes but rather primarily an intrachain kinking.[8] An internal viscosity related to macroscopic plasticity,[9] brittleness and softening has been postulated to cause the absorption. Specific rate constants from the relaxation times can be employed in an absolute rate analysis of the temperature variation of loss. Such treatment, suggested by Eyring,[10] was developed by Frank,[11] and gave a precise correlation in simple alkyl halides with structure and with viscous flow,[12] from which dipole orientation seems to differ considerably in extent of motion.

The linear supercondensation polyesters[13] and polyamides[14] possess many of the desired qualities of model polymers for dielectric studies. These polymers have simple polar groups (ester or amide linkages) regularly spaced along hydrocarbon chains. This intrachain spacing is readily varied, in forming the polymers, by selecting dibasic acids, glycols and diamines of appropriate chain lengths. Thus the effect of articulation or coupling of the orienting units along a given chain may be detected. This variation likewise alters the number of dipoles per cc. and is thus useful in studying the volume polarization. Further, these polymers are generally highly crystalline, and diffraction studies have revealed the relative arrangement of the polar groups in adjacent chains, and whether the dipoles are surrounded by other dipoles or by hydrocarbon groups.[15] The interchain forces constraining dipole motion may be specifically explored by comparing polyesters and polyamides of the same concentration of polar groups per unit of chain length, since the hydrogen bonding from the amido link causes a twofold increase in attraction as estimated from fusion properties. The average chain lengths of the polymers may be determined accurately.[16] Finally, the polymers are prepared essentially chemically pure and of high stability, and the effect of any technically important contaminant such as water may be ascertained and interpreted.

(8) W. Kuhn, *Z. physik. Chem.*, **A161**, 1, 247 (1932); *Kolloid Z.*, **68**, 2 (1934); **76**, 258 (1936).

(9) J. M. Davies, R. F. Miller and W. F. Busse, THIS JOURNAL, **63**, 361 (1941).

(10) A. E. Stearn and H. Eyring, *J. Chem. Phys.*, **5**, 113 (1937).

(11) F. C. Frank, *Trans. Faraday Soc.*, **32**, 1634 (1936).

(12) W. O. Baker and C. P. Smyth, *J. Chem. Phys.*, **7**, 574 (1939).

(13) W. H. Carothers and J. W. Hill, THIS JOURNAL, **54**, 1559 (1932).

(14) W. H. Carothers and J. W. Hill, *ibid.*, **54**, 1566 (1932); W. H. Carothers, U. S. Patents 2,071,250 (1937) and 2,130,523 (1938).

(15) C. S. Fuller, *Chem. Rev.*, **26**, 143 (1940).

(16) W. O. Baker, C. S. Fuller and J. H. Heiss, Jr., THIS JOURNAL, **63**, 2142 (1941).

Experimental

Materials.—The seven polyesters were prepared by Mr. C. J. Frosch and Mr. W. S. Bishop of these Laboratories. Procedures similar to those of Carothers[13] were employed. The products were unfractionated and therefore contained the distribution of molecular weights calculated for a random reaction of end groups,[17] and found experimentally.[16] The molecular weights lay in general in the "superpolyester" range, above $M_w \sim 6000$. The products were free from all oxidation or similar degradation. Their high crystallinity and consequent sharp melting points permitted preparation of test discs of precise and constant geometry. The polyesters were melted in vacuum, thus freed of gas bubbles, and allowed to solidify slowly, between glass plates held apart by shims. The thickness of individual samples was quite uniform, and was determined by numerous micrometer readings. Among the discs, the average thickness varied from 40 to 60 mils. Decamethylene oxalate cracked badly on cooling, so that the dielectric results may be complicated by the presence of voids. All of the samples were annealed to states of maximum crystallinity,[18] and were thoroughly dried.

Dielectric Measurements.—For the frequency range 1 to 100 kc., the dielectric constant and equivalent parallel conductance were measured on a shielded conductance–capacitance bridge.[19] Precise and reproducible contact with the electrodes was obtained in a condenser cell described below in connection with the Q-meter, on which measurements from 100 kc. to 75 megacycles were made.

The type 100A Q-meter,[20] the test cell, measuring technique and corrections described in a previous paper[3] were employed for the measurements on the polyesters. All other measurements were made on the much improved type 160A Q-meter employing a new type test condenser and a special thermostat.

The measuring technique previously described[3] is unsatisfactory for measurements above or below room temperature since it requires removal of the test sample from the test condenser at each frequency. The only alternative is to leave the sample in place, tune the LC circuit with the test condenser connected, disconnect the test condenser and retune the circuit with the internal tuning condenser. This method is less desirable than the former because corrections must be applied at high frequencies for the differences in lead inductance and series resistance of the internal tuning and test condensers in computing the capacity

(17) P. J. Flory, *ibid.*, **58**, 1877 (1936).

(18) C. S. Fuller, W. O. Baker and N. R. Pape, *ibid.*, **62**, 3275 (1940).

(19) W. J. Shackelton and J. O. Ferguson, *Bell System Tech. J.*, **7**, 70 (1928).

(20) The construction, theory and operation of the Q-meter are described in a manual furnished by the manufacturer, Boonton Radio Corporation, Boonton, New Jersey. The type 100A Q-meter is now superseded by the type 160A, which is a much improved model and covers the frequency range from 50 kc. to 75 mc.

and loss of the test specimen. The capacity of the sample is given by

$$C_x = \frac{C_1 - C_2}{D + B(C_1 - C_2)} - C_f$$

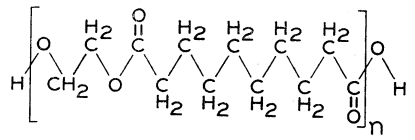
where $D = (1 - \omega^2 L_1C_1)^2$ and $B = (L_2 + L_1(1 - \omega^2 L_1C_1))\omega^2$. C_2 and C_1 denote the capacity of the internal tuning condenser at resonance with the test condenser connected and disconnected, respectively. C_f is the fixed capacity of the test condenser. L_1 and L_2 represent the series inductance of the internal tuning condenser and test condenser, respectively. For the arrangement employed L_1 is 0.00148 μH and L_2 is 0.03 μH. The dielectric loss factor, ϵ'', is given by the equation

$$\epsilon'' = \frac{IZC_{oe}A^2}{C_a}\left[\frac{E_1 - E_2}{E_1E_2} - F_M\right]$$

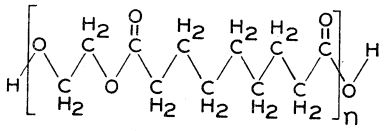
IZ, the voltage impressed on the measuring circuit, was determined experimentally at each test frequency, and a calibration employed for subsequent tests. C_{oe}, the effective capacity necessary to resonate a given coil at a given frequency, is obtained from the relation

$$C_{oe} = C_1/1 - \omega^2L_1C_1$$

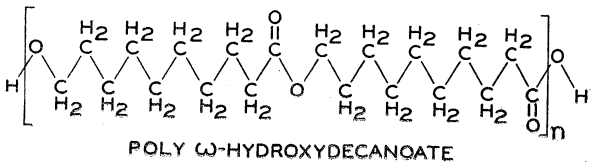
Furthermore, $A = 1 - \omega^2L_2(C_x + C_f)$. E_2 and E_1 represent the readings of the Q-voltmeter in volts at resonance with the test condenser connected and disconnected, respectively. F_M is a factor to correct for series resistance as noted above. It is negligible at frequencies below 10 mc. but increases rapidly with increasing frequency and magnitude of the test capacity. Calibration curves were prepared for F_M *versus* frequency and C_x at room temperature employing the test condenser as a variable air condenser. Although F_M was found to vary somewhat with temperature, this variation was erratic and of a second order so that the room temperature calibration was employed at all temperatures.



POLYETHYLENE SEBACATE



POLYETHYLENE AZELATE



POLY ω-HYDROXYDECANOATE

Fig. 1.—Structural formulas of typical polyesters.

A complete description of the new test condenser and thermostat is omitted for brevity. The test condenser of gold-plated brass was designed so that it may be used either as a clamping condenser for a specimen or as a variable air condenser. The electrodes are 2 inches in diameter, with the variable electrode an integral part of the housing which is connected to ground. The high tension electrode is fixed and insulated from the housing by means of clear, fused quartz. Since it is desirable to minimize the lead inductance of the test condenser, the coaxial type of construction was employed. The high tension lead was brought out through a coaxial tube $^3/_8$" in diameter and 4" long. A coaxial jack was mounted directly over the high tension terminal on the Q-meter and was designed so that the test condenser could be connected or disconnected from the measuring circuit simply by screwing it in or out of the coaxial jack.

Thermostating a test condenser in such close proximity to the Q-meter presented some difficulty. The design finally adopted consists essentially of a metal cylindrical jacket fitted at one end with a heating and cooling chamber and constructed so that it will slide over the test condenser. A small ring heater is employed for heating and provision is made for siphoning liquid nitrogen into the cooling chamber. An air thermo-regulator serves for temperature control. This metal thermostat with the test condenser in place fits into a Dewar flask with an opening in the bottom large enough to permit the coaxial tube of the test condenser to pass through. The entire assembly is mounted on top of the Q-meter directly over the coaxial jack and lined up so that the test condenser can be screwed in and out of the jack. The test condenser is screwed out of the jack and kept in a raised position at all times except during a measurement so as to minimize heat exchange between the Q-meter and test condenser.

The d. c. conductivity was negligibly small for all samples.

Results and Discussion

Figure 1 illustrates the planar zigzag chains which comprise most linear polyesters. Only certain types have been shown; for instance, polyethylene azelate represents an odd-membered dibasic acid which results in the two carbonyl dipoles of a chemical repeating unit being parallel, and evidently this same structure could easily be arranged in other polyesters. Chain oscillations continuously distort instantaneously the planarity of the carbon skeleton. Since such motion normal to the chain axis generally requires twisting about valence bonds, the modes contributing the orientational polarization from the models of Fig. 1 will not be uniformly distributed along the chains, for the potentials hindering rotation about bonds

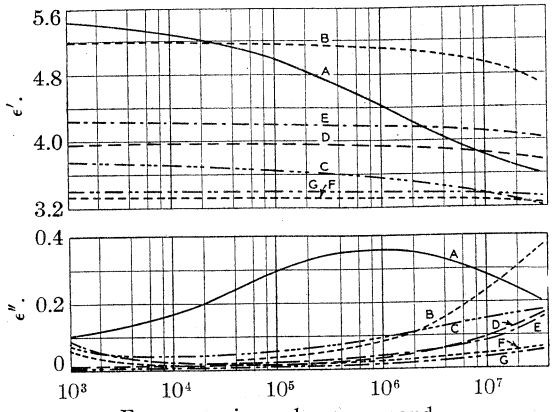


Fig. 2.—Frequency variation of dielectric constant and loss factor of polyesters at 25°: A, polyethylene succinate; B, polyethylene adipate; C, polydecamethylene oxalate; D, polyethylene azelate; E, polyethylene sebacate; F, polydecamethylene sebacate; G, poly-ω-hydroxydecanoate.

at the polar groups probably are lower than for the CH_2–CH_2 bonds.[21] However, the CH_2–O bond may have a high potential.[22] Small segments of the chains may act as relatively stiff units bounded by more flexible linkages. That such chain flexibility does obtain is clearly indicated by the data of Fig. 2, in which the values of ϵ' for such structures as polyethylene sebacate (see Fig. 1) considerably exceed the square of the refractive index, yet successive dipoles along the chain are oppositely directed and should cancel if the whole molecule is rigid. If only the terminal groups on the chains move in the applied field, the static dielectric constant would be virtually independent of the concentration of polar groups in the compound. This is contrary to experimental results, as will appear below. Pelmore and Simons[23] examined this aspect of five linear polyesters containing both opposite and parallel dipoles, as diagrammed in Fig. 1, and likewise concluded from the relaxation times that polar chain segments must be acting.

Although discussion of the effect of polar group concentration would be preferred in terms of specific polarization, there is yet no local field equation adequate for such anisotropic and highly interacting solids.[24] Hence we use simply the static dielectric constant, ϵ_0'. The concentrations are computed as follows.

(21) S. C. Schumann and J. G. Aston, *J. Chem. Phys.*, **6**, 485 (1938).

(22) B. Crawford and Joyce, *ibid.*, **7**, 307 (1939).

(23) D. R. Pelmore and E. L. Simons, *Proc. Roy. Soc.* (London), **A175**, 468 (1940).

(24) J. H. Van Vleck, "Dielectrics" (Annals N. Y. Academy of Sciences **40**, Art. 5), 289 (1940), and other discussions therein.

Let

n_1 = number of —CH_2— groups of molecular weight M_1, per cc.

n_2 = number of polar (ester) linkages of molecular weight M_2, per cc.

ρ = density of the polymer

b = ratio of number of CH_2 to O—C— groups per chemical repeating unit

$$n_1 = bn_2 \qquad (1)$$

N = Avogadro's number

Then

$$\rho = (n_1M_1 + n_2M_2)/N \qquad (2)$$

The experimental values of these quantities appear in Table I. The densities at 25° were from weighing and displacement of a known volume of inert liquid by the solid polymer. Polyethylene is included to represent the limiting case of all —CH_2— and no polar groups.

TABLE I

Compound	ρ, 25°	$n_1 \times 10^{-22}$	$n_2 \times 10^{-22}$	ϵ_0'
Polyethylene	0.924	4.00	0	2.33
ω-Hydroxypolydecanoate	1.064	3.41	0.38	3.40
Polydecamethylene sebacate	1.086	3.48	.39	3.32
Polydecamethylene oxalate	1.130	3.00	.60	3.70
Polyethylene sebacate	1.148	3.05	.61	4.20
Polyethylene azelate	1.172	2.99	.66	3.96
Polyethylene adipate	1.250	2.64	.88	5.16
Polyethylene succinate	1.358	2.29	1.14	5.60

Relations from Table I appear graphically in Fig. 3. The density of the solids increases linearly with the concentration of polar groups. However,

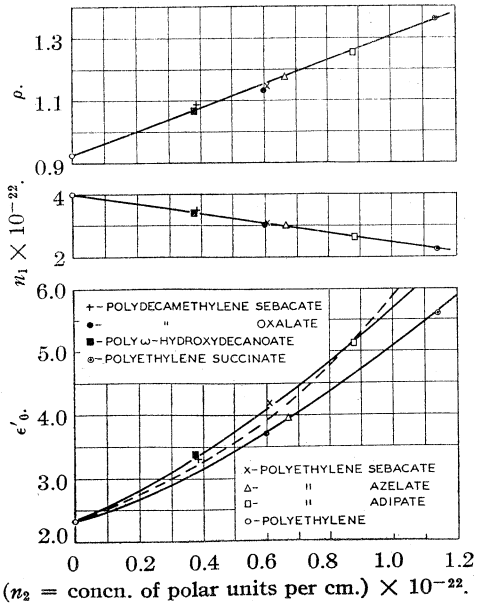


Fig. 3.—Dependence of static dielectric constant and density on concentration of polar groups in polyesters.

this increase in density is actually greater than is caused by the heavier —O—CO— units in the chain. This can be shown by simple calculation, and emphasizes the considerable contribution of the dipole forces to the lattice energy. The proportionality of n_1 to n_2 in agreement with the ratio of the polar to methylene groups *along* the chains agrees with the idea of regular packing in the series. The increase of ϵ_0', the static dielectric constant, with n_2, shown in the lower curves of Fig. 3, emphasizes the comparative independence along the chain of librating polar groups.

The dashed curve on Fig. 3 is the value ϵ_0' would have if the orientation polarization calculated from the equation of Debye for non-interacting dipoles agitated by ordinary Brownian movement, with local fields described by the Lorentz equation, were directly proportional to n_2. However, certainly the above conditions are poor approximations for linear macromolecules in the solid. Hence, we shall not at present discuss the specific polarization, despite the advantages of the Onsager field equation.[25] Also, recent treatments[26] of the internal Brownian motion in randomly-kinked chains[8] require modification for partially crystalline systems, in which considerable sections of the chains are extended in the lattice. In dilute solutions of many chain polymers assignment of effective group moments is less uncertain. There is agreement on highly convolved chains, in which the individual dipoles have almost complete freedom. Further, the molecular dipole moment appears to vary with the square root of the molecular weight.[27–31] The studies of Wyman and Bridgman on the self-polyesters of ω-OH-decanoic acid are especially relevant here, since they concluded that there was nearly complete freedom of group orientation in solutions. Evidence of large interaction (rather than intrachain restraint) reducing the freedom of the dipoles in the solid polymers arises from the two-fold higher specific polarizations (0.8) of polydecanoates found by Bridgman compared to the values (0.4) we estimate for the solid from approximate field equations.

Since the orientation polarization is reduced in the solid compared to the dissolved state, the smooth rise of ϵ_0' with n_2 in Fig. 3 suggests a comparable reduction factor in all of the polyesters. This would agree with the structural evidence[15] of layers of dipole vectors either perpendicular to (odd esters) or inclined at another angle (even esters) with the chain axes. The association of these dipoles may control the solid arrangement. In any case, they occur in layers, and seemingly the interaction is largely in these planes rather than between them, so that the spacing of dipoles *along* the chain is not a predominant factor. However, some interaction along the chain appears in two of the points on the lower solid line on the ϵ_0' curves of Fig. 3. The points on this line for polyethylene succinate and polydecamethylene oxalate show a reduced ϵ_0', expected from the proximity of the dipoles, especially the carbonyl groups, along a given chain. Presumably because of this closeness, the polyethylene succinate chain does not conform to the usual sort of planar zigzag configuration,[15] and polydecamethylene oxalate has an unusual cross-sectional packing.[15] The lower ϵ_0' value for polyethylene azelate is related to another interesting structural change. As noted, the planes containing the polar groups in polyesters having an odd-numbered acid (C_9 for the azelate) are perpendicular to the chain axes. Thus dipoles in adjacent chains come more directly into interaction than when these planes are tilted. Further, the disposition of these resultant dipoles along the chain may actually cause the vertical rather than tilted planes. For in the azelate model of Fig. 1, it is seen that the vector dipoles of the ester groups do not point in the alternately back and forth directions obtaining in the even esters. In the latter, every other dipole along a chain points in the same direction and at the same angle with the chain axis. Thus, the tilted planes containing the carbonyl groups also may be considered to contain rows of "head-to-tail" dipoles. However, in the odd polyesters the vector dipoles all lie on the same side of a given chain. If the chains shifted so that the carbonyl groups in adjacent molecules formed one tilted plane containing "head-to-tail" dipole vectors, the dipoles attached to the other ends of the acid unit (say the azelaic unit) would be uncompensated between chains and would tend to shift the chains back. The vertical form of the odd polyesters with the dipoles shifted neither one way nor the other in adjacent chains probably represents the minimum energy, as indicated by the X-ray

(25) L. Onsager, THIS JOURNAL, **58**, 1486 (1936).
(26) J. G. Kirkwood and R. M. Fuoss, *J. Chem. Phys.*, **9**, 329 (1941).
(27) J. Wyman, *ibid.*, **60**, 328 (1938).
(28) W. B. Bridgman, *ibid.*, **60**, 530 (1938).
(29) I. Sakurada and S. Lee, *Z. physik. Chem.*, **B43**, 245 (1939).
(30) S. Lee, *J. Soc. Chem. Ind.*, Japan, **43**, 190 (1940).
(31) M. Takei and H. Erbring, *Kolloid-Z.*, **94**, 312 (1941).

studies. The same situation occurs for the polydecanoate, and it likewise has the dipole planes perpendicular to the chain axis, in the crystal.

TABLE II

DIELECTRIC PROPERTIES OF POLYETHYLENE SEBACATE

$f \times 10^{-6}$	ϵ' $t = 64.5°$	ϵ'' $t = 64.5°$	ϵ' $t = 26.3°$	ϵ'' $t = 26.3°$	ϵ' $t = -98.5°$	ϵ'' $t = -98.5°$
75	4.03	0.119	3.69	0.305	2.62	0.009
70	4.03	.112	3.60	.298	2.63	.010
60	4.05	.104	3.70	.264	2.70	.010
50	4.03	.094	3.73	.218	2.65	.011
40	4.08	.077	3.80	.203	2.68	.011
30	4.10	.067	3.81	.183	2.72	.015
20	4.08	.053	3.81	.152	2.65	.012
10	4.08	.036	3.87	.115	2.72	.017
5	4.12	.026	3.97	.088	2.59	.010
3	4.13	.020	3.98	.073	2.75	.013
1	4.16	.014	4.01	.051	2.75	.019
0.5	4.15	.010	3.99	.039	2.79	.019
.3	4.17	.008	4.06	.035	2.78	.020
.1	4.16	.005	4.06	.028	2.80	.026
.03	4.13		4.06	.017	2.77	.031
.01	4.15		4.07	.014	2.78	.037
.003	4.15		4.08	.011	2.81	.038
.001	4.13		4.09	.009		

Figure 4 illustrates the frequency dependence of ϵ' and ϵ'' for polyethylene sebacate over a temperature range down to $-98.5°$. Representative data are shown in Table II. As suggested on Fig. 2, absorption maxima occur at the lower temperatures. These are shown as a function of temperature for various frequencies up to 75 mc. in Fig. 5. Wide deviations from the ideal Debye behavior are evident, in agreement with most other polymer systems.[3,7] The ϵ'' *vs.* ln f peaks are much broader, and max. ϵ'' is lower, than expected from the theory for a single relaxation time. However, the concept of group orientation inhibited by interchain potentials is supported by the temperature studies. For it is apparently possible to eliminate absorption and to reduce ϵ' to little more than the square of the refractive index on reducing the kinetic energy of the groups by cooling. The absorption maxima may be readily shifted along the frequency scale by temperature. As the temperature is lowered, the number of groups possessing the energy requisite for surmounting the barriers opposing libration decreases. This means that the absolute reaction rate[32] is reduced, and the polar units are finally unable to follow an alternating field. Thus, at a given temperature, the frequency of maximum ϵ'' indicates about the rate constant at which most of the orienting units are able to oscillate over the barriers. Of course, for gases, on the Debye theory the frequency of maximum absorption equals $1/\tau'$, where τ' is the relaxation time for the dipoles, but in a liquid or solid a given dipole interacts on the surrounding matter to produce an additional polarization so that the relaxation time of the medium, τ, obtains. The familiar expression

$$\tau = \tau' [(\epsilon_0 + 2)/(\epsilon_\infty + 2)] \qquad (3)$$

relates these two relaxation times, where ϵ_0 is the dielectric constant at zero, and ϵ_∞, at infinite frequency. Since the expression above for relating τ to τ' really involves an accurate formula for the local field, which is not yet known for these solids, we shall regard τ for the dielectric as a rough measurement of the rate process for the movement of the atomic groups. It is hoped that subsequently this approximation may be improved. Also, the problem of the distribution of relaxation times about an apparent average value will be omitted from this preliminary discussion.

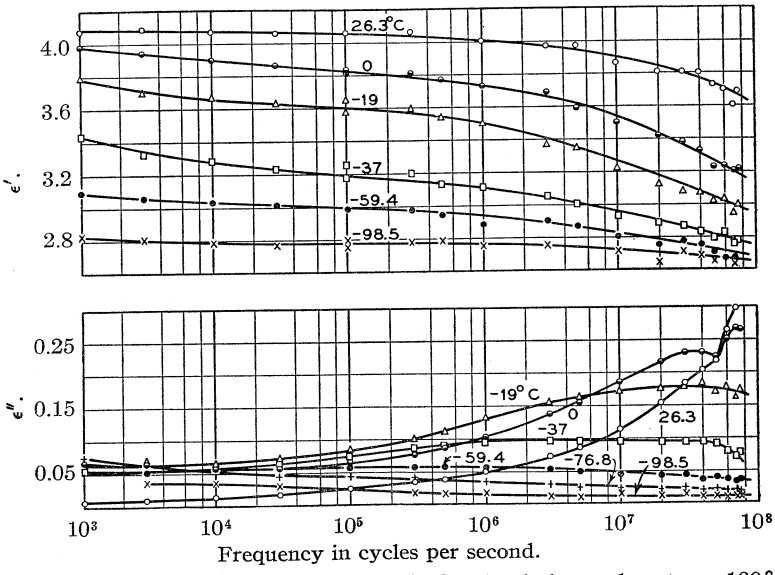


Fig. 4.—Frequency variation of ϵ' and ϵ'' of polyethylene sebacate, $-100°$ to 25°.

The hindered orientation of groups in polyethylene sebacate may then be regarded as analogous to a unimolecular reaction[10,11] whose

(32) S. Glasstone, K. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941.

absolute rate constant, k', is in general given by

$$1/\tau = k' = Ce^{-E/RT} \qquad (4)$$

where C is the "steric" factor, E the activation energy in cal. per mole, T the absolute temperature and R the gas constant.

We assume that E is virtually temperature independent; actually, since E represents a difference between energy levels which does depend on temperature, the corrections of Rushbrooke[33] should properly be applied.

From the loss maximum of Fig. 4, τ is obtained from the frequency producing ϵ'' max. at a given temperature. Although Fig. 5 shows several maxima, the ϵ'' curves here overlap, and do not provide a reliable estimate of the mean τ for a given temperature. A plot of $1/\tau$ against $1/T$ gives a straight line, the slope of which is E/R, and $E =$ 12,100 cal. per mole of orienting groups, for polyethylene sebacate. This value is most significant

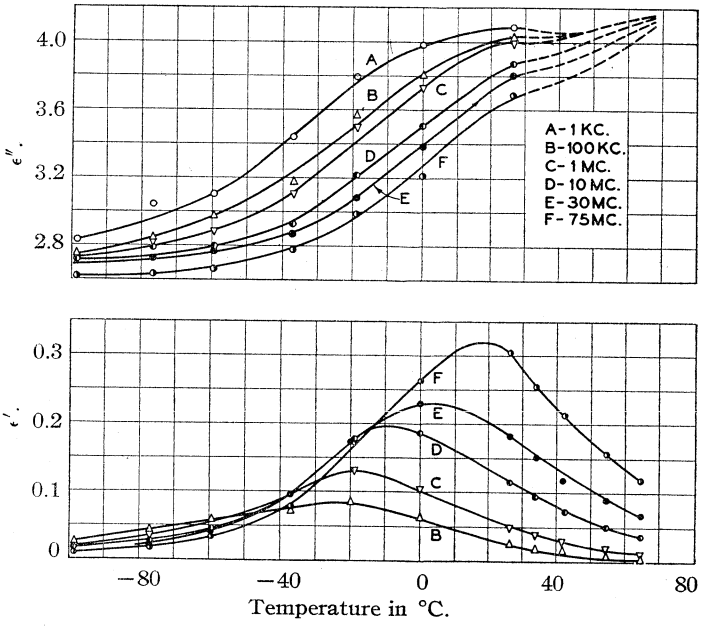


Fig. 5.—Temperature variation of ϵ' and ϵ'' of polyethylene sebacate, 1 kc. to 75 mc.

when compared to the larger value for a polyamide.[34] Further, the entropy term is large; in equation (4), $C = 4.3 \times 10^{18}$. This indicates that the neighbors of an orienting group must cooperate in its motion, such as by momentary displacements to reduce steric hindrance or by concentration of energy in the vicinity, as interpreted previously.[12]

The entropy term in the above expression should be significantly related to the distribution of relaxation times found for a given system. A distribution of relaxation times implies a variety of motions and configurations surrounding the orienting groups and causing different rates of surmounting the restraining barriers. This is just what the entropy of activation, or "activation in many degrees of freedom,"[11] means. Studies connecting explicitly the distribution function with the entropy or "steric" term in the rate equation are in progress.

Reduction in intermolecular coupling appears to give a sharper experimental distribution. Thus, consistent with the above concept, absorption peaks at high temperatures, with high plasticizer contents, or from "soft," weakly interacting polymers at ordinary temperatures are comparatively sharp.

Figure 5 bears interestingly on the phase changes in linear condensation polymers. Their high crystallinity[15,18] precludes a wide softening range, and the rise in ϵ' (accompanied by dispersion) over the broad temperature interval in Figure 5 corresponds to little physical change in the solid. However, the polymer melts (in thermodynamic equilibrium)[35] at ~70°. This is, however, just above the temperature at which the dipoles are able quite freely to follow at least frequencies of 10^8. The ester linkages, or the carbonyl units, are thus undergoing increasingly violent thermal oscillations and are able to surmount the barriers imposed by the lattice array. Figure 5 may thus be regarded as indicating the prelude to fusion. Similar studies on other crystalline polymers including cellulose derivatives give evidence on the role of polar groups in melting. These are also further corroboration of the segment theory of polymer melting.[18]

The occurrence of absorption maxima far below the melting point, as for polyethylene succinate in Fig. 2, simply marks the onset of a particular oscillation—not necessarily that required for breakdown of the lattice.

Summary

The dielectric constant and loss of typical linear polyesters have been determined (over a

(33) G. S. Rushbrooke, *Trans. Faraday Soc.*, **36**, 1055 (1940).
(34) Baker and Yager, THIS JOURNAL, **64**, 2171 (1942)
(35) Baker, unpublished studies.

120° temperature range for one) for the frequency interval 1 kc. to 75 mc. These macromolecular chain polymers are of known structure and composition, so that the observed polarization and dispersion were related to the orientation and concentration of polar groups in the chains and to their relative positions in adjacent chains. The dielectric constants, ϵ', of all of the polymers exceed the refraction value even at room temperature. The oscillation of individual dipole groups (ester linkages) contributes the orientation polarization. These dipoles interact somewhat along a given chain, but chiefly between chains, to cause the observed broad dispersion. The polyesters exhibit principally high frequency absorption, with maxima at low temperatures. This supports the concept of small oscillating units in the chains, in agreement with the observed activation energy of orientation.

The packing of the chains is strongly influenced by the dipoles and the formation of dipole layers makes the interaction, which contributes to dielectric absorption, largely independent of polar group concentration.

The dielectric results reveal thermal motion in the polymers. These chain oscillations are supposed to account for mechanical properties such as thermal retraction associated with chain kinking in long chain molecules.

MURRAY HILL, N. J. RECEIVED NOVEMBER 13, 1941

[CONTRIBUTION FROM BELL TELEPHONE LABORATORIES, INC.]

The Relation of Dielectric Properties to Structure of Crystalline Polymers. II. Linear Polyamides

BY W. O. BAKER AND W. A. YAGER

Linear condensation polymers have been selected as appropriate for study of the effects of molecular structure and molecular order on the dielectric properties of solids.[1] They represent an important class of structural and insulating plastics. Polyesters have been treated previously and the general implications of such an investigation have been reviewed. The present report includes preliminary results on the polyamides, in which the —O— of the ester linkage has been replaced by the —NH— group. Conditions for extensive hydrogen bonding have thus been introduced, and the whole structure resembles that of polypeptides and proteins. The dielectric measurements indicate great mobility in the alternating field of some atomic group, possibly a charged hydrogen. The close analogy of the polyamides to the polyesters allows assignment of the observed differences to the NH group. Certain of the results may be examined for direct evidence of isomerism in the amido linkage. Thus, the linear polyamides may assist, as models, in elucidating the structure of proteins.

Experimental

Materials.—The polyamides were obtained commercially (du Pont Company) or from the procedures of Carothers.[2] They were pure, white polymers with weight average molecular weights greater than 10,000. All were carefully protected from degradation during preparation of the test discs.[1] The co-polyamide was of the 50-50 composition noted in the patent describing it.[3] All samples were annealed to states of maximum crystallinity,[4] unless otherwise noted. The sample discs were molded and machined to a two-inch diameter and 50-mil thickness, were thoroughly dried over phosphorus pentoxide, or conditioned as noted, and equipped with electrodes as previously described.[5]

Dielectric Measurements.—The bridge and Q-meter apparatus and technique used for the polyesters were again employed.

The dielectric loss of polyhexamethylene sebacamide at and above 100°, and of polyhexamethylene adipamide at 100% relative humidity was too high for direct measurement on the Q-meter. Consequently, the top electrode of the test cell was raised above the test specimen, thus introducing a series air gap. The effective capacity, C_m and loss, tan δ_m, of this two-layer arrangement were determined on the Q-meter and the true capacity, C_x, and loss, tan δ_x, calculated from the equations

(1) Yager and Baker, THIS JOURNAL, **64**, 2164 (1942).
(2) Carothers, U. S. Patents 2,071,250 (1937) and 2,130,523 (1938).
(3) Carothers, U. S. Patent 2,191,367 (1940).
(4) Fuller, Baker and Pape, THIS JOURNAL, **62**, 3275 (1940); see also Baker and Fuller, *ibid.*, **64**, October (1942).
(5) Yager, *Trans. Electrochem. Soc.*, **74**, 113 (1938).

$$\tan \delta_x = \frac{C_a}{C_a - C_m} \tan \delta_m$$

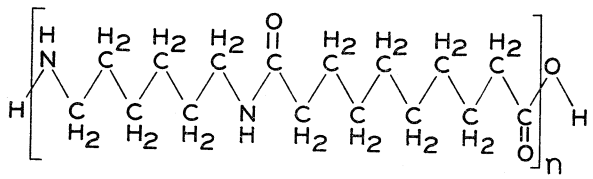
$$C_x = \frac{C_a C_m}{C_a - C_m} \cdot \frac{1}{1 + \tan^2 \delta_x}$$

where C_a represents the series air capacity. C_a was calculated from the above equations by measuring C_m and tan δ_m and then the corresponding C_x and tan δ_x directly on the capacitance and conductance bridge.

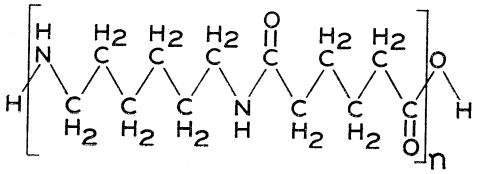
The direct current conductivity of the polyamides was determined after the application of 100 volts for one minute, by use of a Leeds and Northrup H.S. type galvanometer.

Results and Discussion

The structural formulas of two typical polyamides appear in Fig. 1. Evidently, the concentration of polar groups may readily be varied with methylene "spacers," as in the polyesters.[1]



POLYHEXAMETHYLENE SEBACAMIDE



POLYHEXAMETHYLENE ADIPAMIDE

Fig. 1.—Structural formulas of typical linear polyamides.

Likewise, the polar groups in adjacent chains occur in layers,[4] and their interaction includes hydrogen bonding[6] as well as dipole and dispersion forces. The presence of a bonding hydrogen profoundly alters the properties of the polymers. The primary valence chains wander in kinked paths through the crystalline and intercrystalline matter,[4] but in addition a network of secondary forces (hydrogen bonds) obtains. Thus, the interchain forces, and hence the restraints on dipole orientation, should exceed those for the polyesters, as confirmed below. Such predictions of polymer properties from structural formulas have been possible only recently.

Figure 2 shows the dielectric behavior of several polyamides at 25°, with the curves A for polydecamethylene sebacate included for direct comparison. Apparently an appreciable orientation polarization contributed by the motion of the polar groups is present in all of the solids. The polyester has the same concentration of polar links in the chain as the polydecamethylene sebacamide of curve C (9 methylene groups per linkage). The polyamide exhibits significant dispersion at room temperature. The restraint of orientation found in the polyesters[1] appears much increased in the polyamides, in accord with their higher melting points and mole cohesion. The sequence of ϵ' values in Fig. 2 also shows expected increased polarization in the polyamides with increasing concentration of polar groups in the chain. Curve C, for polydecamethylene sebacamide, with 9 CH_2 groups per polar linkage is followed by curve B (polyhexamethylene sebacamide) with 7 and Curve E, for polyhexamethylene adipamide, with 5.

Evidently polyhexamethylene adipamide possesses a broad maximum in ϵ'' at room temperature. This breadth and height of maximum indicate a distribution of relaxation times, generally found in solids. The ϵ'' values for the polyamides have been corrected for d. c. conductivity, which, as noted later, is appreciable for these pure compounds.

The ϵ'' curves in Fig. 2 do not follow the order of the ϵ' for increasing values of the ordinates. This is related to an important aspect of the dielectric behavior of linear polymers. The concentration and resultant moments of the polar groups in the chain determine the essential polarity of the polymer, but it has been emphasized that the interaction with neighboring chains chiefly governs the observed loss. The following discussion indicates some factors causing a variation in interaction and hence in loss. In the melts of these polymers, strong dipole association facilitates the formation of the dipole layers observed in the solid. This layering is distorted, however, in the portions of the polymer which are imperfectly or hardly crystalline, and hence the dipole interaction would be expected to vary with the degree of molecular organization present in the solid studied. This degree of order controls considerably many physical properties of the plastics, such as elastic modulus.[4] Hence, some correlation between physical and mechanical properties and dielectric behavior is a necessary, and observed, consequence of solid structure. The variety of ordered states which may be produced in natural products like

(6) Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, Chap. IX.

cellulose derivatives[7] should likewise be reflected in their dielectric values; the effect is general. Clearly, the dipoles may be disposed differently in adjacent chains either by shifting along the chain, or rotation about its axis. Both of these conditions are present in the non-crystalline regions of linear polymers, as diffraction studies show.[4,7] If the argument above that the longer relaxation time of the polyamides compared to the polyesters is caused by strong intergroup action, principally hydrogen bonding, is correct, then altered relative positions of the groups should alter the dielectric loss. This is shown by Curves C and D of Fig. 2. Curve C is for annealed polydecamethylene sebacamide, in which the polar groups are as efficiently packed and as extensively hydrogen bonded as the lattice-forming deficiencies of long chains permit.[7] The sample of curve D, however, was the same polyamide rapidly quenched from the melt. It contains relatively few crystallites, and the chain segments are rotated so that the hydrogen bonds are, on the average, less efficiently directed and formed than in the annealed compound. They resemble the hydrogen bonding in a liquid rather than in a well-ordered solid. Still, they are strong enough to stabilize the chains in their disordered configurations of higher free energy (compared to the crystal) for long periods, as shown by the rate of crystallization of polyamides in the solid state.[4] However, the reduced forces in the quenched material permit augmented though still hindered dipole freedom, and hence curve D lies clearly above curve C, for ϵ' and ϵ''. These differences were caused not by a change in the composition of the chains, but only in their *relative positions*.

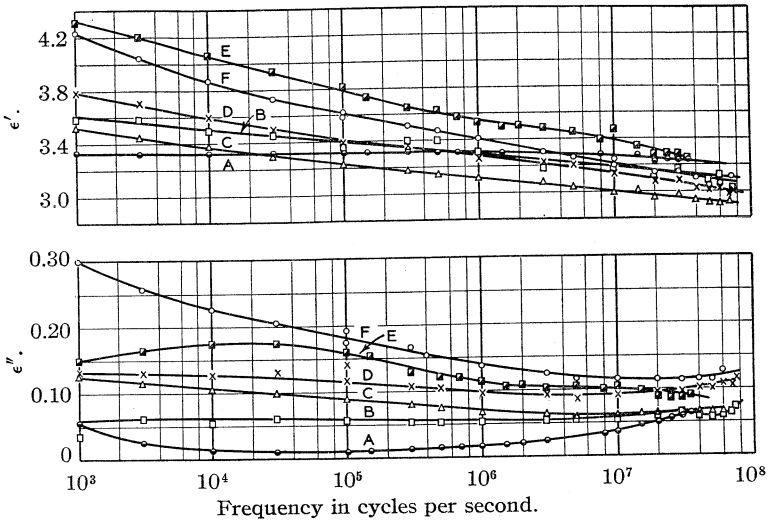


Fig. 2.—Frequency variation of dielectric constant, ϵ', and loss, ϵ'', of polyamides at 25°: A, polydecamethylene sebacate; B, polyhexamethylene sebacamide; C, polydecamethylene sebacamide, annealed; D, polydecamethylene sebacamide, quenched; E, polyhexamethylene adipamide; F, polyhexamethylene–decamethylene adipamide–sebacamide.

The structural variations possible in condensation polymers allow another test of the hypothesis that interaction is modified by relative positions and hydrogen bonding of amido links. If a polyamide is prepared by the intercondensation of two different dibasic acids and two different diamines, say in equimolar ratios, some of the polar groups will associate as usual, but, along a chain, the "repeating units" are quite random in composition, so that many of the dipole groups in adjacent chains will be unable to coincide to form a layer, and will be found surrounded by the hydrocarbon portions of the molecules.[7a] The compound of curve *F* was thus obtained from hexamethylenediamine, decamethylenediamine, adipic acid and sebacic acid.[3] Its average polar group concentration is one per 7 methylene groups, so that it should compare with curve B, yet it shows markedly increased dielectric constant and loss. The average composition of the copolyamide chains is the same as that of polyhexamethylene sebacamide, but the irregular spacing between linkages in the molecule reduces the hydrogen bonding and other interaction in the solid so that ϵ' and ϵ'' are much enhanced. This is further emphatic indication that the chains do not act as units, but that each individual dipole is sensitive to its own environment. Also, the intrachain coupling would be little different in the copolyamides than in the normal polyamides, so seemingly the interchain action alters the dielectric properties. The effect of these changes in interaction in the quenched and co-polyamides on the distribution of relaxation times in the polymer alone forms an extensive study.

The orientation of polar groups is probably not the sole source of high polarization in polyamides, especially at elevated temperatures. A new mechanism which we associate with the isomerism of the amido linkage seems necessary to explain the

(7) W. O. Baker, C. S. Fuller and N. R. Pape, THIS JOURNAL, **64**, 776 (1942).

(7a) W. O. Baker and C. S. Fuller, "Conference on Physics of the Solid State," N. Y. Academy of Sciences, February, 1942.

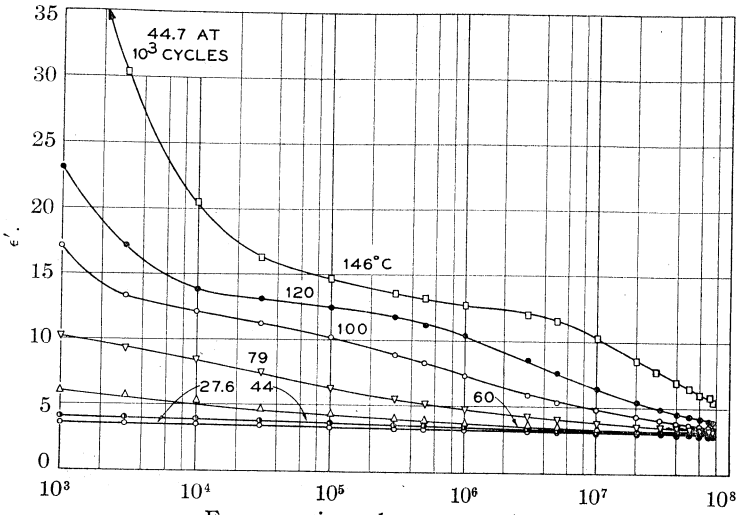


Fig. 3.—Frequency variation of ϵ' of polyhexamethylene sebacamide, 27.6 to 146°.

succeeding results, as in Figs. 3 and 4, for polyhexamethylene sebacamide, which are typical of the series. Some representative values are also given in Table I. At 1 kc. ϵ' has a value at 146° (70° below the melting or softening point of the polymer) of about 48, and ϵ'' is about 27. In addition, as is seen from its temperature variation in Fig. 7, there is a relatively high d. c. conductivity in the compound. The galvanometer behavior indicated that this was not from a space charge. These compounds are likewise free from ionic impurities, as determined by ashing, extraction and quantitative analysis.

The isomerism of the amido linkage has been chiefly considered in the structure of polypeptides and proteins. Hydrogen bonding is important in the molecular configuration of these compounds.[8] A group of the type shown here probably occurs within and between folded polypeptide molecules,[8a] and between the polyamide molecules here treated. Huggins[9] has proposed that the hydrogen in the bridge is virtually ionic. At least one may regard it as in one of two potential minima, one provided by the oxygen and the other by its "own" nitrogen. These two minima are separated by a hump, over which charged hydrogens with requisite energy may oscillate.[10] The dielectric results are consistent with a concept embodying mobile, charged atoms which can contribute an atomic polarization and anomalous dispersion by moving translationally (vibrationally) from one potential minimum to another in the dipole layers. This motion should be strongly temperature-dependent, which is supported by the data of Figs. 3, 4 and 5. The high frequency ϵ'' maxima of Fig. 4 represent a second mechanism and seemingly correspond to the maxima observed at lower temperatures for the polyesters. They occur at elevated temperatures presumably because the oscillations of, say, the carbonyl groups are inhibited by hydrogen bridges of the sort shown in the diagram above. From curve *A* of Fig. 6, obtained as noted before for the polyester[1] (curve B), E =

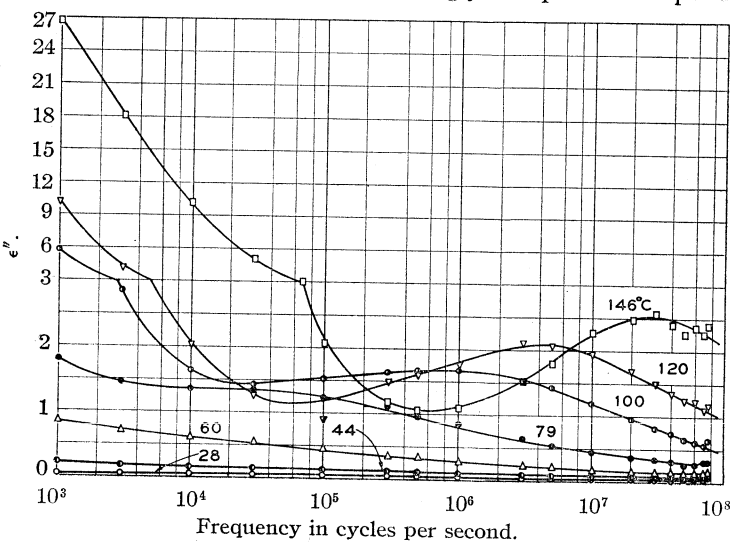
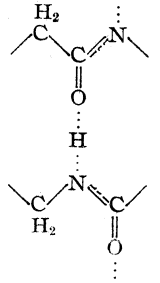


Fig. 4.—Frequency variation of ϵ'' of polyhexamethylene sebacamide 27.6 to 146°.



(8) For a review and discussion see W. T. Astbury, *Trans. Faraday Soc.*, **36**, 871 (1940).

(8a) Frank, *Nature*, **138**, 242 (1936).

(9) M. L. Huggins, *J. Org. Chem.*, **1**, 407 (1937).

(10) This idea was forwarded by M. L. Huggins in a discussion in April, 1939.

TABLE I

DIELECTRIC PROPERTIES OF POLYHEXAMETHYLENE SEBACAMIDE

× 10⁻⁶	ϵ' t = 27.6°	ϵ''	ϵ' t = 79.0°	ϵ''	ϵ' t = 146.0°	ϵ''
75	3.0	0.072	3.49	0.324	5.45	2.39
70	2.93	.065	3.38	.313	5.78	2.26
60	3.12	.060	3.46	.283	6.06	2.35
50	3.09	.058	3.47	.270	6.54	2.27
40	3.12	.061	3.55	.312	6.96	2.40
30	3.17	.063	3.62	.328	7.61	2.56
20	3.13	.061	3.68	.380	8.65	2.47
10	3.19	.057	3.80	.442	10.31	2.27
5	3.28	.055	4.11	.541	11.55	1.79
3	3.19	.053	4.37	.649	12.03	1.51
1	3.31	.052	4.76	.866	12.74	1.10
0.5	3.40	.054	5.18	.964	13.12	1.07
.3	3.40	.054	5.55	1.11	13.52	1.18
.1	3.42	.060	6.32	1.24	14.80	2.07
.03	3.46	.062	7.74	1.33	16.26	5.14
.01	3.50	.056	8.46	1.35	20.44	10.23
.003	3.58	.062	9.35	1.46	30.40	18.12
.001	3.59	...	10.24	1.80	47.66	26.6

23,300 cal. per mole of polyamide polar unit, nearly twice the polyester value of 12,100.

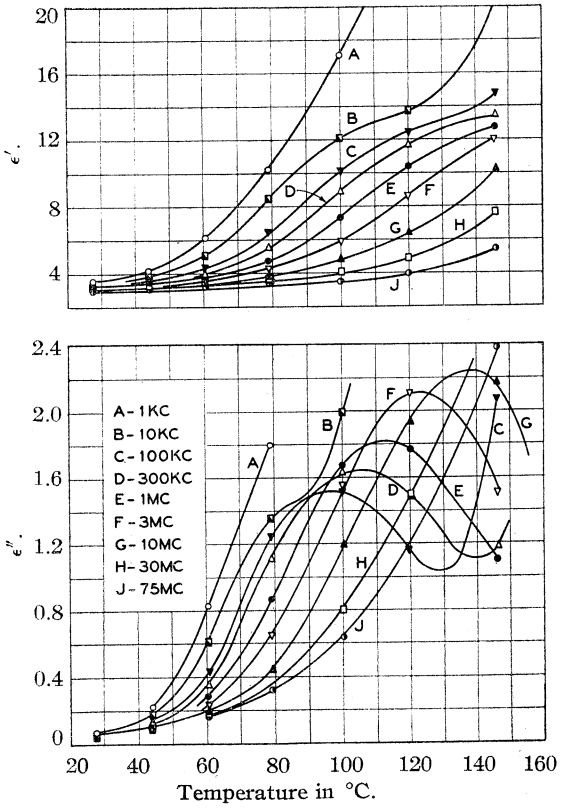


Fig. 5.—Temperature variation of ϵ' and ϵ'' of polyhexamethylene sebacamide, 1 kc. to 75 mc.

Further, the activation process apparently produces another sort of enhanced freedom for the

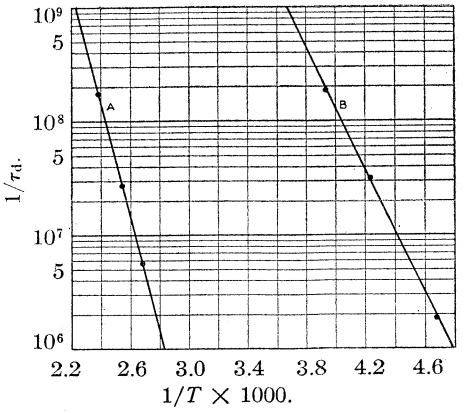


Fig. 6.—Temperature dependence of the relaxation time of the dielectric, τ_d, for polyhexamethylene sebacamide (curve A) and polyethylene sebacate (curve B).

bridge hydrogen. It may pass over to one or the other of the positions near the O or N but possibly it can also acquire even more freedom and act like a migrant ion over very short distances, thus causing the high d. c. conductance. The temperature coefficient of this conductance appears in Fig. 7,

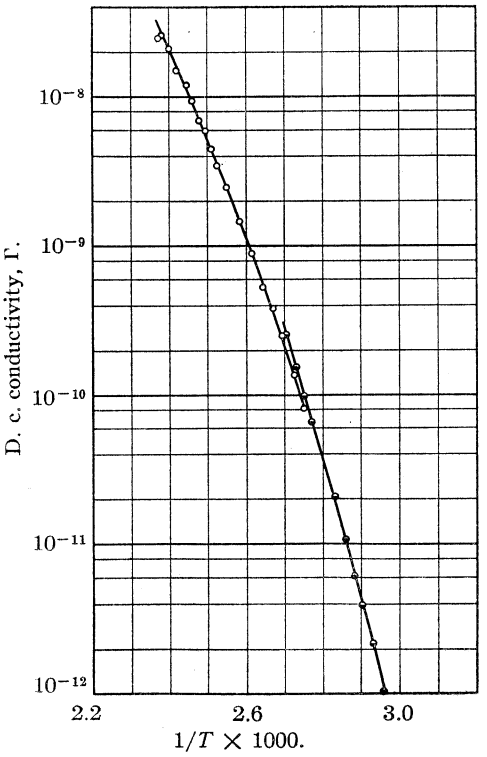


Fig. 7.—Temperature dependence of the d. c. conductivity, Γ, of polyhexamethylene sebacamide.

and corresponds to an activation energy of 29,700 cal. per mole of conducting particle. This value is several fold the dissociation energy for a hydro-

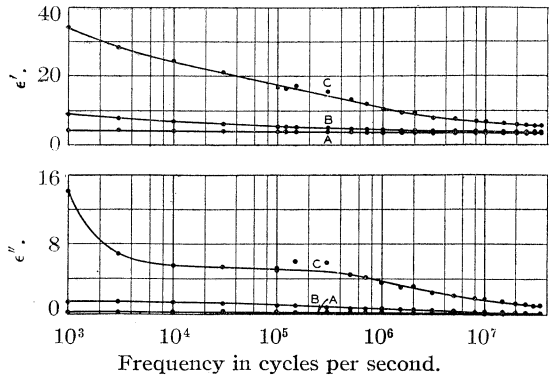


Fig. 8.—Effect of sorbed water on frequency dependence of ϵ' and ϵ'' of polyhexamethylene adipamide at 25°: dry (curves A), 60% R. H. (curves B) and 100% R. H. (curves C).

gen bond,[11] and may well reflect the energy necessary to liberate charged hydrogens from restraining negative force fields around a given N or O atom. It is less than half the energy of the N–H bond, but one would expect this link to be perturbed and weakened by the hydrogen bridges in the solid polyamides and by its adjacent carbonyl. (It should be emphasized that the atomic or nuclei motion cannot contribute, however, to the resonance in the amide linkage.) The d. c. conductance and low frequency loss may thus represent different degrees of the same sort of hydrogen motion. They are not to be regarded as measuring very different phenomena. The low frequency loss may not exhibit a maximum. Molten polyamides and the solids at higher temperatures thus are apparently semi-conducting materials.

It is a striking contrast that the relaxation time of the dielectric is 5×10^{-9} sec. for polyethylene sebacate at −19° and for polyhexamethylene sebacamide at 146°. This large difference may be regarded chiefly as a consequence of the effect of molecular structure on the solid state. The isolated molecules would show no such different kinetic characteristics, nor would they be expected to show diverse intrachain coupling. On the other hand, the polyester melts at 74°, the polyamide at 215°; a 141° interval emphasizes the different forces. The relaxation times reflect thermal motion present in the polymers irrespective of the applied field, and hence are related to the elastic and plastic properties of the solids.

The explanation of hydrogen bridging and charged hydrogen motion in these bridges as the source of the extraordinary dielectric properties of typical linear polyamides suggests that strong hydrogen bonding agents added to the polymers at ordinary temperatures should produce the same effect as elevated temperatures alone. This is confirmed in Fig. 8 for water, whose sorption is of technical importance. Curves A were obtained from polyhexamethylene adipamide dried two weeks over calcium chloride, curves B, for the substance equilibrated (fifty-six days) at 60% relative humidity, and curves C, after immersion in distilled water, all at 25°. Evidently the combination of bound water (about 10% for saturation at room temperature) and the amido groups causes a high dielectric constant and appreciable dispersion. ϵ'' is again corrected for d. c. conductance. Water may be here considered as a loosening (plasticizing) or pseudo-ionizing medium, which substitutes for intermolecular polyamide bonds, and facilitates motion of the whole system.[7] Thus, if the dielectric results are admitted to show enhanced interchain motion directly, the mechanism discussed above could apply to the dependence on *p*H and degree of swelling of the physical properties of polypeptides and proteins. For example, the molecular motion in muscular contraction would be controlled by the degree of interchain force reduction, and hydrogen bonding suppression, as indicated by many other researches. The present results also cause inquiry of how much wandering of hydrogen atoms among peptide linkages, and hence energy exchange, occurs in proteins swollen or thermally agitated. This latter is related to the hypothesis of energy transfer recently proposed by Szent-Györgyi.[12]

We are grateful to Dr. B. S. Biggs and Mr. W. S. Bishop for providing certain of the polyamides studied.

Summary

The dielectric constant and loss have been determined over a 120° temperature interval and over the frequency range 1 kc. to 75 mc. for typical linear polyamides. All of the polymers evidenced dipole orientation accompanied by anomalous dispersion, even at room temperature. The magnitudes of ϵ' and ϵ'' rise with the polar group concentration in the long molecules, but are sharply modified by the interaction between groups in adjacent molecules. The interaction was varied by reducing the crystallinity by quenching, and by forming co-polymers in which the polar groups

(11) See review in J. J. Fox and A. E. Martin, *Trans. Faraday Soc.*, **36**, 897 (1940).

(12) Szent-Györgyi, *Nature*, **148**, 157 (1941); see also London, *J. Phys. Chem.*, **46**, 305 (1942).

were displaced from their usual layer structure. Reduced interaction always caused enhanced polarization.

The dielectric properties of the polyamides show steep temperature coefficients; at 146°, 70° below its melting point, polyhexamethylene sebacamide has $\epsilon' \sim 48$, $\epsilon'' \sim 27$, at 1 kc. This compound also has a high frequency absorption associated with a relaxation process of activation energy 23.3 kcal. per mole, about twice the value for the analogous polyesters. Further, the polyamides show a high d. c. conductivity at elevated temperatures, which may be caused by mobile, charged atoms, such as hydrogen, resulting from isomerism in the amido linkage.

MURRAY HILL, NEW JERSEY RECEIVED JANUARY 6, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

The Dropping Mercury Electrode in Acetic Acid. II. Electrocapillary Curves and the Theory of Maxima[1,2]

BY G. BRYANT BACHMAN AND MELVIN J. ASTLE[3]

In a preceding paper[4] it was shown that ions and molecules with low polarographic reduction potentials give discontinuous current–voltage curves in acetic acid solutions. In the present investigation this phenomenon has been related to the adsorption processes occurring on the drop through a study of electrocapillary curves.

Discontinuities in anhydrous acetic acid are fundamentally the same phenomena as maxima in water systems. They differ in that they seem to be limited to substances of rather low reduction potential. Since the occurrences of maxima in aqueous solutions have been associated with the adsorption of ions and molecules on the mercury drop, it is reasonable to assume that a similar association exists in acetic acid solutions. A convenient method of studying adsorption on charged mercury surfaces is through the medium of electrocapillary curves.

The electrocapillary curve for ammonium acetate in anhydrous acetic acid shows a marked difference from the same curve in water in that the top of the curve is broad and rather flat and two maxima instead of one are present. Double maxima are very uncommon in water although Kemula and Beer[5] observed them in some cases using the dynamic drop weight method. Addition of water causes the two maxima in acetic acid to approach each other and to blend into one well-defined maximum at 50 mole per cent. water (Fig. 1).

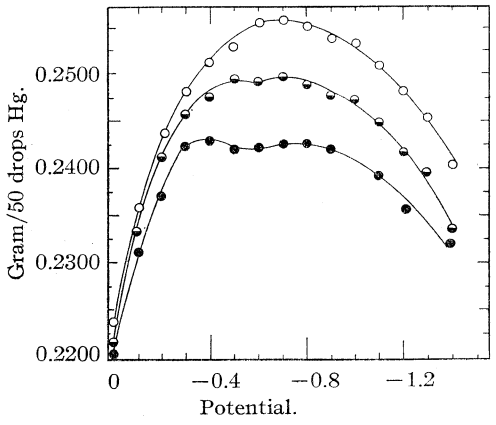


Fig. 1.—The effect of solvent composition on the electrocapillary curve for mercury in ammonium acetate solutions: ●, 0.25 *M* NH_4OAc in acetic acid; ◒, 0.25 *M* NH_4OAc in acetic acid and water (35 mole %); ○, 0.25 *M* NH_4OAc in acetic acid and water (50 mole %).

When salts are added to a solution of ammonium acetate in acetic acid, the effect on the electrocapillary curve depends on the reduction potential of the cation of the salt. If the cation has a half-wave reduction potential more negative than the *first* electrocapillary maximum for solutions of ammonium acetate in acetic acid (about −0.3 volt) then the resulting curves have the same general shape as the electrocapillary curve for ammonium acetate alone. Such cations are designated as Class I cations and include Zn^{++}, Pb^{++}, Cd^{++}, Co^{++}, Sb^{+++}, Ni^{++}, Cr^{+++} and Bi^{+++}. Figure 2 shows typical curves of this sort for Zn^{++} together with the corresponding current–

(1) Presented before the Physical and Inorganic Section at the Atlantic City meeting of the American Chemical Society, September 8–12, 1941.

(2) From the Ph.D. thesis of Melvin J. Astle.

(3) Present address: University of Kentucky, Lexington, Kentucky.

(4) Bachman and Astle, THIS JOURNAL, **64**, 1303 (1942).

(5) W. Kemula and E. Beer, *Roczniki Chem.*, **16**, 259 (1936).

voltage curves. Solutions of these cations give normal S-shaped curves after degassing and can be determined polarographically in the usual fashion.

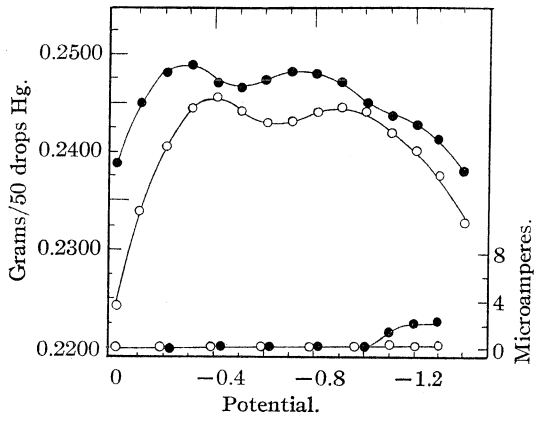


Fig. 2.—Electrocapillary curves (top) and current–potential curves (bottom): O, 0.25 *M* ammonium acetate; ●, 0.25 *M* ammonium acetate, 1.2 × 10^{-3} *M* zinc acetate.

Cations whose half-wave reduction potentials lie at more positive values than the first electrocapillary maximum for solutions of ammonium acetate in acetic acid give irregular and distorted electrocapillary curves. Such cations are designated as Class II cations and include Cu^{++}, Fe^{+++}, Pb^{++++} and Hg^{++}. The behavior of cations of this class is illustrated in Fig. 3 with electrocapillary and current–voltage curves for Cu^{++}. Class II cations cannot be determined polarographically in acetic acid even after their solutions are thoroughly degassed.

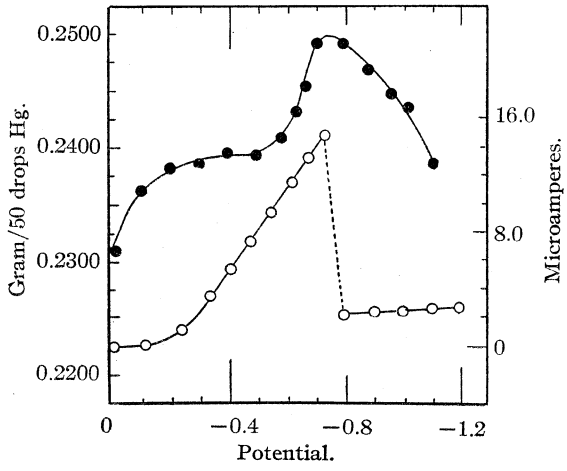


Fig. 3.—Electrocapillary and current–potential curves for the system ammonium acetate–copper acetate–acetic acid, 0.2 *M* ammonium acetate, 1.2 × 10^{-3} *M* copper acetate; ●, electrocapillary curve; O, current–potential curve.

An examination of Fig. 3 reveals that between −0.2 and −0.6 volt the surface tension remains practically constant.[6] In this region then there is no change in the degree of polarization and hence no change in the surface potential of the electrode. This is a result of the fact that the electrons flowing into the mercury drop from the external source are being neutralized by the reduction process. As the discontinuity potential is approached, however, the interfacial tension and the surface potential change very rapidly. Copper ions no longer reach the electrode in sufficient numbers to neutralize the flow of externally impressed electrons. Finally, the electrocapillary maximum is reached and passed, the mechanism of reduction changes radically as evidenced by the abrupt decrease in the current, and the electrocapillary curve becomes normal as the interfacial tension begins to parallel its decline in the absence of Cu^{++} ions.

Two important theories to account for maxima in current–voltage curves have been proposed. The first of these is that of Heyrovsky,[6] who attempted to explain them on the basis of the adsorption of the reducible substance on the growing drop. Ilkovic[7] also considers maxima as being caused by the adsorption of reducible substances on the mercury drop, but differs concerning the force responsible for it. The Heyrovsky and Ilkovic interpretations of maxima meet with much the same difficulties in attempting to explain the electrolysis of salts in acetic acid. In the first place, they do not take into account the change in sign of the drop charge at the maximum of the electrocapillary curve, and hence they do not explain the difference in the behavior of such ions as Cu^{++} and Zn^{++}. In the second place, it is difficult to understand, on the basis of this theory, the abrupt decline in the current which takes place in the reduction of Class II ions. Finally, it is probable that the thickness of the adsorption layer is insufficient to account for the manifold increase in adsorption required to produce the currents observed.[8]

A more recent theory of maxima has been put forward by Antweiler.[9] This theory is based on the observation that there is a vigorous stirring action around the mercury drop at potentials

(6) A similar phenomenon has been observed in aqueous solutions. *Cf.* Heyrovsky, "Actualités scientifiques et industrielles," No. 90, Hermann et Cie., Paris, 1934 .

(7) Ilkovic, *Coll. Czech. Chem. Commun.*, **8**, 13 (1936).

(8) Antweiler, *Z. Elektrochem.*, **44**, 831 (1938).

(9) Antweiler, *ibid.*, **44**, 663 (1938).

below that of the electrocapillary maximum, but that the stirring ceases and a well-defined diffusion layer forms at the potential of the maximum.[10] Streaming around the drop destroys the diffusion layer responsible for the concentration polarization and results in the carrying of many more ions to the drop than would otherwise reach it. The stirring action is electro-osmotic in nature and is caused by a tangential potential gradient which arises from a difference in current density between the top and bottom of the drop. The difference in current density is explained by Antweiler as being caused by a preferential adsorption of ions on the under side of the drop. The glass of the electrode partially shields the top of the drop and thus lengthens the path which the ions must travel in diffusing from the solution to the drop surface. Hence, the rate at which the ions are adsorbed is greater at the bottom than at the top of the drop.

The above reasoning accounts for the great increase in the current preceding the maximum but does not explain the sudden fall of the current beyond the maximum. To understand this it is necessary to consider the role of the supporting electrolyte. Taking as an example the electrolysis of Cu^{++} ions in the presence of Na^{+} ions, it is clear that the Na^{+} ions will wander to the cathode along with the Cu^{++} ions but that they will not be discharged, because of their higher reduction potential. The concentration of the Na^{+} ions builds up, especially on the under side of the drop, with the result that the tangential potential is augmented still further and the streaming becomes still more rapid. This is accompanied by a rapid rise in the current. Eventually, however, the concentration of Na^{+} ions becomes so high that the Cu^{++} ions are effectively screened out. When this occurs the current declines, the streaming ceases and normal concentration polarization sets in.

With certain additions and limitations this picture of current–voltage maxima can be carried over quite satisfactorily to reduction phenomena in acetic acid. In the electrolysis of Class II cations a maximum in the current–voltage curve is to be expected as a result of the streaming effect described above. The stirring brings to the drop an ever-increasing number of reducible cations. The current therefore rises more rapidly than would be expected on the basis of normal diffusion. Two different processes now interrupt this rapid increase in the current. (1) The concentration of the supporting cations surrounding the drop may become so high that the ions being reduced are screened out. In this event reduction practically ceases, the current decreases, streaming stops, and a normal diffusion process of reduction is all that remains. (2) The maximum of the electrocapillary curve may be reached. If this occurs the charge on the drop surface becomes nil, and as a result the streaming ceases, the current drops abruptly, and once more a normal diffusion current is all that remains. It is evident that the second process is the one which applies to Class II cations. Our investigations indicate that the electrocapillary maximum always coincides with the potential of the discontinuity, even though the electrocapillary maximum may be shifted to more negative potentials as a result of the reduction process.

The addition of surface active substances would be expected to influence the nature of current–voltage curves to a considerable degree. All such substances are preferentially adsorbed on the mercury drop. They thus interfere with the adsorption of ions from the solution and prevent the establishment of a very high potential gradient. The result is that a more nearly normal diffusion process accompanied by less vigorous stirring is attained. Similar results would be expected with materials which raise the viscosity of the solution sufficiently to make streaming difficult. In Fig. 4 will be seen the effect of gelatin (saturated solution) on the reduction of copper in acetic acid. On the left there is a partially completed copper

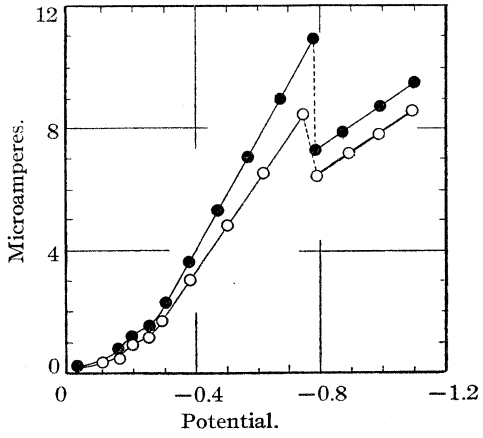


Fig. 4.—Current–potential curves in 0.25 molar sodium acetate solution in acetic acid containing gelatin: ○, 10^{-2} molar copper acetate; ●, 2×10^{-2} molar copper acetate.

(10) Antweiler, *Z. Electrochem.*, **44**, 719 (1938).

wave. This wave is almost normal, although the failure to level off at the top indicates that some streaming is occurring. Eventually the curve becomes discontinuous at the potential of the electrocapillary maximum.

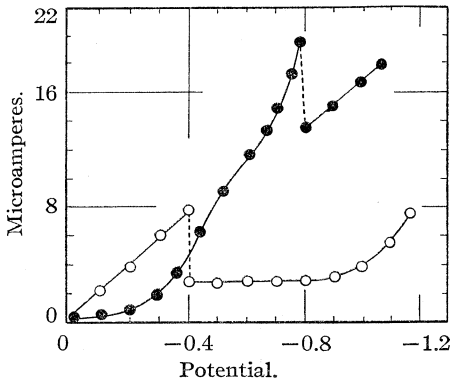


Fig. 5.—The effect of shifting the electrocapillary maximum on the current–potential curves in 0.25 molar ammonium acetate solutions in acetic acid: ○, 1.14×10^{-3} *M* benzil in presence of I^-; ●, 2×10^{-4} *M* Bi^{+++} in the presence of NO_3^-.

On the negative side of the electrocapillary maximum the mercury drop is surrounded by adsorbed cations. The concentration of the adsorbed particles will again be greater at the bottom than at the top of the drop. *In water solutions* this results in a potential gradient and a streaming of the electrolyte. As before, a rapid rise in the current takes place as the reduction of the next ion begins. This is interrupted only when the concentration of the supporting ions becomes so great around the mercury drop that the ions being reduced are screened out. From this point on, the process follows the pattern previously discussed (Process 1 for ions of Class I). *In acetic acid* no maxima are observed on the negative side of the electrocapillary maximum. This arises from the fact that the electrocapillary curve in acetic acid is practically flat over the whole voltage range here studied. It was mentioned before that the adsorption of neutral molecules depresses and flattens electrocapillary curves. In this case neutral acetic acid molecules are probably adsorbed on the negative side of the maximum in sufficient concentration to prevent an appreciable adsorption of ions from the solution. Hence the established potential gradient is small, the stirring is negligible and maxima do not occur. The failure of surface active substances, which are often effective in reducing maxima in water solution, to function satisfactorily in acetic acid may be explained in the same way. These substances only tend to cause a broadening of the electrocapillary maximum such as is commonly observed in acetic acid without the addition of other substances. They, therefore, add nothing and detract nothing from the processes already occurring.

The addition of an ion which shifts the position of the electrocapillary maximum to more negative potentials causes the current–voltage curves for certain cations and other substances belonging to Class I to revert to Class II. Thus iodide ion causes the normal curves for bismuth ion and for benzil to become discontinuous (Fig. 5). These substances have half-wave reduction potentials which lie just beyond the electrocapillary maximum on the negative side. In the case of bismuth ions even nitrate ions, which are less powerful than iodide ions in shifting the maximum, can cause a discontinuity to appear.

In aqueous solutions most maxima are rounded in appearance although discontinuous maxima are also observed, especially in solutions of low ionic concentration. Usually discontinuous maxima can be made continuous by the addition of strongly adsorbed substances or by increasing the ionic concentration. Rayman[11] obtained discontinuous maxima for oxygen in 0.001 *N* potassium chloride solution. These became rounded humps when various dyes were added. Similarly, Dillinger[12] added barium chloride to make the discontinuous maxima of dilute mercurous cyanide solutions continuous. The discontinuous maxima in acetic acid are probably a result of the high resistances brought about by the low ionic concentrations possible in a medium of such low dielectric constant. The addition of water permits greater ionization and lower resistance and results in the occurrence of normal rounded maxima. The greater the concentration of the supporting ion, the less water is needed to effect this transformation.

The removal of all traces of oxygen is a *sine qua non* for the obtaining of satisfactory current–voltage curves in acetic acid. Even with relatively concentrated solutions of zinc salts the zinc wave is so small that it is completely obscured by the oxygen normally dissolved in the solution. Since there is ordinarily no discontinuity in the oxygen curve it is evident that it is reduced at potentials more negative than the electrocapillary maximum

(11) B. Rayman, *Coll. Czech. Chem. Commun.*, **3**, 314 (1931).
(12) Dillinger, *ibid.*, **1**, 638 (1929).

and hence belongs to the substances of Class I. However, it is thrown into Class II by the addition of small amounts of iodide ion (Fig. 6). Its reduction potential in acetic acid is therefore not far from that of bismuth ions.

Conclusions

1. The relationship which exists between the electrocapillary maximum of the medium and the half-wave potential of a reducible substance determines to a considerable degree the nature of the current–voltage curves of the substance in acetic acid and probably also in other solvents.

2. Class I substances, which are reduced at potentials more negative than the electrocapillary maximum, exhibit normal electrocapillary curves. They also give normal S-shaped current–voltage curves (after thorough degassing) and can be determined polarographically in the usual fashion. Class II substances, which are reduced at potentials more positive than the electrocapillary maximum, exhibit distorted electrocapillary curves. They also give discontinuous maxima in their current–voltage curves and cannot be determined polarographically.

3. Maxima in acetic acid can be explained satisfactorily on the basis of a streaming of the electrolyte around the mercury drop of the type observed by Antweiler for aqueous solutions. The decline in current following the maximum is caused by a screening out of the reducible ions by the supporting ions, or by the neutralization of charge on the drop occurring at the electrocapillary maximum, whichever occurs first.

4. Ions (like iodide) which shift the position of the electrocapillary maximum to more negative potentials cause certain reducible substances (like oxygen, bismuth ion and benzil) to change from Class I to Class II. Such substances have half-wave reduction potentials close to and on the negative side of the electrocapillary maximum.

5. Things which act to decrease the amount of adsorption of ions on the drop or the amount of streaming around the drop decrease the heights of the maxima. The addition of high molecular weight substances (like gelatin) which increase the viscosity, and the addition of capillary active substances (like methyl red) which decrease the adsorption of small ions by being adsorbed themselves both tend to decrease maxima heights. None of these substances is as effective in acetic acid solutions as in water because acetic acid molecules are themselves adsorbed fairly strongly.

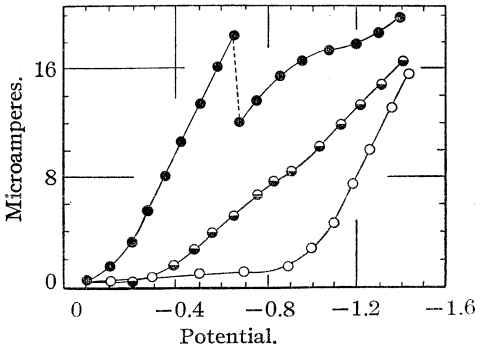


Fig. 6.—Current–potential curves for oxygen in acetic acid solutions: ◒, 0.25 molar ammonium acetate; ●, 0.25 molar ammonium acetate to which a small crystal of KI was added; O, the latter solution after degassing for one hour.

Apparatus and Materials

The electrocapillary curves were determined by the drop weight method.[13] An electrolysis cell constructed in such a way as to make it possible to catch the drops falling from the dropping mercury cathode was attached to a Fisher Elecdropode identical with the one employed in our previous work. The dropping electrode was also identical with the one previously described. The capillary used had a value for $m^{2/3}t^{1/6}$ of 1.1 mg.$^{2/3}$ sec.$^{-1/2}$. After thoroughly degassing the solution to be studied, 50 drops of mercury were collected at each of a number of successively increased potentials. The mercury was then washed, dried and weighed. Since the surface tension is directly proportional to the drop weight, it is only necessary to plot this latter quantity against the potential to obtain curves which are strictly analogous to true electrocapillary curves and which do not differ from them in any detail of form or shape. The potentials plotted were corrected for the *IR* drop of the solutions. This correction is large in the case of acetic acid solutions.

The acetic acid was the "99.5%" acid of the J. T. Baker Chemical Company and was employed without further purification. The salts were all C. P. grade and were carefully dried at 110° before use. The organic materials were Eastman Kodak Co. grade, and were recrystallized once before use. Degassing was accomplished as before with purified natural gas.

Summary

A study of the electrocapillary curves of mercury in acetic acid solutions of various salts reveals some important differences from similar curves in aqueous solutions. With the aid of such curves it has been possible to explain the current–potential curves of various cations and other reducible substances in acetic acid.

LAFAYETTE, INDIANA RECEIVED APRIL 9, 1942

(13) Heyrovsky and Dillinger, *Coll. Czech. Chem. Commun.*, **2**, 626 (1930).

[CONTRIBUTION FROM THE MALLINCKRODT CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Polarographic Investigation of Rhenium Compounds. II. Oxidation of −1 Rhenium at the Dropping Electrode and the Potential of the Re^{+2}–Re^{-1} Couple

BY JAMES J. LINGANE

The reduction of perrhenate ion at the dropping mercury electrode has been discussed in a previous paper from this Laboratory,[1] in which evidence was presented that the −1 oxidation state of rhenium is produced at this electrode under certain conditions. The existence of −1 rhenium was discovered quite recently by Lundell and Knowles,[2] who obtained it by the reduction of perrhenate ion by amalgamated zinc in *cold* dilute sulfuric acid solutions from which air had been carefully excluded. The experiments of Lundell and Knowles were later confirmed by Tomiček and Tomiček.[3] Since the existence of Re^{-1} is of interest from several points of view, and since very little is known about the potentials of the lower oxidation states of rhenium compounds, it seemed worth while to investigate the oxidation of solutions of −1 rhenium at the dropping electrode by the polarographic technique. This study has furnished some interesting information concerning the course of the oxidation of reduced rhenium solutions, and in particular it has supplied data which lead to a fairly accurate estimate of the potential of the Re^{+2}–Re^{-1} couple in dilute sulfuric and perchloric acid solutions.

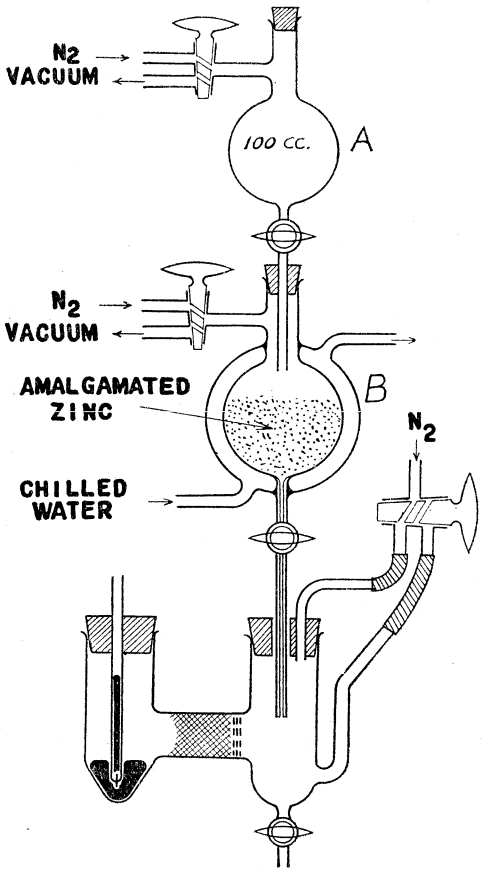


Fig. 1.—Zinc reductor and polarographic cell.

Experimental

Solutions of −1 rhenium were prepared by reducing perrhenate ion with amalgamated zinc in dilute sulfuric acid or perchloric acid. Lundell and Knowles[2] have shown that successful production of Re^{-1} requires the complete absence of oxygen and ice-cold solutions. In the present study it was necessary to work with moderately small volumes of quite dilute solutions since only a small quantity of potassium perrhenate was available, and it was also desired to perform the reductions in an initially dry reductor so that the concentrations of the solutions would remain unchanged. After numerous trials it was finally found that these conditions were fulfilled most satisfactorily by the reductor shown in Fig. 1.

Vacuum technique was employed to free the reductor and solutions from dissolved air, and the reductions were performed in an atmosphere of nitrogen that had been purified by passage over copper gauze at 500°. The reductor proper consisted of the double walled bulb B, the inner bulb of which (125 cc.) was about two-thirds filled with very pure 20-mesh amalgamated zinc. Previous to use the reductor was washed out with dilute sulfuric acid, water, and acetone, and was dried by evacuating to a pressure below 2 mm. for a few minutes. Pure nitrogen was then admitted. The potassium perrhenate solution to be reduced, contained in the 100-cc. reservoir bulb A, was freed from dissolved air by evacuating rapidly until boiling just began and then admitting nitrogen. This was repeated two or three times to ensure complete removal of air. Care was taken to minimize evaporation of water from the solution by evacuating very rapidly and maintaining vacuum for only a few seconds. The solution was then run into the reductor, which had previously been chilled to below 5° by passage of ice-water through the outer jacket. The volume of solution was such (50 cc.) that it covered the amalgamated zinc to a depth of less than a centimeter, and thus intimate contact was obtained between the two phases. Finally the reduced solution was run into the polarographic cell from the capillary delivery tube under an atmosphere of nitrogen, and with the cell

(1) J. J. Lingane, THIS JOURNAL, **64**, 1001 (1942).

(2) G. E. F. Lundell and H. B. Knowles, *J. Research Nat. Bur. Standards*, **18**, 629 (1937).

(3) O. Tomiček and F. Tomiček, *Coll. Czech. Chem. Commun.*, **11**, 626 (1939).

in an ice- and water-bath at 0°. The reductor was then withdrawn and the capillary of the dropping electrode inserted through the same hole in the stopper, which was oversize to act as an exit for the nitrogen. The polarogram of the reduced solution was taken without delay, and, unless otherwise specified, at 0°.

The H-type polarographic cell that was used was similar to that previously described.[4] A medium porosity sintered glass disk (2-cm. diameter) was sealed into the cross tube as close as possible to the right-hand compartment, and this was backed with a plug of 4% agar gel containing 0.2 *M* sodium sulfate. This arrangement provides a good low resistance electrolytic contact between the two halves of the cell and at the same time effectively prevents streaming of one solution into the other. A mercury–mercurous sulfate electrode in the left-hand compartment, with 1 *N* sulfuric acid as electrolyte, was used as the working reference electrode of the cell. The potential of this electrode was measured at frequent intervals against a saturated calomel electrode, and all potential data are referred to the latter electrode as a standard.

The dropping electrode was of the same type described by Lingane and Laitinen,[4] and the rate of flow of mercury (*m*) was determined by means of the volumetric instrument described elsewhere.[5] It was found, as the average of a number of experiments, that the ratio of the rate of mercury flow at 25° to that at 0° was 1.075 in 2 *N* sulfuric acid. This corresponds to an average temperature coefficient for *m* of +0.0030 deg.$^{-1}$ between 0° and 25°. In most experiments the value of *m* was determined at 25° and divided by 1.075 to obtain its value at 0°.

Polarograms were recorded according to the usual technique[6] with a Sargent–Heyrovsky polarograph.

Standard solutions of potassium perrhenate (0.002 to 0.003 *M*) were prepared directly by weight from a pure sample of the salt (obtained from A. D. Mackay Co., New York) which had been dried at 110°.

Results and Discussion

In order to establish the fact that quantitative formation of −1 rhenium was actually obtained under the reduction conditions that were employed, several of the reduced solutions were titrated with a standard ceric sulfate solution. In preliminary experiments samples of the reduced solutions from the reductor were delivered under the surface of an excess of ferric sulfate solution in dilute sulfuric or perchloric acid, and the solution was then titrated with a standard ceric sulfate solution using *o*-phenanthroline ferrous sulfate ("Ferroin") as indicator. This procedure yielded unsatisfactory results because the rate of reaction of ceric ion with the reduced solution was surprisingly slow, even when the solutions were warmed to 40–50° prior to titration. These observations confirm the results of Geilmann and Wrigge,[7] who found that the oxidation of solutions of +3 and +4 rhenium by permanganate, dichromate and ceric ions is quite slow under certain conditions, particularly when substances, such as chloride ion, which form stable complexes with +4 rhenium are present. The following procedure was finally adopted and it led to correct results. The reduced solutions were run directly from the reductor into an excess of standard ceric sulfate solution *under an atmosphere of nitrogen*, and, after standing for at least fifteen minutes under nitrogen, the excess ceric ion was titrated back with a standard ferrous ammonium sulfate solution from a microburet, using Ferroin as indicator. Removal of air from the collecting ceric sulfate solution was found to be essential, and, when it was not done, low and erratic results were obtained, indicating that the rate of reaction of dissolved oxygen with the reduced rhenium compounds is more rapid than that of ceric ion with these compounds.

In order to determine the volume of the reduced solution taken for analysis, the collecting flask (Erlenmeyer flask with drawn out neck) was calibrated for total volume, and at the end of a titration the volume of water required to fill to the mark was measured. This volume was added to the known volumes of ceric solution and ferrous solution used, and the sum was subtracted from the total volume of the flask. The volume of the sample of reduced solution was known with an accuracy of ± 0.1 cc. The results are summarized in Table I.

TABLE I

OXIDATION STATE OF REDUCED RHENIUM SOLUTIONS

Solutions of potassium perrhenate in 2.0 *N* sulfuric acid reduced for 10 min. under nitrogen at a temperature near 5°.

$KReO_4$ Millimolar	Vol. reduced soln., cc.	0.01 *N* $Ce(SO_4)_2$, cc.	Equiv. Ce^{IV} per mole total rhenium
0.105	37.6	3.26	8.3
.209	33.3	5.28	7.6
.418	36.4	12.1	8.0
.836	35.2	23.0	7.8
			Av. 7.9

These results, which confirm the conclusions of Lundell and Knowles[2] and those of Tomiček and Tomiček,[3] show that, within the limits of the experimental error, 8 equivalents of ceric ion were required to oxidize the reduced solutions up to

(4) J. J. Lingane and H. A. Laitinen, *Ind. Eng. Chem., Anal. Ed.*, **11**, 504 (1939).

(5) J. J. Lingane, *ibid.*, **14**, 655 (1942).

(6) I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1941.

(7) W. Geilmann and F. W. Wrigge, *Z. anorg. allgem. Chem.*, **222**, 56 (1935).

perrhenate ion. Hence there is no doubt that the solutions reduced under the present conditions contain all of the rhenium in the −1 oxidation state. No definite statement can yet be made concerning the actual ionic or molecular state of the −1 rhenium in these solutions, but since the chemistry of rhenium is similar in a number of respects to that of the halogens, it seems reasonable to assume that hydrorhenic acid is a strong acid and that the −1 rhenium is present as rhenide ion, Re^-.

A typical polarogram of a reduced rhenium solution in dilute sulfuric acid at 0° is shown by curve 1 in Fig. 2. In accordance with the usual conventions a negative sign is used to indicate anodic current (electroöxidation), and the sign prefixed to the potential of the dropping electrode, $E_{d.e.}$, signifies the polarity of this electrode with respect to the saturated calomel electrode.

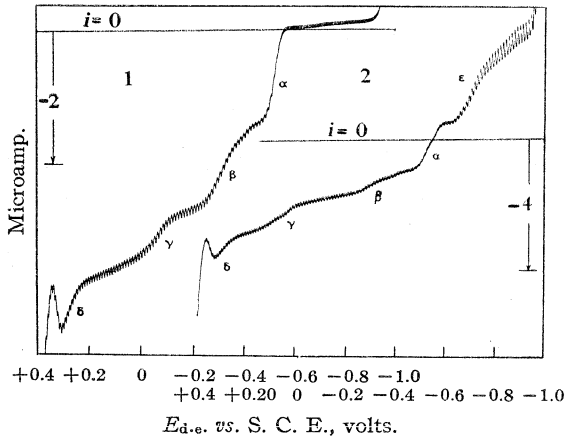


Fig. 2.—Curve 1: Polarogram of a 2.09 × 10^{-4} *M* solution of −1 rhenium in 2.0 *N* sulfuric acid at 0°. Curve 2: Polarogram obtained (at 0°) after partial oxidation by warming to 50° for sixty-five minutes in absence of oxygen.

It is seen that the polarogram (curve 1) consists of three distinct anodic waves, with half-wave potentials of −0.54, −0.3 and −0.05 v. *vs.* the S. C. E., which for the sake of convenient discussion will be referred to as α-, β-, and γ-waves, respectively. These waves correspond to oxidation of rhenide ion to successively higher oxidation states. The abrupt increase in cathodic current at about −0.9 v. results from the discharge of hydrogen ion, and the final increase in anodic current beginning at about +0.35 v. is caused by the oxidation of the mercury of the dropping electrode to mercurous ion. A fourth increase in anodic current, which at first glance appears to be the beginning of a fourth stage in the oxidation of the −1 rhenium, is also observable at +0.25 v. (δ in Fig. 2), and this is followed by an abrupt decrease in current just prior to the final anodic dissolution current of the mercury. Actually, data discussed below disprove the hypothesis that this δ-wave is the beginning of a fourth stage in the oxidation. Since mercurous perrhenate is only slightly soluble, we also considered the possibility that the δ-wave might be caused by the depolarization of the dropping electrode by perrhenate ion (formed in the preceding stage of the oxidation) according to the equation $2Hg + 2ReO_4^- = Hg_2(ReO_4)_2(s) + 2e$. However, this possibility was excluded by polarograms of solutions of potassium perrhenate itself in 1.8 *N* sulfuric acid which showed no indication of such a wave.

The abrupt decrease in current immediately preceding the anodic dissolution current of the mercury has been observed on the anodic waves of other substances, notably hydroquinone,[6,8] and it appears to be a rather general phenomenon in which the inception of the oxidation of the mercury itself inhibits the oxidation of other substances at the dropping electrode.

The significance of curve 2 in Fig. 2 is discussed in a following section.

A polarogram of a reduced rhenium solution in dilute perchloric acid is shown in Fig. 3. It possesses the same general features as the polaro-

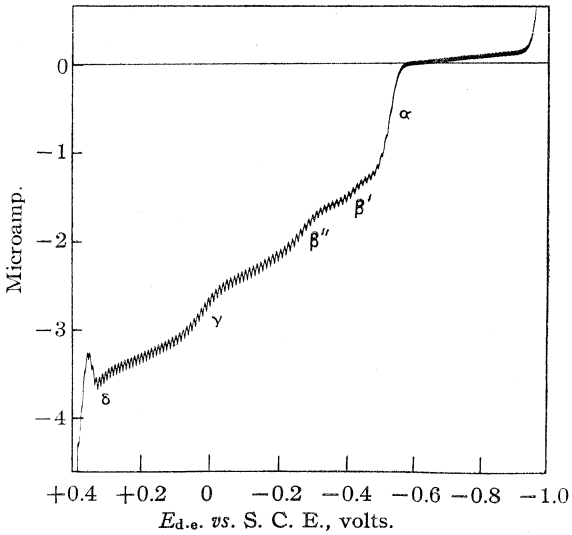


Fig. 3.—Polarogram of a 2.09 × 10^{-4} *M* solution of −1 rhenium in 1.2 *N* perchloric acid at 0°.

(8) O. H. Müller and J. P. Baumberger, *Trans. Am. Electrochem. Soc.*, **71**, 169, 181 (1937).

TABLE II

DIFFUSION CURRENT DATA FOR REDUCED RHENIUM SOLUTIONS

Polarograms were recorded at 0°, and the diffusion currents have been corrected for the residual current and for the change of drop time—and hence current—with the potential of the dropping electrode. The α-, β-, and γ- diffusion currents were measured at *ca.* −0.45, −0.15, and +0.2 v., respectively, *vs.* the S. C. E. $m^{2/3}t^{1/6} = 2.26$ mg.$^{2/3}$ sec.$^{-1/2}$ at 0° at −0.6 v. The values of i_d/C refer to the *total*, rather than separate, diffusion currents.

Re^{-1}, millimolar	i_d/C, microamp./mole/l. γ	β''	β'	α	Ratio γ	β''	β'	α
	(a) In 1.0 N H_2SO_4; reduced for 30–60 min.							
0.151	14.4	11.5		6.0	1.25	1		0.52
.302	15.4	12.7		6.7	1.21	1		.53
.604	13.6	10.8		5.6	1.26	1		.52
	Av. 14.5	11.7		6.1	1.24	1		0.52
	(b) In 2.0 N H_2SO_4; reduced for 10 min.							
0.105	16.2	12.8		6.7	1.27	1		0.52
.209	17.0	13.3		6.9	1.28	1		.52
.836	14.9	11.6		5.5	1.29	1		.47
	Av. 16.0	12.6		6.4	1.28	1		0.50
	(c) In 1.2 N $HClO_4$; reduced for 5–10 min.							
0.209	15.3	11.4	7.7	5.9	1.34	1	0.68	0.52
.418	15.3	11.7	7.8	6.0	1.31	1	.67	.51

gram in dilute sulfuric acid, with the marked exception that instead of a single β-wave the two separate waves indicated in Fig. 3 by β' and β'' are obtained. The sum of these two waves is equal to that of the single β-wave in dilute sulfuric acid. The separate β'-wave is one-half the height of the separate β''-wave, or one-third the height of the α-wave (see Table II), and hence the electron change in the reaction responsible for the β'-wave must be one-third that for the α-wave. This point is important in the interpretation of the oxidation states to which the waves pertain (*vide infra*). There is some indication on the original polarograms that the β-wave in sulfuric acid medium is also composite in nature, but the two parts of the wave are not clearly separated as they are in perchloric acid medium.

A summary of diffusion current data for various concentrations of the reduced rhenium solutions in dilute sulfuric and perchloric acids at 0° is given in Table II.

The diffusion currents have been corrected for the residual current of the acid solution alone in each case. Since the diffusion current depends directly on the sixth root of the drop time,[6,9] and since the latter changes considerably over the potential range involved in the present measurements, a correction for this effect was also made. The requisite data for this correction were obtained by measuring the electrocapillary curve of mercury (drop time *vs.* $E_{d.e.}$) in 1.8 N sulfuric acid at 0°. Values of $(t/t_{max.})^{1/6}$ obtained in this way at +0.2, −0.15 and −0.45 v. were 0.966, 0.992 and 1.00, respectively, and the maximum in the electrocapillary curve was at −0.58 v. The measured diffusion currents were referred to the value of the drop time at the electrocapillary maximum, $t_{max.}$, by dividing by the appropriate value of $(t/t_{max.})^{1/6}$.

From the data in Table II it is evident that the diffusion currents of all the anodic waves are directly proportional to the concentration of −1 rhenium, and hence are diffusion controlled. Since the values of i_d/C are essentially the same in dilute sulfuric and perchloric acids, it is clear that corresponding waves pertain to the same oxidation states in the two media. Although the precision of the data in Table II leaves something to be desired, there is no systematic trend in the values of i_d/C with concentration. It is believed that the variations observable in the values of i_d/C were caused by unequal amounts of evaporation of water from the solutions during the evacuation prior to reduction, in spite of the precautions that were taken to minimize this effect. Similar variations, probably due to the same cause, are noticeable in the data in Table I.

For the present purpose the *ratio* of the diffusion currents of the various waves is of more importance than their absolute values, and it is seen that the values of the ratios in the last columns of Table II are satisfactorily concordant. The rela-

(9) I. M. Kolthoff and E. F. Orlemann, THIS JOURNAL, **63**, 2085 (1941).

tive heights of the anodic waves (*i. e.*, the ratios in Table II) are determined by the oxidation states to which the -1 rhenium is oxidized as each limiting current is attained. When a polarographic limiting current is diffusion controlled the ratio i_d/C is expressible by the Ilkovic equation[6,10]

$$i_d/C = knD^{1/2}m^{2/3}t^{1/6} \quad (1)$$

In this equation, i_d/C is the diffusion current constant (microamperes per millimole per liter), n is the number of electron equivalents per molar unit of the electrode reaction, D is the diffusion coefficient (cm.^{2} sec.$^{-1}$) of the substance that is being reduced or oxidized, m is the rate of mercury flow from the dropping electrode (mg. sec.$^{-1}$), t is the drop time (sec.), and k is a constant whose numerical value is 605 at 25° and 603 at 0°. Unfortunately this equation cannot be applied directly in the present case to determine the n-values of each of the anodic waves, because nothing is known about the diffusion coefficient of rhenide ion under the conditions of the present experiments. However, since the rhenium in these reduced solutions is present entirely in the -1 state, it will be evident that each of the diffusion currents results from the oxidation of the -1 rhenium from the same concentration to successively higher oxidation states, and therefore each is controlled by the rate of diffusion of the rhenide ion. Consequently the ratio of the *total* diffusion currents is the same as the ratio of the n-values of the various waves, and this ratio must be expressible as a ratio of simple integers. Furthermore, the maximum possible value of n is 8, for complete oxidation of rhenide ion to perrhenate ion.

It is immediately evident from the data in Table II, and the polarograms in Figs. 2 and 3, that the n-value for the α-wave is equal to that for the individual β-wave in dilute sulfuric acid, or equal to the combined n-values of the β'- and β''-waves in dilute perchloric acid. Furthermore, since the individual γ-wave is smaller than the individual α- or β-waves, the latter must each correspond to at least a 2-electron oxidation, but the sum of the α- and β-waves cannot correspond to more than a 6-electron change without exceeding the maximum possible n-value of 8 for the total combined diffusion currents. Hence the only patterns of n-values that need be considered are 8/6/3 and 5/4/2. The 8/6/3 pattern requires a ratio of 1.33/1/0.5, and the 5/4/2 pattern a ratio of 1.25/1/0.5, for the cumulative heights of the γ-, β- (or $\beta' + \beta''$), and α-waves. The average observed value of the ratio in dilute sulfuric acid is 1.26/1/0.51, whereas in dilute perchloric acid, with the β-wave resolved into its component β' and β'' parts, the observed ratio is 1.33/1/0.68/0.52. From Figs. 2 and 3 it is seen that the γ-diffusion current increases appreciably with increasing positive potential, even when proper allowance is made for the residual current and the effect of changing drop time with changing potential. Consequently, values for the ratio of the γ- to the β-diffusion current ranging from 1.25 to 1.33 can be obtained depending on the potential at which the γ-diffusion current is measured. The key to the correct pattern of n-values is found in the resolution of the β-wave into its component β' and β'' parts in dilute perchloric acid, and the fact that the individual β'-wave is only half the height of the individual β''-wave, or one-third the height of the α-wave. It seems reasonable to conclude that the correct pattern of n-values is 8/6/4/3. Hence the α-wave corresponds to oxidation of the -1 rhenium to the $+2$ state, the β'-wave to the $+3$ state, the β''-wave to the $+5$ state, and the γ-wave to complete oxidation to the $+7$ state (ReO_4^-).

In order to test the foregoing conclusion an amperometric titration[11] of a reduced rhenium solution with a standard solution of ammonium hexanitratocerate was carried out, with the result shown in Fig. 4. In this experiment a completely reduced rhenium solution was titrated with an air-free 0.01 N $(NH_4)_2Ce(NO_3)_6$ solution at 0°, and individual polarograms were recorded five to ten minutes after each addition of the ceric solution. Curve 1 in Fig. 4 is a polarogram of 35.0 cc. of the original reduced solution, and the other curves were recorded after successive additions of 3.00-cc. increments of the 0.01 N ceric solution, corresponding to the addition of 0, 2.0, 4.1, 6.2, 8.2, and 10.3 equivalents of oxidant for curves 1 to 6, respectively. It is seen that the anodic current, measured at a potential of $+0.2$ v. corresponding to the γ-diffusion current, decreased to zero after the addition of somewhat less than 8.2 equivalents of oxidant. The cathodic diffusion current obtained with larger amounts of the oxidant (curve 6) results from the

(10) D. Ilkovic, *Coll. Czech. Chem. Commun.*, **6**, 498 (1934); *J. chim. phys.*, **35**, 129 (1938).

(11) See Ref. 6 for a discussion of the principles of amperometric titrations.

reduction of the excess ceric ion to the cerous state. This experiment constitutes conclusive proof that the correct pattern of n-values is 8/6/4/3, and that the -1 rhenium is completely oxidized to perrhenate ion at potentials at which the γ-diffusion current is attained.

It should be pointed out that the slow reaction of ceric ion with the reduced rhenium compounds should not seriously influence the validity of the conclusions that are drawn from this type of amperometric titration. Consider, for example, an extreme case in which the reaction between the oxidant and reductant is so very slow that it actually only proceeds to a slight extent during the time of a titration. At any point in the titration relatively large amounts of unreacted oxidant and reductant will then be present, and the net current will be the resultant of a cathodic current of the oxidant and an anodic current of the reductant, provided, as in the present case, that the measurements are made at a potential where both diffusion currents are separately attained with pure solutions of the oxidant and reductant. If the diffusion coefficients of the oxidant and reductant are equal, the *net* current will decrease to zero (corrected for the residual current) after an equivalent amount of oxidant has been added, just as if the reaction had been rapid and complete. This unique characteristic of amperometric oxidation–reduction titrations should permit their application to a number of reactions which cannot be followed by other methods that require the establishment of equilibrium conditions throughout the titration.

TABLE III

HALF-WAVE POTENTIALS OF REDUCED RHENIUM SOLUTIONS

The half-wave potentials were measured at 0°, and are referred to the saturated calomel electrode at room temperature.

Re^{-1} Millimolar	γ	$E_{1/2}$, *vs.* the S. C. E., v. β''	β'	α
		(a) In 1.0 N H_2SO_4		
0.151	−0.10	−0.34		−0.547
.302	.10	.34		.546
.604	.09	.33		.545
		(b) In 2.0 N H_2SO_4		
0.105	−0.07	−0.33		−0.524
.209	.06	.34		.540
.836	.04	.34		.536
		(c) In 1.2 N $HClO_4$		
0.209	+0.03	−0.26	−0.42	−0.542
.418	.03	.26	.42	.527
				Av. −0.538 ± 7

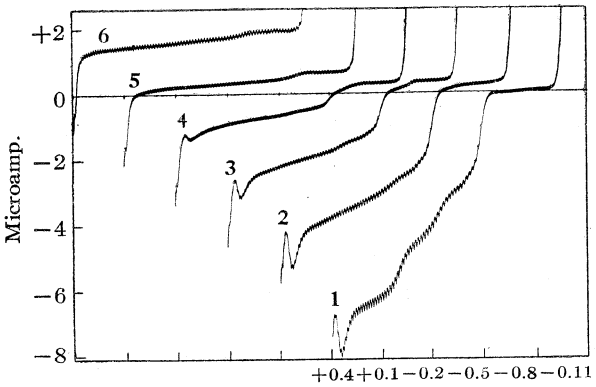


Fig. 4.—Amperometric titration of -1 rhenium with ceric ion: 35.0 cc. of a 4.18 × 10^{-4} M solution of Re^{-1} in 1.2 N perchloric acid at 0° plus: (1) none, (2) 3.0 cc. (2.0 equiv.), (3) 6.0 cc. (4.1 equiv.), (4) 9.0 cc. (6.2 equiv.), (5) 12.0 cc. (8.2 equiv.), and (6) 15.0 cc. (10.3 equiv.) of 0.01 N $(NH_4)_2Ce(NO_3)_6$.

Data concerning the half-wave potentials of the reduced rhenium solutions are presented in Table III. The values pertaining to the sulfuric acid solutions in the β''-column refer to the single β-wave in these media, and it will be noted that these values are about midway between the half-wave potentials of the separate β'- and β''-waves in the 1.2 N perchloric acid solution. It will also be noted that the half-wave potential of the γ-wave is about 0.1 v. more positive in perchloric acid medium than in sulfuric acid solutions. It is evident that the half-wave potentials of all the waves are constant in a given medium and independent of the concentration of rhenium.

From the slopes of the β- and γ-waves it seems clear that the corresponding reactions do not proceed with thermodynamic reversibility at the dropping electrode. However, the slope of the α-wave indicates that the oxidation of Re^{-1} to Re^{+2} does approach reversibility. If this is actually the case, then the equation of the anodic α-wave should be[6]

$$E_{d.e.} = E_{1/2} - \frac{RT}{3F_y} \ln \frac{i_d - i}{i} \qquad (2)$$

where i is the anodic current at any point on the wave and i_d is the anodic diffusion current. The half-wave potential should be given by

$$E_{1/2} = E^0_{+2,-1} - \frac{RT}{3F_y} \ln \left(\frac{D_2}{D_1}\right)^{1/2} \qquad (3)$$

where $E^0_{+2,-1}$ is the reversible standard potential for the reaction written in the direction $Re^{+2} + 3e = Re^{-1}$, and D_2 and D_1 are, respectively, the diffusion coefficients of the Re^{+2} and Re^{-1}. Ac-

tually the second term in Eq. 3 is of very minor importance, and hence $E_{1/2}$ should be practically equal to $E^0_{+2,-1}$. From Eq. 2 the following relation should apply to the difference between the potentials at the one-fourth and three-fourths points on the α-wave at 0°, provided that the reaction proceeds reversibly

$$E_{3/4} - E_{1/4} = \frac{0.0546}{3} \log 9 = 0.017 \text{ v.} \qquad (4)$$

From measurements of several polarograms in both dilute sulfuric and perchloric acids, the averaged observed difference between $E_{3/4}$ and $E_{1/4}$ was found to be 0.030 ± 3 v. It appears, therefore, that the oxidation of Re^{-1} to Re^{+2} does not occur with perfect thermodynamic reversibility. On the other hand, the observed slope of the α-wave is sufficiently close to the theoretical value to indicate that the degree of irreversibility cannot be very great. This is also evident from the character of the composite cathodic–anodic α-wave in partially oxidized solutions (curve 2 in Fig. 2), which displays a smooth transition from anodic to cathodic current without any pronounced inflection at the zero current point. Hence it seems safe to conclude that the reversible potential of the $Re^{+2} - Re^{-1}$ couple must be very nearly equal to the half-wave potential of the α-wave, namely, −0.54 v. *vs.* the S. C. E., or slightly more negative. Rhenide ion is thus a considerably stronger reducing agent than titanous ion, and is about equal to chromous ion in this respect.

In this connection it should be mentioned that Lundell and Knowles[2] performed a potentiometric titration of a solution of −1 rhenium in 1.8 *N* sulfuric acid with a standard permanganate solution, using a *platinum* indicator electrode. The titration curve they obtained showed only two points of inflection, the first after the addition of 2 equivalents of oxidant and the second after the addition of 8 equivalents. However, it is the author's experience from several such titrations with different oxidants that constant potential is established quite slowly, if at all, and since Lundell and Knowles apparently titrated rapidly the significance of the potential break after the addition of two equivalents of oxidant is doubtful and may well be fortuitous. It should be noted that a platinum indicator electrode cannot be expected to indicate the correct potential in a strongly acid solution of −1 rhenium, because the potential of the Re^{+2}–Re^{-1} couple is considerably more negative than the discharge potential of hydrogen ion on a platinum surface. Consequently, Re^{-1} will reduce hydrogen ion at the surface of a platinum electrode, the measured potential will lie between the hydrogen potential and that of the Re^{+2}–Re^{-1} couple, and its actual value will depend on the rate of oxidation of Re^{-1} by hydrogen ion. This effect is evident from the titration curve given by Lundell and Knowles, in which the potential of the platinum indicator electrode was about −0.4 v. *vs.* the saturated calomel electrode at a point midway to the first break, or more than 0.1 v. more positive than the potential observed in the present study. The above conclusion is also borne out by the fact that quantitative deposition of metallic rhenium, with no indication of the formation of Re^{-1}, is obtained when strongly acid solutions of potassium perrhenate are reduced electrolytically at a platinum cathode under such conditions that hydrogen is simultaneously evolved.[2,12,13]

Lundell and Knowles[2] discovered that solutions of −1 rhenium in 1.8 *N* sulfuric acid were slowly oxidized, and acquired a straw-yellow color, when they were warmed to about 50° for thirty to sixty minutes in the absence of oxygen. They found that the partially oxidized solutions required 6 equivalents of permanganate for oxidation to perrhenate ion, and they concluded that the rhenium had been oxidized to the +1 state. These investigators passed pure carbon dioxide through the solutions during the warming process and discovered that the effluent gas contained a volatile sulfur compound which very likely was sulfur dioxide. Tomiček and Tomiček[3] have reported the evolution of hydrogen sulfide, as well as sulfur dioxide, from reduced rhenium solutions in sulfuric acid medium. It thus appears that sulfuric acid, or bisulfate ion, rather than hydrogen ion, is the oxidant responsible for the oxidation of the −1 rhenium under these conditions.

The experiments of Lundell and Knowles led to very concordant results and they leave no doubt that the *average* oxidation state of the rhenium in the warmed solutions was +1. However, a titration technique such as they employed does not prove that all of the rhenium in the partially oxidized solutions is present in a single oxidation state, and their results can be interpreted equally well by assuming that the partially oxidized solu-

(12) C. G. Fink and P. Deren, *Trans. Am. Electrochem. Soc.*, **66**, 471 (1934).

(13) O. Tomiček and F. Tomiček, *ibid.*, **76**, 105 (1939).

tions contained a mixture of two or more oxidation states in proportions that would be equivalent to an average oxidation state of +1. The polarograms obtained in the present study show no indication of a wave corresponding to the +1 state, which would lead one to expect that the +1 rhenium is unstable in respect to disproportionation into higher and lower states. In order to obtain further information on this point the experiment represented by curve 2 in Fig. 2 was performed. After the polarogram of the original reduced solution was recorded (curve 1 in Fig. 2), the solution was heated to 50° under an atmosphere of nitrogen for sixty-five minutes (the conditions employed by Lundell and Knowles) and it was then cooled back to 0° and curve 2 was recorded. The solution acquired the straw-yellow color reported by Lundell and Knowles. One marked effect of the warming process was the production of a new cathodic wave, designated by ϵ in Fig. 2. This wave increased to an abnormally great extent when the polarogram was recorded at 25° instead of 0°, which is fairly good evidence that it is catalytic in nature and similar to the catalytic waves described in a previous paper.[1] It will be noted that the γ-wave in curve 2 has become quite extended, and inspection of the original polarogram shows that it is composite and consists of two parts. The diffusion currents (corrected for the residual current) of the partially oxidized solution are compared with those of the original solution in Table IV.

TABLE IV

COMPARISON OF ORIGINAL DIFFUSION CURRENTS WITH THOSE OF SOLUTION PARTIALLY OXIDIZED BY WARMING

	i_d, microamp.		
	γ	β	α
Curve 1, Fig. 2.	3.55	2.73	1.42
Curve 2, Fig. 2	2.63	1.70	0.93[a]
Decrease, microamp.	0.92	1.03	0.49

[a] Anodic part of the α-wave. The cathodic part is equal to 0.50 microamp.

It is seen that the α-wave became approximately one-third cathodic and two-thirds anodic after warming, which indicates that two-thirds of the rhenium was still present as the Re^{-1} and the remainder in a higher oxidation state or states. The sum of the heights of the cathodic and anodic portions of the α-wave (0.50 + 0.93 = 1.43 microamp.) is the same as the height of the original anodic α-wave.

The *cumulative* γ-diffusion current at +0.2 v. decreased by 0.92 microamp., which is 0.92/3.55 = 0.26, or one-fourth of its original value within the limit of accuracy of the measurements. Assuming for the sake of simplicity that the average diffusion coefficient of the rhenium compounds in the mixed oxidation states in the partially oxidized solution is the same as that of Re^{-1}, we conclude that the one-fourth decrease in the original 8-electron γ-diffusion current corresponds to a 2-electron oxidation. Hence the *average* oxidation state of the rhenium in the partially oxidized solution was +1; a value in agreement with the results that Lundell and Knowles obtained by direct oxidimetric titration.

From the data in Table IV it is seen that the *individual* height of the γ-wave of the partially oxidized solution (2.63 − 1.70 = 0.93 microamp.) is the same, within the limits of the experimental error, with that of the original solution (3.55 − 2.73 = 0.82 microamp.). On the other hand, the individual height of the β-wave decreased by about one-third from 1.31 microamp. (2.73 − 1.42) to 0.77 microamp. (1.70 − 0.93), and this decrease of 0.54 microamp. is equal to the cathodic portion of the α-wave. Since the height of the γ-wave, which corresponds to the oxidation of Re^{+5} to ReO_4^-, remained constant, it appears that none of the rhenium was present in an oxidation state higher than +5. The fact that the individual height of the β-wave, which results from the oxidation of Re^{+2} to Re^{+5}, decreased to about two-thirds of its original value indicates that part of the rhenium was present in an oxidation state greater than +2, because if only Re^{-1} and Re^{+2} had been present the height of the β-wave should not have differed markedly from its original value. It seems reasonable to conclude from these data that the partially oxidized solution still contained about two-thirds Re^{-1}, with the remainder of the rhenium present as Re^{+3}, Re^{+4} or Re^{+5}, or a mixture of these three. A more specific statement of the composition of such solutions must await the acquisition of more extensive data, which we expect from experiments now in progress in this Laboratory.

The existence of −1 rhenium raises an interesting question in regard to its electronic configuration. In the rhenium atom itself the first four quantum levels are completely filled, and the configuration of the outer fifth and sixth levels is $5s^2 5p^6 5d^5 6s^2$. Hence the addition of an electron to produce −1 rhenium could lead to either of the

configurations, (A) $5s^25p^65d^66s^2$, or (B) $5s^25p^66s^26p^6$. It is a significant and generally accepted fact that the negative oxidation states of all other elements involve the formation of stable s^2p^6 octets, and on this basis one is inclined to assign configuration B to Re^{-1}. This configuration, which requires the promotion of all of the original $5d$ electrons to the $6p$ orbital, would be in accord with the marked instability and strong reducing character of Re^{-1}.

Summary

A zinc reductor is described in which reduction can be performed conveniently at a controlled temperature and in the absence of oxygen. The fact that −1 rhenium is produced when ice-cold and air-free solutions of perrhenate ion in dilute sulfuric and perchloric acids are reduced with zinc has been confirmed by oxidimetric titration of the reduced solutions.

Polarograms of solutions of −1 rhenium in 1 to 2 *N* sulfuric acid at 0° display three anodic waves, whose half-wave potentials are (α) −0.54 v., (β) −0.34 v., and (γ) −0.07 v. *vs.* the saturated calomel electrode. A similar polarogram is obtained in 1 *N* perchloric acid with the following exceptions: (a) the β-wave is resolved into two separate waves, β' and β'', whose half-wave potentials are −0.42 and −0.26 v., and (b) the half-wave potential of the γ-wave is about 0.1 v. more positive than in sulfuric acid medium. Diffusion current data show that corresponding waves in the two media pertain to the same oxidation states and in both media the diffusion currents are directly proportional to the concentration of −1 rhenium. From the ratio of the heights of the various waves it is concluded that the α-wave results from the oxidation of −1 rhenium to the +2 state, the β'-wave to the +3 state, the β''-wave to the +5 state and the γ-wave to complete oxidation to the +7 state (ReO_4^-). This conclusion has been confirmed by amperometric titration of the reduced solutions with ceric ion. Evidence is presented which indicates that the reversible potential of the reaction $Re^{+2} + 3\,e = Re^{-1}$ is equal to, or slightly more negative than, −0.54 v. *vs.* the saturated calomel electrode in dilute sulfuric or perchloric acid medium at 0°.

Partially oxidized solutions, obtained by warming dilute sulfuric acid solutions of −1 rhenium to about 50° for an hour in the absence of oxygen, show an *average* oxidation state of +1. However, the polarogram of such a solution indicates that the rhenium is not actually present in the +1 state, but as a mixture of Re^{-1} and higher states in proportions that are equivalent to an average oxidation state of +1.

CAMBRIDGE, MASSACHUSETTS RECEIVED JUNE 15, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI]

The Accommodation Coefficient of Mercury on Platinum and the Heat of Vaporization of Mercury

BY LLOYD B. THOMAS AND FRANCOIS G. OLMER

Introduction

We have been interested in applying the Pirani type pressure gage as a means of determining small total pressures of pure gases and as a means of following quantitatively the progress of gas reactions at low pressure. Such an application to mixtures in which some gaseous compounds are consumed and others produced requires an accurate knowledge of the free molecule heat conductivity of each gas from the surface of the specified filament material. This actual heat conductivity is conveniently expressed in terms of the calculated free molecule heat conductivity and the accommodation coefficient. Since there is available only an admittedly rough estimate of the accommodation coefficient of mercury[1] on platinum and since, in this case, pressures are established in equilibrium with liquid mercury and the measurements apparently lead to a precise method of determining the heat of vaporization which should be generally applicable, we are submitting this work under separate title.

Experimental

A diagram of the tube used is shown in Fig. 1. The filament consists of 31.5 cm. of 0.004 inch C. P. platinum wire (Bishop Company) hung in a loop from tungsten leads in a Pyrex tube 3.0 cm. in diameter. At a distance of 4.5 cm. from the ends of the filament, potential leads of 0.001 inch C. P. platinum wire of 3.0 cm. length are welded on the

(1) W. B. Mann, *Proc. Roy. Soc.* (London), **A146**, 786 (1934).

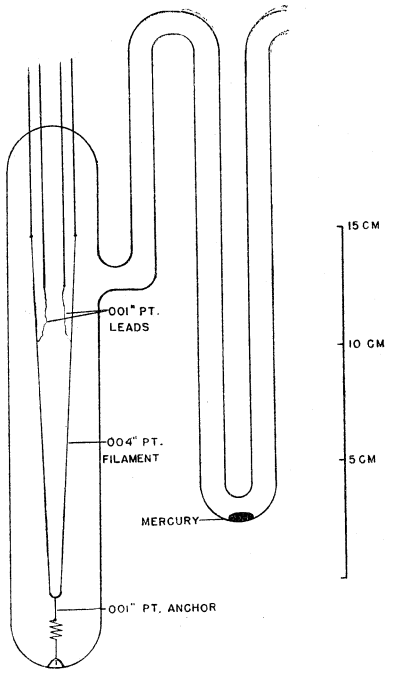


Fig. 1.—Tube I.

main filament and these are led out through two more tungsten seals. At the bottom of the loop a third 0.001 inch platinum wire was attached and this was anchored to the bottom of the tube. This latter was found necessary to eliminate vibration and to prevent the filament being pulled to the glass by electrostatic forces.

A diagram of the electrical circuits is shown in Fig. 2. The temperature coefficient of resistance of the filament was determined with the tube immersed in an oil-bath at temperatures from 0 to 150°. The resistance of the filament at any temperature is given by $R_t = R_0(1 + 0.0039055t)$ where R_0 is the resistance at 0°, t is the centigrade temperature of the filament, and 0.0039055 is the temperature coefficient. To operate the apparatus, the resistance between the potential leads at the desired filament temperature was calculated by the preceding equation and this value was set to the nearest 0.1 ohm on R_2. Current in the filament was then adjusted by means of R_3 (two dial boxes in parallel) until the fall in potential over the filament and R_2 became equal. The current in the circuit and the temperature of the filament were then established accurately by measuring the potential drop across R_1, a N. B. S. type 10 ohm standard resistor with potential contacts. Upon addition of gas the temperature of the filament was again adjusted to the original value by decreasing R_3 and the measurements for determining the new power loss were taken for the new condition.

The experimental tube was connected through a "U" tube and mercury cut-off to a high vacuum system employing the usual condensation pump, mercury cut-offs, McLeod gage, etc. No stopcocks were in the high vacuum line. The mercury vapor pressure was controlled by adjusting the temperature of a droplet of mercury in the "U" tube by means of a Dewar partially filled with water. When necessary this temperature was held constant and the bath stirred by passing air cooled in ice-water into the Dewar at the proper rate to counter the heat leak. The tube itself was immersed in a thermostat containing kerosene held at 30°, about 5° above room temperature.

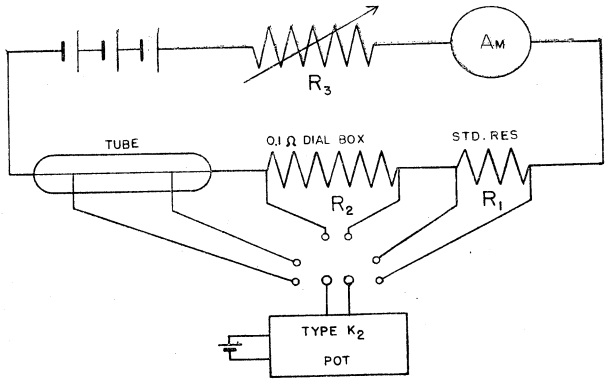


Fig. 2.—Electrical circuit of tube I.

Measurements and Treatment of Data.—The power loss from the filament is measured for a series of mercury vapor pressures from 0 to 15×10^{-4} mm. The filament current is increased with each increase of mercury vapor pressure to bring the temperature of the filament to its original value in order to keep the radiation losses constant. The power losses are plotted against the vapor pressures of mercury at the various control bath temperatures according to the values given in the "International Critical Tables," Vol. III. These vapor pressures are corrected for the thermal transpiration pressure according to the formula $P_t = P_u \sqrt{T_t/T_u}$, in which P_t and P_u are the pressures of mercury in the experimental tube and in the "U" tube, respectively, and T_t and T_u are the corresponding absolute temperatures. To check the applicability of the above formula measurements were made using a 2-mm. capillary as the left arm of the "U" tube of Fig. 1, but no difference could be observed between these measurements and the ones using the uniform 9-mm. "U" tube shown in Fig. 1. The capillary was removed for the data reported here to facilitate thorough evacuation. The mean free path of the mercury atoms at the highest pressures used is at least three times the diameter of the tubes in which the temperature gradients occur, thus giving conditions under which the above transpiration formula holds.

A typical plot of power loss from the filament against corrected mercury vapor pressure (for a filament temperature of 224° in this case) is shown in Fig. 3. The points are seen to fall on a well defined straight line. To obtain such a line

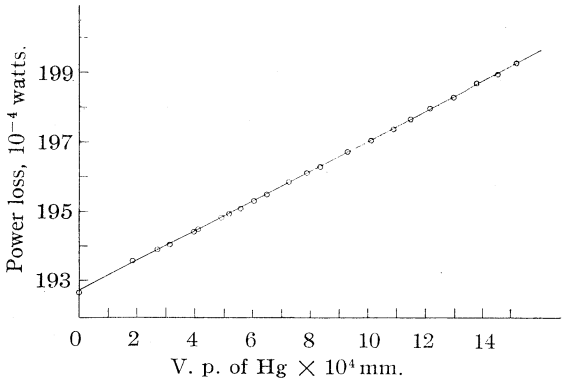


Fig. 3.

it was necessary to make measurements with the mercury cut-off which separates the system of Fig. 1 from the vacuum system closed. Runs made with the system open to the pumps showed a consistent behavior which we have been unable to explain. The observed behavior in such a case may be described with reference to Fig. 3. If the straight line is the best line which can be put through the points, the points lie regularly on an arc below the line from 0 to 6×10^{-4} mm., cross over at 6×10^{-4} and form an arc above the line from 6×10^{-4} to about 10×10^{-4}, and then cross back below the line and appear to lie on a third arc. The deviation of the arcs at the midpoints from the line is of the order of two to three times the radius of the circles of Fig. 3. Each of the four curves taken in this manner has the same form.

The slope of the curves as shown in Fig. 3 is the actual energy lost from the filament surface per second by gas conduction per unit of mercury vapor pressure. This, of course, may be reduced to the power lost per square centimeter of filament surface, per degree temperature difference between the wall and filament per bar of mercury pressure. This quantity will be designated by "$\Lambda_{obs.}$." The theoretical heat conduction, designated as "$\Lambda_{calcd.}$" from a square centimeter of surface per second per degree per bar, assuming complete temperature equilibrium of the rebounding molecules with the surface, has been calculated from kinetic theory to varying degrees of refinement. We have used the expression[2]: $\Lambda_{calcd.} = {}^1/_2(\gamma + 1)C_vP'/(2\pi RT')^{1/2}$ in which γ is the ratio of specific heats, C_v the specific heat at constant volume, P' the pressure, T' the temperature of the gas concerned. In this case with mercury T' is practically the same as the temperature of the wall since the mean path of mercury atoms is of the order of the radius of the tube at the highest pressures used, and the ratio of area of wall to area of filament is of the order of 150. We have used the values $\gamma = 1.67$, $C_v = {}^3/_2 R$, $R = 8.316 \times 10^7/200.6$ ergs/deg. × gram. The accommodation coefficient is the ratio of $\Lambda_{obs.}/\Lambda_{calcd.}$. The values which we have obtained for the accommodation coefficient of mercury are tabulated below. For completeness under the title of this paper and to throw evidence on a point discussed below we have included a set of accommodation coefficients measured with a tube, designated Tube II, in which filament lead losses have been eliminated.[3]

Tube I		Tube II	
ΔT^4	a	ΔT^4	a
36.6	0.967	36.3	0.969
114	.910	112	.905
194	.840	199	.844
		202	.828
		275	.757

These values of a are plotted against the corresponding values of ΔT in Fig. 4. The curve has two notable features, namely: the limiting accommodation coefficient as ΔT approaches zero is very close to unity assuming the extrapolation to be valid; and the accommodation coefficient falls off in approximately linear fashion as ΔT increases. This is the only case which we have seen of a simple molecule for which an accommodation coefficient of unity is reported. A high accommodation coefficient is generally associated with a long time of contact of the molecules with the surface or, *i. e.*, strong adsorption tendencies.

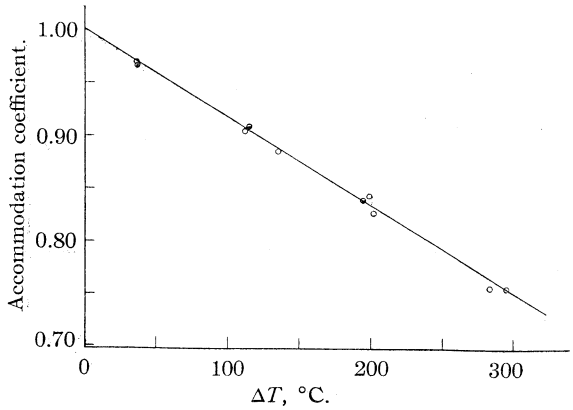


Fig. 4.—○, Values with tube II; ◒, values with tube I.

(2) Kennard, "Kinetic Theory of Gases," McGraw-Hill Book Co., Inc., New York, N. Y., 1938.

(3) Description of Tube II to be published currently.

(4) ΔT is the temperature difference between the filament and wall, the latter being 30°.

Keesom and Schmidt[5] have investigated the accommodation coefficients of several gases on glass and have drawn the conclusion that below the critical temperature the heat conduction in a rarified gas becomes independent of the surfaces and the accommodation coefficient becomes unity. From this point of view it is not surprising that the value for mercury is unity since its critical temperature is above 1500°. It is commonly assumed that the accommodation coefficient is independent of the temperature difference, ΔT, of the filament and the impinging gas molecules.[6] This seems to be tacitly assumed at least in defining the accommodation coefficient in which no restriction is made that ΔT approach zero for the determination of its value. In view then of the fact that a value of unity is obtained for the coefficient as $\Delta T \rightarrow 0$ and that, according to Keesom and Schmidt's generalization, it should remain unity to high filament temperature, we are inclined to doubt that the accommodation coefficient is independent of the ΔT at which it is measured. It would be quite improbable that the wall temperature, 30°, chosen in this work happened to be the unique temperature at which the accommodation coefficient of mercury on platinum begins to digress from unity. We suspect that the fall in accommodation coefficient is due primarily to an increasing ΔT rather than an increasing filament temperature. The work of Mann[1] and Mann and Newell[7] on platinum filaments points toward the possibility of another cause of the observed behavior. Their filament surfaces have been freed from contamination, presumably, by heating to high temperature and accommodation coefficient measurements have been taken as soon as possible after lowering the temperature. The initial values obtained in this way are much lower than those obtained before heating the wire, and the values rise with time and approach the original value. This behavior is attributed to the cleaning and subsequent contamination of the surface with adsorbed gas. The behavior observed in the present work could be due to the decreasing extent of adsorption at higher temperature of some gas present in the system—water vapor for example or mercury itself—and hence a changing surface upon which the accommodation coefficient is measured. However, all such effects, if present, must have been rapidly reversible as no inconsistencies or erratic behavior commonly associated with filament surfaces of varying degree of cleanness were evident. In our work the tube was frequently baked out thoroughly at 400°, the tubing of the vacuum system heated with a large brush flame, and the filament temperature raised to 800° during the course of the experiments.

Some points concerning the accuracy of the measurements should be considered. The diameter of the filament was checked by two methods—comparing the observed resistance at 0° and length of the filament with the resistivity of platinum (60.0 ohms per mil. foot), and comparing the mass of a portion of the filament material of known length with the density. Both methods agree with the specified diameter to well within one per cent The filament shows some striation and general roughness under the microscope. No attempt was made to determine the extent of increase in area (above that calculated) due to roughness, but it should be mentioned in this connection that the accommodation coefficients of hydrogen and helium on the same filament material are 0.23 and 0.17, respectively, and the emissivity from this filament material is approximately 20% greater than that given for bright platinum in the "International Critical Tables" over the temperature range 300 to 700°K. The temperature of the filament as measured in this work is a mean value between the potential leads. The resistance of platinum has a very nea ly linear dependence on temperature and the heat conducted to the wall by the gas has a similar dependence on the temperature of the filament. The temperature distribution over the portion of the filament between the potential leads is far from constant in vacuum, and this distribution will be modified with addition of gas giving rise to concealed changes in power loss not due to gas conduction itself but due to changes in the temperature gradients in the filament at the leads and in the potential leads themselves and due to changes in the radiation loss, which is proportional to the temperature to the fourth power, over the new temperature distribution. It is believed that the errors from this source are negligibly small in these measurements on mercury for the following reasons: first, the slope of the power loss *vs.* pressure curves is constant both with mercury and with permanent gases up to pressures corresponding to

(5) Keesom and Schmidt, *Physica*, **3**, 590 and 1085 (1936); **4**, 828 (1937).

(6) See for example J. K. Roberts, *Proc. Roy. Soc.* (London), **A129**, 146, 147 (1930).

(7) Mann and Newell, *ibid.*, **158**, 401 (1937).

many times the gas heat conduction attained in these experiments on mercury vapor; second, values of the accommodation coefficient obtained in a tube constructed to eliminate end losses, and hence having constant filament temperature over the entire length, agree with those obtained with this tube; third, the approximate calculations of the temperature distributions with and without gas show that the above suspected uncertainties would be very small for mercury. Concerning the accuracy of the electrical measurements it should be said that all voltages were read to the limit of the L. and N. Type K-2 potentiometer using a L. & N. galvanometer of 0.005 μ a. sensitivity and 33-ohm resistance. The 10-ohm resistor is guaranteed to a tolerance of 0.01%, and the standard cell was checked against cells recently certified by the Bureau of Standards. The resistance of the filament was adjusted for each measurement in a set to within 0.0005 ohm of the chosen value and the value of R_0 for the filament was checked from time to time. The power loss by gas conduction varied from 11% of the total with the filament at 66° to 3.3% with the filament at 225°.

Measurement of the Heat of Vaporization of Mercury at 10°.—A great many sets of values for the vapor pressure of mercury are in the literature. If we use sets of vapor pressure data differing from that of the "International Critical Tables," different slopes for the curves of the type plotted in Fig. 3, and hence different values for the accommodation coefficient will be obtained. The vapor pressure and accommodation coefficient are mutually indeterminate by the method of this paper, but the measurements allow a determination of the heat of vaporization of mercury which of course has its bearing on any set of vapor pressure data through the equation

$$\frac{\mathrm{d} \ln p}{\mathrm{d} T} = \frac{\Delta H_v}{RT^2}$$

By subtracting the power loss in vacuum, W_{vac}, from that at each temperature of the vapor pressure control bath, W_T, one obtains numbers which are proportional to the pressure of mercury vapor P_T in the experimental tube at the temperature of the thermostat bath, 30°. One has then $W_T - W_{vac.} = \Delta W_T$. The assumption can then be made that $\Delta W_T = kP_T$ which is justified by the experimental fact that it is found to be true with permanent gases for which the pressure can be measured directly with the McLeod gage To determine the heat of vaporization one is interested in the pressure of mercury vapor in contact with the liquid mercury in the "U" tube and this is less than P_T by a thermal transpiration correction factor as mentioned earlier. Designating the equilibrium vapor pressure in the "U" tube by P_T (eq.) one may write

$$\Delta W_T \sqrt{\frac{T}{303}} = kP_T \text{ (eq.)}$$

$$\ln \Delta W_T + {}^1/_2 \ln (T/303) = \ln k + \ln P_T \text{ (eq.)}$$

$$\ln \Delta W_T \text{ (cor.)} = \ln k + \ln P_T \text{ (eq.)}$$

$$\frac{\mathrm{d} \ln P_T \text{ (eq.)}}{\mathrm{d}T} = \frac{\mathrm{d} \ln \Delta W_T \text{ (cor.)}}{\mathrm{d}T} = \frac{\Delta H}{RT^2} \quad \text{or}$$

$$\frac{\mathrm{d} \log_{10} \Delta W_T \text{ (cor.)}}{\mathrm{d}\, 1/T} = -\frac{\Delta H}{R \times 2.303}$$

The values of $\log_{10} \Delta W_T$ (cor.) for five sets of data were plotted against $1/T$ and the slopes of these curves multiplied by $R \log_{10} e$ (4.575 cal./deg.) give $-\Delta H_{vap.}$ for mercury. The points lie in regular fashion and seem to show a slight curvature in the proper direction to give smaller values of $\Delta H_{vap.}$ at the higher temperatures. We have taken the slopes of the best lines we could put through the points over the temperature range 0–20°, and our results give the heat of vaporization at approximately 10°. The results of five runs from both Tube I and Tube II are tabulated below.

$T_{fil.}$, °C.	Tube	$\Delta H_{vap.}$
66	I	14898
144	I	14897
224	I	14923
232	II	14951
315	II	14930

The mean deviation from the average is 0.12%. We have not made a critical study of the measurements of others on this $\Delta H_{vap.}$ value, but we can say that our value, 14920 calories, is not outside the probable limits for the correct value.

This method seems to us to offer attractive possibilities as a means of determining heats of vaporization or sublimation of compounds over temperature ranges such that the vapor pressure varies from 10^{-5} up to 10^{-2} mm. If desired, the thermostat could be operated at any temperature and the filament can be operated from a few degrees above this up to as high as desired as long as it does not cause decomposition of the compounds investigated. We hope to test the method on some organic compounds of convenient volatility.

Summary

The accommodation coefficient of mercury on

platinum has been measured at low mercury pressures. It has been found to approach unity as the temperature difference between the filament and wall approaches zero and to fall off about 0.08 for each 100° of this temperature difference. The data obtained in the measurements allow a calculation of the heat of vaporization of mercury. It is suggested that the method might be developed into a precise and convenient one of wide applicability for determining heats of vaporization and sublimation.

COLUMBIA, MISSOURI RECEIVED JUNE 25, 1942

[CONTRIBUTION FROM PHYSICAL CHEMISTRY LABORATORY, DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, CASE SCHOOL OF APPLIED SCIENCE]

Equation of State for Gases at High Pressures Involving Only Critical Constants

BY SAMUEL H. MARON AND DAVID TURNBULL

Several years ago F. G. Keyes,[1] starting with an equation of state involving PV as a linear function of pressure, deduced generalized equations for polar and non-polar gases at low pressures. More recently the authors,[2] using the principle of corresponding states, presented a method for estimating the Beattie–Bridgeman constants of any gas from those of a reference gas. The only supplementary data required were the critical pressures and temperatures of a gas and of the reference, for which nitrogen was taken. The success thus attained suggested that the pressure range over which calculations could be made could be extended appreciably provided an equation of state were available covering a wider range of pressures than that of Beattie–Bridgeman. Consequently an empirical equation of state for nitrogen was deduced, covering the temperature range of −70 to 600°, and for pressures up to 1000 atmospheres.[3] The purpose of this paper is to show how this equation for nitrogen may be extended to other gases, and to present evidence for the validity of such an extension.

Derivation of Equation of State

The nitrogen compressibility data within the temperature and pressure ranges specified are represented with good reproducibility by the equation,[3]

$$PV = RT + \alpha_1' P + \alpha_2' P^2 + \alpha_3' P^3 + \alpha_4' P^4 \quad (1)$$

where the virial coefficients α_1', α_2', α_3', α_4' are functions of the temperature only, and are given by

$$\alpha_1' = a_1 + \frac{a_2}{T} + \frac{a_3}{T^3} \quad (2)$$

$$\alpha_2' = \frac{b_1}{T^2} + \frac{b_2}{T^4} + \frac{b_3}{T^6} \quad (3)$$

$$\alpha_3' = \frac{c_1}{T^2} + \frac{c_2}{T^4} + \frac{c_3}{T^6} \quad (4)$$

$$\alpha_4' = \frac{d_1}{T^2} + \frac{d_2}{T^4} + \frac{d_3}{T^6} \quad (5)$$

a_1, a_2, . . ., b_1, b_2, . . ., etc., are constants independent of temperature and pressure. From (1) the expression for the compressibility coefficient, Z, of nitrogen follows as

$$Z = \frac{PV}{RT} = 1 + \frac{\alpha_1' P}{RT} + \frac{\alpha_2' P^2}{RT} + \frac{\alpha_3' P^3}{RT} + \frac{\alpha_4' P^4}{RT} = 1 + \left[\frac{\alpha_1' P_c'}{RT_c'}\right]\frac{P_r}{T_r} + \left[\frac{\alpha_2'(P_c')^2}{RT_c'}\right]\frac{P_r^2}{T_r} + \left[\frac{\alpha_3'(P_c')^3}{RT_c'}\right]\frac{P_r^3}{T_r} + \left[\frac{\alpha_4'(P_c')^4}{RT_c'}\right]\frac{P_r^4}{T_r} \quad (6)$$

where the substitutions $T = T_c' T_r$ and $P = P_c' P_r$ have been made for T and P. T_c' and P_c' are the critical constants of nitrogen, while T_r and P_r are the reduced temperature and pressure corresponding to T and P.

Now, the indications of various attempts at generalized correlation of compressibilities of gases[4,5] are that Z is, to a fairly close approximation, a function of T_r and P_r only. If this statement be accepted provisionally, then it must follow that at any given values of T_r and P_r Z is the same for different gases, and hence the quantities in brackets in equation (6) must have the same values for all gases obeying the principle of corresponding states. Applying this identity condition to the first quantity in brackets in (6), we obtain for the relation between the primed quantities for nitrogen and the unprimed quantities for any other gas

$$\frac{\alpha_1 P_c}{T_c} = \frac{\alpha_1' P_c'}{T_c'}$$

$$\alpha_1 = \left(\frac{\alpha_1' P_c'}{T_c'}\right)\frac{T_c}{P_c} \quad (7)$$

(1) Keyes, THIS JOURNAL, **60**, 1761 (1938).
(2) Maron and Turnbull, *Ind. Eng. Chem.*, **33**, 408 (1941).
(3) Maron and Turnbull, THIS JOURNAL, **64**, 44 (1942).
(4) Dodge, *Ind. Eng. Chem.*, **24**, 1353 (1932).
(5) Lewis, *ibid.*, **28**, 257 (1936).

Substituting now $T = T_c'T_r$ for T in (2), and inserting the result in (7), we find for α_1

$$\alpha_1 = \frac{T_c}{P_c}\left\{\left[\frac{a_1P_c'}{T_c'}\right] + \left[\frac{a_2P_c'}{(T_c')^2}\right]\frac{1}{T_r} + \left[\frac{a_3P_c'}{(T_c')^4}\right]\frac{1}{T_r^3}\right\}$$
$$= \frac{T_c}{P_c}\left[\beta_1 + \frac{\beta_2}{T_r} + \frac{\beta_3}{T_r^3}\right] \quad (8)$$

where β_1, β_2 and β_3 are constants given by the quantities in brackets involving the a's and the critical pressure and temperature for nitrogen.

By extending this procedure to the other α's, it can readily be shown that

$$\alpha_2 = \frac{T_c}{P_c^2}\left\{\left[\frac{b_1(P_c')^2}{(T_c')^3}\right]\frac{1}{T_r^2} + \left[\frac{b_2(P_c')^2}{(T_c')^5}\right]\frac{1}{T_r^4} + \left[\frac{b_3(P_c')^2}{(T_c')^7}\right]\frac{1}{T_r^6}\right\}$$
$$= \frac{T_c}{P_c^2}\left[\frac{\beta_4}{T_r^2} + \frac{\beta_5}{T_r^4} + \frac{\beta_6}{T_r^6}\right] \quad (9)$$

$$\alpha_3 = \frac{T_c}{P_c^3}\left\{\left[\frac{c_1(P_c')^3}{(T_c')^3}\right]\frac{1}{T_r^2} + \left[\frac{c_2(P_c')^3}{(T_c')^5}\right]\frac{1}{T_r^4} + \left[\frac{c_3(P_c')^3}{(T_c')^7}\right]\frac{1}{T_r^6}\right\}$$
$$= \frac{T_c}{P_c^3}\left[\frac{\beta_7}{T_r^2} + \frac{\beta_8}{T_r^4} + \frac{\beta_9}{T_r^6}\right] \quad (10)$$

$$\alpha_4 = \frac{T_c}{P_c^4}\left\{\left[\frac{d_1(P_c')^4}{(T_c')^3}\right]\frac{1}{T_r^2} + \left[\frac{d_2(P_c')^4}{(T_c')^5}\right]\frac{1}{T_r^4} + \left[\frac{d_3(P_c')^4}{(T_c')^7}\right]\frac{1}{T_r^6}\right\}$$
$$= \frac{T_c}{P_c^4}\left[\frac{\beta_{10}}{T_r^2} + \frac{\beta_{11}}{T_r^4} + \frac{\beta_{12}}{T_r^6}\right] \quad (11)$$

If the above considerations are valid, equations (8), (9), (10), and (11) should give the α's for any gas in terms of the constants for nitrogen as they appear in the β's, and the critical pressure and temperature of the gas in question. These α's, then, when substituted in equation (1) for the α's for nitrogen should permit a calculation of the compressibility of various gases from a knowledge of their critical constants and the β's for nitrogen. In other words, the equations for the α's should give the virials of any gas whose PV behavior as a function of P is represented by equation (1).

Results and Discussion

Table I gives the β values calculated from the constants of equations (2) to (5) as published,[3] and from the critical constants of nitrogen, $T_c' = 126.0$°K. and $P_c' = 33.5$ atmospheres. From these β's and the appropriate critical constants α's were determined for a number of gases at various reduced temperatures, and these, in turn, were employed with equation (1) to estimate the volumes of these gases at various temperatures and pressures. In line with Newton,[6] the critical temperatures for hydrogen and helium were taken as $T_c + 8$, with the critical pressures as $P_c + 8$, since these definitions for the critical constants were found necessary to generalize the thermodynamic behavior of these gases. The results thus obtained with nine gases are summarized in Table II. Column 1 gives the temperature in °C., column 2 the corresponding reduced temperature, while column 3 the maximum pressure to which the calculations were extended. Finally, columns 4 and 5 give, respectively, the maximum and average percentage deviation of the volumes calculated in this manner from the observed.

TABLE I

β VALUES FOR EQUATIONS (8) TO (12)[a]

β_1 =	1.01961×10^{-2}	β_7 =	-1.2516×10^{-4}
β_2 =	-2.1420×10^{-2}	β_8 =	4.6408×10^{-4}
β_3 =	-3.2548×10^{-2}	β_9 =	-1.5573×10^{-3}
β_4 =	3.6991×10^{-3}	β_{10} =	1.7019×10^{-6}
β_5 =	-4.3022×10^{-3}	β_{11} =	-1.1221×10^{-5}
β_6 =	1.8289×10^{-2}	β_{12} =	3.2830×10^{-5}

[a] These constants are for V in liters, P in atmospheres, and $T = (t$°C. $+ 273.18)$°K.

Before considering these results it should be pointed out that the equation for nitrogen, from which the more general equation presented here is derived, was set up from data which cover the reduced temperature interval 1.61–7 and up to $P_r = 30$. Therefore, in extending this equation through the principle of corresponding states to other gases, it is to be anticipated that the proposed equation will be strictly applicable over the same reduced temperature and pressure interval. Actually it has been found that the equation may be extended to T_r values lower than 1.6 although in such extension the maximum and average deviations which appear are higher than within the specified interval.

The results in Table II indicate that within the range of equations, compressibilities of various gases can be calculated with a maximum deviation no greater than about 4%, and an average deviation less than 2%, up to pressures of 1000 atmospheres in many instances. The reason for not extending all calculations to this pressure is lack of data for comparison. However, in the case of helium, where data are available, the limitation is the high reduced pressure, which is already 58.5 at 600 atmospheres. Any attempts to carry the calculations beyond this large P_r extrapolation result in an appreciable decrease in concordance with observed data.

(6) Newton, *Ind. Eng. Chem.*, **27**, 302 (1935).

TABLE II

COMPARISON OF CALCULATED AND OBSERVED VOLUMES FOR SOME GASES[a]

t, °C.	T_r	Max. press., atm.	% Dev. max.	% ± Dev. av.
Hydrogen—T_c = 41.28, P_c = 20.8				
−175	2.378	75	−0.55	0.22
−100	4.195	100	0.10	.06
− 50	5.406	1000	2.00	.60
0	6.617	1000	2.10	.33
100	9.040	1000	2.55	.36
300	13.885	1000	1.30	.24
500	18.730	1000	2.43	.53
Methane—T_c = 190.68, P_c = 45.8				
0	1.432	1000	7.12	3.60
25	1.563	1000	3.70	1.71
50	1.694	1000	2.89	1.21
100	1.957	1000	3.28	1.02
150	2.219	1000	3.14	1.32
200	2.481	1000	2.99	1.42
Helium—T_c = 13.28, P_c = 10.26				
− 70	15.299	600	1.84	0.70
0	20.570	600	2.12	0.88
200	35.631	600	2.64	1.46
Propane—T_c = 369.99, P_c = 42.01				
225	1.346	104.2	4.83	2.17
250	1.414	266.06	3.13	1.53
275	1.481	303.03	1.90	0.79
Ethane—T_c = 305.28, P_c = 48.8				
125	1.304	111.46	9.45	4.05
175	1.468	222.44	3.05	0.88
225	1.631	311.09	3.10	1.12
250	1.713	345.38	2.99	1.17
275	1.795	345.30	2.32	1.63
Carbon Dioxide—T_c = 304.28, P_c = 73.0				
137	1.348	225	4.85	2.01
198	1.548	1000	4.35	2.30
258	1.745	400	−2.91	1.18
Nitric Oxide—T_c = 179.18, P_c = 65				
9	1.574	160	3.27	1.80
Ethylene—T_c = 282.88, P_c = 50.9				
137.5	1.451	500	3.13	1.43
198.5	1.667	900	2.82	1.24
Oxygen—T_c = 154.38, P_c = 49.7				
0	1.77	1000	2.30	0.85
99.5	2.41	1000	1.10	0.41
199.5	3.06	900	2.10	1.14
Carbon Monoxide—T_c = 134.18, P_c = 35.0				
− 70	1.51	800	4.4	1.75
− 50	1.66	1000	4.2	1.75
− 25	1.85	1000	2.9	1.18
0	2.04	1000	3.2	0.86
100	2.78	1000	1.0	.27
200	3.53	1000	1.1	.52

[a] Sources of P–V–T data: hydrogen—Otto and Holborn, *Z. Physik*, **33**, 1 (1925); Bartlett, Cupples and Tremearne, THIS JOURNAL, **50**, 1275 (1928); methane—Kvalnes and Gaddy, *ibid.*, **53**, 394 (1931); helium—Wiebe, Gaddy and Heins, *ibid.*, **53**, 1721 (1931); propane—Beattie, Kay and Kaminsky, *ibid.*, **59**, 1589 (1937); ethane—Beattie, Hadlock and Poffenberger, *J. Chem. Physics*, **3**, 93 (1935); carbon dioxide—Amagat, *Ann. chim. phys.*, **29**, 68 (1893); nitric oxide—Briner, Biedermann and Rother, *Helv. chim. acta*, **8**, 923 (1925); ethylene—Amagat, *Ann. chim. phys.*, **29**, 68 (1893); oxygen—*ibid.*; carbon monoxide—Bartlett, Hetherington, Kvalnes and Tremearne, THIS JOURNAL, **52**, 1374 (1930).

The results for hydrogen and helium indicate that the equation is suitable for extrapolation to values of T_r much higher than seven. In fact, the agreement for hydrogen at T_r = 18.7 and helium at T_r = 35.6 is not very much worse than at the lower T_r's. On the other hand, the calculations do indicate that extrapolation to values of T_r lower than 1.6 cannot be made as freely. With some sacrifice in accuracy the equation may be applied to T_r values as low as 1.3, although in such cases it is found necessary to decrease the pressure range to be covered. All things considered, it does not seem advisable to recommend the equation for its full pressure range below T_r = 1.55. At T_r = 1.3 the equation should be used only up to pressures of 100 atmospheres, with progressive increase in pressure range up to P_r = 30 as T_r approaches 1.55. Above T_r = 1.55 the equation seems to hold very well even at pressures considerably higher than the reduced pressure range for which the original nitrogen equation was deduced.

To show the superiority of the equation proposed here over a simple equation of state such as van der Waals, Table III gives a comparison of PV's observed and calculated by means of the two equations. Throughout the equation proposed here reproduces the observed compressibility data with a much higher fidelity than does the van der Waals equation. Further, when extended to pressures beyond the upper limits given in the table the van der Waals equation gives deviations which are above 15% and which reach 200–300% as the pressures approach 1000 atmospheres, whereas the equation of this paper still reproduces the data within a few per cent. A further comparison of the present equation with those of van der Waals, Dieterici, and Berthelot with data on hydrogen and oxygen at 0°[7] also shows that up to 1000 atmospheres our equation reproduces much more satisfactorily the data for these gases than do the other equations.

(7) Maron and Turnbull, *Ind. Eng. Chem.*, **34**, 544 (1942).

TABLE III

COMPARISON OF OBSERVED AND CALCULATED PV'S

Gas	Pressure range,[a] atm.	Reduced temp., T_r	PV van der Waals % Max. dev.	PV van der Waals % Av. dev.	PV this paper % Max. dev.	PV this paper % Av. dev.
Methane	30–300	1.694	7.67	3.66	2.14	0.96
Ethane	38.64–311.09	1.631	− 8.43	4.81	−3.10	1.12
Propane	41.23–303.03	1.481	14.05	6.07	−1.90	0.79
Ethylene	50–300	1.667	− 6.44	4.10	−1.57	0.61
Carbon monoxide	25–200	1.663	− 7.16	4.54	−2.57	0.90
Carbon dioxide	75–500	1.548	11.33	6.26	−3.64	2.17

[a] Above the upper limits of pressure indicated the van der Waals equation gives deviations which are 15% or higher, and which reach 200–300% at pressures approaching 1000 atmospheres.

From the equations given in this paper it is readily possible to derive a generalized equation for the compressibility coefficients of gases obeying the principle of corresponding states. If the values of the α's given by equations (8) to (11) be substituted into equation (1), and Z solved for, the result is

$$Z = 1 + \left[\frac{\beta_1}{T_r} + \frac{\beta_2}{T_r^2} + \frac{\beta_3}{T_r^4}\right]\frac{P_r}{R} + \left[\frac{\beta_4}{T_r^3} + \frac{\beta_5}{T_r^5} + \frac{\beta_6}{T_r^7}\right]\frac{P_r^2}{R} + \left[\frac{\beta_7}{T_r^3} + \frac{\beta_8}{T_r^5} + \frac{\beta_9}{T_r^7}\right]\frac{P_r^3}{R} + \left[\frac{\beta_{10}}{T_r^3} + \frac{\beta_{11}}{T_r^5} + \frac{\beta_{12}}{T_r^7}\right]\frac{P_r^4}{R} \quad (12)$$

This equation should reproduce the generalized compressibility coefficient curves deduced empirically by various authors within the ranges specified. That it will do so is evidenced by the comparisons of calculated and observed volumes given in this paper.

Summary

1. Employing the principle of corresponding states, an equation of state for gases is deduced requiring only the critical temperature and pressure of a gas.

2. The equation is shown to be applicable to pressures as high as 1000 atmospheres and reduced temperatures of $T_r = 1.55$ and above.

3. Below $T_r = 1.55$ the equation proposed is applicable down to $T_r = 1.30$ provided the pressure interval covered is reduced to 100 atmospheres at the lower temperature.

4. A comparison of the proposed equation with several other common equations of state shows the present equation to be superior to these.

5. A generalized equation for compressibility coefficients of gases is deduced.

CLEVELAND, OHIO RECEIVED JUNE 11, 1942

[CONTRIBUTION FROM THE MORLEY CHEMICAL LABORATORY, WESTERN RESERVE UNIVERSITY]

Systems with Boron Trifluoride[1]

BY HAROLD SIMMONS BOOTH AND DONALD RAY MARTIN

The boron atom of boron trifluoride has been found to be an acceptor to form a large number of coördinate compounds. The number of donor atoms has been found so far to be quite small, being confined to the seven elements carbon, nitrogen, oxygen, fluorine, phosphorus, sulfur and argon.

One of the best procedures for the identification of these coördinate compounds is thermal analysis, particularly as applied to liquefied gases. The object of the present investigation was to extend our knowledge of the coördinate compounds of boron trifluoride and various gases by means of therma analysis.

Apparatus and Procedure

The apparatus shown in Fig. 1 is similar in principle and operation to that described in detail by Germann and Booth,[2] save for the following features.

1. Boron trifluoride[3] from the cylinder B was purified by fractional distillation in the fractionating column[4] LH and stored in ampoule T_2 separated by the mercury cut-off MC to prevent contamination from stopcock grease or from leakage.

(1) From a part of a thesis submitted by Donald Ray Martin to the Graduate Faculty of Western Reserve University, May, 1941, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Germann and Booth, *J. Phys. Chem.*, **30**, 369 (1926).

(3) Obtained through the kindness of the Harshaw Chemical Company.

(4) Booth and Bozarth, *Ind. Eng. Chem.*, **29**, 470 (1937).

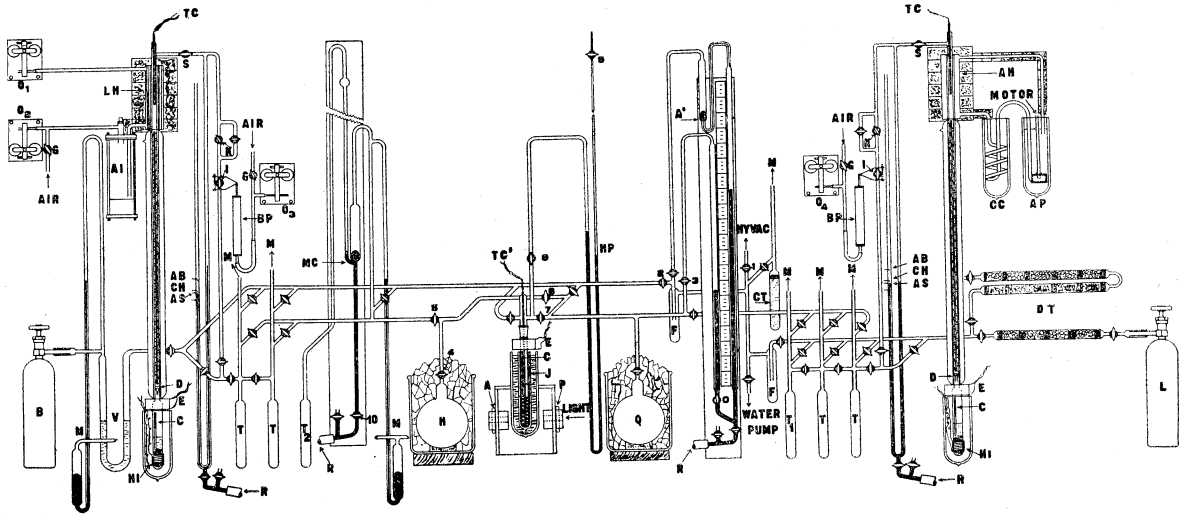


Fig. 1.—Apparatus.

2. In a corresponding fashion the right side of the apparatus contained the fractionating column AH for purifying the gases whose systems with boron trifluoride were to be studied.

3. The freezing points of the liquefied gas mixtures were determined by a triple junction copper–constantan thermocouple TC in a thin-walled glass well (3 mm. in diameter) immersed in the freezing point cell J and recorded on a special Leeds and Northrup Micromax recording potentiometer yielding freezing point determinations accurate to ±0.25 degree (see Fig. 2).

4. The first appearance of crystals on cooling was established in two ways: by the appearance of points of light in the field when the cell was placed between crossed nicols A, P, mounted in a light-proof box, and by the inflection in the cooling curves recorded on the potentiometer.[5]

In the early part of this investigation, on the system methyl chloride–boron trifluoride, we enjoyed the coöperation of Professor W. C. Fernelius of Ohio State University. In applying the procedure as described by Germann and Booth[2] to this system, difficulties in obtaining reproducible results were encountered which led us to undertake a study of the various sources of error in this method.

The following points presented themselves as factors which might in some way affect the accuracy of the determination of freezing points; (1) rate of cooling, (2) chart rate in the recording potentiometer, (3) diameter of freezing point cell, (4) immersion depth of thermocouple, and (5) closeness of the thermocouple to the bottom of the freezing point cell.

Rate of Cooling.—By the use of a partially exhausted Dewar type container for the freezing point cell, it was possible to maintain a cooling rate of three to three and one-half degrees per minute. The moment when crystal formation started was detected by means of polarized light, using polarized disks as shown in Fig. 2.

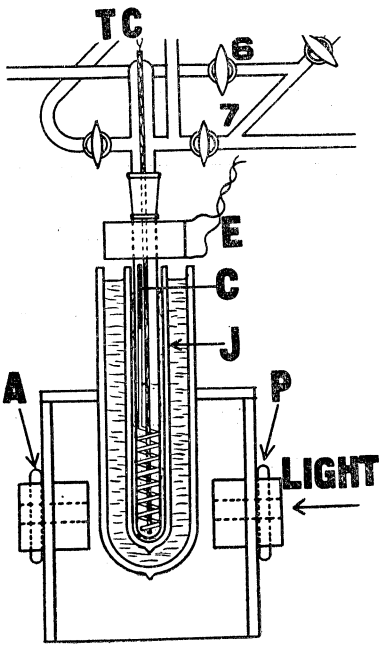


Fig. 2.

Chart Rate in Recording Potentiometer.—The recording potentiometer was found to give

(5) Booth and Willson, THIS JOURNAL, 57, 2273 (1935).

optimum results at a chart rate of eight inches per hour corresponding to 4° min.$^{-1}$.

Diameter of Freezing Point Cell.—In this Laboratory it has been customary to build the freezing point cell of as small a diameter as possible, being just large enough to enable a glass spiral stirrer to operate smoothly between the inner wall of the freezing point cell and the outer wall of the glass thermocouple well. The small diameter freezing point cell was advantageous because it required less gas to give reliable freezing point data.

A study was made with two freezing point cells, one being 14 mm. outside diameter while the other was 19 mm. Provided the thermocouple was sufficiently immersed, reliable freezing point data could be obtained with either freezing point cell.

Immersion Depth of Thermocouple.—It has been reported that a sample depth of 7 cm. above the uppermost thermocouple junction is necessary to obtain reliable freezing point data.[4] With the 14-mm. freezing point cell, an immersion depth of 3.2 cm. above the uppermost thermocouple junction was necessary while the 19-mm. cell required an immersion depth of 3.8 cm. (see Fig. 3). We have found it a safe rule that the uppermost junction of the thermocouple using number thirty-two gage copper and constantan wire, should be immersed at least 4 cm. when the cell is to be used at temperatures around −100°.

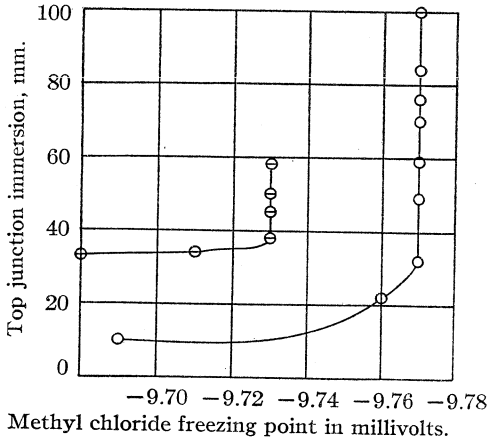


Fig. 3.—Effect of depth of thermocouple immersion on the freezing point: O, 14-mm. cell; ⊖, 19-mm. cell.

Closeness of Thermocouple to the Bottom of the Freezing Point Cell.—It was found that the distance of the thermocouple from the bottom of the freezing point cell had no effect upon the recorded temperature of the freezing point up to a distance of 2 cm. The effect for more than 2 cm. was not studied.

The System Methyl Chloride–Boron Trifluoride

Since fluorine in its compounds is the only member of Group VII of the Periodic Table which has been found capable of donating to the boron atom of boron trifluoride, and since members of the third period of Groups V and VI were found also to donate, it was of interest to determine the behavior of chlorine in methyl chloride.

Second, acetyl chloride has been found to coordinate with boron trifluoride but there is a question as to whether it is the carbonyl oxygen[6] or the chlorine[7] which is donating to the boron atom of boron trifluoride.

Third, earlier work upon this system left some uncertainty as to whether or not a compound was formed. Germann and Cleaveland[8] working in this Laboratory in 1921 studied this system and reported that they obtained a maximum at 15 and 33 mole per cent. of boron trifluoride and an "angular point" at 50 mole per cent. Since they made their own methyl chloride from concentrated sulfuric acid, methyl alcohol and sodium chloride, they postulated that these maxima might be due to methyl ether which might have been present as an impurity. Since methyl ether and methyl chloride boil within 0.3° of each other, they are difficult to separate by distillation.

They continued the work later using some methyl chloride which had been made by chlorinating gas and after five distillations the system was reinvestigated. A simple curve with no maxima and with a eutectic point at 70 mole per cent. boron trifluoride was found.[9] An uncalibrated propane thermometer was used in their study for the determination of the freezing points and as a result all of the values were high.

The methyl chloride used in this investigation was obtained from the Ohio Chemical Company, dried over barium oxide, and fractionally distilled. The freezing points for various mixtures of boron trifluoride and methyl chloride are given in Table I and are plotted in the phase rule diagram, Fig. 4.

The methyl chloride was condensed and stored as a liquid using dry-ice as the refrigerant because when it was solidified, it made a crackling noise

(6) Brown, Schlesinger and Burg, THIS JOURNAL, **61**, 673 (1939).
(7) Meerwein and Maier-Hüser, *J. prakt. Chem.*, **134**, 51 (1932).
(8) Germann and Cleaveland, *Sci.*, **53**, 582 (1921).
(9) Marion Cleaveland, unpublished laboratory notes, Western Reserve University, Cleveland, Ohio, 1921.

TABLE I

DATA FOR SYSTEM METHYL CHLORIDE–BORON TRIFLUORIDE

Mole fraction[a] BF_3	Freezing point, °C.	Mole fraction[a] BF_3	Freezing point, °C.	Eutectic temp., °C.	Mole fraction[a] BF_3	Freezing point, °C.	Eutectic temp., °C.
0.000	− 96.7	0.348	−112.5		0.630	−140.5	
.000	96.6	.354	112.8		.638	144.4	
.036	98.2	.360	113.3		.651	144.1	
.067	99.3	.392	115.6		.666	144.1	
.094	100.2	.412	116.8		.688	143.1	
.117	101.1	.431	117.8		.702	142.4	
.128	101.3	.449	120.2		.725	141.0	
.160	102.7	.464	120.4		.751	138.9	−144.8
.194	104.0	.476	121.5		.776	137.2	
.225	105.4	.483	121.3		.807	135.6	
.253	107.0	.486	121.6		.833	134.0	
.279	108.3	.498	122.6		.845	133.3	
.302	109.6	.511	122.6		.845	133.0	
.308	109.9	.526	124.3		.858	132.2	
.318	110.6	.526	126.0		.873	132.4	
.323	111.0	.541	125.8		.885	131.4	
.327	111.5	.562	129.4		.905	130.7	
.331	111.6	.569	130.4		.925	130.0	
.335	111.7	.593	133.6		.948	129.2	
.339	111.8	.616	136.0		.973	128.1	
.342	112.2	.618	136.3	−144.7	1.000	126.8	
					1.000	126.6	

[a] Mole fractions were established according to the equation used by Germann and Booth.[2] This equation becomes $X_{BF_3} = cP_{BF_3}/(P_h + cP_{BF_3})$ where X_{BF_3} is the mole fraction of BF_3, c is the ratio of the volumes of the calibrated flasks = 1.18910, P_{BF_3} is the pressure exerted by the number of moles of BF_3 introduced into the freezing point cell, and P_h is the pressure exerted by the number of moles of other gaseous component introduced.

and occasionally broke the glass vessel into which it was being condensed.

The freezing point of the pure methyl chloride was found to be −96.65° and that of the pure boron trifluoride to be −126.7 ± 0.25°. A eutectic point was found at 65.5 mole per cent. boron trifluoride and −144.8 ± 0.25°. The curve is of the same type as found by Cleaveland.[9]

The results of the investigation of this system show that the chlorine atom of methyl chloride does not donate to the boron atom of boron trifluoride to form an addition compound at a pressure of one atmosphere.

Since it is the carbonyl oxygen of aldehydes and ketones which donates to the boron atom of boron trifluoride to form addition compounds, and since the chlorine atom has not been found to donate in methyl chloride, it seems logical to expect that it is the carbonyl oxygen of acetyl chloride which is donating to the boron atom of boron trifluoride to form that addition compound.

The System Hydrogen Chloride–Boron Trifluoride

Hydrogen fluoride has been found to form three

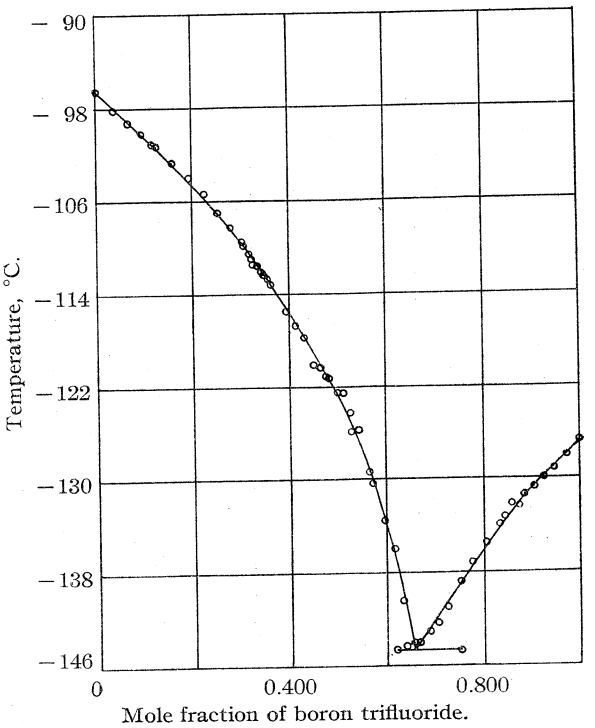


Fig. 4.—The system methyl chloride–boron trifluoride.

addition compounds with boron trifluoride.[10] In each case, however, water was present so that it was the fluoride ion which was donating to the boron atom. It was of interest to see whether anhydrous hydrogen chloride would combine with boron trifluoride. Also, it was of interest to find out if the replacement of the methyl group of methyl chloride by hydrogen in the form of hydrogen chloride would affect the coördinating power of the chlorine atom. For these reasons the system hydrogen chloride–boron trifluoride was investigated.

The hydrogen chloride used in this investigation was prepared from hydrochloric acid and sulfuric acid, dried over phosphorus pentoxide, and fractionally distilled. Care had to be exercised in condensing the hydrogen chloride in the usual manner with liquid air as the condensing agent because when it solidified it broke the glass vessels. It was possible to avoid breakage of the freezing point cell by preventing the temperature of the pure hydrogen chloride from dropping more than 20° below its freezing point. This practice had to be followed until a mole fraction of about two-tenths boron trifluoride was reached.

Pure hydrogen chloride was found to freeze at

(10) Berzelius, *Pogg. Ann.*, **2**, 113 (1824); Landolph, *Compt. rend.*, **86**, 601 (1878); Hantzsch, *Ber.*, **63**, 1789 (1930).

TABLE II

DATA FOR SYSTEM HYDROGEN CHLORIDE–BORON TRIFLUORIDE

Mole fraction BF_3	Freezing point, °C.	Eutectic temp., °C.	Mole fraction BF_3	Freezing point, °C.	Eutectic temp., °C.
0.000	−113.0		0.500	−129.2	−134.2
.000	113.2		.500	129.4	134.2
.047	116.9		.525	129.4	134.1
.075	118.6		.551	130.1	134.2
.098	120.2		.569	130.3	134.1
.126	121.2		.600	131.2	134.2
.148	122.2		.622	131.4	134.1
.179	123.1		.647	132.2	134.2
.203	124.1		.675	133.3	134.1
.223	124.1		.698	133.7	134.2
.251	125.0		.723	134.1	
.285	125.5		.749	133.9	
.301	125.8		.778	133.2	133.7
.324	126.2		.795	133.3	
.350	126.8		.832	131.9	
.378	126.9		.850	131.6	
.403	127.8	−134.1	.897	130.5	
.425	127.8		.917	129.8	
.454	128.4	134.1	.953	128.7	
.485	128.5	133.3	1.000	127.0	
			1.000	127.0	

−113.1° and pure boron trifluoride at −127.0 ± 0.25°. A phase rule diagram was obtained with a eutectic point at 72.3 mole per cent. boron trifluoride and at a temperature of −134.15 ± 0.25°. The data are given in Table II and shown in Fig. 5.

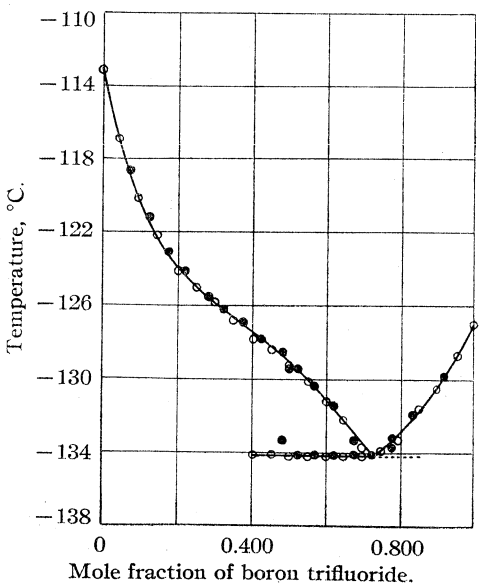


Fig. 5.—The system hydrogen chloride–boron trifluoride: O, first analysis; ●, second analysis.

In most systems where only one eutectic is found, the curve drops slowly with relation to the temperature in the vicinity of the pure components, and then drops rapidly in the vicinity of the eutectic point. The curve obtained with hydrogen chloride and boron trifluoride did just the opposite. This curve dropped rapidly in temperature in the vicinity of the pure components and more slowly in the vicinity of the eutectic point. A similar curve was found by Graff[11] for the system hydrogen chloride–boron trichloride.

As no addition compound was found, it appears that ionization may be the explanation of the difference between the action of hydrogen fluoride with boron trifluoride on the one hand, and of hydrogen chloride and boron trichloride, and of hydrogen chloride and boron trifluoride on the other hand. Also, Wiberg and Sütterlin[12] tried the reaction between hydrogen fluoride and boron trichloride and obtained as reaction products hydrogen chloride on the one hand and boron trifluoride on the other. An additional fraction having a vapor pressure between that of boron trifluoride and that of hydrogen chloride was obtained which had a molecular weight corresponding to the addition compound $BF_3 \cdot 3HCl$ analogous to $BF_3 \cdot 3HF$. They postulated that the reaction between hydrogen fluoride and boron trichloride took place because the fluorine atom of the hydrogen fluoride, through its residual valence, reacted with the boron trichloride, probably forming as a first product in the liquid state $BF_3 \cdot 3HCl$. If such a compound exists in the liquid state, it should have given a maximum in the phase rule diagram at 25 mole per cent. boron trifluoride. No maximum was found and we believe that they were mistaken in their conclusion.

It has been shown that the chlorine atom in both methyl chloride and in hydrogen chloride does not coördinate with the boron atom of boron trifluoride.

The System Nitrous Oxide–Boron Trifluoride

Over one hundred years ago, Kuhlmann[13] noted a reaction between the oxides of nitrogen and their respective acids with boron trifluoride, with the exception of nitrous oxide which he reported did not react. Germann and Booth[2] mention a reaction between nitric oxide and boron trifluoride. One would expect a reaction between nitrous oxide and boron trifluoride in the light of the addition compounds to which each of its constituents

(11) Graff, *Compt. rend.*, **197**, 754 (1933).

(12) Wiberg and Sütterlin, *Z. anorg. allgem. Chem.*, **202**, 37 (1931).

(13) Kuhlmann, *Ann. chim. phys.*, [3] **2**, 116 (1841); *Ann.*, **39**, 319 (1841).

give rise in their respective compounds. The nitrogen atom and the oxygen atom in their respective compounds have been found to donate to the boron atom of boron trifluoride to form addition compounds. Therefore, it was of interest to study the system nitrous oxide–boron trifluoride.

Anhydrous nitrous oxide, of anesthesia quality, from the Ohio Chemical Company, was dried over barium oxide before being fractionally distilled.

In order to fractionate this gas, because of the narrow liquidus range of 2.3°,[14] it was necessary to distil at a pressure of one and one-half atmospheres.

Due to the short liquidus range of nitrous oxide, the freezing point procedure was modified slightly. With pure nitrous oxide or with mixtures on that side of the system, the technique for melting the solid was modified. It was found best to warm gently the wall of the freezing point cell with acetone from the top of the cell to the bottom until it was certain that there was a very small space between the solid and the wall of the freezing point cell. Then the bottom of the cell was warmed rapidly by raising a small bottle of acetone around the bottom. In this manner, the solid at the bottom of the cell was all melted before the liquid on top had acquired too high a vapor pressure. Also, the stirrer was freed more rapidly and could stir the liquid, which prevented an excessive pressure building up due to the liquid on top vaporizing.

The freezing point of the pure nitrous oxide was found to be −91.05° and that of the pure boron trifluoride −126.8 ± 0.25°. The phase rule diagram was a smooth curve with the eutectic occurring at 76.6 mole per cent. boron trifluoride and at a temperature of −138.0 ± 0.25° (see Table III and Fig. 6).

TABLE III

DATA FOR SYSTEM NITROUS OXIDE–BORON TRIFLUORIDE

Mole fraction BF_3	Freezing point, °C.	Eutectic temp., °C.	Mole fraction BF_3	Freezing point, °C.	Eutectic temp., °C.
0.000	− 91.0		0.501	−116.7	
.000	91.1		.522	118.3	−137.9
.050	92.3		.550	121.0	
.079	93.7		.576	122.3	138.1
.111	94.8		.598	124.4	138.0
.131	95.8		.626	126.1	138.0
.151	96.9		.650	128.4	138.1
.178	97.7		.664	129.5	
.197	98.4		.675	130.4	138.3
.240	100.8		.701	132.9	137.9
.251	101.2		.724	135.6	138.0
.273	102.5		.754	137.7	
.303	104.0		.771	137.9	138.4
.327	105.7		.802	135.8	137.7
.350	106.7		.826	134.5	137.0
.375	108.2		.847	133.2	137.7
.400	109.8		.871	132.3	
.425	111.3		.898	130.0	
.450	113.0		.949	128.7	
.451	113.3		.950	128.5	
.480	115.3	−137.2	1.000	126.8	
			1.000	126.8	

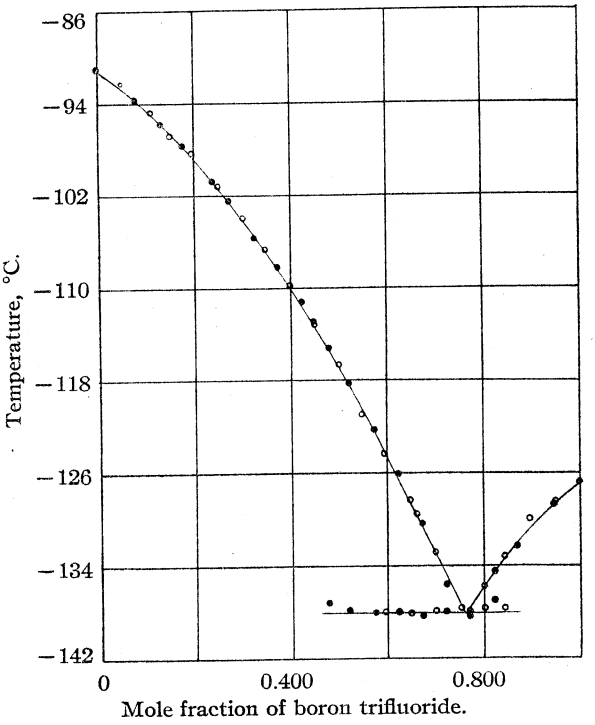


Fig. 6.—The system nitrous oxide–boron trifluoride: O, first analysis; ●, second analysis.

The investigation of this system confirmed the report of Kuhlmann[13] that nitrous oxide and boron trifluoride do not react. The explanation for this is not clear.

The System Sulfur Dioxide–Boron Trifluoride

The sulfur atom and the oxygen atom in their respective compounds have been found to donate to the boron atom of boron trifluoride to form coördination compounds. A compound made up of these two atoms would be expected to coördinate with boron trifluoride. Therefore, the system sulfur dioxide–boron trifluoride was investigated.

The anhydrous sulfur dioxide was obtained from the Ohio Chemical Company, dried over phosphorus pentoxide, and fractionally distilled.

The freezing point of the pure sulfur dioxide was

(14) Blue and Giauque, THIS JOURNAL, 57, 991 (1935).

found to be −73.5° and that of the pure boron trifluoride to be −126.75 ± 0.25°. A maximum was found at 50 mole per cent. of boron trifluoride, indicating a one to one addition compound between sulfur dioxide and boron trifluoride, whose freezing point was found to be −96.0 ± 0.25°. Eutectic points were found on each side of this maximum. One was found to exist at 38.0 mole per cent. boron trifluoride and at a temperature of −97.15 ± 0.25°, while the other eutectic point was found at 95.2 mole per cent. of boron trifluoride and −128.6 ± 0.25° (see Table IV and Fig. 7).

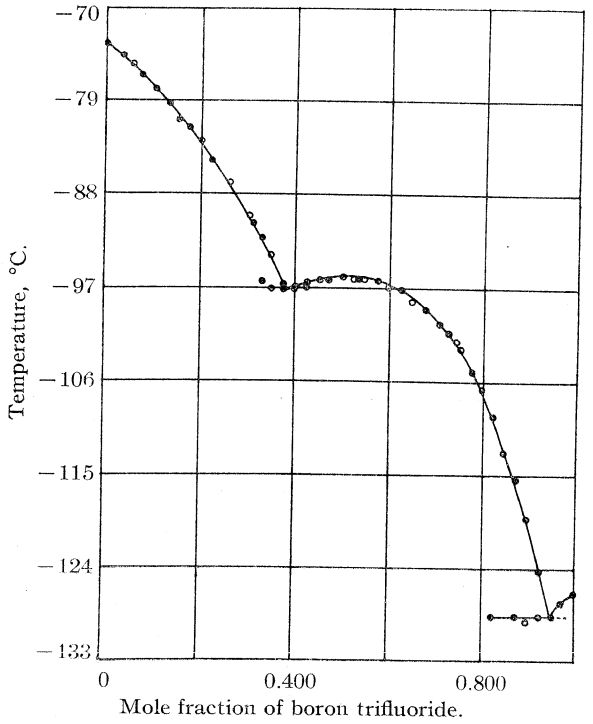


Fig. 7.—The system sulfur dioxide–boron trifluoride: O, first analysis; ●, second analysis.

From the flatness of the maximum obtained it is obvious that the compound is somewhat dissociated above the melting point.

Liquid sulfur dioxide has been found to be a solvent analogous to water and liquid ammonia. Extensive work has been done in this field since 1936 by Jander and his co-workers.[15] Liquid sulfur dioxide is a good solvent for organic and inorganic substances, the solutions being good electrical conductors, while sulfur dioxide itself is a poor conductor. The solutes have been found to be more or less dissociated. The results of their

(15) Jander and Wickert, *Z. physik. Chem.*, **A178**, 57 (1936), is the first article of a series. The last to appear is Part 10, Jander and Mesech, *ibid.*, **A183**, 277 (1939).

TABLE IV

DATA FOR SYSTEM SULFUR DIOXIDE–BORON TRIFLUORIDE

Mole fraction BF_3	Freezing point, °C.	Eutectic temp., °C.	Mole fraction BF_3	Freezing point, °C.	Eutectic temp., °C.
0.000	−73.5		0.524	−96.2	
.000	73.5		.535	96.2	
.034	74.6		.547	96.2	
.055	75.4		.576	96.4	
.077	76.5		.598	97.0	
.105	77.8		.625	97.2	
.132	79.2		.648	98.4	
.154	80.8		.676	99.2	
.177	81.5		.705	100.5	
.201	82.8		.725	101.4	
.223	84.7		.742	102.2	
.261	86.9		.750	102.9	
.303	90.1		.774	105.0	
.311	90.8		.798	106.8	
.331	92.3	−96.4	.823	109.3	−128.6
.350	93.9	97.1	.847	112.8	
.378	96.7	97.1	.874	115.4	128.6
.400	97.0	97.2	.898	119.2	129.2
.426	96.5	97.1	.926	124.2	128.6
.453	96.2		.952	128.6	
.473	96.3		.972	127.3	
.500	96.0		1.000	126.8	
.501	96.0		1.000	126.7	

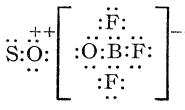
experiments have been explained on the assumption of the following types of dissociation of other solvents

$$2\,H_2O \rightleftharpoons H_3O^+ + OH^-$$
$$2\,NH_3 \rightleftharpoons NH_4^+ + NH_2^-$$
$$2\,SO_2 \rightleftharpoons SO^{++} + SO_3^{--}$$

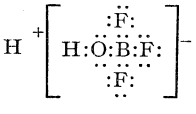
Wickert,[16] who also has been working with liquid sulfur dioxide, suggested that the dissociation of sulfur dioxide might also be written

$$SO_2 \rightleftharpoons SO^{++} + O^{--}$$

The structure of this compound with boron trifluoride might be



analogous to the monohydrate of boron trifluoride

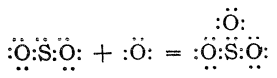


It is this dissociation which would have to take place in order to form the above addition compound with boron trifluoride. This addition compound would fit into the "sulfito" system of acids, bases and salts as developed by Jander.[15] The boron trifluoride addition compound would

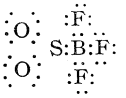
(16) Wickert, *Z. Elektrochem.*, **44**, 410 (1938).

be an acid in the sulfur dioxide system just as it is an acid in the water system.

Hägg[17] has explained the ease of oxidation of sulfur dioxide up to sulfur trioxide as being due to the electron pair on the sulfur. Thus



Thus, we could write the one to one addition compound with boron trifluoride



The fact that hydrogen sulfide formed the compound $H_2S \cdot BF_3$,[2] where only the sulfur can be the donor, would permit this latter mechanism.

Regardless of which structural formula represents sulfur dioxide, it is possible to account for the addition compound between the given structure and boron trifluoride.

(17) Hägg, *Z. physik. Chem.*, **B18**, 199 (1932).

Summary

In the present investigation it has been found that hydrogen chloride and methyl chloride give eutectics and no compounds with boron trifluoride, showing that, at least in these two compounds, chlorine does not act as a donor to boron trifluoride, thus refuting the existence of the reported compound $BF_3 \cdot 3HCl$.

It has been found further that nitrous oxide also will form no compound with boron trifluoride although it has been reported that nitric oxide does. Sulfur dioxide, just as the other parent solvents, water and ammonia, forms a one to one compound with boron trifluoride and two eutectics.

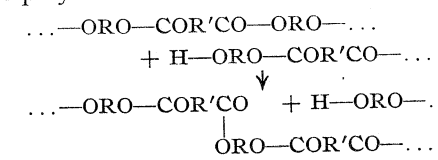
CLEVELAND, OHIO RECEIVED FEBRUARY 16, 1942

[CONTRIBUTION FROM ESSO LABORATORIES, CHEMICAL DIVISION, STANDARD OIL DEVELOPMENT COMPANY]

Random Reorganization of Molecular Weight Distribution in Linear Condensation Polymers[1]

BY PAUL J. FLORY

In a recent publication[2] concerned with the viscosities of molten polyesters, it was observed that the viscosity of a mixture of two polyesters decreases when heated. This decrease was attributed tentatively to a change in the distribution of molecular species in the mixture, brought about by the occurrence of ester interchange between terminal hydroxyl groups and ester groups of the polymer chains



where —ORO— and —COR′CO— represent, respectively, the glycol and the dibasic acid residues of a linear polyester formed through polycondensation of a glycol and a dibasic acid. As the result of such an interchange process, an x-mer may react with a y-mer to yield a $(y + z)$-mer and an $(x - z)$-mer. There is no net change in the number of molecules; hence, the number average molecular weight will be unaffected by reorganization processes of this sort. On the other hand, the distribution of species may be altered, and changes in distribution will produce corresponding changes in the weight average molecular weight. Since the viscosity of the molten polyester, composed of a mixture of polymeric species, depends directly on the weight average molecular weight,[2] the viscosity will be sensitive to changes in distribution caused by ester interchange, and these changes can be observed conveniently through viscosity measurements.

Investigations of rates of formation of polyesters and of their degradation[3] by monomeric alcohols have shown that the rate constant for alcoholysis, though somewhat smaller, is similar in magnitude to that for esterification under the same conditions. The two reactions are similarly affected by catalysts and temperature. After polyesterification has proceeded to the point where the average molecular weight is large, the free carboxyls are so overwhelmingly outnumbered by ester groups that the rate of reaction of the free hydroxyls with ester groups will exceed their rate

(1) A portion of this work has been discussed briefly by H. Mark and R. Raff, "High Polymeric Reactions," Interscience Publishers, Inc., New York, 1941, p. 147.

(2) P. J. Flory, THIS JOURNAL, **62**, 1057 (1940).

(3) P. J. Flory, *ibid.*, **62**, 2255, 2261 (1940).

of reaction with acid groups, despite the superiority of the esterification velocity constant. Thus, it is conceivable that ester interchange might exert a profound effect on the distribution of species obtained in the course of a polyesterification process.

It is the purpose of this paper to examine, both theoretically and experimentally, the consequences of interchange processes such as may occur in various linear condensation polymers. It will be shown that ester interchange, or any other analogous process in other polymers, provides a route to the most probable distribution of species. This happens to be the same distribution normally obtained by polycondensation without the occurrence of interchange.

Theoretical

The Equilibrium Distribution.—From a consideration of the kinetics of condensation polymerization, it has been shown that the molecular size distribution in linear condensation polymers containing equal numbers of the two co-reacting functional groups (*e. g.*, OH and COOH) is given by

$$N_x = Np^{x-1}(1-p) \qquad (1)^4$$

where N_x is the number of molecules composed of x monomer units, N is the total number of molecules and p is the extent of reaction, *i. e.*, the fraction of the functional groups which have condensed. Rate of reaction measurements[5] show the reactivity of a terminal functional group to be independent of the size of the molecule. Hence, the probability that any particular functional group has reacted is equal to the extent of reaction p. Equation (1) follows directly from statistical considerations.

In deriving (1) from this point of view it is assumed that once a given pair of functional groups condense, they remain forever united. If an interchange process such as ester interchange occurs, the ultimate distribution will be determined by the equilibria between the various polymer species, not by the rates of their initial formation through condensation. If the free energy of formation of a linkage between an x-mer and a y-mer is independent of x and y, then after equilibrium has been established through interchange, the probability that a particular functional group constitutes a part of an inter-unit linkage remains equal to the degree of conversion p, and the distribution (1) should obtain as before.[6]

The distribution (1) for the "equilibrated" linear polyester can be derived in a manner analogous to the derivation of the Maxwell–Boltzmann energy distribution law. We consider a polymer wherein interchange may occur freely, but in which the net degree of advancement of the inter-unit condensation process is fixed. Here

$$\sum_{x=1}^{\infty} N_x = N \qquad (2)$$

$$\sum_{x=1}^{\infty} xN_x = n_0 \qquad (3)$$

where n_0 is the total number of units and

$$N = n_0(1-p) \qquad (4)$$

Both n_0 and N are constant under the conditions. Equations (2) and (3) are analogous, respectively, to the conditions of conservation of matter and of energy in the Maxwell–Boltzmann derivation.[7] Here we define a micro state as one in which the size x of each molecule is specified. A macro state is defined merely by the numbers of molecules of the various sizes, *i. e.*, by N_1, N_2, N_3, etc. For a given macro state there are

$$W = N!/\Pi N_x! \qquad (5)$$

micro states. Solution of (5) for the maximum value of W consistent with (2) and (3) by the usual variational method yields (1) for the most probable macro state. Thus, under the assumption that the thermodynamic stability of a given inter-unit bond is independent of the size of the molecule and of its position along the chain, the equilibrium distribution ultimately attained by interchange processes is identical with that obtained by random synthesis. The difference in entropy between a mole of a heterogeneous polymer and a mole of the single species of molecular weight equal to the number average molecular weight for the heterogeneous polymer is given by the entropy of mixing expression

$$\Delta S_h = -R\Sigma(N_x/N)\ln(N_x/N) \qquad (6)$$

which may be called the molar entropy of hetero-

(4) P. J. Flory, THIS JOURNAL, **58**, 1877 (1936).

(5) P. J. Flory, *ibid.*, **61**, 3334 (1939).

(6) "Equilibration" of the distribution of species in a polyester containing a small amount of water, which impedes further increase in p, could take place through simultaneous hydrolysis and esterification as well as by ester interchange. In this connection, see G. V. Schulz, *Z. physik. Chem.*, **A182**, 127 (1938).

(7) F. T. Wall, THIS JOURNAL, **62**, 803 (1940), has applied this method to the derivation of the distribution of sequences of like units in random vinyl copolymers. In as much as no interchange subsequent to formation of the polymer chains may occur in this case, it is not immediately obvious that the "most probable" state will be obtained.

geneity. For the most probable distribution, substitution of (1) in (6) gives

$$\Delta S_h = R[\ln(p/1-p) - (\ln p)/(1-p)] \quad (7)$$

which also can be obtained directly from the Boltzmann relation $S = k \ln W$, where W is taken to be $W_{\max.}$ in (5). For a high molecular weight polymer p is near unity and

$$\Delta S_h \cong R[1 - \ln(1-p)] \quad (7.1)$$

or

$$\Delta S_h \cong R[1 + \ln(\overline{DP}_n)] \quad (7.2)$$

since the number average degree of polymerization is given by

$$\overline{DP}_n = 1/(1-p) \quad (8)$$

For the entropy of heterogeneity per mole of *structural units*, we have

$$\Delta S_h' = \Delta S_h/\overline{DP}_n \quad (9)$$

These equations express the maximum entropy of heterogeneity, or entropy of mixing, for a given degree of polymerization. Any distribution other than (1) will yield a lower entropy of heterogeneity. The entropy per mole of *polymer* molecules ΔS_h increases without limit as p approaches unity and $\overline{DP}_n$ approaches infinity; the entropy per mole of *structural units* $\Delta S_h'$, after reaching a maximum at a very low degree of polymerization, decreases asymptotically toward zero as $\overline{DP}_n$ increases.

Reorganization in Mixtures.—Since direct synthesis by polycondensation gives at once an equilibrium distribution, in order to observe the effects of interchange it is first of all necessary to obtain some other distribution. A product of greater homogeneity could be obtained by fractional precipitation. When subjected to interchange conditions, its distribution should broaden into the most probable one. An alternative method has been used here. Mixtures of greater heterogeneity have been obtained by mixing two normal products of synthesis, one of low and the other of high average molecular weight. The ensuing homogenization toward the most probable distribution was followed by means of viscosity measurements on the molten mixture.

The viscosity of the melt depends on the weight average chain length $\overline{Z}_w$ according to the relationship[2]

$$\log \eta = A + C\,\overline{Z}_w^{1/z} \quad (10)$$

where A and C are constants, and the weight average chain length is defined by

$$\overline{Z}_w = \Sigma w_x Z_x \quad (11)$$

where w_x is the weight fraction of x-mer. Whereas the number average chain length

$$\overline{Z}_n = \Sigma(N_x/N)Z_x \quad (12)$$

is unaffected by interchange, a transformation in the distribution will produce changes in the weight average chain length $\overline{Z}_w$, which may be calculated from viscosities using (10).

The decamethylene adipate polyesters which have been used are of two types. In the one case, the polymers possessed carboxyl and hydroxyl groups in equivalent quantities; in the other, an excess of glycol was used and the reaction was carried to completion, yielding a product having hydroxyl end-groups exclusively. For polymers of the former type

$$w_x = xp^{x-1}(1-p)^2 \quad (13)$$

which can be derived from (1),[2,4] and

$$\overline{Z}_n = z/(1-p) \quad (14)$$

$$\overline{Z}_w = z(1+p)/(1-p) \quad (15)^4$$

$$= 2\,\overline{Z}n - z \quad (16)^2$$

where z is the mean number of chain atoms per unit. ($z = 9$ for polydecamethylene adipate.) For the mixture composed of weight fractions f_1 and f_2 of polymers characterized by p_1 and p_2, respectively, the averages for the initial mixture are

$$\overline{Z}_n' = \overline{Z}_{n,1}\,\overline{Z}_{n,2}/(f_1\overline{Z}_{n,2} + f_2\overline{Z}_{n,1}) \quad (17)$$

$$= z/(1-p') \quad (17.1)$$

where $p' = f_1p_1 + f_2p_2$

$$\overline{Z}_w' = f_1\overline{Z}_{w,1} + f_2\overline{Z}_{w,2} \quad (18)$$

After equilibration through ester interchange (in the absence of either further esterification or of hydrolysis) $\overline{Z}_n'$ remains unchanged, but $\overline{Z}_w'$ becomes

$$\overline{Z}_w'' = z(1+p')/(1-p') = 2\overline{Z}_n' - z \quad (19)$$

Under the conditions of the experiments reported below, esterification occurs simultaneously with ester interchange, though at a slower rate. Consequently, p' increases slowly during the experiments. Nevertheless, the weight average chain length ultimately should reach a value given by (19), wherein p' is time dependent.

For polyesters prepared from r moles of dibasic acid per mole of glycol, the reaction being carried to completion[3,4]

$$w_x = [(zx + \alpha)r^{(x-1)/2}(1-r)^2]/[z(1+r) + \alpha(1-r)] \quad (20)$$

and

$$\overline{Z}_n = z(1+r)/(1-r) + \alpha \quad (21)$$

where α is an "end-group correction" which may be taken equal to three in the present instance.[3]

From statistical considerations analogous to those used in the derivation of (1) and (15)[2,3]

$$\bar{Z}_w = 2z(1 + r)/(1 - r) = 2(\bar{Z}_n - \alpha) \qquad (22)$$

For the mixture of two such polymers, $\bar{Z}_n'$ is given by (17). In this case further esterification is not possible, and equilibration of the mixture through ester interchange yields

$$\bar{Z}_w'' = 2(\bar{Z}_n' - 3) \qquad (23)$$

Experimental Results

The methods used for the preparation of the polyesters and for the measurement of their viscosities in the molten state have been described previously.[2,3] Polymers A and B were prepared by heating excess quantities of decamethylene glycol with adipic acid at 109° in the presence of about 0.1% by weight of *p*-toluenesulfonic acid until the viscosity showed no further change, indicating complete esterification of the adipic acid. In the preparation of Polymer A the mixture was heated sixty hours; for Polymer B twenty-five hours was sufficient for substantially complete esterification.

Data pertaining to these polymers are given in the second and third columns of Table I. The reactants were of high purity,[2] and the quantities used were carefully weighed. At the low temperature of reaction the amounts of glycol removed with effluent water vapor formed in the esterification were negligible. For these reasons the values of r given in the first row of Table I are believed to be accurately representative of the final products. The number average chain lengths given in the second row have been calculated directly from r. Computation of the weight average chain lengths from r (third row of Table I) involves acceptance of the size distribution relationship (20). The constants which have been used in equation (10), *i. e.*

$$\log \eta = -1.435 + 0.1144\, \bar{Z}_w^{1/2} \qquad (10')$$

for the calculation of the viscosities given in the fourth row of the table have been established at 109° for decamethylene adipate polymers having hydroxyl and carboxyl end-groups in equal numbers.[2] The discrepancies between observed and calculated viscosities for the two polymers are doubtless due to minor dependence of the viscosity relationship on the end-groups.[8]

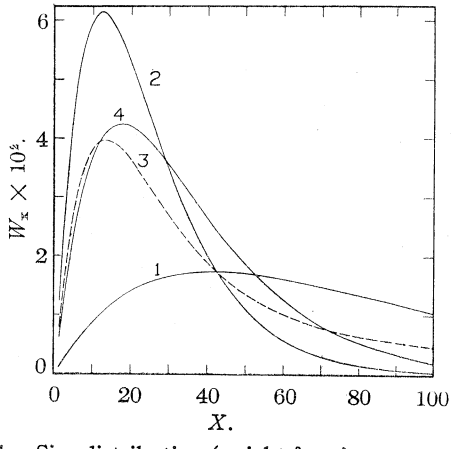


Fig. 1.—Size distribution (weight fraction *vs.* number of units) for the initial polymers A and B (curves 1 and 2, respectively), for the mixture composed of 42.4% of A and 57.6% of B (curve 3), and for the calculated equilibrium distribution for the mixture (curve 4).

TABLE I

	Polymer A	Polymer B	Calcd. for mixture[a] Initial	Calcd. for mixture[a] Equilibrium
Molar ratio r of acid to glycol	0.955	0.855	0.896	0.896
$\bar{Z}_n$ calcd. from r using (21)	394	118	168	168
$\bar{Z}_w$ calcd. from r using (22)	782	230	464[b]	330
η at 109°, calcd. from $\bar{Z}_w$ using (10')	58.2	2.00	10.7	4.40
η at 109°, poises (obs.)	51.9	1.78		4.15
$\bar{Z}_w$ calcd. from η (obs.) using (10')	758	217		322

[a] The mixture composed of 42.4 weight per cent. of Polymer A and 57.6% of Polymer B. [b] Calculated for the initial mixture prior to interchange using (18).

The distributions of species calculated from (20) for Polymers A and B are shown by curves 1 and 2 in Fig. 1. A mixture consisting of 42.4% by weight of A and 57.6% of Polymer B was employed in the interchange experiment. The distribution curve for the initial mixture, computed by multiplying ordinate values of curve 1 by 0.424 and those of curve 2 by 0.576 and taking the sum, is represented by the broken curve 3. Computed initial values of r, $\bar{Z}_n'$, $\bar{Z}_w'$ and η are given in Table I. Inasmuch as there is no possibility for an increase in the number of inter-unit bonds in the mixture, $\bar{Z}_n'$ must remain fixed during interchange. According to the theory presented above, the distribution of species should be transformed by interchange to the most probable distribution (20), r having the value given in Table I. This distribution is shown by curve 4 in Fig. 1.

(8) See pp. 2256, 2259 of ref. 3.

The weight average chain length for the final distribution 4 is considerably less than that for the initial distribution 3; the calculated viscosities differ correspondingly (see Table I).

The experimental results of this interchange experiment carried out at 109° are given in Table II. As has been observed previously in experiments on polyester mixtures, from fifteen to thirty minutes is required before complete mixing has occurred.[2] Interchange in the present instance is quite rapid due to the presence of an acid catalyst.[3] Hence, a valid extrapolation to the initial viscosity of the mixture prior to interchange is not possible from these data. The final viscosity is somewhat lower than that calculated from (10′) for the most probable distribution (see Table I), but the discrepancy is of the order of that to be expected to result from the inaccuracy of (10′) as applied to hydroxyl terminated polymers.[8]

TABLE II

Time, minutes	Viscosity, poises at 109°
29	6.85
62	5.80
103	5.06
156	4.72
200	4.52
281	4.38
345	4.33
420	4.27
535	4.17
840	4.15

Other interchange experiments have been carried out on decamethylene adipate polyesters having equivalent quantities of hydroxyl and carboxyl end-groups. These were prepared by heating equimolar quantities of the pure glycol and dibasic acid, in the absence of catalyst, until the desired degree of polymerization was reached. Glycol carried out of the reaction mixture with the slow stream of dry nitrogen, used to remove water, was carefully replaced in order to assure sufficiently precise balance between the two end-groups. Polymer C, prepared by heating the reactants at 202° for twenty-nine hours, had a viscosity at 109° of 164 poises. According to (10′) and (16), $\overline{Z}_w = 1017$ and $\overline{Z}_n = 513$. For Polymer D, prepared by heating for two hours at 166°, $\eta_{109°} = 0.532$ poise; accordingly, $\overline{Z}_w = 103.0$ and $\overline{Z}_n = 56.0$. Neutral equivalents of the polymers were in close agreement with those calculated from these values of $\overline{Z}_n$, indicating satisfactory equivalence of the end-groups.

Table III presents a portion of the data for the interchange experiment performed on a mixture consisting of 40% of Polymer C with 60% of Polymer D. The mixture was heated at 109° in a dry nitrogen atmosphere.[9] The weight average chain lengths given in the third column have been computed, using equation (10′), from the measured viscosities given in the second column. Interchange is much slower than in the preceding experiment, due to the absence of an acid catalyst other than is furnished by the unreacted carboxyl end-groups. During the course of the experiment some inter-esterification continued to take place, as is shown by the neutral equivalents given in the fourth column. These were determined by titration of samples removed from the mixture. Values of $\overline{Z}_n$ calculated directly from the neutral equivalents, or number average molecular weights, are given in the fifth column. If interchange equilibrium were fully established, the weight average chain length should equal $2\,\overline{Z}_n' - 9$, according to the theory given above. These "equilibrium" values are presented in the sixth column. The corresponding viscosities calculated using (10′) are given in the last column. The above theory requires that eventually the weight average chain lengths given in the third and sixth columns should coincide; or, the viscosities in the second and last columns should become identical.

TABLE III

INTERCHANGE BETWEEN MIXTURE CONSISTING OF 40 PARTS POLYMER *C* AND 60 PARTS POLYMER *D* (PARTIAL TABULATION ONLY

Time, minutes	η poises, 109°	$\overline{Z}_w$	Neutral equivalent	$\overline{Z}_n'$	$\overline{Z}_w''$ (equil.)	η (equil.)
0	(11.0)[a]	(468.6)[a]		87.0	165.0	1.08
29	9.60	446.5				
68	7.85	414.8				
72			1392	87.5	166.0	1.09
109	6.38	383.3				
187	4.73	340.1				
315	3.54	300.8				
448	2.93	276.1				
625	2.53	258.4				
784	2.43	253.3	1599	101.2	193.4	1.43
947	2.40	251.7				
1125	2.42	252.7				
1270	2.44	253.6	1767	111.8	214.6	1.74

[a] Values computed for the initial mixture.

The data from this experiment are shown in full

(9) The experiments on mixtures of Polymers C and D are continuations of two of those reported previously[2] in connection with determinations of viscosities of polyester mixtures prior to interchange. It may be noted that the chain lengths of Polymers C and D differ slightly from those employed previously (Ref. 2, Table II, Series II). This discrepancy, which is of no real significance in either investigation, is due to inadvertent use, in the earlier tabulation, of constants in (10) which differ slightly from those used here.

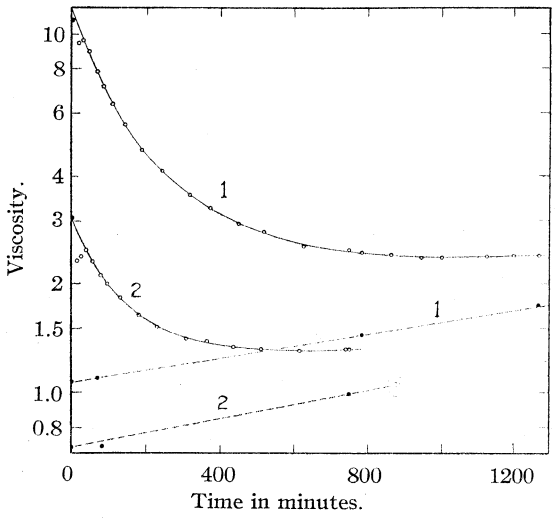


Fig. 2.—Experimental results for mixtures of Polymers C and D.

in Fig. 2. The solid curve 1 represents the observed viscosities (second column of Table III), plotted on a log scale merely for convenience. The dashed curve represents the viscosities (last column of Table III) calculated for interchange equilibrium for the observed neutral equivalent. Similar results obtained at 109° using a mixture composed of 19.7% of Polymer C and 80.3% of Polymer D are represented by the solid and dashed curves 2 in Fig. 2. In each experiment the observed viscosity decreases to a minimum and then increases. During this latter stage the effect on the viscosity of the rate of change in distribution due to interchange is outweighed by the rate of interesterification. When interchange equilibrium has been established, the solid and dashed curves should coincide according to the theory presented herein. To the extent that they are asymptotic, this theory is confirmed.

Discussion

The similarity in rates of ester interchange and esterification assures simultaneous occurrence of interchange during the synthesis of a polyester by interesterification. The distributions of species in normal products of synthesis, such as those from which the mixtures were prepared, are determined to a large extent by interchange equilibria. It could be contended, therefore, that if it is permissible to assume, as has been done above, that the distributions in the initial polymers A, B, C and D are correctly represented by (1) and (13), or (20), these equations necessarily will apply to their mixtures after equilibration through interchange. The above experimental results cannot be regarded as *explicit* experimental proof of adherence to (1), (13) and (20). They demonstrate convincingly, however, that the ultimate transformations of the size distributions in the mixtures are consistent with these equations. To this extent, these results confirm implicitly the correctness of the statistically calculated distributions. Previously they have received indirect substantiation from their applicability to the analysis of viscosities of polymer mixtures,[2] and to the degradation of polyesters by alcohols.[3]

The question may arise as to how one might synthesize a linear polyester having some other distribution. The conversion of cyclic esters to linear polyesters, investigated extensively by Carothers and co-workers,[10,11] is of particular interest in this connection. They have shown[10] that the conversion of the cyclic monomer to linear polymer is conditioned by the presence of small amounts of substances capable of providing functional groups to which the monomers may add successively. For example, in the case of a cyclic ester such as δ-valerolactone, a trace of water may yield the hydroxy acid, with which the lactone may then react as follows

$$\text{HORCOOH} \xrightarrow{+\ \overline{\text{ORCO}}} \text{HORCOORCOOH} \xrightarrow[\text{etc.}]{+\ \overline{\text{ORCO}}} \quad (24)$$

The addition of the lactone to the linear molecule of increasing length is an ester interchange,[12] which may be very rapid or negligibly slow, depending on the stability of the cyclic monomer, which in turn depends on the size of the ring.[10,11] Bezzi and co-workers[13] have found that lactide is similarly converted to a linear polymer of lactic acid and at a rate which depends directly on the amount (very small) of water added. On the basis of this observation they have discarded the Carothers mechanism (24) in favor of a process consisting of hydrolysis of the lactide followed by polymerization by interesterification. Actually their results do not contradict the much more plausible mechanism (24). Addition of water merely in-

(10) W. H. Carothers, G. L. Dorough and F. J. van Natta, THIS JOURNAL, **54**, 761 (1932).

(11) See also, W. H. Carothers, J. A. Arvin and G. L. Dorough, *ibid.*, **52**, 3292 (1930); W. H. Carothers, *Chem. Rev.*, **8**, 353 (1931); J. W. Hill and W. H. Carothers, THIS JOURNAL, **55**, 5031 (1933); F. J. van Natta, J. W. Hill and W. H. Carothers, *ibid.*, **56**, 455 (1934).

(12) Since esters generally interchange with alcohols much more readily than with acids, it is presumed that addition of lactone in (24) occurs predominantly at the hydroxyl end of the chain.

(13) S. Bezzi, L. Ricoboni and C. Sullam, *Mem. accad. Italia, Classe sci. fis., mat. nat.*, **8**, 127 (1937); S. Bezzi and B. Angeli, *Gazz. chim. ital.*, **68**, 215 (1938).

creases the concentration of functional groups to which monomers may add, thereby increasing the over-all rate of conversion of monomer to polymer.

Successive addition of cyclic ester monomers to a fixed number of molecules bearing a suitable functional group (*e. g.*, OH) as in (24) is strictly analogous to the polymerization of ethylene oxide,[14] for which the distribution of species is represented by Poisson's distribution function[15]

$$N_x = Ne^{-\nu}\nu^x/(x-1)! \qquad (25)$$

where

$$\nu = \overline{DP}_n - 1$$

The entropy of heterogeneity for this distribution, obtained by substituting equation (25) in (6) (see Appendix), is given to a close approximation when the degree of polymerization is large by

$$\Delta S_h = \frac{R}{2}[1 + \ln(2\pi\overline{DP}_n)] \qquad (26)$$

The distribution (25) covers a much narrower range than the equilibrium distribution. Correspondingly, its entropy of heterogeneity is less than for the equilibrium distribution as given by equation (7.2). Therefore, if interchange between polymer molecules occurs, the distribution (25) will be broadened toward the equilibrium distribution (1).

The actual distribution of species which will be obtained from the conversion of a cyclic monomer to linear polymer will depend on the extent to which polymer–polymer interchange accompanies the primary addition process (24). If the latter process, an ester interchange between a terminal functional group and a cyclic monomer, is much more rapid than interchange with ester groups of the polymer molecules, the comparatively sharp Poisson distribution (25) will be obtained. In the opposite situation, the more heterogeneous equilibrium distribution (1) should be found. In intermediate cases, distributions of intermediate heterogeneity will be produced.

Other condensation polymers, *e. g.*, the polyamides and polyanhydrides investigated by Carothers and co-workers,[11] are subject to analogous interchange processes. These doubtless can be treated in complete analogy with the polyesters. The concept of a most probable distribution is equally applicable to three-dimensional condensation polymers, although the situation here becomes much more complex. The most probable distributions for equal stability of all possible interunit linkages have been treated by statistical methods in previous publications[16] on three-dimensional polymers.

(14) H. Staudinger, "Die hochmolekularen organischen Verbindungen," J. Springer, Berlin, 1932; S. Perry and H. Hibbert, THIS JOURNAL, **62**, 2599 (1940).

(15) P. J. Flory, THIS JOURNAL, **62**, 1561 (1940).

Appendix

Entropy of Heterogeneity for a Poisson Distribution of Species.—Substituting equation (25) in (6)

$$\Delta S_h = Re^{-\nu}\sum_{x=1}^{\infty}\left\{\frac{\nu^{x-1}}{(x-1)!}[\nu - (x-1)\ln\nu + \ln(x-1)!]\right\}$$

Shifting the lower limit on the summation to $x = 0$ and replacing x by $x + 1$, and introducing Stirling's approximation for $\ln x!$

$$\Delta S_h = R\left[e^{-\nu}\sum_{x=0}^{\infty}\frac{\nu^x}{x!}\left(\nu - x + \frac{1}{2}\ln 2\pi\right) + e^{-\nu}\sum_{x=0}^{\infty}\frac{\nu^x}{x!}x\ln(x/\nu) + \frac{e^{-\nu}}{2}\sum_{x=0}^{\infty}\frac{\nu^x}{x!}\ln x\right] \qquad (27)$$

Since $\sum_{x=0}^{\infty}\frac{\nu^x}{x!} = e^{\nu}$, the first summation reduces readily to $\frac{R}{2}\ln(2\pi)$. The second and third terms may be evaluated by approximate methods valid when ν is large. Nearly all of the contributions to these sums come in the vicinity of $x = \nu$. Hence, in the case of the second term, we expand $\ln(x/\nu)$ about $(x/\nu) = 1$, giving

$$e^{-\nu}\sum_{x=0}^{\infty}\left\{\frac{\nu^x}{x!}x\left[\left(\frac{x}{\nu}-1\right) - \frac{1}{2}\left(\frac{x}{\nu}-1\right)^2 + \frac{1}{3}\left(\frac{x}{\nu}-1\right)^3 - \ldots\right]\right\}$$

Summation over five terms of the series yields

$$1 - \tfrac{1}{2}(1 + 1/\nu) + \tfrac{1}{3}(4/\nu + 1/\nu^2) - \tfrac{1}{4}(3/\nu + 11/\nu^2 + 1/\nu^3) + \tfrac{1}{5}(25/\nu^2 + 26/\nu^3 + 1/\nu^4)$$

To a very close approximation when ν is large, the second term is given therefore by

$$^1/_2(1 + {}^1/_{6\nu}) \cong {}^1/_2$$

The third term may be written

$$\frac{e^{-\nu}}{2}\sum_{x=0}^{\infty}\frac{\nu^x}{x!}[\ln(x/\nu) + \ln\nu]$$

Expanding $\ln(x/\nu)$ in series as above and summing each term, we obtain a power series in $1/\nu$ the first term of which is $-1/2\nu$. Hence, the contribution of the third term is

$$1/2[\ln\nu - 1/2\,\nu + \ldots]$$

(16) P. J. Flory, *ibid.*, **63**, 3083, 3091, 3096 (1941).

Combining the above values for the three terms in (27)

$$\Delta S_h = \frac{R}{2}[\ln(2\pi\nu) + 1 - 1/3\nu - \ldots] \quad (28)$$

Equation (28) reduces to (26) when ν is replaced by $\overline{DP}_n$ and series terms of the order of $1/\nu$ or smaller are neglected.

Summary

The individual molecules of a linear polyester have only a temporary existence when heated to a suitable temperature, due to the occurrence of ester interchange between an ester group of one polymer molecule and the terminal functional group of another. While such processes have no effect on the number average degree of polymerization, they may modify the distribution of species. Such considerations lead to the concept of an entropy of heterogeneity and of an equilibrium size distribution; the latter is identical with that obtained directly by random poly-condensation.

The transformation in the distribution of species in a mixture of polyesters has been observed by viscosity measurements. The results confirm the theoretical predictions.

The conversion of a cyclic ester (lactone) to a linear polyester should yield a much narrower distribution of species than is obtained by poly-condensation, but if ester interchange occurs between the polymer molecules subsequent to their initial formation, the distribution will be broadened.

ELIZABETH, NEW JERSEY RECEIVED JUNE 5, 1942

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Dipole Moments in the Vapor State and Resonance Effects in Some Substituted Benzenes

BY EVERETT C. HURDIS AND CHARLES P. SMYTH

The influence of resonance upon the dipole moment of a molecule containing a single polar group has been observed in both aromatic and unsaturated aliphatic molecules and the mutual effects of two polar groups in an aromatic molecule have been noted in a few cases, such as that of *p*-nitroaniline. In the case of two identical groups para to one another on the benzene ring, these mutual effects upon the dipole moments cancel each other and cannot, therefore, be detected, while in the ortho position, the mutual inductive effects of the two groups tend to obscure any effect of the resonance of one upon that of the other. It was hoped that, in spite of the smallness of the differences between the different carbon–halogen moments, accurate determinations in the vapor state of the moments of para-dihalogenated benzenes containing two different halogens might give quantitative evidence of the differences in resonance effects of the halogens. Unfortunately, the possibility of the presence of small quantities of the ortho-disubstituted benzenes as impurities in the samples of the para-compounds, which were too small for extensive purification, reduces the presumed accuracy of the results obtained for these compounds. Measurements upon iodobenzene and confirmation of moment values already in the literature for chloro- and bromobenzene were carried out to check the precision of the measurements and facilitate the interpretation of the results for the dihalogenated benzenes. Measurements were also made upon very pure samples of *o*-xylene and *p*-xylene with the object of observing possible small mutual induction or resonance effects of two adjacent methyl groups and of checking the group moment value to be assigned to a methyl group attached to a benzene ring.

Purification of Materials

Chlorobenzene.—Material from the Eastman Kodak Company was dried over calcium chloride and fractionally distilled; b. p. 130.5° (755 mm.).

Bromobenzene.—Material from the Eastman Kodak Company was dried over calcium chloride and fractionally distilled; b. p. 154.7° (753 mm.).

Iodobenzene, Sample I.—Material from the Paragon Testing Laboratories was fractionally distilled in a column of fourteen theoretical plates; b. p. 188.3° (762 mm.).

Iodobenzene, Sample II.—Iodobenzene was prepared by the method of "Organic Syntheses," Collective Volume I, p. 316, an all glass system being used. Fractionation gave 234 g. of material boiling between 188.2 and 188.5° (760 mm.). This was further distilled under low pressure, the main fraction (b. p. 98° at 37 mm.) being used for the measurements. The freezing point of this sample was measured by means of a platinum resistance thermometer

and found to be −31.8° ("International Critical Tables" gives −31.4°).

p-**Fluorobromobenzene.**—About twelve grams of material from the Eastman Kodak Company (n^{20}D 1.5279, $n^{21.8}$D, 1.5270) was sealed into a trap connected with the gas apparatus. For measurement, a simple fractionation was made by distilling the first 3 g. under vacuum into another trap, and the middle 6 g. into the U-tube from which vapor was introduced into the gas cell.

p-**Fluoroiodobenzene.**—Ten grams of material from the Eastman Kodak Company ($n^{21.8}$D 1.5794) was purified by vacuum distillation in the gas apparatus directly before each measurement, as in the case of the *p*-fluorobromo compound.

p-**Fluoronitrobenzene.**—Material from the Eastman Kodak Company ($n^{23.6}$D 1.5304, n^{25}D 1.5294) was purified by vacuum distillation by the method used for the two dihalogenated benzenes.

o-**Dichlorobenzene.**—A special 99.4% grade of material kindly given us by the Heyden Chemical Corporation was used without further purification; b. p. 180.3° (750 mm.); m. p. −17.1°; n^{25}D 1.5486; n^{20}D 1.5513. "International Critical Tables" gives normal boiling point 179°, melting point −17.6°, n^{20}D 1.549.

o- **and** *p*-**Xylene.**—The hydrocarbons used in this work were supplied as a part of the American Petroleum Institute Pure Hydrocarbon Program. They were prepared and purified at the Pure Hydrocarbon Laboratory, Department of Chemistry, operating as project No. 31 of the Ohio State University Research Foundation. A full description of these products will be published at a later date.

Experimental Results

The dielectric constants of the vapors were measured with the apparatus and, essentially, the same technique that has been previously described.[1] A polarization value, P, was obtained at an absolute temperature, T, by measurements over a wide range of pressure. The value of P given by each such run is shown in Table I, as is also the corresponding value of the dipole moment μ calculated as $\mu = 1.281 \times 10^{-20}[(P - MR_D)T]^{1/2}$. For the dihalogenated benzenes, many of the values represent the averages of two or more runs. The molar refraction for the sodium D line, MR_D, is listed for each compound in Table II together with the average of the moment values in Table I. The moment of fluorobenzene, which is included in Table II for purposes of comparison, has been recalculated from previous measurements,[2] by the use of MR_D instead of the total induced polarization given by temperature dependence without consequent alteration in value. The few measurements on chloro- and bromobenzene were run primarily as a check upon the absolute accuracy of the determinations. The polarization values for chlorobenzene, 72.2 and 72.3 at 436.1°K., are in excellent agreement with

(1) Wiswall and Smyth, *J. Chem. Phys.*, **9**, 352 (1941).
(2) McAlpine and Smyth, *ibid.*, **3**, 55 (1935).

TABLE I

DIPOLE MOMENTS AND DEPENDENCE OF POLARIZATION UPON TEMPERATURE

T, °K.	P	$\mu(\times 10^{18})$
	Chlorobenzene	
435.8	73.1	1.73
436.1	72.2	1.72
436.1	72.3	1.72
	Bromobenzene	
455.8	75.8	1.77
455.8	75.7	1.77
	Iodobenzene (Sample I)	
476.1	78.2	1.75
476.1	79.7	1.78
495.4	76.8	1.75
495.4	75.5	1.72
495.4	72.6	1.65
495.4	76.5	1.74
508.3	74.8	1.73
523.2	75.2	1.76
	Iodobenzene (Sample II)	
433.0	77.1	1.64
433.0	78.5	1.67
433.0	80.0	1.70
458.9	75.0	1.64
463.1	72.9	1.60
463.1	79.3	1.75
472.3	74.6	1.66
473.0	74.4	1.66
487.1	75.2	1.70
487.1	76.0	1.71
	p-Fluorobromobenzene	
436.1	37.4	0.51
444.1	37.6	.53
449.0	37.8	.55
454.7	37.4	.53
461.6	37.3	.52
490.5	37.1	.52
523.9	37.4	.57
	p-Fluoroiodobenzene	
470.1	49.4	0.89
492.4	49.1	.89
	p-Fluoronitrobenzene	
487.9	135.1	2.865
499.4	132.3	2.86
509.3	131.0	2.87
523.7	128.2	2.87
	o-Dichlorobenzene	
444.9	122.3	2.51
473.3	117.5	2.52
493.1	114.4	2.52
	113.7	2.50
	113.7	2.50
507.6	111.6	2.51
522.7	109.4	2.51

TABLE I (*Concluded*)

T, °K.	P	$\mu(\times 10^{18})$
p-Xylene (A. P. I. Hydrocarbon Laboratory, Manifest No. 15-P)		
447.4	37.7	(0)
447.4	37.7	(0)
447.4	37.6	(0)
o-Xylene (A. P. I. Hydrocarbon Laboratory, Manifest No. 13-P)		
412.5	(43.7)	(0.65)
433.1	43.2	.63
462.1	42.8	.62
497.3	42.3	.61
512.1	42.2	.62

TABLE II

MOLAR REFRACTIONS AND AVERAGE MOMENT VALUES

	MR_D	$\mu(\times 10^{18})$
Fluorobenzene	26.0[a]	1.57
Chlorobenzene	31.1[b]	1.72
Bromobenzene	34.0[b]	1.77
Iodobenzene	39.2[b]	1.70
p-Fluorobromobenzene	33.7[c]	0.5
p-Fluoroiodobenzene	39.2[c]	.9
p-Fluoronitrobenzene	32.4[e]	2.87
p-Xylene	36.0[d]	(0)
o-Xylene	35.8[d]	0.62
o-Dichlorobenzene	36.0[c]	2.51

[a] Calculated from data in "International Critical Tables." [b] Landolt–Börnstein (5th ed.). [c] Measured in this Laboratory. [d] Calculated from data furnished by Professor C. E. Boord. [e] Calculated from refractions in Landolt–Börnstein (5th ed.).

the value 72.5 obtained from the data of McAlpine and Smyth[2] by interpolation at this temperature and the values for bromobenzene, 75.8 and 75.7 at 455.8°K. are indistinguishable from the value 75.8 obtained from the data of Groves and Sugden[3] by interpolation. The moment values calculated from these polarizations are slightly higher, 0.02 for chlorobenzene and 0.06 for bromobenzene, than the values obtained in the earlier work by the use of total induced polarization instead of molar refraction. This neglect of the small atomic polarization which may cause the total induced polarization to be slightly higher than MR_D, is evidently unimportant in the case of the monohalogenated benzenes, but is serious in that of the *p*-dihalogenated benzenes. In view of the symmetry of the *p*-xylene molecule, its moment may safely be assumed to be zero. Its polarization was measured only in order to obtain a total induced polarization value, which, as a fair approximation, could be taken equal to that of *o*-xylene and thus used, instead of the MR_D value, to calculate the dependable value for the latter compound in Table II. The difference of 0.2 in the MR_D values for the two compounds indicates that the total polarization of *p*-xylene may differ by a few tenths of a unit from the induced polarization of *o*-xylene. Decomposition of the iodobenzene limits the range of temperature over which the measurements may be made and, probably, causes the unusually large variation in the moment value for it in Table I. The two samples of satisfactory purity give mean moment values differing by 0.07 from each other. The average of these two in Table II is from 0.10 to 0.15 higher than the value to be expected for the vapor on the basis of the values obtained from solution measurements.[4,5] In view of this, the value 1.70 may be high, but it is, probably, less than 0.1 high.

(3) Groves and Sugden, *J. Chem. Soc.*, 971 (1935).

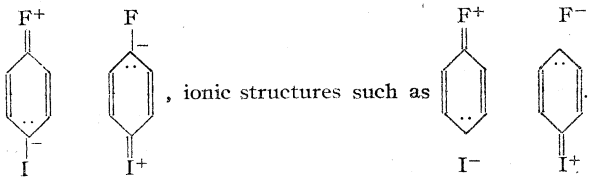
Discussion of Results

It happens that the chloro-, bromo- and iodobenzene moment values in Table II have almost the same differences from one another as the corresponding butyl halides.[6] The fluorobenzene moment is lower than that of chlorobenzene, as the alkyl fluoride moment is lower than that of the alkyl chloride.[7] The slight increases in the values of the bromobenzene and iodobenzene moments lessen the calculated reduction in moment by contributions from structures with double-bonded positive halogens and, hence, show the amounts of double bond character in the C–Cl, C–Br, and C–I bonds to be more nearly equal than previously supposed.[6]

The moment value of *p*-fluorobromobenzene in Table II is 0.3 higher than the difference between the moments of fluoro- and bromobenzene, to which it should be equal in the absence of complicating factors. The presence of a small amount of *o*-fluorobromobenzene as an impurity together with a larger atomic polarization than is assumed in the use of MR_D as the total induced polarization could account for this discrepancy, which is, however, a little large to arise from these causes. The moment value for *p*-fluoroiodobenzene is 0.8 higher than the small difference 0.1 between the moments of fluorobenzene and iodobenzene. It would require about 10% of *o*-fluoroiodobenzene present as an impurity to account for this discrepancy, or, at least, 5% of the ortho compound plus an abnormally high atomic polarization

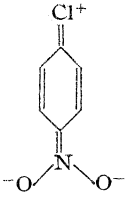
(4) Parts, *Z. physik. Chem.*, **B10**, 264 (1930).
(5) Tiganik, *ibid.*, **B13**, 425 (1931).
(6) Smyth, THIS JOURNAL, **63**, 57 (1941).
(7) Smyth and McAlpine, *J. Chem. Phys.*, **2**, 499 (1934).

value, both of which possibilities are somewhat remote. The larger moment of the *p*-fluoroiodobenzene seems to correspond to the fact that the electronegativity difference between fluorine and iodine is greater than that between fluorine and bromine, the difference between the two moments coinciding with the I-Br bond moment, 0.4.[8] The moments of the two compounds could be accounted for by writing for their molecules, in addition to their normal covalent structures and their quinoid structures of the type



The much greater electronegativity of the fluorine would make the ionic structure with negative fluorine predominate over that with negative iodine or bromine, giving a moment opposite in direction to that to be expected from the small differences between the moments of the monosubstituted benzenes. These combinations of structures should lead to small moments of the order of magnitude of those observed and differing in value according to the electronegativity differences as observed.

In order to obtain a moment value for nitrobenzene directly comparable with the values in Table II, the previous data[2] were recalculated with MR_D instead of the total induced polarization. The difference between the moment value, 4.25, thus obtained and the moment of fluorobenzene in Table II gives a value 2.68 for *p*-fluoronitrobenzene, 0.19 lower than the observed value in Table II. Although part of this difference could arise from the presence of *o*-fluoronitrobenzene as an impurity in the para compound, it has been previously pointed out[9] that the moment of *p*-chloronitrobenzene, 2.78, measured[10] for the vapor of a carefully purified sample is high, probably because of contributions from highly polar structures such as



The elevation, 0.25, of the moment above the calculated value, 2.53, is slightly larger than that in the case of *p*-fluoronitrobenzene, 0.19, which, because of possible impurity, represents an upper limit for the elevation. It appears that, in the case of these two compounds, the presence of the nitro group effects a greater increase in the amount of double bond character in the C–Cl than in the C–F bond.

The polarization of the *p*-xylene vapor in Table I is 0.6 higher than the value 37.07 found for the same sample in the liquid state at 293.1°K. by Dr. P. F. Oesper, a difference of the magnitude and direction normally found between liquid and vapor values. The absence of error due to impurity and to neglect of atomic polarization should make the moment value of *o*-xylene in Table II extremely accurate. It differs by only 0.01 from the value previously used for the moment of two *o*-methyl groups[9] and the natural assumption of an angle of 60° between the two group moments leads to a calculated value 0.36 for the group moment of methyl on a benzene ring in excellent agreement with the moment of toluene, 0.35,[11] on which the above-mentioned value for the two *o*-methyl groups was based. The excellence of this agreement shows, in harmony with previous conclusions, that any mutual inductive or resonance effects between the two ortho-methyl groups are too small to detect by means of dipole moments. It may be mentioned that the use of MR_D instead of the *p*-xylene polarization in calculating the *o*-xylene moment would give a value 0.73 instead of 0.62 and 0.42, instead of 0.36, for the methyl–benzene group moment. Similar use of MR_D instead of the total induced polarization for toluene would give a moment value 0.45 instead of 0.35. This does not mean, however, that the group moment value 0.42 or 0.45 should be used for consistency in calculating the moments of more polar molecules, for which MR_D values have been used in obtaining the moment from the experimental data, since large moment values are little affected by neglect of atomic polarization. The value 0.36 is, therefore, to be regarded as correct for the group moment produced by the attachment of a methyl group to a benzene ring.

The moment of *o*-dichlorobenzene was measured because of the fact that the value, 2.16, obtained by Groves and Sugden[10] from vapor meas-

(8) Smyth, *J. Phys. Chem.*, **41**, 209 (1937).
(9) Smyth and Lewis, THIS JOURNAL, **62**, 721 (1940).
(10) Groves and Sugden, *J. Chem. Soc.*, 1782 (1937).
(11) McAlpine and Smyth, THIS JOURNAL, **55**, 453 (1933).

urements was 0.1 lower than the value found by several investigators from measurements in solution, although the solvent effect, which, in the case of chlorobenzene, lowers the solution value to such an extent that the gas value is 10% higher than that measured in solution, should lead to a similarly lower value for *o*-dichlorobenzene.[9] Since addition of 10% to the solution value, 2.27, for *o*-dichlorobenzene gives a value, 2.50, practically identical with the newly determined gas value, 2.51, in Table II, it is evident that there is no anomaly in the solvent effect for this compound.

The writers wish to express their thanks to Professor C. E. Boord of Ohio State University and Dr. George Calingaert of the Ethyl Gasoline Corporation for the xylenes and to Dr. P. D. Hammond of the Heyden Chemical Corporation for the *o*-dichlorobenzene used in this investigation.

Summary

The dielectric constants of the vapors of chloro-, bromo-, iodo-, *p*-fluorobromo-, *p*-fluoroiodo-, *p*-fluoronitro- and *o*-dichlorobenzene, and of *p*- and *o*-xylene have been measured and used to calculate the dipole moments of the molecules. The moment values found for chlorobenzene and bromobenzene agree closely with those in the literature, while that for iodobenzene is slightly higher than would be expected on the basis of previous measurements in solution. The moment value of *o*-dichlorobenzene is much higher than the one in the literature and in excellent agreement with that obtained by correcting the solution value for solvent effect. The data for the two xylenes give an accurate value, 0.36, for the group moment produced by the attachment of a methyl group to a benzene ring. The moments found for the *p*-disubstituted benzenes are larger than the differences between the corresponding mono-substituted compounds by amounts which may be accounted for by resonance.

PRINCETON, NEW JERSEY RECEIVED JUNE 22, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Condensation Products of Ketene with Ketones[1]

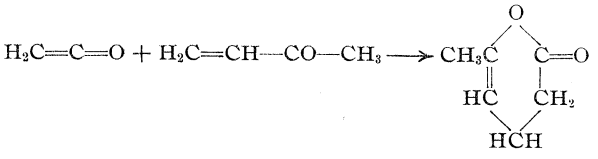
BY B. H. GWYNN WITH ED. F. DEGERING

The reactions of ketene have been studied rather extensively. It has been found to act as the anhydride of acetic acid. Although it is commonly prepared from acetone and therefore contaminated with it to some extent, no one appears to have noted a reaction between the two. Investigations have been reported in which the reactivity of ketene with ketones was studied without a catalyst[2] and in the presence of anhydrous sodium or potassium acetate.[3] No reaction was noted. Acetone has been used as a solvent in the acid catalyzed acetylation of carbohydrates[4] with ketene. A reaction undoubtedly took place in these cases but escaped notice. Similarly, in the acid catalyzed acetylation of butyl alcohol,[5] the ketene was contaminated with acetone, and the two probably reacted to a limited extent.

This investigation has shown that ketene does react with ketones. In the presence of a small amount of sulfuric acid the product is the acetate of the enol form of the ketone, as indicated by the equation

$$H_2C{:}C{:}O + H{\cdot}O{\cdot}C(CH_3){:}CH_2 \left(\rightleftarrows CH_3{\cdot}CO{\cdot}CH_3/H_2SO_4\right) \longrightarrow CH_3{\cdot}CO{\cdot}O{\cdot}C(CH_3){:}CH_2$$

Since the completion of this work, ketene has been reported to react with vinyl ketones to yield cyclic esters of the enol form of *delta* keto acids,[6] an entirely different type of reaction from that observed in this study, as indicated



Experimental Part

Apparatus.—Ketene was generated in a lamp which was constructed in the same manner as one described by Hurd.[7] In order to separate acetone from the ketene, the

(1) Abstract of a thesis by B. H. Gwynn, submitted to the faculty of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry, June, 1942. Present address, Westvaco Chlorine Products Corp., Carteret, New Jersey.

(2) Staudinger and Klever, *Ber.*, **41**, 594 (1908).

(3) Hurd and Williams, THIS JOURNAL, **58**, 962 (1936).

(4) Hurd, Cantor and Roe, *ibid.*, **61**, 426 (1939).

(5) Morey, *Ind. Eng. Chem.*, **31**, 1129 (1939).

(6) U. S. Patent 2,265,165, Dec. 9, 1941; *C. A.*, **36**, 1614 (1942).

(7) Hurd, *J. Org. Chem.*, **5**, 122 (1940).

pyrolysis gases were passed through two water-cooled spiral condensers, then through two cold traps. The first of these cold traps was kept at 0°, the second at −35 to −40°. The resultant gas was practically acetone-free and was passed into the material with which it was desired to have it react. The inlet tube was placed in such a manner as to direct the entering gas into a rapidly revolving stirrer. The temperature of the reaction tube was maintained at the desired point by means of an oil-bath. An expansion chamber surrounded by an ice-bath was placed so as to return volatile liquids to the reactor. The output of the generator, determined by absorption in caustic,[7] was approximately 0.25 mole (hr). All fractionations were made with a modified Podbielniak column.

Materials Used.—The ketones used in this work were either purchased or prepared by standard methods. In either case they were distilled or fractionated before use except for the acetone, which was Mallinckrodt analytical reagent grade, and the acetophenone, which was Eastman Kodak Company white label grade. The 2,4-dinitrophenylhydrazones were prepared from each of the ketones except 2,6-dimethyl-4-heptanone and 2,4-dimethyl-3-pentanone and found to melt properly. The semicarbazides were prepared from 2,6-dimethyl-4-heptanone and 2,4-dimethyl-3-pentanone and the melting points checked with those in the literature.

Reaction of Ketene with Acetone.—Ketene was passed into a well-stirred solution of one mole of acetone and a trace of sulfuric acid at the rate of 0.25 mole per hour. Forty-one runs were made to determine optimum conditions. The best reaction temperature at atmospheric pressure was found to be about 55°, and the optimum yield of the enol acetate was obtained with 0.007 mole of sulfuric acid and 0.81 mole of ketene per mole of acetone.

In a run which approximated optimum conditions, 0.87 mole of ketene was passed into a solution of 0.007 mole of sulfuric acid in one mole of acetone at 55°. The product was then fractionated to give 39.5 ml. of product boiling in the range 90–96.5°, leaving 8.5 ml. of residue; conversion, 45%. The residue was shown to be principally diketene with some higher polymers and acetic anhydride.

Identification of Product.—Several 90–96.5°-fractions were refractionated and a material obtained which boiled at 96° (750 mm.). This had a sharp, ester-like odor. It reacted quite vigorously with bromine and reduced alkaline permanganate readily. Metallic sodium appeared to induce polymerization. These qualitative observations suggested that the product might be 1-propen-2-ol acetate. This compound was previously prepared by Nieuwland[8] from acetic acid and methylacetylene. He reported a b. p. of 92–94° (736 mm.). The saponification equivalent, as determined, was 106.0, 105.3. Calculated value for 1-propen-2-ol acetate is 100.07. The method is reported to give high values for esters of tertiary alcohols.[9] The 2,4-dinitrophenylhydrazone was prepared by the standard method[10] and a derivative, m. p. 125°, obtained. The derivative prepared from pure acetone melted at 126°, and a mixture of the two melted at 125.5°, thereby indicating the identity of the two. The formation of this derivative occurs in acid solution so that 1-propen-2-ol acetate should revert to acetic acid and acetone.

Anal. Calculated for $C_5H_8O_2$: C, 59.96; H, 8.06. Found: C, 60.03; H, 8.18.

Reaction of Ketene with 2-Butanone.—Several runs were made in which catalyst concentration, temperature and amount of ketene introduced were varied. Optimum conditions, however, were not determined. Best results were obtained by passing ketene, at the rate of 0.25 mole per hour, into a solution of 70 ml. of 2-butanone and 0.007 mole of sulfuric acid for two and one-half hours at 75°. The product was fractionated and 40 ml. of a fraction, b. p. 112–122°, obtained, leaving 5.5 ml. of residue. Refractionation of the 112–122°-fraction gave principally material with a b. p. of 118–120° (751.5 mm.), which could not be further purified by this method. The 2,4-dinitrophenylhydrazone was prepared and found to melt at 110°. A similar derivative prepared from the starting ketone melted at 112°, and a mixture of the two melted at 111.25°. The saponification equivalent was determined.[9] Calculated value for 1-buten-2-ol acetate or 2-buten-2-ol acetate is 114.08. Found: fraction boiling 118–19°, 118.4, 116.4; fraction boiling 119–20°, 113.9, 114.8. The product is, therefore, the acetate of the enol form of 2-butanone but, probably, is a mixture of both possible forms; conversion, 47%.

Phosphoric Acid and *p*-Toluenesulfonic Acid as Catalysts.—Ketene was passed into a solution of 70 ml. of 2-butanone and 3 drops of 85% phosphoric acid for five hours at 55°. The product was fractionated and found to yield only 2 ml. of material, b. p. 112–122°. A similar run using 3 drops of sulfuric acid gave 20 ml. of material boiling in this range. Another run was made in which ketene was passed into 70 ml. of 2-butanone for three and one-half hours at 55° and a small amount of *p*-toluenesulfonic acid. The product was fractionated and it was found to yield no distillate in the range 112–122°.

Reaction of Ketene with Acetophenone.—Ketene was passed through a solution of 3 drops of sulfuric acid in 70 ml. of acetophenone for three and one-half hours at 64°. This product was fractionated and 25 ml. of product obtained, b. p. 85° (2 mm.). The saponification equivalent was determined.[9] Calculated for 1-phenylethenol acetate, 162.08. Found: 160.4. The 2,4-dinitrophenylhydrazone was prepared[10] and found to melt at 243°; derivative from acetophenone, m. p. 244°, mixed m. p. 243.5°, conversion, 19%.

Reaction of Ketene with Mesityl Oxide.—Ketene was passed into a solution of 3 drops of sulfuric acid in 70 ml. of mesityl oxide for three and one-half hours at 75°. The product was fractionated to give 62 ml. of material with a b. p. of 57.5–58° (10 mm.). Calculated saponification equivalent[9] for 4-methyl-1,3-pentadiene-2-ol acetate 140.10. Found: 146.4, 147.0. The 2,4-dinitrophenylhydrazone[10] melted at 200°; derivative from mesityl oxide, m. p. 199°, mixed m. p. 199°. Since this is close to the melting point of the reagent, a mixed melting point was determined for a mixture of reagent and derivative prepared from the ester (m. p. 177–180°). Whereas the derivative formed immediately when the ketone was used, a period of several minutes was necessary when the ester was used. This was the behavior noted with all of these

(8) Nieuwland, THIS JOURNAL, **56**, 1802 (1934).

(9) Redeman and Lucas, *Ind. Eng. Chem., Anal. Ed.*, **9**, 521 (1937).

(10) Shriner and Fuson, "Identification of Organic Compounds," J. Wiley and Sons, Inc., New York, N. Y., 1940.

esters. Conversion, 46.8%. This ester showed some tendency to polymerize to a tar when heated at too high a temperature.

Reaction of Ketene with 2,4-Dimethyl-3-pentanone.—A total of three runs was made with 2,4-dimethyl-3-pentanone at temperatures up to 117°. In one of these runs ketene was passed through a solution of 5 drops of sulfuric acid in 70 ml. of the ketone for four and one-quarter hours at 117°. Upon fractionating only the ketone and a small amount (1.4 ml.) of diketene were obtained. The conditions employed in the other runs were less severe and likewise yielded no ester.

Reaction of Ketene with Pinacolone.—Ketene was passed into a solution of 15 drops (0.007 mole) of sulfuric acid in 70 ml. of pinacolone for two and two-thirds hours (0.66 mole) at 110°. Upon fractionation, 3.5 ml. of a fraction was obtained, b. p. 134–135° (752 mm.). The saponification equivalent[9] of this was only 88.3 as compared with a calculated value of 142 for 3,3-dimethyl-1-buten-2-ol acetate. This probably indicates contamination with diketene, boiling only a few degrees lower. The 2,4-dinitrophenylhydrazone was prepared[10] and separated into two fractions, one of which melted high, the other at 123.5°. The derivative prepared from the ketone melted at 125° and a mixture of the two at 124.5°.

Determination of Physical Properties.—The boiling points, densities and refractive indices for the compounds (or mixtures of isomers) were determined and are shown in Table I.

TABLE I

PHYSICAL PROPERTIES OF ENOL ACETATES

Acetate of	B. p. °C.	Mm.	$n^{20}D$	d^{25}_{25}
Acetone	96	750	1.4001	0.9308
2-Butanone	118–120	751.5	1.4111	.9043
Mesityl oxide	57.5–58	10	1.4611	.9250
Acetophenone	85	2	1.5329	1.0715
4-Methyl-2-pentanone	143–145	741.5	1.4164	0.8695
2-Heptanone	112–114	93	1.4262	.7488
2-Octanone	108	42.5	1.4283	.8692
2,6-Dimethyl-4-heptanone	74	12	1.4281	.8541
Cyclohexanone	99	48	1.4573	.9952

Discussion

In nearly all of the cases investigated, ketene reacted with ketones to form the acetate of the enol form. The exceptions are worthy of mention since they are those which would be expected to react with most difficulty. Diisopropyl ketone, with only two *alpha* (or 4-position) H-atoms to the carbonyl group, did not react at all, whereas pinacolone with three *alpha* (or 4-position) H-atoms, reacted only slightly. In every case where four or more *alpha* (or 4-position) H-atoms were present, reaction occurred to an appreciable extent. Acetophenone, with only three such groupings, reacted quite readily but an additional factor is present in this case—namely, the formation of a conjugated system upon enolization. Although the evidence is not complete, the results strongly indicate that ease of reaction with ketene parallels the ease of enolization of the ketone. This is well illustrated by the much greater ease of reaction of mesityl oxide than of 4-methyl-2-pentanone. Mesityl oxide, in one form at least, is a substituted vinyl ketone and in this investigation it did not show any differences in behavior from the saturated ketones. Although both types of derivative would give the same saponification equivalent, the lactone would not be expected to give a 2,4-dinitrophenylhydrazone identical with that of the starting material.

Summary

Ketene has been found to react with ketones possessing three or more *alpha* (or 4-position) H-atoms to yield the enol acetates. The tendency to react appears to be dependent upon the ease of enolization. The presence of a catalyst is necessary, sulfuric acid being the best of those investigated. Optimum conditions were determined for the reaction with acetone. It was found that higher temperatures favor the acetylation reaction whereas at lower temperatures considerable polymerization of the ketene occurs. The amount of catalyst present is also critical.

LAFAYETTE, INDIANA RECEIVED JUNE 8, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

The Halogenation of Certain Esters in the Biphenyl Series. I. The Chlorination of 4-Phenylphenyl Acetate[1]

BY CORA MAY SEGURA SAVOY[2] AND JOHN LEO ABERNETHY

A recent review[3] on the relationship of bactericidal activity to structure of substituted phenols suggested the need for a more direct method of preparation of the 4-(4-halophenyl)-phenols. The bactericidal activity of these substances has not been studied. This paper presents a procedure for direct introduction of chlorine into the desired position of the biphenyl nucleus, namely, the 4′-position, when the 4-position contains an acetyloxy group.

It has been shown that bromination of 4-phenylphenylbenzenesulfonate[4] and 4-phenylphenylbenzoate[5] introduces bromine into the 4′-position of the biphenyl nucleus. Hydrolysis of these brominated esters yields 4-(4-bromophenyl)-phenol. On the other hand, bromination of 4-phenylphenyl acetate[6] introduces bromine in an ortho position to the acetyloxy group, and hydrolysis of this ester yields 2-bromo-4-phenylphenol. This difference has been attributed to the difference in sizes of the groups. Thus, the benzenesulfonyloxy and benzoyloxy groups, being much larger than the acetyloxy group, exhibit greater steric hindrance to bromine. Therefore, bromine is shifted to the 4′-position of the biphenyl nucleus in the case of the larger groups, whereas it enters the 3-position in case of the smaller group.

On the basis of these results it was anticipated that chlorination of 4-phenylphenyl acetate would result in an introduction of chlorine in an ortho position to the acetyloxy group. Such was not found to occur. In contrast to bromination, the halogen in this instance entered the 4′-position. This is indeed surprising, if steric hindrance is the predominant factor, in view of the fact that the chlorine atom is considerably smaller than the bromine atom and presumably less steric hindrance should exist to entrance ortho to the acetyloxy group.

(1) From a portion of a thesis to be submitted by Mrs. Savoy to the Graduate Faculty of the University of Texas in partial fulfillment of the requirements for the degree of Master of Arts.

(2) Present address: Department of Chemistry, Southwestern Louisiana Institute, Lafayette, Louisiana.

(3) Suter, *Chem. Rev.*, **28**, 269 (1941).

(4) Hazlet, THIS JOURNAL, **59**, 1087 (1937).

(5) Hazlet, Alliger and Tiede, *ibid.*, **61**, 1447 (1939).

(6) Hazlet and Kornberg, *ibid.*, **61**, 3037 (1939).

4-Phenylphenyl acetate (II) was prepared from 4-phenylphenol (I) by the method of Kaiser.[7] Chlorination of II in the presence of iodine catalyst gave rise to 4-(4-chlorophenyl)-phenylacetate (III). Hydrolysis of this ester took place readily to give a good yield of the desired 4-(4-chlorophenyl)-phenol (IV). That the chlorine had entered the 4′-position was proved by an independent synthesis of IV.

Benzidine (VII) was converted to 4-(4-chlorophenyl)-aniline (VIII), by means of the Sandmeyer reaction, according to the method used by Täubner[8] as modified by van Alphen[9] for the corresponding iodo compound. Diazotization of VIII gave rise to IV. A mixed melting point of the chlorophenylphenol obtained from VII caused no depression. Furthermore, when the chlorophenylphenol obtained from benzidine was acetylated and a mixed melting point was taken with the chlorination product of II, no depression was noted. This is conclusive evidence that chlorination of II resulted in substitution in the 4′-position.

Previous to the independent synthesis of IV from benzidine, it was noted that the melting point (145–146°) of IV was somewhat close to the melting point (133.5–137°) of 4-(4-chlorophenyl)-2,6-dichlorophenol (XI) as obtained by Colbert, Meigs and Mackin.[10] A mixed melting point of these two substances showed them to be different.

During the course of this investigation it was desirable to prepare 2-chloro-4-phenylphenyl acetate (VI) as well as 4-(4-chlorophenyl)-2,6-dichlorophenyl acetate (XII). This was readily accomplished by acetylation of V and XI, respectively, with acetic anhydride and sodium acetate.

Synthesis of 4-(4-chlorophenyl)-phenol leaves only the fluoro compound unsynthesized in this list of 4-(4-halophenyl)-phenols. The corresponding bromo compound has been prepared from 4-phenylphenyl benzenesulfonate[4] and 4-phenylphenylbenzoate[5] as well as from 4-nitro-4′-bromobiphenyl.[11] The iodo compound has been prepared from benzidine.[9]

(7) Kaiser, *Ann.*, **257**, 95 (1890).

(8) Taübner, *Ber.*, **27**, 2627 (1894).

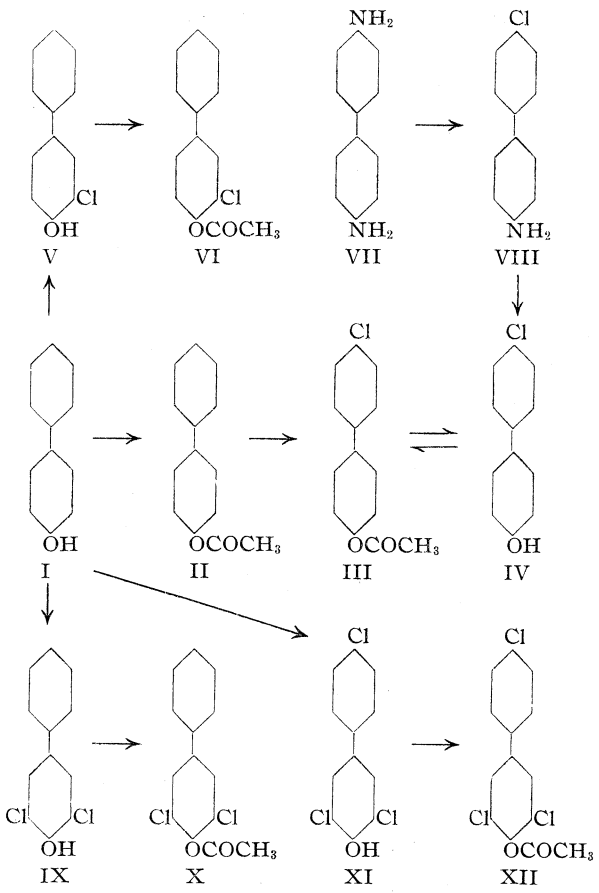
(9) van Alphen, *Rec. trav. chim.*, **50**, 1112 (1931).

(10) Colbert, Meigs and Mackin, THIS JOURNAL, **56**, 202 (1934)

(11) Bell and Robinson, *J. Chem. Soc.*, 1127 (1927).

The essential reactions of this investigation are correlated in Chart I.

CHART I



Experimental Part

4-(4-Chlorophenyl)-phenyl Acetate (III).—Twenty grams of 4-phenylphenyl acetate, prepared in quantitative yield from 4-phenylphenol,[6] was suspended in 100 cc. of carbon tetrachloride. A trace of iodine was added, and a solution of 7.4 g. (10% excess) of chlorine in 75 cc. of carbon tetrachloride was then added, drop by drop, over a period of two hours. The reaction mixture was stirred during this period and for an additional two hours. When the solvent was removed by distillation under reduced pressure, the crude product crystallized out. After two recrystallizations from methanol, the product, obtained as white plates in 47% yield, melted at 113°. This compound has also been recrystallized from ethanol in approximately the same yield.

An attempt to chlorinate 4-phenylphenyl acetate in sunlight without the use of iodine gave only the original ester.

Anal. Calcd. for $C_{14}H_{11}O_2Cl$: Cl, 14.39. Found: Cl, 14.10, 14.22.

Hydrolysis of 4-(4-Chlorophenyl)-phenyl Acetate.—Five grams of the ester (III) was suspended in a solution of 50 cc. of water, 50 cc. of ethanol, and 5 g. of potassium hydroxide, and refluxed for five minutes; the reaction mixture was allowed to cool and poured into twice its volume of water. The clear solution obtained was acidified, and the white precipitate which formed was filtered and washed with water. The product, which was obtained in nearly quantitative yield, melted at 145–146°. (This was identified as 4-(4-chlorophenyl)-phenol by synthesis from benzidine.) Acetylation of the 4-(4-chlorophenyl)-phenol obtained by hydrolysis of III gave an ester which melted at 113° and which did not depress the melting point of III.

Anal. Calcd. for $C_{12}H_9OCl$: Cl, 17.34. Found: Cl, 17.11, 17.19.

4-(4-Chlorophenyl)-phenol (IV).—Twelve and one-half grams of benzidine was suspended in a dilute solution of hydrochloric acid, cooled, and allowed to react with a solution containing 10 g. of sodium nitrite. An additional 12.5 g. of benzidine was added to the reaction mixture, and the liquid was kept in the ice-box for three days.[8] A cold solution of 10% cuprous chloride in hydrochloric acid was then added. The mixture was allowed to come to room temperature, after which it was heated at 60° for two hours.

The 4-(4-chlorophenyl)-aniline hydrochloride which separated as a brown solid was filtered and washed with water. This product was suspended in a dilute solution of hydrochloric acid, cooled, and allowed to react with a solution containing 10 g. of sodium nitrite. After two hours, the mixture was heated to 60° and kept at this temperature for one hour. A dark brown tarry material separated; the product was extracted from this tar with boiling water. After three recrystallizations from chloroform and petroleum ether, the purified product (IV), obtained in 4% yield on the basis of the benzidine used, melted at 145.5°. A mixture of this compound and the chlorophenylphenol obtained from the hydrolysis of 4-(4-chlorophenyl)-phenyl acetate melted at 146°. Acetylation of 4-(4-chlorophenyl)-phenol obtained from benzidine gave an ester which, after recrystallization from ethanol, melted at 113° and did not depress the melting point of the ester prepared by the chlorination of II.

Anal. Calcd. for $C_{12}H_9OCl$: Cl, 17.34. Found: Cl, 17.21, 17.30.

2-Chloro-4-phenylphenyl Acetate (VI).—A mixture of three grams of 2-chloro-4-phenylphenol[10] and one-fourth molecular proportion of anhydrous sodium acetate was gently refluxed for ten minutes in an excess of acetic anhydride. The reaction mixture was allowed to cool and poured into five volumes of water. The ester was collected by filtration and twice recrystallized from ethanol. The white needles obtained in 92% yield melted at 68°.

Anal. Calcd. for $C_{12}H_9OCl$: Cl, 14.39. Found: Cl, 14.17, 14.22.

2,6-Dichloro-4-phenylphenyl Acetate (X).—A mixture of three grams of 2,6-dichloro-4-phenylphenol[10] and one-fourth molecular proportion of anhydrous sodium acetate was refluxed gently for ten minutes in an excess of acetic anhydride. The reaction mixture was allowed to cool and poured into five volumes of water. The ester was collected by filtration in quantities representing a quantitative yield. Two recrystallizations from ethanol reduced the yield of 73%. The white rhombic crystals melted at 64°.

Anal. Calcd. for $C_{14}H_{11}O_2Cl$: Cl, 25.24. Found: Cl, 25.08, 25.16.

4-(4-Chlorophenyl)-2,6-dichlorophenol (XI).—The impure 4-(4-chlorophenyl)-2,6-dichlorophenol was prepared according to the method of Colbert, Meigs and Mackin.[10] This was crystallized several times from carbon tetrachloride, thus yielding the pure compound with a constant melting point of 144°. (A 9% yield was obtained.) When a melting point was taken on a mixture of this compound with the chlorophenylphenol obtained from III it was lowered to 120°.

4-(4-Chlorophenyl)-2,6-dichlorophenyl Acetate (XII).—This product was obtained by acetylating 2,6,4′-trichlorophenylphenol in the same manner used to prepare VI and X. After two recrystallizations from ethanol, the product was obtained as white needles which melted at 79.5°, in a yield of 75%.

Anal. Calcd. for $C_{14}H_9O_2Cl_3$: Cl, 33.72. Found: Cl, 33.50, 33.57.

Acknowledgment.—The writers wish to express their appreciation for the helpful suggestions of Mr. Harry Kornberg during the progress of this investigation and for the assistance of Mr. T. R. Thompson in the analyses of the compounds.

Summary

1. Chlorination of 4-phenylphenyl acetate in the presence of iodine catalyst gave rise to 4-(4-chlorophenyl)-phenyl acetate. Hydrolysis of this ester gave a quantitative yield of 4-(4-chlorophenyl)-phenol. Proof of the structure of 4-(4-chlorophenyl)-phenol was given by an independent synthesis of this compound from benzidine.

2. Purification of 4-(4-chlorophenyl)-2,6-dichlorophenol to a constant melting point (144°) was accomplished by several recrystallizations of the impure substance (m. p. 135.5–137°) previously reported. The acetates of 4-(4-chlorophenyl)-phenol, 2-chloro-4-phenylphenol, 2,6-dichloro-4-phenylphenol and 2,6-dichloro-4-(4-chlorophenyl)-phenol were prepared in good yield.

AUSTIN, TEXAS RECEIVED MAY 5, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

A Method for the Synthesis of Certain 2-Substituted Phenanthrenes

BY BYRON RIEGEL, MARVIN H. GOLD[1] AND MICHAEL A. KUBICO

A good general method for the preparation of a number of 2-acyl and amino phenanthrenes was required for the synthesis of polynuclear hydrocarbon derivatives. A few such derivatives have been prepared from phenanthrene, but in low yields because the orientation for substitution is chiefly to the 3-position. Not only are the yields low but the separation is quite often difficult.

By the use of the Friedel–Crafts reaction on phenanthrene a 15% yield of the 2-acetylphenanthrene has been obtained. The major product of this reaction[2] was a 65% yield of the 3-acetylphenanthrene. It is possible to separate readily the 2-acetyl derivative because it has the higher melting point and is less soluble. Using the same method, the 2-propionylphenanthrene could be isolated only in an 8% yield,[3] while with succinic anhydride no 2-succinoylated phenanthrene could be isolated.[4] When there is no particular need for the 3-acylphenanthrenes such reactions constitute an unnecessary waste of laboriously purified phenanthrene.

It has been shown that the 2-position is exclusively involved in the substitution reactions[5] of 9,10-dihydrophenanthrene. The reactions with 9,10-dihydrophenanthrene are not accompanied by the usual resinous products encountered with phenanthrene. We have found that 2-acyl-9,10-dihydrophenanthrenes could be easily dehydrogenated by means of sulfur. Although this method requires three steps in contrast to one step by the older method, they are all readily performed in over-all yields as listed in Table I. The amino derivative was made in four steps from phenanthrene, through the 2-amino-9,10-dihydrophe-

TABLE I

2-Substituted phenanthrene	Over-all yield, %
Acetyl	53
Propionyl	45
Isobutyryl	48
Methoxysuccinyl	70
Amino	25

(1) Anna Fuller Fund Research Associate.

(2) E. Mosettig and J. van de Kamp, THIS JOURNAL, **52**, 3704 (1930); **54**, 3328 (1932).

(3) W. E. Bachmann and W. S. Struve, *ibid.*, **58**, 1659 (1936).

(4) R. D. Haworth and C. R. Mavin, *J. Chem. Soc.*, 1012 (1933).

(5) A. Burger and E. Mosettig, THIS JOURNAL, **58**, 1857 (1936), **59**, 1302 (1937).

nanthrene, previously reported by Krueger and Mosettig.[6]

Experimental[7]

2-Acetylphenanthrene.[2]—The 9,10-dihydrophenanthrene used in this work was prepared by the method described by Fieser and Johnson.[8] The crude 2-acetyl-9,10-dihydrophenanthrene[5] obtained from the reaction of 65 g. of 9,10-dihydrophenanthrene and 31 g. of acetyl chloride was transferred to a 250-ml. Claisen-head sabre flask. After heating the flask to 250°, 12 g. of sulfur was added in 1–2 g. quantities over a period of ten minutes. Heating was continued at 260–280° for about one hour or until no more hydrogen sulfide was evolved. The reaction mixture was allowed to cool somewhat and then distilled at 1–2 mm. By dissolving the crude solid distillate in boiling benzene and adding an equal volume of petroleum ether (b. p. 60–90°), 47 g. of crystalline material (in two crops), m. p. 138–142°, was obtained. This was sufficiently pure for further work and represented an over-all yield of 59% for the two steps or a 53% yield based on phenanthrene. Pure material, m. p. 142–143°, could be obtained by two crystallizations. A high boiling viscous oil remained in the mother liquors.

2-Propionylphenanthrene.—The distillate, from the dehydrogenation of 2-propionyl-9,10-dihydrophenanthrene,[5] gave crystalline material, m. p. 99–102°, from ethanol. An over-all yield of 45%, based on phenanthrene, was obtained. Recrystallization from ethanol raised the m. p. to 103–104°. Bachmann and Struve[3] reported its m. p. as 104–105°.

2-Isobutyryl-9,10-dihydrophenanthrene.—The crude reaction product from 30 g. of 9,10-dihydrophenanthrene and 19.4 g. of isobutyryl chloride was distilled at 2 mm. giving 36.8 g. (88%) of distillate, a sample of which gave crystals, from ethanol, melting at 71.6–72.6°.

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.36; H, 7.24. Found: C, 86.90; H, 7.34.

2-Isobutyrylphenanthrene.—Dehydrogenation of a 10.1-g. sample of the previously described distillate gave a product which crystallized from benzene–ethanol giving 6.06 g. (61%), m. p. 116.8–117.6°. This represents an over-all yield of 48% for the three steps.

Anal. Calcd. for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found: C, 86.83; H, 6.75.

Methyl β-[2-Phenanthroyl]-propionate.—To a suspension of 8 g. of β-[9,10-dihydro-2-phenanthroyl]-propionic acid[5] in 100 ml. of methanol was added slowly, while swirling, 10 ml. of acetyl chloride. The reaction mixture became hot and the solid acid dissolved. After standing for three hours at room temperature, water and ether were added. The ether extract was washed with a dilute solution of sodium carbonate and treated with Norite and anhydrous sodium sulfate. It was then filtered and the solvent removed under reduced pressure. The residual oil crystallized from methanol giving 7.6 g. (90%) of material sufficiently pure for further reactions. Recrystallization from methanol gave prisms melting at 73.5–74°. Fieser and Johnson[9] reported the m. p. 77–78°. The above esterification is most convenient and is similar to the method described by Freudenberg and Jakob.[10]

Dehydrogenation of a 2.756-g. sample of the methyl β-[9,10-dihydro-2-phenanthroyl]-propionate gave 2.382 g. of crude material which crystallized from acetone–methanol giving 2.185 g. (80%) of product melting 105–107°. Two crystallizations including a treatment with Norite gave glistening white plates, m. p. 112.2–112.6°.

Anal. Calcd. for $C_{19}H_{16}O_3$: C, 78.06; H, 5.53. Found: C, 78.43; H, 5.96.

A small sample was hydrolyzed giving the free acid melting at 203–206° (reported[4] 205–206°).

2-Aminophenanthrene.—2-Amino-9,10-dihydrophenanthrene[6] was smoothly dehydrogenated by means of sulfur. The reaction product was isolated in the form of its hydrochloride in a 68% yield. Liberation of the free amine by the addition of alkali gave a product melting at 85–86°. This amine has been prepared by Bachmann and Boatner[11] through the Beckmann rearrangement of the oxime of 2-acetylphenanthrene.

Summary

1. A convenient and improved method for the preparation of 2-acyl and amino phenanthrenes has been described. This method involves the dehydrogenation of the easily prepared 9,10-dihydrophenanthrene derivatives.

EVANSTON, ILLINOIS RECEIVED MAY 26, 1942

(6) J. W. Krueger and E. Mosettig, *J. Org. Chem.*, **3**, 340 (1938–1939).

(7) All melting points are corrected. Microanalyses by Dr. T. S. Ma, University of Chicago.

(8) L. F. Fieser and W. S. Johnson, THIS JOURNAL, **61**, 168 (1939).

(9) L. F. Fieser and W. S. Johnson, *ibid.*, **61**, 1647 (1939).

(10) K. Freudenberg and W. Jakob, *Ber.*, **74**, 1001 (1941).

(11) W. E. Bachmann and C. H. Boatner, THIS JOURNAL, **58** 857 2194 (1936).

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

A Convenient Procedure for the Preparation of Deuterium Chloride

BY HERBERT C. BROWN AND CORNELIUS GROOT[1]

In the course of an investigation upon which we have been engaged, the need arose for considerable quantities of deuterium chloride of high purity. Examination of the literature reveals that many methods for the preparation of the substance have been reported. In the main, however, these methods, such as the action of deuterium oxide on anhydrous magnesium chloride at 600°,[2] the reduction of silver chloride with deuterium at 700°,[3] the combination of chlorine with deuterium,[4] or the treatment of sodium chloride with deutero sulfuric acid,[5] either require the prior preparation of intermediates or involve such difficult techniques as to be unsuitable for the preparation of more than small quantities of deuterium chloride.

The procedure based on the reaction of deuterium oxide with thionyl chloride ($SOCl_2 + D_2O \rightarrow SO_2 + 2\ DCl$) has received careful attention as a means of preparing deuterium chloride in appreciable quantities,[6] and the process would be entirely satisfactory but for the difficulty involved in the separation of the product from the accompanying sulfur dioxide. In the recommended procedure, two traps cooled by dry-ice–acetone mixtures are used to remove the greater portion of the sulfur dioxide. However, since this gas possesses an appreciable vapor pressure at −80° (10 mm.), it is evident that the deuterium chloride thus obtained must be contaminated with not inconsiderable quantities of sulfur dioxide. Moreover, the solubility of deuterium chloride in liquid sulfur dioxide at −80° causes losses as high as 15% of the product.

In casting about for a more satisfactory procedure, we examined the possibility of utilizing benzoyl chloride for transforming deuterium oxide into the desired product. Study revealed that at somewhat elevated temperatures deuterium oxide reacts smoothly with the reagent to liberate *two* equivalents of deuterium chloride. The reaction occurs in accordance with the equations

$$C_6H_5COCl + D_2O \longrightarrow C_6H_5COOD + DCl$$
$$C_6H_5COCl + C_6H_5COOD \longrightarrow (C_6H_5CO)_2O + DCl$$

The yield of the gaseous chloride is practically quantitative, the product is analytically pure deuterium chloride, and, finally, the rate at which the gas is generated is readily controlled throughout the preparation.

The apparatus used in the preparation is shown in Fig. 1. The deuterium oxide is contained in the dropping funnel where the long length of capillary tubing serves to maintain the rate of addition of the deuterium oxide constant despite small fluctuations in pressure within the flask.

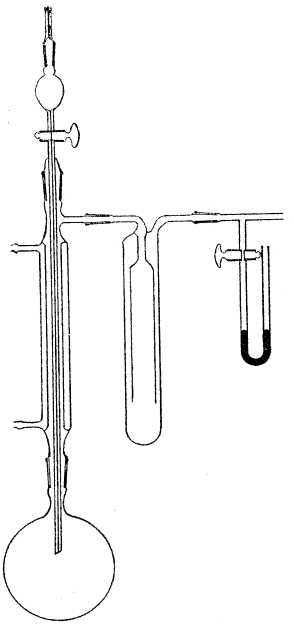


Fig. 1.—Apparatus.

The trap is immersed in an ice-bath to remove traces of benzoyl chloride which are carried past the condenser by the stream of gas. The open manometer is used to indicate the pressure at which the system is operating and to act as a safety valve should the delivery tube become blocked. It also aids in following the course of the reaction. If the delivery tube is closed momentarily (by means of a pinch clamp on a rubber connection), the action of the manometer reveals whether gas is being evolved.

(1) This paper is taken from a dissertation submitted by Cornelius Groot to the Faculty of the Division of the Physical Sciences of the University of Chicago in partial fulfillment of the requirements for the degree of Master of Science.

(2) Lewis, MacDonald and Schutz, THIS JOURNAL, **56**, 494 (1934).

(3) Steiner and Rideal, *Proc. Roy. Soc.* (London), **A173**, 504 (1939).

(4) Bawn and Evans, *Trans. Faraday Soc.*, **31**, 1394 (1935).

(5) Frivold, Hassel and Rustad, *Physik. Z.*, **38**, 193 (1937).

(6) Langseth and Klit, *Kgl. Danske Videnskab. Selskab. Math. fys. Medd.*, **15**, No. 13. 4 (1937).

A few drops of the deuterium oxide is run from the funnel into the flask containing a two to three mole excess of benzoyl chloride (reagent grade). The flask is gently heated until deuterium chloride is evolved at a satisfactory rate, and the temperature is maintained at this level until all of the deuterium oxide has been added and the evolution of gas has noticeably slackened. The temperature is then slowly raised to the boiling point of the benzoyl chloride and maintained there until gas is no longer produced.

At the end of the reaction, a slow stream of dry air is passed into the system through the dropping funnel (the refluxing of the reaction mixture is not interrupted) to force the last traces of deuterium chloride to the outlet. At all times the evolution of deuterium chloride is smooth, easily controlled (the addition of a few chips of porous plate to the reaction flask is advisable), and may be halted simply by removing the source of heat.

The details of one test preparation will be given to illustrate the yields and degree of purity which may be expected.

Five ml. (0.550 equiv.) of deuterium oxide (99.6%) were treated with an excess (*ca.* 1.5 moles) of benzoyl chloride. The deuterium chloride obtained was dissolved in distilled water (contained in a 250-ml. volumetric flask), the solution in the flask diluted to the mark, and samples removed for analysis. Total acidity found was 0.528 equiv. (average of three determinations: 0.526, 0.527, 0.531), representing a yield of 96% of the theoretical. The solution was analyzed volumetrically for chloride ion by the Volhard method; found: 0.529 equiv. (average of three determinations: 0.528, 0.530, 0.530). The deuterium content was determined by the temperature float method on a portion of the solution after the acid had been carefully neutralized with barium oxide and the water distilled; found: 0.528 equiv. of deuterium (average of two determinations: 0.530, 0.526). It is evident that, within the accuracy of the experiment, a nearly quantitative yield[7] of pure deuterium chloride had been obtained

Acknowledgment.—The authors wish to express their thanks to Mr. D. C. Sayles for the chloride ion analyses and to Mr. K. Wilzbach for the deuterium analyses. They also wish to acknowledge gratefully the deuterium oxide generously donated by Professor M. S. Kharasch for this and other investigations.

Summary

Deuterium chloride may be prepared conveniently by the action of benzoyl chloride on deuterium oxide at elevated temperatures. The product is analytically pure and the yields (based on the available deuterium) are practically quantitative.

(7) In three preliminary experiments in which 9 to 18 g. of water (1.0 to 2.0 equiv.) were transformed into hydrogen chloride by this method, the yields obtained were 98.5, 100, 99%.

CHICAGO, ILL. RECEIVED MAY 8, 1942

NOTES

Physical Constants of Methyl Isopropenyl Ketone

BY JOSEPH H. BRANT

The literature dealing with methyl isopropenyl ketone[1-8] shows a considerable variance with respect to the physical constants of this ketone. Two methods of preparation have been described in the recent literature. The liquid phase synthesis from methyl ethyl ketone and formalin has been studied extensively by Morgan and coworkers[2,3] and also by Rutovskii and coworkers.[4,5,6] A vapor phase synthesis has been described by Brant and Hasche[7] in which the ketone is produced in one step starting with methyl ethyl ketone and formalin or paraformaldehyde.

More recently Marvel, Riddle and Corner[8] reported the boiling point of methyl isopropenyl ketone as 45–46° at 40 mm. It would appear that this value is considerably too high.

(1) Beilstein IV, Vol. I, p. 733, Supp., 381.
(2) Morgan, Megson and Pepper, *Chemistry and Industry*, **57**, 390 (1938).
(3) Morgan, Megson and Pepper, *ibid.*, **57**, 885 (1938).
(4) Rutovskii and Yakobson, *J. Applied Chem.*, (U. S. S. R.), **14**, 528 (1941).
(5) Rutovskii and Dmitrieva, *ibid.*, **14**, 535 (1941).
(6) Rutovskii and Goncharov, *ibid.*, **14**, 542 (1941).
(7) Brant and Hasche, U. S. Patent 2,245,567.
(8) Marvel, Riddle and Corner, THIS JOURNAL, **64**, 92 (1942).

In order to help clarify this situation regarding the physical constants the following table is presented which shows the effect of time on the physical constants of methyl isopropenyl ketone. The first determinations listed were made within a few minutes after the completion of a careful vacuum distillation. The fraction studied was the middle 75 cc. from an 800-cc. batch and collected in a brine cooled receiver at about −10°. The material used in these tests was stored in a clear glass bottle without an inhibitor present and at room temperature. This sample contained less than 0.01% H_2O.

TABLE I

Age, days	$n^{20}D$	d^{20}_{20}	Age, days	$n^{20}D$	d^{20}_{20}
	1.4163	0.8459	12	1.4242	0.8710
1	1.4162	.8458	13	1.4260	.8758
2	1.4163	.8465	14	1.4280	.8809
3	1.4166	..	15	1.4293	.8862
4	1.4168	..	16	1.4310	.8884
5	1.4170	.8485	17	1.4328	.8954
6	1.4174	..	18	1.4360	..
7	1.4183	..	19	1.4380	..
8	1.4190	.8566	20	1.4400	..
9	1.4208	.8604	21	1.4424	..
10	1.4214	.8632	22	Too viscous to examine	
11	1.4230	.8670	30	Glass-like	solid

Other samples have shown comparable behavior except that the change has set in more quickly. One other sample on record was as much polymerized after thirteen hours as the one above was in seven days based on the density and refractive index values. No doubt some catalyzing impurities present in very small amounts account for this variation in rate of polymerization.

It appears necessary that physical constants of pure methyl isopropenyl ketone be determined as soon after distillation as possible even when inhibitors have been added.

The following are constants obtained for pure freshly vacuum distilled methyl isopropenyl ketone made by the vapor phase process.[7]

$n^{20}D$	1.4163
d^{20}_{20}	0.8459
Molecular refraction, calculated	24.84
Molecular refraction, observed	25.05
Boiling point (735 mm.), ° C.	98.5
Boiling point (100 mm.), ° C.	45–46
Boiling point (75 mm.), ° C.	37–38
Boiling point of the water azeotrope	
(735 mm.)	82
(100 mm.)	34–35

TENNESSEE EASTMAN CORPORATION
KINGSPORT, TENNESSEE

RECEIVED JULY 2, 1942

The Further Nitration of Certain Dinitrobiphenyls

BY FRANCIS H. CASE

2,3′,4,4′-Tetranitrobiphenyl has been obtained by Blakey and Scarborough[1] by the nitration of either 2,3′- or 3,4′-dinitrobiphenyl. These authors were, however, unable to obtain the corresponding trinitro derivatives. In this Laboratory, 2,3′,4-trinitrobiphenyl (m. p. 137–138°, from alcohol) was the sole product isolated after heating 2,3′-dinitrobiphenyl with nitric acid (sp. gr. 1.5) for three minutes.

Anal. Calcd. for $C_{12}H_7N_3O_6$: N, 14.54. Found: N, 14.77.

When 3,4′-dinitrobiphenyl (6 g.) was heated for one hour with nitric acid (50 cc., sp. gr., 1.5), the reaction mixture poured into water, and the precipitate crystallized from benzene, 3,4,4′-trinitrobiphenyl (1.1 g., m. p. 205–206°) was first obtained.

Anal. Calcd. for $C_{12}H_7N_3O_6$: N, 14.54. Found: N, 14.70.

On evaporation of the benzene mother liquors and crystallization from alcohol, 2,3′,4-trinitrobiphenyl (1.5 g., m. p. 136–137°) separated. This product melted unchanged when mixed with the trinitro isomer from 2,3′-dinitrobiphenyl. The structure of the isomer melting at 137–138° follows from its dual method of synthesis; that of the isomer (m. p. 205–206°) depends on the fact that it is different from II, and yet yields the known 2,3′,4,4′-tetranitrobiphenyl on further nitration.

When 3,3′-dinitrobiphenyl (5 g.) was nitrated under the conditions described above for the 3,4′-compound, and the product was crystallized from a mixture of acetone and alcohol, 3,3′,4-trinitrobiphenyl (2.4 g., m. p. 179–180°) was obtained.

Anal. Calcd. for $C_{12}H_7N_3O_6$: N, 14.54. Found: N, 14.53.

The structure of this compound was evident from the fact that on further nitration with mixed acids (1:1) at 100°, 3,3′,4,4′-tetranitrobiphenyl, m. p. 203–204° (from alcohol–acetone), identical (mixed m. p. undepressed) with a sample prepared by Ullmann's method[2] from 3,4-dinitroiodobenzene, was obtained.

Anal. Calcd. for $C_{12}H_6N_4O_8$: N, 16.77. Found: N, 16.90.

(1) Blakey and Scarborough, *J. Chem. Soc.*, 3000 (1927).

(2) *Cf.* Ullmann and Bielecki, *Ber.*, **34**, 2179 (1901). These authors, apparently through an error, record the m. p. of this compound as 186°.

TEMPLE UNIVERSITY
PHILADELPHIA, PA.

RECEIVED MAY 18, 1942

Preparation of *p*-Aminobenzenesulfonyl Urea

BY EDWARD H. COX

The procedure for the preparation of the arylsulfonyl ureas[1] has now been applied in making

(1) Cox and Raymond, THIS JOURNAL, **63**, 300 (1941).

p-aminobenzenesulfonyl urea. The therapeutic properties of this compound and some of its salts are under investigation.

***p*-Acetaminobenzenesulfonyl Ethyl-isourea.**—In a five-liter flask provided with a mechanical stirrer was placed 600 g. of anhydrous potassium carbonate, 2 liters of acetone and 100 cc. of water. The suspension of carbonate–acetone–water was stirred and cooled in an ice-bath. To this suspension 272 g. (2.2 moles) of ethyl-isourea hydrochloride was added gradually over a period of one-half hour. With each addition some water was added until the total amount was 400 cc. The ice-bath was removed after the addition and the reaction mixture stirred at room temperature for four hours.

The reaction material was then poured into five liters of water, and the crude product filtered and washed. The weight of the crude dried product was 458 g. (87% yield). It crystallized from 50% acetic acid as white needles and melted at 223–224°.

Anal. Calcd. for $C_{11}H_{15}O_4N_3S$: N, 14.71. Found: N, 14.76, 14.79.

***p*-Aminobenzenesulfonyl Urea.**—One mole (285 g.) of *p*-acetaminobenzenesulfonyl ethyl-isourea (crystallized once from dilute acetic acid) was placed in a two liter flask and covered with 700 cc. of concentrated hydrochloric acid. The isourea first dissolved and then reprecipitated as the hydrochloride. The flask was immersed in a boiling water-bath and the reaction mixture stirred until solution took place (fifteen to twenty minutes). Decolorizing charcoal was added while still hot and the solution was filtered. After the addition of an equal volume of alcohol the filtrate was set aside to crystallize. The dried crystalline product weighed 200 g. (80% yield). White needles were produced when the product was recrystallized from dilute acetic acid. The compound melted with gas formation (ammonia) at 140–146°.[2,3]

Anal. Calcd. for $C_7H_9O_3N_3S$: N, 19.54. Found: N, 19.53, 19.59.

Salts of *p*-Aminobenzenesulfonyl Urea.—The ammonium, potassium and sodium salts were prepared by treating slightly more than one equivalent of the *p*-aminobenzenesulfonyl urea with one equivalent of the metallic carbonate in 50% alcohol. After the addition of the carbonate, ether was added to produce the maximum yield of the salt.

Ammonium Salt. *Anal.* Calcd. for $C_7H_{12}O_3N_4S$: N, 24.12. Found: N, 24.09, 24.19.

Potassium Salt. *Anal.* Calcd. for $C_7H_8O_3N_3SK$: N, 16.59. Found: N, 16.54, 16.56.

Sodium Salt. *Anal.* Calcd. for $C_7H_8O_3N_3SNa$: N, 17.71. Found: N, 17.59, 17.64.

Acknowledgment.—The author thanks the Monsanto Chemical Company for a generous supply of *p*-acetoaminobenzenesulfonyl chloride.

DEPARTMENT OF CHEMISTRY
SWARTHMORE COLLEGE
SWARTHMORE, PA.

RECEIVED JUNE 16, 1942

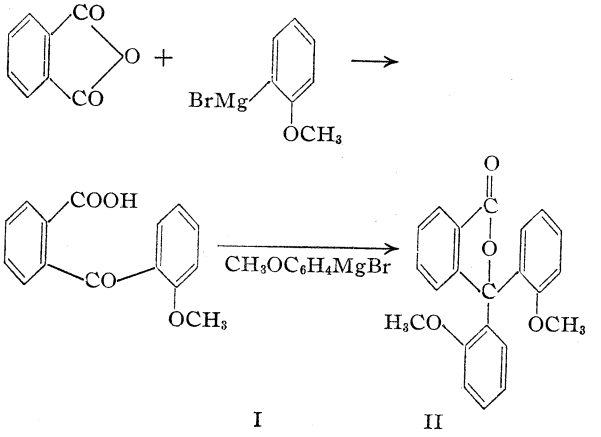
(2) The properties of this compound as given by Geigy, British Patent 538,884, are not in agreement with those recorded here.

(3) Since the completion of this work, *p*-aminobenzenesulfonyl urea has been reported by Roblin and his co-workers, THIS JOURNAL, **64**, 1683 (1942).

A Synthesis of 2-(2′-Methoxybenzoyl)-benzoic Acid

BY BRADFORD P. GEYER[1]

In the course of a projected synthesis of 1-hydroxyfluorenone it became necessary to prepare a quantity of 2-(2′-methoxybenzoyl)-benzoic acid (I). This keto acid was prepared previously by Sieglitz[2] by methylation of 2-salicylylbenzoic acid. The synthesis of I has now been accomplished, using phthalic anhydride and *o*-bromoanisole as starting materials.



I II

A by-product formed in the Grignard reaction of *o*-anisylmagnesium bromide with phthalic anhydride is 2,2-di-*o*-anisylphthalide (II), reported earlier by Ferrario[3] and by Blicke and Weinkauff.[4]

Experimental

Before preparing the Grignard reagent, *o*-anisylmagnesium bromide, the flask containing 9.6 g. (0.4 mole) of magnesium was heated with a low, free flame to expel traces of moisture. A 20-ml. portion of anhydrous diethyl ether, freshly distilled from an ethereal ethylmagnesium bromide solution and containing 10 drops of ethyl bromide, was placed in the flask with the magnesium. To this mixture, agitated by means of a mercury-seal stirrer, 63 g. (0.34 mole) of *o*-bromoanisole in 100 ml. of diethyl ether, the latter likewise freshly distilled from the same ethylmagnesium bromide solution, was added dropwise. After complete addition of the *o*-bromoanisole, the solution of the arylmagnesium halide was heated under reflux for one-half hour. This Grignard reagent was then introduced slowly, dropwise, to a vigorously stirred, hot solution of 37 g. (0.25 mole) of phthalic anhydride in 600 ml. of thiophene-free benzene, ether being removed simultaneously by distillation. Pale yellowish-white solid formed immediately. After the addition of all of the re-

(1) Present address: Shell Development Company, Emeryville, California.

(2) Sieglitz, *Ber.*, **57**, 316 (1924).

(3) Ferrario, *Gazz. chim. ital.*, **41**, I, 1 (1911).

(4) Blicke and Weinkauff, THIS JOURNAL, **54**, 1452 (1932).

agent, the resulting mixture was stirred for several minutes longer, heated under reflux for two hours and then allowed to cool and stand overnight at room temperature. The reaction flask was cooled in an ice–water-bath and the pale yellow product decomposed with dilute hydrochloric acid. A 300-ml. quantity of diethyl ether was added to dilute the benzene solution of 2-(2′-methoxybenzoyl)-benzoic acid and 2,2-di-*o*-anisylphthalide. The ether–benzene layer was extracted with potassium carbonate solution, and the carbonate extract then run dropwise into vigorously stirred, ice-cold hydrochloric acid. In this way the keto acid first separated as a pasty mass which soon became solid. This pale fawn-colored, granular solid was filtered off and washed with cold diethyl ether. Upon drying, 34.5 g. (54%) of crude acid was obtained. After four recrystallizations from glacial acetic acid, 2-(2′-methoxybenzoyl)-benzoic acid was secured in the form of short, colorless, small prisms; m. p. 143–143.5°; yield 30 g. (47%, based on phthalic anhydride). Sieglitz[2] reported 144–145° as the m. p. of this acid.

Anal. Neutralization equivalent, calcd. for $C_{15}H_{12}O_4$: 256.2. Found: 257.9.

From the above-mentioned benzene–ether layer, after the potassium carbonate extraction and concentration of the solution to a small volume, a colorless powder was obtained. This material, 2,2-di-*o*-anisylphthalide, when recrystallized three times from glacial acetic acid, formed small, colorless crystals, m. p. 148–149°; yield 10.5 g. (18%, based on *o*-bromoanisole). The phthalide was found to be soluble in concentrated sulfuric acid with a very deep violet color which gradually changed to ruby-red and finally to orange.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF WASHINGTON
SEATTLE, WASHINGTON

RECEIVED JUNE 24, 1942

The Dissociation of Hexaarylethanes. XIV.[1] Ethanes Derived from Mixtures of Triaryl Halides

BY C. S. MARVEL AND CHESTER M. HIMEL

Since symmetry seemed to be important in connection with the influence of substituents on the degree of dissociation of triarylmethyls, it occurred to us that treating an equimolecular mixture of two triarylmethyl halides with silver might produce a truly unsymmetrical ethane rather than a mixture of ethanes. Table I contains a list of some mixtures of chlorides which were thus treated and the degree of dissociation calculated from magnetic susceptibility measurements on the assumption that a mixed ethane was formed. In one case (the first in the table) the mixed ethane was prepared by mixing preformed solutions of the individual ethanes rather than by action of silver on the mixed halides.

(1) For the thirteenth communication see *J. Org. Chem.*, **7**, July (1942).

TABLE I

DISSOCIATION OF SOME MIXED HEXAARYLETHANES

Chlorides used	$-\chi \times 10^6$	α at 0.1 *M*, %	α of corresponding ethane at 0.1 *M*, %	Ref.
o-Chlorophenyldiphenylmethyl	0.6620	14 ± 2	12 ± 1	1
o-Bromophenyldiphenylmethyl			17 ± 1	1
o-Tolyldiphenylmethyl	.6320	26 ± 2	25 ± 1	2
α-Naphthyldiphenylmethyl			27 ± 2	3
o-Tolyldiphenylmethyl	.6282	27 ± 2	25 ± 1	2
Di-*o*-tolylphenylmethyl			82 ± 2	4
Tri-*p*-diphenylmethyl	.6765	25 ± 3[a]	25 ± 5	3
Tri-β-naphthylmethyl			25 ± 5	3
p-*t*-Amylphenyldiphenylmethyl	.6985	3.5 ± 1	8.0 ± 1	4
Phenyl-di-*p*-*t*-amylphenylmethyl			9.0 ± 1	4
Tri-*p*-*t*-butylphenylmethyl	.6997	3.5 ± 1	20 ± 4	4
p-*t*-Butylphenyldiphenylmethyl			7.5 ± 1	4

[a] The actual measurement was made at 0.025 *M* and the dissociation at this concentration was 43 ± 4%. The value in the table was calculated by means of the mass law.

The method and apparatus have been described in previous papers in this series. It can be seen readily that the observed degrees of dissociation are not the average of the two simple ethanes, but in general are lower than this value. There are several equilibria possible in this complicated system and a complete appraisal of the significance of these experimental results will not be possible until these equilibria are more thoroughly studied. Since it seems unlikely that this can be done soon, these results are recorded.

(2) Marvel, Mueller, Himel and Kaplan, THIS JOURNAL, **61**, 2771 (1939).
(3) Marvel, Shackleton, Himel and Whitson, *ibid.*, **64**, 1824 (1942).
(4) Marvel, Kaplan and Himel, *ibid.*, **63**, 1892 (1941).

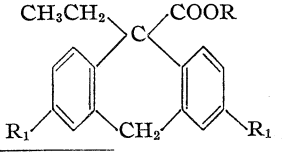
DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

RECEIVED JUNE 17, 1942

The Reaction of Furoic Acid with Aromatic Compounds. III

BY CHARLES C. PRICE, E. C. CHAPIN AND MARTIN RIEGER

The isolation of methyl 9-ethyl-9,10-dihydro-9-anthroate (I) from the aluminum chloride catalyzed reaction of methyl furoate with benzene[1] suggests the presence of the corresponding acid (II) in the mixture obtained from a similar re-



I (R = CH_3, R_1 = H)
II (R = R_1 = H)
III (R = H, R_1 = CH_3)

(1) Price and Huber, THIS JOURNAL, **64**, 2136 (1942).

action with furoic acid.[2] Oxidation of the crude mixture from the latter reaction to yield anthraquinone has already been presented as evidence for the formation of an acid with an anthracene nucleus.[2] This observation has now been substantiated by degradation of the crude reaction mixture to anthracene by subjecting it to soda-lime distillation. Crystallization from benzene of the oily distillate so obtained yielded anthracene in 10% yield, m. p. 208–210°. Its identity was checked by a mixed melting point determination.

Thus, although the pure acid has yet to be isolated, analogy with the methyl furoate reaction supports the suggestion that the anthroic acid present in the mixture of acids formed from benzene and furoic acid is 9-ethyl-9,10-dihydro-9 anthroic acid (II).

The oily residue left after crystallization of anthracene from the soda-lime distillate was dehydrogenated with sulfur to yield 1,4-diphenylnaphthalene, previously obtained as a degradation product of the acid mixture. It is believed to be derived from 1,4-diphenyl-1,2,3,4-tetrahydro-1-naphthoic acid.[2]

Soda-lime distillation of the crude acid mixture obtained by reaction of toluene and furoic acid yielded 2,7-dimethylanthracene, m. p. 238–239°, which showed no depression in melting point when mixed with an authentic sample. Isolation of this hydrocarbon indicates that this reaction also gives rise to an anthroic acid. Again, the pure acid has yet to be isolated, but analogy with the product from benzene, as well as consideration of the simplest product of the reaction, 6-methyl-1-naphthoic acid, suggests that the anthracenic component of the toluene-furoic acid reaction may be 3,6-dimethyl-9-ethyl-9,10-dihydro-9-anthroic acid (III).

Repeated efforts to isolate a substance from the crude toluene product, corresponding to the 1,4-diphenylnaphthalene obtained from the benzene product, have failed. Attempted decarboxylation of the toluene product by heating with copper chromite in quinoline, successful for the benzene product, yielded a black, intractable tar from the toluene product. Evidently the tar was formed by oxidation, since the black powdery copper chromite catalyst was transformed to a mixture of green chromium oxide powder and small bright balls of metallic copper. Treatment with sulfur or selenium of the pale yellow oil from the mother liquor of the soda-lime distillate led to copious evolution of hydrogen sulfide or selenide, but no crystalline product could be isolated.

(2) Price, Chapin, Goldman, Krebs and Shafer, THIS JOURNAL, **63**, 1857 (1941).

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

RECEIVED APRIL 14, 1942

A Color Test for Citrinin and a Method for its Preparation

BY HENRY TAUBER, STEPHEN LAUFER AND MILTON GOLL

The following is a color test for citrinin and a method for the preparation of the anti-bacterial substance.

The Color Test.—One mg. of citrinin (prepared as given below) is dissolved in 0.5 cc. of 95% alcohol and 0.3 cc. of 3% hydrogen peroxide is added. The mixture is agitated for one minute. The intense yellow solution becomes first colorless, then light brown. Hereafter, 0.3 cc. of 0.2 *N* sodium hydroxide is added. A deep wine-red color forms at once. On the addition of 0.3 cc. of 0.2 *N* sulfuric acid the wine-red color turns orange-yellow and on the addition of a further 0.3 cc. of 0.2 *N* sodium hydroxide the wine-red color reappears again. In a control tube in which water is substituted for hydrogen peroxide an orange-yellow color develops. This color reaction with sodium hydroxide from intense yellow to orange-yellow was also noted by A. C. Hetherington and H. Raistrick [*Trans. Roy. Soc.*, London, **B220,** 279 (1931)] who stated that "Citrinin is readily soluble in aqueous NaOH giving rise to an orange-yellow solution which on standing changes color to orange-red." This is indeed the case when a fairly concentrated sodium hydroxide solution is added to a citrinin solution. We found, however, that when 0.25 to 0.5 cc. of 0.02 *N* sodium hydroxide is added to 1 mg. of citrinin in 0.5 cc. of ethyl alcohol, a very light pink color forms which does not change in intensity on further addition of the alkali or on standing. H. W. Hirschy and Ruoff [THIS JOURNAL, **64,** 1490 (1942)] have recently observed that above *p*H 9.9 the color of a citrinin solution changed from orange-pink to cherry-red.

Continued exposure of citrinin to dioxane results in a hydrogen peroxide-like reaction. On long exposure to air alcoholic citrinin solutions undergo certain changes which do not appear to be identical with hydrogen peroxide-oxidation.

The hydrogen peroxide–sodium hydroxide color reaction is also given by the original cultures, by the acid precipitated crude citrinin, and after it had been recrystallized from 95% alcohol. Citrinin solutions that have been treated with sodium hydroxide and readjusted to the original *p*H do not give the hydrogen peroxide–sodium hydroxide reaction.

Penicillin obtained from *P. notatum* (A. T. C. C.) gives a lemon-yellow color with this test.

Preparation of Citrinin.—1500 cc. of the filtrate of a fourteen-day old culture of *P. citrinum* prepared according to H. Raistrick and G. Smith [*Chemistry and Industry,* **60,** 828 (1941)] is adjusted to *p*H 3.0 to 2.5 with *N* hydro-

chloric acid. After about five minutes the crystals of crude citrinin are centrifuged off, dissolved in 30 cc. of dioxane at room temperature, and the solution is centrifuged. A small amount of insoluble material is discarded, and to the clear supernatant fluid one volume of distilled water is added. Citrinin crystallizes out immediately in long microscopic needles or plates. If the citrinin concentration is low, it is necessary to add more water in order to effect crystallization. The citrinin is centrifuged off and dried in vacuum at room temperature (yield, 1.5 g.). The melting point is at 163 to 166°. We were able to confirm fully the action of citrinin on *Streptococcus aureus* as reported by Raistrick and associates.

P. citrinum (P25 and ad95) was very kindly sent by Dr. H. Raistrick and forwarded to us through the courtesy of Dr. C. Thom of U. S. Department of Agriculture.

RESEARCH DEPARTMENT
SCHWARZ LABORATORIES, INC.
NEW YORK, N. Y.

RECEIVED JUNE 24, 1942

Acidic and Basic Catalysis in Urethan Formation

BY D. S. TARBELL, R. C. MALLATT AND J. W. WILSON

Urethans, because of their favorable characteristics, are frequently used to identify alcohols and phenols. They are usually prepared by heating an alcohol or phenol in the absence of a catalyst.[1] However, scattered statements indicate that this formation of urethans, particularly from phenols, is catalyzed not only by bases[2] but by aluminum chloride[3] and hydrogen chloride.[4] A general survey of the effect of acidic and basic catalysts on urethan formation has therefore been undertaken, but, as this work has been interrupted, the present brief report is now submitted.

Experiments in which equivalent amounts of *o*-cresol and phenyl isocyanate were heated without solvent but with catalyst at 100° and the urethan which had formed after varying times isolated, showed that the following substances have a catalytic effect: sodium carbonate, sodium acetate, pyridine, acetic acid, trichloroacetic acid, zinc chloride and hydrogen chloride. Without a catalyst a yield of less than 50% was obtained after nine hours of heating. The addition of 2% of either zinc chloride or pyridine gave a 100% yield in less than fifteen minutes.

Similar experiments with other phenols varying greatly in acid character, from *p*-nitrophenol to *p*-triphenylmethylphenol, gave in fifteen minutes without a catalyst zero, with the same catalysts, practically 100% yields of urethan. On the other hand, 2,4-dinitrophenol, 2,6-dinitro-4-chlorophenol and picric acid did not form urethans under any conditions tried.

More exact experiments using purified *o*-cresol and α-naphthyl isocyanate were made as follows: solutions of 9.2 mmol. of each reagent and a small amount of a catalyst in 3.00 cc. of purified ligroin (b. p. 60–65°) in stoppered test-tubes, were heated in the vapors of refluxing methanol (65°) and after a definite time cooled in ice and filtered. The resultant crystals were washed twice with 2-cc. portions of cold ligroin in which they are practically insoluble, dried and weighed.

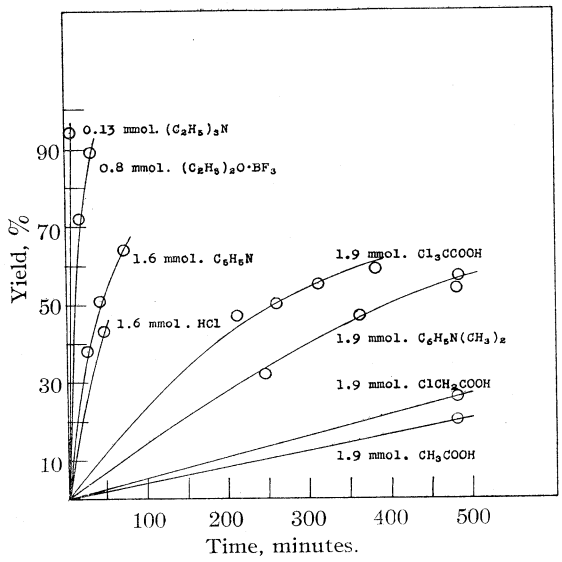


Fig. 1.

The results are shown as curves in Fig. 1, and from them it can be seen that triethylamine is by far the most effective catalyst tried. It is probably significant that it is a much stronger base than the less effective catalysts pyridine and dimethylaniline.[5] Boron fluoride etherate is the most active acid tested, and the catalytic activity of the other acids tested is roughly in the order of their acid strengths in water. When no catalyst was used, only an 11% yield was obtained after nine days, a result which could not be shown on the graph.

An 80% yield of the urethan (m. p. 141–142.5°)[6] was obtained by mixing the above quantities of *o*-cresol and α-naphthyl isocyanate in 30 cc. of ligroin with two drops of triethylamine, and letting the mixture stand for two and one-half hours at room temperature. From this it appears that an excellent and rapid procedure for preparing urethans from phenols in general would be to use the above quantities of materials, reflux the solution a few minutes and cool slowly to allow crystallization.

Phenylurethans of Tertiary Alcohols.—These compounds were prepared by heating a mixture of 2 or 3 g. of the *t*-alcohol with an equivalent quantity of phenyl isocyanate and 0.1 g. of anhydrous sodium acetate for four to five hours on a steam-bath. In each case the reaction product was contaminated with some diphenylurea and unreacted phenyl isocyanate. If the oily product failed to crystal-

(1) Shriner and Fuson, "Identification of Pure Organic Compounds," 2nd Edition, John Wiley and Sons, Inc., New York, N. Y., 1940, p. 136.

(2) Dieckmann, Hoppe and Stein, *Ber.*, **37**, 4627 (1904); Michael and Cobb, *Ann.*, **363**, 64 (1908); Vallee, *Ann. chim. phys.*, (7) **15**, 331 (1908); Claisen, *Ann.*, **418**, 82 (1919); French and Wirtel, THIS JOURNAL, **48**, 1736 (1926).

(3) Leuckart, *Ber.*, **18**, 873 (1885); Farinholt, Harden and Twiss, THIS JOURNAL, **55**, 3383 (1933).

(4) Tarbell and Kincaid, *ibid.*, **62**, 728 (1940).

(5) Hall, *ibid.*, **52**, 5115 (1930).

(6) French and Wirtel, ref. 2, give 141–142°.

lize, it was purified by distillation in vacuum. In this manner the phenylurethans in Table I were obtained.

TABLE I

Phenylurethan of	M. p., °C. (uncor.)	Formula	Analyses,[a] % Calcd. C	Calcd. H	Found C	Found H
Dimethylbutylcarbinol	62–63	$C_{14}H_{21}NO_2$	71.5	8.9	71.8	8.9
Diphenylmethylcarbinol	124–125	$C_{21}H_{19}NO_2$	79.5	6.0	79.7	5.7
Triethylcarbinol	61–61.5	$C_{14}H_{21}NO_2$	71.5	8.9	70.9	8.8
Methylethylbenzylcarbinol	83.5–84	$C_{18}H_{21}NO_2$	76.3	7.5	75.9	7.3
Diethylbenzylcarbinol	96–96.5	$C_{19}H_{23}NO_2$	76.7	7.8	76.7	7.4

[a] Analyses by R. W. King.

Discussion of the mechanism of the catalysis will be deferred, but it seems to be a case of general acid–base catalysis. The tests for determining general acid–base catalysis which are employed in aqueous systems cannot be used readily here, since the isocyanates must be kept in inert solvents.

It is hoped to study this catalysis effect in greater detail and to include the reactions of alcohols and isocyanates.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ROCHESTER
ROCHESTER, NEW YORK

RECEIVED MAY 25, 1942

Optical Properties of 2-Sulfanilamidopyrimidine (Sulfadiazine)

BY ALBERT S. WILKERSON

Thanks to the courtesy of Mr. Leonard Dhein of the American Cyanamid Company, Bound Brook, New Jersey, we have been able to determine the optical and related properties of a sample of sulfadiazine (m. p. 254°)[1] with the following results: monoclinic, colorless, transparent to translucent; luster vitreous. Cleavage pinacoidal at right angles, perfect. $H = 1$–2. Solubility 0.0123 g./100 cc.,[1] H_2O at 37°. Optically biaxial positive; $\alpha = 1.680$, $\beta = 1.695$, $\gamma = 1.788$; all ± 0.002, $2V = 45$–$46°$, $Y//b$, $Z \wedge c = 20°(?)$, elongation$//b$.

(1) R. O. Roblin, *et al.*, THIS JOURNAL, **62**, 2002 (1940), found 255–256° with decomposition; they found the solubility to be 0.0123 g./100 cc.

RUTGERS UNIVERSITY
NEW BRUNSWICK, NEW JERSEY

RECEIVED JUNE 12, 1942

NEW COMPOUNDS

Certain Naphthylidene Sulfanilamide Derivatives

The procedures employed for the preparation of the following compounds were modifications of methods used in the preparation of the aniline derivatives of the sulfonated α- and β-naphthoquinones.[1,2] To conform with *Chemical Abstracts* the nomenclature of these compounds was suggested by Dr. Austin M. Patterson.

N^4-(3-Hydroxy-4-oxo-1(4)-naphthylidene)-sulfanilamide.—A solution of 8.6 g. of sulfanilamide (Eastman Kodak Co.) in 200 cc. of water at 60–65° was added with stirring to a solution of 13.0 g. of 1,2-naphthoquinone-4-sodium sulfonate (Eastman purified by the method of Folin[3]) in 300 cc. of water at 45–50°. The reaction mixture after standing for fifteen minutes at room temperature was kept in the ice box overnight. The reddish orange precipitate was filtered off, washed with water and dried in a vacuum desiccator over sulfuric acid; yield, 9.9 g. (60%). The compound melted at 271–273° (uncor.). It is insoluble in cold water, very difficultly soluble in hot water, very soluble in alkali, formic acid, slightly soluble in hydrochloric acid, alcohol, dioxane and acetone.

Anal. Calcd. for $C_{16}H_{12}O_4SN_2$: N, 8.53. Found: N, 8.41.

N^4-(3-Hydroxy-4-oxo-7-sulfo-1(4)-naphthylidene)-sulfanilamide, Sodium Salt.—To a solution containing 2.7 g. of 1,2-naphthoquinone-4,6-sodium disulfonate[1] in 75 cc. of water, 1.7 g. of sulfanilamide was added. The mixture was stirred mechanically until all the solid went into solution. This required fifteen minutes. Then 1.5 cc. of superoxol was added and stirring continued for an additional ten minutes. The deep red-brown solution was clarified with a small amount of Merck activated charcoal to remove the brown impurity. Upon addition of 10 g. of powdered sodium chloride the solution became a thick paste in a few minutes. After cooling in the ice box for two hours, the dark red needles were filtered off and dried in a vacuum desiccator over sulfuric acid. The weight of the crude material (contaminated with sodium chloride) was 4.6 g. It was recrystallized by solution in 50 cc. of water at 60° and subsequent chilling. The crystalline compound was filtered off, washed with ice-cold water, ice-cold 95% alcohol, ether and dried in a vacuum desiccator over sulfuric acid; yield, 2.2 g. (41%).

Anal. Calcd. for $C_{16}H_{11}O_7S_2N_2Na$: N, 6.50. Found: N, 6.51.

N^4-[4-Oxo-3-(*p*-sulfamylanilino)-2-sulfo-1(4)-naphthylidene]-sulfanilamide.—A solution of 1.7 g. of sulfanilamide in 100 cc. of water at 80° was added with stirring to a solution of 1.6 g. of 1,4-naphthoquinone-2-potassium sulfonate[4] in 50 cc. of water at 55°. As soon as the temperature of the mixture reached 50°, a small amount of yellow orange crystals (not identified) separated. These were filtered off by suction and discarded. To the filtrate at 30° was added 1 cc. of concentrated hydrochloric acid and the reaction mixture cooled in the ice box for three hours. The bright red needles that separated were filtered off, washed with cold water and dried in a vacuum desiccator over sulfuric acid; yield, 1.4 g. (50%). The material was recrystallized from 40 cc. of boiling water. It is fairly soluble in hot water. Dried in a vacuum desic-

(1) M. Böniger, *Ber.*, **27**, 23, 3050 (1894).
(2) P. Seidel, *ibid.*, **25**, 423 (1892).
(3) O. Folin, *J. Biol. Chem.*, **51**, 377 (1922).
(4) L. F. Fieser and M. Fieser, THIS JOURNAL, **57**, 491 (1935).

cator over sulfuric acid the compound melted at 276–278° (uncor.).

Anal. Calcd. for $C_{22}H_{18}S_3O_8N_4$: N, 9.96; S, 17.09. Found: N, 9.54; S, 16.85.

CHEMO-MEDICAL RESEARCH INSTITUTE
GEORGETOWN UNIVERSITY FILADELFO IRREVERRE
WASHINGTON, D. C. M. X. SULLIVAN

RECEIVED JUNE 25, 1942

Some Diamino Peptides

Dimethylamine reacted with *p*-nitro-β-bromopropionanilide to form *p*-nitro-β-dimethylaminopropionanilide, m. p. of the hydrochloride, 200–201°. A portion of this was transformed into the methochloride and both substances were reduced catalytically in alcohol containing hydrogen chloride to give, respectively, *p*-amino-β-dimethylaminopropionanilide dihydrochloride (I), colorless felted needles, m. p. 218–219°, and *p*-amino-β-dimethylaminopropionanilide methochloride hydrochloride (II), hygroscopic crystals, m. p. 211–212°.

N,N-Diethylethylenediamine,[1] prepared by the reduction (sodium and alcohol) of diethylglycine nitrile, reacted with *p*-nitrobenzoyl chloride, forming β-[*p*-nitrobenzoylamidoethyl]-diethylamine hydrochloride, colorless needles melting at 164–5°. This substance and its ethochloride were reduced catalytically in alcoholic hydrogen chloride to β-[*p*-aminobenzoylamidoethyl]-diethylamine dihydrochloride (III), m. p. 176.5–178°, and to β-[*p*-aminobenzoylamidoethyl]-triethylammonium chloride, hydrochloride (IV), which forms stubby prisms melting at 228°.

Reduction of β-dimethylaminopropionitrile gave γ-dimethylaminopropylamine, m. p. of the dihydrochloride, 182–184° The base reacted with *p*-nitrobenzoyl chloride to form γ-[*p*-nitrobenzoylamidopropyl]-dimethylamine hydrochloride, m. p. 190–192°. This was reduced catalytically in alcoholic hydrogen chloride solution to γ-[*p*-aminobenzoylamidopropyl]-dimethylamine dihydrochloride (V), m. p. 184–185°.

Reduction of the *p*-nitrophenylurethan of β-hydroxyethyltriethylammonium chloride yielded β-[*p*-aminophenylcarbamatoethyl]-triethylammonium chloride, hydrochloride (VI), which forms irregular prisms melting at 138–139°.

By the reduction of β-[*p*-nitrobenzoyloxyethyl]-triethylammonium chloride, there was obtained β-[*p*-aminobenzoyloxyethyl]-triethylammonium chloride, hydrochloride (VII), m. p. 214–215°. This has been reported[2] previously, but the synthesis used was not free from ambiguity.

The salts described here were crystallized from absolute alcohol or from alcohol–ethyl acetate mixtures. The analytical data are in the table.

No.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
I	$C_{11}H_{19}ON_3Cl_2$	47.12	6.84	47.38	6.61
II	$C_{12}H_{21}ON_3Cl_2$	48.96	7.20	48.67	7.27
III	$C_{13}H_{23}ON_3Cl_2$	50.63	7.52	50.67	7.80
IV	$C_{15}H_{27}ON_3Cl_2$	53.56	8.13	53.45	8.04
V	$C_{12}H_{21}ON_3Cl_2$	48.96	7.20	49.05	7.51
VI	$C_{15}H_{27}O_2N_3Cl_2$	51.12	7.73	51.27	7.75
VII	$C_{15}H_{26}O_2N_2Cl_2$	53.39	7.77	53.02	7.62

BURROUGHS WELLCOME & CO., U. S. A. RICHARD BALTZLY
EXPERIMENTAL RESEARCH LABORATORIES WALTER S. IDE
TUCKAHOE, NEW YORK JOHANNES S. BUCK

RECEIVED MAY 18, 1942

Some New Quaternary Salts

Methylaniline and octadecyl iodide reacted to yield methyloctadecylaniline, a yellow oil, b. p. (3 mm.), 234°. This was treated in benzene solution with methyl iodide forming octadecylphenyldimethylammonium iodide which crystallized in leaflets from ethyl acetate.

Cyclohexylethylamine (prepared from cyclohexylacetic acid by the sequence: acid → acid chloride → amide → nitrile → amine) was methylated by the Clarke–Eschweiler method. The resulting tertiary amine reacted with benzyl chloride in ether to give cyclohexylethylbenzyldimethylammonium chloride.

Benzyl-β-bromoethyldimethylammonium bromide was prepared from benzyldimethylamine and ethylene bromide.

Triethylamine and α-menaphthyl chloride (α-naphthylmethyl chloride) yielded α-menaphthyltriethylammonium chloride. Data on these substances are presented in the subjoined table.

Formula	M. p., °C.	Composition	Analyses, % Calcd. C	Calcd. H	Found C	Found H
(*n*-$C_{18}H_{37}$)$C_6H_5NMe_2I$	93–94	$C_{26}H_{48}NI$	62.25	9.65	62.12	9.69
($C_6H_{11}CH_2CH_2$)($C_6H_5CH_2$)NMe_2Cl	206 dec.	$C_{17}H_{28}NCl$	72.44	10.02	72.15	10.16
($C_6H_5CH_2$)($BrCH_2CH_2$)NMe_2Br	174	$C_{11}H_{17}NBr_2$	40.87	5.31	40.91	5.61
(α-$C_{10}H_7CH_2$)NEt_3Cl	197 dec.	$C_{17}H_{24}NCl$	73.49	8.71	73.41	8.62

BURROUGHS WELLCOME & CO., U. S. A.
EXPERIMENTAL RESEARCH LABORATORIES
TUCKAHOE, NEW YORK RICHARD BALTZLY
CLAYTON W. FERRY
JOHANNES S. BUCK

RECEIVED MAY 18, 1942

Some Mono- and Disubstituted Guanidines

The guanidines here described were all prepared by conventional methods. The S-methyl-isothiourea sulfate method (generally applicable with amines of moderate strength and water solubility) was used to prepare the five following: β-[N-morpholinoethyl]-guanidine sulfate (from aminoethylmorpholine), β,β-diethoxyethylguanidine sulfate (from amino acetal), N,N-dicyclohexylguanidine sulfate (from dicyclohexylamine), N-benzyl-N-methylguanidine sulfate (from benzylmethylamine) and δ-phenoxybutylguanidine sulfate (from δ-phenoxybutylamine prepared by reduction of γ-phenoxybutyronitrile). In all these cases the salt was isolated by evaporation of the reaction mixture

(1) Ristenpart, *Ber.*, **29**, 2526 (1896).
(2) Einhorn and Uhlfelder, *Ann.*, **371**, 138 (1909).

and crystallized from mixtures of polar and non-polar solvents. Diethoxyethylguanidine sulfate crystallized best from *n*-butanol–ethyl acetate. The others were crystallized from alcohol–ether.

N-Benzyl-N-α-naphthylguanidine Hydrochloride.—Benzyl-α-naphthylamine was refluxed in amyl alcohol with 1 mol of cyanamide and 1.2 mols of hydrogen chloride. On cooling, ether was added and the hydrochlorides separated as a purple sirup. Attempts to crystallize having failed, the mixture was dissolved in water and ammonia added. Some unreacted benzylnaphthylamine separated together with most of the color. The aqueous layer was then basified with sodium hydroxide and the precipitated guanidine taken into ether. After drying over potassium carbonate, alcoholic hydrogen chloride was added. The salt was recrystallized from alcohol–ether mixtures.

N,N′-Dihomoanisylguanidine Hydrochloride.—To a solution of 2 mols of homoanisylamine in absolute ether was added, with shaking and ice-cooling, a solution of 1 mol of cyanogen bromide in ether. After standing one-half hour the ether was evaporated by a stream of dry air, a little absolute alcohol added to homogenize the mixture and the whole was heated three hours in an oil-bath at 150°. The material was then dissolved in water, the base liberated with alkali, and extracted with ether. On drying over potassium carbonate a crystalline solid appeared on the surface of the drying agent. The ether was decanted off, the solid dissolved in chloroform and transformed into the hydrochloride by alcoholic hydrogen chloride. It was recrystallized from alcohol–ether, forming lustrous plates.

N-Methyl-N′-α-naphthylguanidine.—Methylamine and α-naphthylisothiocyanate yielded N,N′-methylnaphthylthiourea. Methylation with methyl sulfate gave the S-methyl derivative which was desulfurized in the usual manner with lead oxide and ammonia.

Data on these compounds are presented in the table.

Substance	M. p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
β-N-Morpholinoethylguanidine sulfate	197	$C_7H_{16}ON_4(H_2SO_4)_{1/2}$	37.99	7.75	38.33	7.52
β,β-Diethoxyethylguanidine sulfate	154	$C_7H_{17}O_2N_3(H_2SO_4)_{1/2}$	37.47	8.09	37.38	7.99
N,N-Dicyclohexylguanidine sulfate	195	$C_{13}H_{25}N_3(H_2SO_4)_{1/2}$	57.28	9.62	57.05	9.28
N-Benzyl-N-methylguanidine sulfate	252 dec.	$C_9H_{13}N_3(H_2SO_4)_{1/2}$	50.90	6.65	50.87	6.59
δ-Phenoxybutylguanidine sulfate	199–199.5	$C_{11}H_{17}ON_3(H_2SO_4)_{1/2}$	51.53	7.08	51.32	7.33
N-Benzyl-N-α-naphthylguanidine hydrochloride	223–224	$C_{18}H_{17}N_3 \cdot HCl$	69.33	5.82	69.19	5.80
N,N′-Dihomoanisylguanidine hydrochloride	125.5–126.5	$C_{19}H_{25}O_2N_3 \cdot HCl$	62.69	7.21	62.63	7.05
N-α-Naphthyl-N′-methylguanidine hydrochloride	220–220.5 dec.	$C_{12}H_{13}N_3 \cdot HCl$	61.12	5.99	61.06	5.99

BURROUGHS WELLCOME & CO., U. S. A. JOHANNES S. BUCK
EXPERIMENTAL RESEARCH LABORATORIES
TUCKAHOE, NEW YORK RICHARD BALTZLY
CLAYTON W. FERRY

RECEIVED MAY 18, 1942

Some Quaternary Salts from β-Dimethylamino-β′-cymoxydiethyl Ether

A concentrated aqueous solution of sodium thymolate or sodium *p*-chlorothymolate was heated under reflux with β,β′-dichlorodiethyl ether. After separation of the aqueous layer, unreacted dichlorodiethyl ether was removed *in vacuo*, and the residue was heated for seven hours at 145° (*p* = *ca.* 150 lb.) in a glass-lined bomb with 33% methanolic dimethylamine. After removal of volatile materials on the steam-bath under diminished pressure, the residual tertiary amines were partially purified by solution in acid and extraction with ether; on liberation with alkali, they were obtained as oils which could not be distilled *in vacuo*, but were converted directly into quaternary salts by warming on the steam-bath with the appropriate halides. The salts crystallized from acetone or alcohol on addition of ether.

$[p\text{-}XC_{10}H_{12}OCH_2CH_2OCH_2CH_2N^+(CH_3)_2R]Y^-$

R	X	Y	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
CH_3	Cl	I	152	$C_{17}H_{29}O_2NClI$	46.19	6.62	46.20	6.42
$C_6H_5CH_2$	H	Cl	122–123	$C_{23}H_{34}O_2NCl$	3.58[a]	9.05[b]	3.91[a]	9.21[b]
$p\text{-}ClC_6H_4CH_2$	H	Cl	166–166.5	$C_{23}H_{33}O_2NCl_2$	64.76	7.80	64.85	7.80
$p\text{-}ClC_6H_4CH_2$	Cl	Cl	160	$C_{23}H_{32}O_2NCl_3$	59.92	7.00	60.12	7.01
$p\text{-}BrC_6H_4CH_2$	Cl	Cl	156.5–157	$C_{23}H_{32}O_2NCl_2Br$	54.64	6.38	54.95	6.35

[a] N. [b] Cl.

BURROUGHS WELLCOME AND CO., U. S. A.
EXPERIMENTAL RESEARCH LABORATORIES
TUCKAHOE, NEW YORK CLAYTON W. FERRY
ALAN E. ARDIS
JOHANNES S. BUCK

RECEIVED MAY 18, 1942

N,N-Dimethylethylenediamine and Some Derivatives

The readily available dimethyl glycine nitrile[1] can be reduced by sodium and absolute alcohol to give N,N-dimethylethylenediamine. This is a colorless liquid boiling, when anhydrous, at 107°. As its dehydration is difficult and its dihydrochloride (melting around 160°) is also hygroscopic, it is better characterized through a derivative. The following compounds were prepared as outlined, nitro derivatives being reduced with Adams catalyst in alcoholic solution containing hydrogen chloride. β-[*p*-Nitrobenzoylamidoethyl] dimethylamine hydrochloride (I), formed from *p*-nitrobenzoyl chloride and the diamine, was hydrogenated catalytically yielding β-[*p*-aminobenzoylamidoethyl]-dimethylamine dihydrochloride (II). The methochloride of I was reduced to β-[*p*-amino-

(1) v. Braun, *Ber.*, **40**, 3937 (1907).

benzoylamidoethyl]-trimethylammonium chloride, hydrochloride (III).

The diamine reacted with *p*-nitrophenyl isocyanate to give β-[*p*-nitrophenylureidoethyl]-dimethylamine; m. p. of the hydrochloride, 247–248.5°. From this were obtained β-[*p*-aminophenylureidoethyl]-dimethylamine dihydrochloride (IV) and the corresponding trimethylammonium chloride, hydrochloride (V). The diamine with *p*-nitrophenylacetyl chloride gave the *p*-nitrophenylacetamide, m. p. of the hydrochloride, 190–192.5°, and reduction of this yielded β-[*p*-aminophenylacetamidoethyl]-dimethylamine dihydrochloride (VI). Reduction of the methochloride of the nitro compound gave β-[*p*-aminophenylacetamidoethyl]-trimethylammonium chloride hydrochloride (VII).

With phenyl isothiocyanate the diamine formed N-phenyl-N′-β-dimethylaminoethyl thiourea (VIII) and with *p*-acetamidobenzenesulfonyl chloride it formed the *p*-acetamidobenzenesulfonamide which was hydrolyzed with hydrochloric acid to β-[*p*-aminophenylsulfonamidoethyl]-dimethylamine dihydrochloride (IX). The thiourea was crystallized from benzene–hexane; the hydrochlorides from absolute alcohol.

DERIVATIVES OF N,N-DIMETHYLETHYLENEDIAMINE

No.	Formula	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
I	$O_2NC_6H_4CONHCH_2CH_2NMe_2 \cdot HCl$	182.5–183.5	48.24	5.89	48.09	5.90
II	$H_2NC_6H_4CONHCH_2CH_2NMe_2 \cdot 2HCl$	190–191	47.12	6.84	47.23	6.89
III	$H_2NC_6H_4CONHCH_2CH_2NMe_3Cl \cdot HCl$	dec. > 230	48.96	7.20	49.37	7.39
IV	$H_2NC_6H_4NHCONHCH_2CH_2NMe_2 \cdot 2HCl$	182–184 dec.	44.73	6.83	44.88	6.87
V	$H_2NC_6H_4NHCONHCH_2CH_2NMe_3Cl \cdot HCl$	186	46.59	7.17	46.59	7.40
VI	$H_2NC_6H_4CH_2CONHCH_2CH_2NMe_2 \cdot 2HCl$	209.5–210.5	48.96	7.20	49.12	7.13
VII	$H_2NC_6H_4CH_2CONHCH_2CH_2NMe_3Cl \cdot HCl$	155–156 dec.	50.63	7.52	50.49	7.61
VIII	$C_6H_5NHCSNHCH_2CH_2NMe_2$	83–83.5	59.15	7.68	58.97	7.69
IX	$H_2NC_6H_4SO_2NHCH_2CH_2NMe_2 \cdot 2HCl$	211.5–213 dec.	37.96	6.06	37.86	6.02

BURROUGHS WELLCOME & CO., U. S. A.
EXPERIMENTAL RESEARCH LABORATORIES
TUCKAHOE, NEW YORK
RICHARD BALTZLY
JOHANNES S. BUCK
WALTER S. IDE

RECEIVED JUNE 6, 1942

Some Unsymmetrical Disubstituted Ureas

The substances, data on which are presented in the subjoined table, were prepared by the action of nitrourea on the corresponding secondary amines.[1] They crystallize in colorless prisms from alcohol or benzene–petrol ether.

UNSYMMETRICAL DISUBSTITUTED UREAS

$R,R'NCONH_2$

Substituents R	Substituents R′	Formula	M. p., °C.	Analyses, % Calcd. N	Found N
CH_3	$(n)C_6H_{13}$	$C_8H_{18}ON_2$	75	17.72	17.92
$(4)CH_3OC_6H_4$	$C_2H_5(CH_3)CH$	$C_{12}H_{18}O_2N_2$	140	12.61	12.70
$(4)CH_3OC_6H_4$	$C_2H_5(CH_3)CHCH_2$	$C_{13}H_{20}O_2N_2$	130	11.86	12.17
$(4)CH_3OC_6H_4$	$(CH_3)_3CCH_2$	$C_{13}H_{20}O_2N_2$	155	11.86	12.13
$(4)CH_3OC_6H_4$	$(CH_3)_2CHCH_2(CH_3)CH$	$C_{14}H_{22}O_2N_2$	110	11.19	11.25

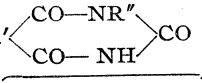
(1) *Cf.* Buck and Ferry, THIS JOURNAL, **58**, 854 (1936).

BURROUGHS WELLCOME & CO., U. S. A.
EXPERIMENTAL RESEARCH LABORATORIES
TUCKAHOE, NEW YORK
JOHANNES S. BUCK
WALTER S. IDE
RICHARD BALTZLY

RECEIVED JUNE 6, 1942

Some N-Substituted Barbituric Acids

The subjoined table contains data on five new compounds of this type. 1-*p*-Nitrophenyl-5-*i*-butyl-5-ethyl barbituric acid was obtained by nitration[1] of 1-phenyl-5-*i*-butyl-5-ethyl barbituric acid[2] and in turn was reduced catalytically[1] to the *p*-amino derivative. The other three substances were prepared by the conventional method from the corresponding ureas and malonic esters. All crystallized in colorless prisms, the 1-*n*-hexyl derivative from hexane, the others from alcohol.

DERIVATIVES OF BARBITURIC ACID R,R′ 

Substituents R	Substituents R′	Substituents R″	Formula	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_2H_5	C_2H_5	$(n)C_6H_{13}$	$C_{14}H_{24}O_3N_2$	41	62.64	9.02		62.79	9.09	
C_2H_5	$(n)C_4H_9$	$(4)C_2H_5C_6H_4$	$C_{18}H_{24}O_3N_2$	107	68.31	7.65		68.21	7.81	
C_2H_5	$(CH_3)_2CHCH_2$	$(4)H_2NC_6H_4$	$C_{16}H_{21}O_3N_3$	153	63.33	6.98		63.58	7.32	
H	H	$(2)C_2H_5OC_6H_4$	$C_{12}H_{12}O_4N_2$	193.5			11.29			11.47
C_2H_5	$(CH_3)_2CHCH_2$	$(4)O_2NC_6H_4$	$C_{16}H_{19}O_5N_3$	188			12.61			12.89

(1) *Cf.* Buck, THIS JOURNAL, **59**, 1249 (1937).
(2) Hjort and Dox, *J. Pharmacol.*, **35**, 155 (1929).

BURROUGHS WELLCOME & CO., U. S. A.
EXPERIMENTAL RESEARCH LABORATORIES
TUCKAHOE, NEW YORK
JOHANNES S. BUCK
WALTER S. IDE
RICHARD BALTZLY

RECEIVED JUNE 6, 1942

Some Quaternary Salts Containing Aryloxyethyl and Aryloxypropyl Groups

A number of salts of the two types

$$[p\text{-}ClC_{10}H_{12}O(CH_2)_nN^+Me_2R]Y^- \quad I$$

$$(p\text{-}ClC_{12}H_{16}O)NC_5H_5Br \quad II$$

have been prepared by the following general procedure. Thymol and *p*-chlorothymol, reacting as the sodium salts with ethylene and trimethylene bromohydrins, gave ether alcohols which were transformed into bromides by phosphorus tribromide in the usual manner and the bromides were allowed to react with dimethylamine in methanol at 120–125°. The resulting tertiary amines on treatment with appropriate alkyl halides produced the quaternary salts of type I. As a variant chlorocymoxyethyl bromide was allowed to act on pyridine and 2,4-dimethylthiazole, yielding the members of type II. The quaternary salts were purified by crystallization from absolute alcohol with addition of ether or ethyl acetate.

R	Y	*n*	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
				$[p\text{-}ClC_{10}H_{12}O(CH_2)_nN^+Me_2R]Y^-$				
CH_3[a]	I	2	176	$C_{15}H_{26}ONI$	49.57	7.22	49.45	7.41
CH_3	I	2	228	$C_{15}H_{25}ONClI$	45.27	6.34	45.21	6.50
$C_6H_5CH_2$	Cl	2	194	$C_{21}H_{29}ONCl_2$	65.95	7.65	65.86	7.90
p-$ClC_6H_4CH_2$	Cl	2	216	$C_{21}H_{28}ONCl_3$	60.49	6.77	60.62	6.99
o-$ClC_6H_4CH_2$	Cl	2	175	$C_{21}H_{28}ONCl_3$	60.49	6.77	60.28	6.89
CH_3	I	3	229	$C_{16}H_{27}ONClI$	46.65	6.61	46.50	6.61
p-$ClC_6H_4CH_2$	Cl	3	204	$C_{22}H_{30}ONCl_3$	61.31	7.02	61.37	7.13
p-$BrC_6H_4CH_2$	Cl	3	191	$C_{22}H_{30}ONCl_2Br$	55.57	6.37	55.71	6.62
p-$ClC_{10}H_{12}O(CH_2)_3$	Cl	3	184–187	$C_{28}H_{42}O_2NCl_2Br$	58.41	7.36	58.67	7.52
				p-$ClC_{10}H_{12}OCH_2CH_2RBr$				
N-Pyridyl			119–120	$C_{17}H_{21}ONClBr$	55.05	5.72	55.18	6.00
N-2,4-Dimethylthiazolyl			214	$C_{17}H_{23}ONSClBr$	50.42	5.73	50.53	6.03

[a] Nuclear Cl replaced by H.

BURROUGHS WELLCOME AND CO., U. S. A.
EXPERIMENTAL RESEARCH LABORATORIES
TUCKAHOE, NEW YORK
WALTER S. IDE
RICHARD BALTZLY
JOHANNES S. BUCK

RECEIVED MAY 18, 1942

Basic Indium Salicylates

Insoluble basic indium salicylate analogous to the basic indium salts reported for a number of organic acids[1] results from the interaction of indium salt solutions with those of soluble salicylates.

Basic Indium Salicylate Tri-hydrate.—To 2.0000 g. of anhydrous indium sulfate dissolved in 50 ml. of water was added 25 ml. of a solution containing 4.5553 g. of sodium salicylate (mole ratio of 1 to 3). The resulting finely divided white precipitate was removed by filtration, washed until sulfate and sodium free, and air dried by suction. The product consists of microcrystalline needles which are very slightly soluble in water, ethanol and methanol, insoluble in benzene and toluene, but readily soluble in hot dilute acids. On ignition, the solid chars and is converted quantitatively to indium oxide. Prolonged drying at 110° yields the anhydrous compound.

Anal. Calcd. for $In(C_7H_5O_3)_2OH\cdot 3H_2O$: In, 24.95. Found: In (by ignition), 24.83.

Anhydrous Basic Indium Salicylate.—Two grams of the trihydrate was dehydrated by boiling with absolute methanol. The residue was washed successively with methanol and ether and dried for one hour at 110°. In appearance and behavior it resembles the hydrate.

Anal. Calcd. for $In(C_7H_5O_3)_2OH$: In, 28.27; salicylate, 67.54. Found: In, 28.23; salicylate (bromate titration), 67.64.

(1) Ekeley and Johnson, THIS JOURNAL, **57**, 773 (1935).

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS
THERALD MOELLER

RECEIVED JUNE 29, 1942

COMMUNICATIONS TO THE EDITOR

ON THE CHEMICAL BEHAVIOR OF CAFESTEROL

Sir:

In view of the recent publication of Wettstein, *et al.* [*Helv. Chim. Acta*, **24**, 332E (1941)], which we have just received, it appears desirable to record some of our observations in this field. The existence of a benzenoid ring in cafesterol, as suggested by Slotta and Neisser [*Ber.*, **71**, 2342 (1938)], is highly improbable, since nitric acid oxidation of this compound gives neither benzene tetra- or dicarboxylic acid; from the reaction mixture was obtained only a non-acidic substance, apparently a nitro derivative, m. p. 220–230°. Cafesterol possesses a highly reactive conjugated double bond system in one ring, a fact shown by the formation of the maleic anhydride adduct (m. p. 185–192°), in benzene solution at room temperature or on *gentle* warming. Boiling such a solution promptly causes decomposition. In absolute alcoholic solution cafesterol takes up two moles of hydrogen in presence of palladized charcoal (20% Pd) giving a tetrahydro derivative, m. p. 153–155°, acetate 150–152°. Neither this tetrahydrocafesterol nor its acetate gives any coloration with concentrated hydrochloric acid, while cafesterol in alcoholic solution gives an intense blue to blue-green color reaction with this reagent (Slotta and Neisser). Contrary to the observations of Wettstein, *et al.*, and Slotta and Neisser, on treatment with sodium and alcohol (or amyl alcohol), cafesterol gives a new product, m. p. 153–156°, acetate 162–165°. Despite similar melting points, the difference of this product from cafesterol is shown by the fact that with concentrated hydrochloric acid, its alcoholic solution gives a purple coloration which *does not turn blue even on boiling*. Its acetate on the other hand gives a yellow to orange coloration with the same reagent. Sodium–alcohol treatment does not appear to affect the conjugated double bond system, because the acetate of the product gives a maleic anhydride adduct, m. p. 185°. The adduct gives no coloration with hydrochloric acid at room temperature.

A detailed report will be published at a later date.

THE RESEARCH LABORATORIES
THE UPJOHN COMPANY PURNENDU NATH CHAKRAVORTY
KALAMAZOO, MICHIGAN MILDRED M. WESNER

RECEIVED JULY 29, 1942

DERIVATIVES OF ESTRONE CONTAINING OXYGEN AT POSITION 16

Sir:

The interesting hypothesis, recently advanced by Marrian,[1] that 16-ketoestrone is an estrogen metabolite in the human, leads to the speculation that estriol (theelol) may be formed from estrone by the reduction of 16-ketoestrone. If such a reduction occurs, it is logical to assume that 16-hydroxyestrone may also lie on this metabolic pathway as an intermediate between the dione and glycol forms. In the reduction of 16-ketoestrone, two stereoisomeric 16-hydroxyestrones and four stereoisomeric estriols are theoretically possible. The question also arises whether or not a compound in this series may be regarded as an abnormal estrogen metabolite, which might conceivably play a role in the etiology of carcinoma of the uterus and of the mammary gland.

We have succeeded in preparing (i) the methyl ether of 16-ketoestrone, (ii) a compound believed to be one of the two epimeric 16-hydroxyestrones, and (iii) an estriol which is isomeric with the naturally-occurring theelol.

Estrone was converted to the 16-isonitroso derivative by the method of Litvan and Robinson,[2] and this derivative on reduction with zinc and acetic acid[3] yielded a mixture of α-ketols, from which there was isolated in pure form a compound which is probably a 16-hydroxyestrone (m. p. 234–237°; $[\alpha]^{29.5}D$ −102° in ethanol). This compound was characterized by the following derivatives: oxime (m. p. 222.5–223°), monobenzoate (m. p. 241.5–243.5°), methyl ether (m. p. 174–177°), and oxime of the methyl ether (m. p. 175–177°).

Reduction of a similar α-ketol mixture with hydrogen and Adams catalyst yielded a mixture of estriols, one of the components of which proved to be an isomer of theelol. The isomer of estriol obtained has m. p. of 267–269° and $[\alpha]^{29.5}D$ +88° (in ethanol). A mixed melting point with theelol shows a depression of 10°. It gives a methyl ether melting at 141–142° and a triacetate melting at 152°.

(1) Marrian, *Bul. New York Acad. Med.*, **15**, 27 (1939).
(2) Litvan and Robinson, *J. Chem. Soc.*, 1997 (1938).
(3) Stodola, Kendall and McKenzie, *J. Org. Chem.*, **6**, 841 (1941).

Oxidation with copper acetate of the mixture of α-ketols obtained from estrone methyl ether gave 16-ketoestrone methyl ether, obtained as flat needles, orange in color (m. p. 176–178°). It gives a dioxime (m. p. 230°) identical with that prepared by oximating 16-isonitrosoestrone methyl ether. The dione gives an intense violet color with concentrated sulfuric acid.

The dioxime of 16-ketoestrone (free phenol) was also prepared in the hope that this derivative might be useful in detecting the dione in tissue or fluid, should it be present as predicted by Marrian. 16-Ketoestrone dioxime (m. p. 230–231°) gives no colored complex with nickelous or cobaltous ions, but produces a yellowish-green solution with alcoholic copper acetate. The copper complex may be extracted with chloroform, and the color intensity is such that the eye can detect it at the level of 10 γ per cc.

The melting points listed above are uncorrected.

We are now attempting to prepare the other isomeric 16-hydroxyestrone and the remaining two isomeric estriols.

DEPARTMENT OF BIOCHEMISTRY
COLLEGE OF PHYSICIANS AND SURGEONS
COLUMBIA UNIVERSITY, NEW YORK, N. Y.
MAX N. HUFFMAN
National Research Fellow in the Medical Sciences, 1941–1942

RECEIVED JULY 31, 1942

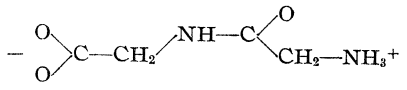
THE CRYSTAL STRUCTURE OF β-GLYCYLGLYCINE

Sir:

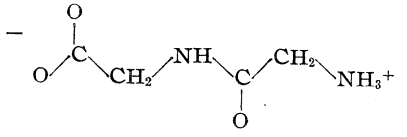
Some time ago the determination of the crystal structure of glycylglycine was undertaken as a continuation of the X-ray diffraction studies[1] which are a part of a program of research upon the constitution and configuration of proteins. This determination, the first concerned with a linear peptide, was stopped last year because of the war, and in view of the uncertainty of completing the work the results at hand are briefly described in this letter.

The crystals were grown from aqueous *n*-propyl alcohol and all three modifications described by Bernal[2] were eventually obtained, although not simultaneously as in his crystallization. Because of the shortness of the *b* axis the needle-like beta form was selected for investigation. Using Cu Kα rays complete sets of oscillation pictures were prepared about *a* and *b* and some oscillations were made about *c* to confirm the length of that axis. Weissenberg pictures of the [010] zone were made for intensity comparisons. The cell has a = 17.89 Å., b = 4.62 Å. and c = 17.06 Å., with β = 125°10′, and contains eight molecules. This *c* is twice that given by Bernal and the space-group instead of $P2_1/a$ as given by him, is either Aa or $A2/a$. The latter was tentatively assumed and present results indicate it is probably correct.

A Patterson projection parallel to *b* yielded preliminary *x* and *z* parameters. The configurations I, suggested by Bernal, and II were tried, and it was found that only with II could the projection be interpreted. The parameters were



I



II

improved by Fourier projections and least squares,[3] the latter to resolve CO groups not resolved in the projections. The present agreement between calculated and observed intensities in this zone is good, but minor discrepancies indicate that there may be a few errors in signs or that the contributions from hydrogen atoms should be considered. A tentative set of *y* parameters has also been selected so as to yield reasonable interatomic distances both within and between molecules and these give qualitative agreement between calculated and observed intensities in the [100] zone.

Because of the approximate nature of the parameters, particularly the *y*'s, there is no point in listing interatomic distances. The chief results are first, that the configuration is that of II with the molecule coplanar within present errors except for the terminal nitrogen atom, which lies out of the plane by several tenths of an ångström, and, second, that the zwitterion form is correct. The terminal nitrogen is surrounded at the usual N–H $\cdots$O distance by three oxygen atoms of other molecules, two carboxyl and one carbonyl. All the indicated hydrogen bond angles about the nitrogen are tetrahedral to within 10°. The imino nitrogen is also forming a hydrogen bond to a carboxyl oxygen of a neighboring molecule.

(1) Diketopiperazine, R. B. Corey, THIS JOURNAL, **60**, 1598 (1938); glycine, G. Albrecht and R. B. Corey, *ibid.*, **61**, 1087 (1939); *dl*-alanine, H. A. Levy and R. B. Corey, *ibid.*, **63**, 2095 (1941).

(2) J. D. Bernal, *Z. Krist.*, **78**, 363 (1931).

(3) E. W. Hughes, THIS JOURNAL, **63**, 1737 (1941).

The hydrogen bonds satisfactorily account for the binding together of the crystal.

Although the structure has not yet been completely checked by quantitative comparisons of intensities, particularly with regard to the y parameters, it is probably substantially correct.

THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIFORNIA EDWARD W. HUGHES
WALTER J. MOORE
(National Research Fellow 1940–1941)

RECEIVED JULY 15, 1942

NEW BOOKS

Thorpe's Dictionary of Applied Chemistry. By JOCELYN FIELD THORPE and M. A. WHITELEY, Assisted by Eminent Contributors. Fourth Edition (Revised and Enlarged), Vol. V, FEH.-Glass, including an Abridged Index to Volumes I-V of the New Edition. Longmans, Green and Company, Inc., 55 Fifth Avenue, New York, N. Y., 1942. xxiii + 610 pp. With illustrations. 15.5 × 23 cm. Price, $25.00.

The earlier volumes of this Fourth Edition have already been reviewed in THIS JOURNAL (**59,** 2477; **61,** 222; **62,** 237; **63,** 884). This fifth volume of 609 pages covers a part of the alphabet which required 275 pages in the earlier edition. The new edition is almost completely rewritten. There has been a noticeable deterioration in the quality of the paper which is far from uniform in color and texture in the different parts of the book. But there has been no deterioration in the quality of the text. This excellent book has been issued promptly in spite of difficulties modestly described, "When, owing to war conditions, the work of the Dictionary could no longer be carried on in London it was transferred to the University Chemical Laboratory, Cambridge." Another obstacle was the death of the Editor-in-Chief, Sir Jocelyn Thorpe, which occurred on June 10, 1940, the day of publication of Volume IV of the Dictionary. M. A. Whiteley, formerly Associate Editor, has had the editorial responsibility for the completion of this volume, which, however, was well advanced at the time of the death of Sir Jocelyn Thorpe. It is a pleasure to express appreciation and admiration for the typically British determination to carry on successfully in spite of hindrances which would stop many a less resolute people.

GRINNELL JONES

Liebig and after Liebig. A Century of Progress in Agricultural Chemistry. Publication of the American Association for the Advancement of Science, No. 16. Publication Committee: CHARLES A. BROWNE, Chairman, RICHARD BRADFIELD, HUBERT B. VICKERY. Edited by FOREST RAY MOULTON. American Association for the Advancement of Science, Smithsonian Institution Building, Washington, D. C., 1942. 111 pp. 19.5 × 26.5 cm.

The ten papers which make up this volume constitute a well-integrated account of the announced subject of the book, namely, of a century of progress in agricultural chemistry. The Introduction by Charles A. Browne on "Justus von Liebig—Man and Teacher" is followed by Section I, "Organic Chemistry, Enzymes and Nutrition," which contains four papers, "Liebig's Influence in the Promotion of Agricultural Chemical Research" by Henry R. Kraybill, "Liebig and the Chemistry of Proteins" by Hubert B. Vickery, "Liebig and the Chemistry of Enzymes and Fermentation" by Arnold K. Ball, and "Liebig and the Chemistry of Animal Nutrition" by Paul E. Howe, and Section II, "Soils, Fertilizers and the Mineral Requirements of Plants," which contains five papers, "Liebig and the Chemistry of the Soil" by Richard Bradfield, "Liebig—The Humus Theory and the Rôle of Humus in Plant Nutrition" by Selman A. Waksman, "Liebig and the Chemistry of Mineral Fertilizers" by Harry A. Curtis, Liebig and the Law of the Minimum" by Charles A. Browne, and "Liebig and the Mineral Requirements of Plants as Indicated by Means of Solution Cultures" by Burton Livingston. For the chemist who is not familiar with the subject of agricultural chemistry, the book will supply an interesting introduction to it, a general account of the field and of the manner in which it has been cultivated and made to fructify. It is a book which is not by any means to be reserved for the library of the specialist.

The book is clearly printed, two columns to the page, and is fully documented. It is illustrated with five pictures and ten diagrams.

TENNEY L. DAVIS

The Amphoteric Properties of Proteins. Vol. XLI, Art. 4 of the Annals of the New York Academy of Sciences. By R. Keith Cannon, A. Kibrick, John G. Kirkwood, L. G. Longsworth, A. H. Palmer and Jacinto Steinhardt. The New York Academy of Sciences, care of the American Museum of Natural History, New York, N. Y. 87 pp. Price $1.25. This monograph is one of several, which if purchased as a set, may be had at a reduced price.

This contribution to protein literature consists of a series of papers presented at a recent symposium sponsored by the New York Academy of Sciences. It conforms to the usual high standards of other symposia sponsored by this Academy.

The first paper of the series, titled "The Amphoteric Properties of Egg Albumin," by Cannon, Kibrick and Palmer "is devoted to a discussion of the contribution

which electrode titrations may make to the quantitative definition of the amphoteric properties of a protein." A considerable body of data showing the effect of the protein concentration, temperature, ionic strength, and nature of the added ions upon the titration curve of acid or base bound *vs.* *p*H is presented for egg albumin solutions. The discussion of these results correlates the observed titration curves with those estimated on the basis of amino-acid composition studies. In the studies of the effect of added electrolyte, it is found that the slopes of the titration curves vary with ionic strength but are nearly independent of the nature of the ions present, while the isoionic point depends upon both the nature and concentration of the ions present. These empirical results are considered in terms of the Linderstrøm-Lang electrostatic theory, and may be quantitatively reconciled only if certain empirical corrections are applied.

Longsworth's contribution, "The Influence of *p*H on the Mobility and Diffusion of Ovalbumin" attempts a correlation of mobilities with other physical properties. He presents mobility and diffusion constant measurements over a wide *p*H range of from 1.8 to 12.8. All buffers used were monovalent, and of 0.1 ionic strength. Protein concentrations were about one-half per cent. These values are compared with net charges as estimated from the titration data of Cannon, Kibrick and Palmer. A study of the ratio of charge (as estimated from titration measurements) to mobility showed that this quantity "is sufficiently constant to warrant the conclusion that, except for minor secondary effects, the mobility of ovalbumin is proportional to the number of equivalents of acid bound by the protein at constant ionic strength at any *p*H within its stability range." The observed value for this ratio does not agree with that computed from the measured frictional coefficient and molecular weight, however, and this discrepancy is discussed. Dr. Longsworth's paper also contains a rather detailed discussion of certain problems relating to the computation of mobilities from electrophoretic patterns.

The paper of Steinhardt on "Participation of Anions in the Combination of Proteins with Acids" describes an extensive study of "the combination of wool with nineteen different acids," and attempts to "establish a quantitative measure of the relative affinities of the anions of various strong acids for proteins on the basis of a small number of measurements of acid combined and *p*H." Steinhardt points out that certain advantages gained by using a protein such as wool keratin, makes possible the analysis of the specific anion effects. A variation in affinity of several thousand fold in going from hydrochloric acid to picric and flavianic acids is postulated. Data showing a similar variation of affinities computed from measurements upon egg albumin solution are also given, although these data are of considerably less quantitative nature. The nature of these protein–anion combinations and other possible significance is also discussed.

A final paper by Kirkwood, "Acid–Base Equilibrium in Solutions of Ampholytes," outlines methods and presents tables which make possible the calculation of the charge separation, or dipole moment, of dipolar ions from measurements of Δp_K, defined as $\log_{10} K_2^0/K_2$ where K_2^0 and K_2 are the acid ionization equilibrium constants for the ionization of HZ^{0+} and HZ, respectively. Here Z^0 and Z^- differ in structure only by the negative charge. Charge separations are presented for some seven amino acids and peptides, using NH_3^+-$RCOO^-$ for HZ and NH_3^+-$RCOO$-CH_3 for HZ^{0+}. Extensions of these simple relations to models containing arbitrary numbers of acidic and basic groups are presented.

J. L. ONCLEY

BOOKS RECEIVED

July 10, 1942–August 10, 1942

FREDERICK BERNHEIM. "The Interaction of Drugs and Cell Catalysts." Burgess Publishing Company, 426 South Sixth Street, Minneapolis, Minn. 85 pp. $2.25.

M. J. BUERGER. "X-Ray Crystallography." John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y. 531 pp. $6.50.

GUSTAV EGLOFF, GEORGE HULLA and V. I. KOMAREWSKY. "Isomerization of Pure Hydrocarbons." (A. C. S. Monograph Series.) Reinhold Publishing Corporation, 330 West 42nd Street, New York, N. Y. 499 pp. $9.00.

WILLIAM F. EHRET, Editor. "Physical Science." The Macmillan Company, 60 Fifth Avenue, New York, N. Y. 639 pp. $3.90.

H. W. HAGGARD and E. M. JELLINEK. "Alcohol Explored." (American Association for the Advancement of Science Series.) Doubleday, Doran and Company, Inc., Garden City, New York, N. Y. 297 pp. $2.75.

WILLIAM HAYNES. "The Stone That Burns." D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N. Y. 345 pp. Illustrated. $3.75.

MERLE RANDALL and LEONA ESTHER YOUNG. "Elementary Physical Chemistry." Randall and Sons, 2512 Etna Street, Berkeley, California. 455 pp. $4.50.

HUGH STOTT TAYLOR, ERNEST O. LAWRENCE and IRVING LANGMUIR. "Molecular Films, the Cyclotron and the New Biology." Rutgers University Press, New Brunswick, New Jersey. 95 pp. $1.25.

EDWARD STAUNTON WEST. "Physical Chemistry for Students of Biochemistry and Medicine." The Macmillan Company, 60 Fifth Avenue, New York, N. Y. 368 pp. $5.75.

"The Entire Electromagnetic Spectrum (Chart)." Compiled by Westinghouse Research Laboratories, East Pittsburgh, Pennsylvania. $2.00. (Orders should be sent to Publications Section, 6-N-17, Westinghouse Electric and Manufacturing Company, East Pittsburgh, Pa. Glossy print of the seven-color electromagnetic spectrum chart available on request.)

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

VOLUME 64 OCTOBER 7, 1942 NUMBER 10

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 262]

Condensations by Sodium. XXI. *n*-Octyl- and *n*-Decylsodium

BY AVERY A. MORTON, JOHN B. DAVIDSON AND ROBERT J. BEST

Propyl, butyl and amyl chlorides, condensed with sodium in petroleum ether, produce, respectively, some 10, 14 and 57% of total acids, the ratios of malonic to monobasic acids being 1.5, 1.3 and 0.3, and form alkylbenzenes to the extent of 43, 70 and 61%.[1] We have now carried out similar condensations with octyl and decyl chlorides, following the usual procedure.

***n*-Octylsodium (J. D.).**—The conventional[2] apparatus and process were used with 25 ml. (0.15 mole) of *n*-octyl chloride and 15 g. (0.65 g. atom) of fine sodium sand in 635 ml. of petroleum ether at −10°. Carbonation by bubbling carbon dioxide below the surface gave yields of pelargonic acid, *n*-heptylmalonic and *n*-hexadecane of 49% (11.7 g.), 15% (2.3 g.) and 7% (1.2 g.), respectively; while allowing it to drift over the surface of the mixture, following Gilman and Pacevitz,[3] gave corresponding yields of 23, 26 and 6%, respectively. Separation of the mono- and di-carboxylic acids in these experiments could not be effected in the usual manner because the malonic acid was soluble in petroleum ether, particularly in the presence of the mono acid. The fatty acid was, therefore, steam-distilled and identified as pelargonic acid by its boiling point 250° (uncor.) (lit.[4] 254°) and its *b*-bromophenacyl ester melting at 65.0–66.2° (lit.[5] 68.5°). The heptylmalonic acid was identified by its melting point 94.8–95.2° (uncor.) (lit.[6] 96.5–98°) and by its neutralization value.

The pink-colored octylsodium product in suspension in petroleum ether was centrifuged, the clear supernatant liquid separated and carbonated, but no acid was recovered after acidification and extraction with ether.

Nonylbenzene (J. D.).—To 16 g. of sodium, suspended with stirring in 200 ml. of sulfur-free toluene at 72°, 25 ml. of alkyl chloride was added dropwise over a one-hour period. There was obtained 7.7 g. of nonylbenzene (51%); b. p. 280–281°; α^{20} 1.485, which gave a *p*-sulfonamide derivative, m. p. 94.5–95°.[7]

***n*-Decylsodium (R. B.).**—Under the same conditions as above, the yield of undecylic acid was 28.4%; that of nonylmalonic acid was 2.3%. The melting points of the undecylic acid and of its *p*-bromophenacyl derivatives were 29.5° and 68.1°, respectively.[8] The melting point of the nonylmalonic acid was 100.5–102.0° (uncor.); temperature of decarboxylation, 140°. It was only slightly soluble in water, very soluble in ether, neutralization equivalent, 116 (calcd. 115). One hour at 160° converted it to undecylic acid.

Undecylbenzene (R. B.).—To 15 g. of sodium in 500 ml. of sulfur-free toluene 60 g. of decyl chloride was added as above. There was obtained 25.3 g. (74%) of undecyl benzene; b. p. 296 ± 1°; α^{20} 1.4824; mol. wt. by the Rast method 235, calculated 232; and *p*-sulfonamide derivative, m. p. 95.7–96.2.

Anal. Calcd. for $C_{17}H_{29}O_2NS$: N, 4.5. Found: N, 4.6 and 4.7.

Attempted Alkylation of Benzene and Anisole (J.D.).—The quantities and procedure for addition of octyl chloride to toluene, but with replacement of the toluene by benzene or anisole, gave after carbonating only 0.2 g. of liquid boiling within the range for octylbenzene. The products from benzene: 11.7 g. (68%) of octane, 6.2 g. (33%) of benzoic acid and 130 mg. of triphenylcarbinol; from anisole, 6.5 g. of phenol and 1.1 g. of an impure yellow acid.

Discussion.—These results show that *n*-octyl- and *n*-decylsodium are formed in about the same quantities and have about the same properties

(1) Morton, Richardson and Hallowell, THIS JOURNAL, **63**, 327 (1941).
(2) Morton and Richardson, *ibid.*, **62**, 123 (1940).
(3) Gilman and Pacevitz, *ibid.*, **62**, 1301 (1940).
(4) Deffet, *Bull. soc. chim. Belg.*, **40**, 388 (1931).
(5) Moses and Reid, THIS JOURNAL, **54**, 2101 (1932).
(6) Verkade and Coops, *Rec. trav. chim.*, **49**, 568 (1930).
(7) Huntress and Autenrieth, THIS JOURNAL, **63**, 3446 (1941).
(8) Huntress and Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941.

as amylsodium.[1] The major differences between these chlorides and the lower members of the series are the greater tendency of the reaction mixtures to gel and the occurrence of a pink to gray-white color in place of a blue during the condensation. No evidence could be found of any true solution of these substances in petroleum ether.

Summary

n-Octylsodium and *n*-decylsodium have been prepared by condensation in petroleum ether. The yields and properties were similar to those observed with amylsodium rather than with propyl- or butylsodium.

CAMBRIDGE, MASSACHUSETTS RECEIVED MARCH 18, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, NO. 263]

Condensations by Sodium. XXII. The General Theory of the Wurtz Reaction. The Initial Step

BY AVERY A. MORTON, JOHN B. DAVIDSON AND HERBERT A. NEWEY

This and the following communication record results of a critical inquiry into the mechanism of the Wurtz reaction, particularly as regards the issue of a free radical *vs.* an organometallic intermediate. The latter is deemed adequate. This first paper will show that there is no need for assuming existence of a free radical prior to formation of this organo-sodium compound; the second will show there is no need afterward. The contention that the organometallic intermediate can be regarded as the sole necessary first product will be based on the facts that (a) there is only one organosodium compound formed, and (b) it is formed in essentially quantitative yield. A view that the sodium metal serves as a trap for the free radical is judged unnecessary.

The Organosodium Compound.—The excellent work of Gilman and Pacevitz,[1] in which the organosodium compound was poured on solid carbon dioxide, has shown that there was one amyl radical for every combined sodium atom rather than a mixture of amylsodium and an "amylidene disodium" as previously assumed.[2] Their results have been confirmed in this Laboratory, not only with amylsodium, but also with butylsodium which has shown[3] a greater tendency to form a malonic acid under ordinary conditions of carbonation, *i. e.*, when passing carbon dioxide into the mixture. The result is important because it brings the mechanism of formation of alkylmalonic acids into line with that previously observed[4] for phenylmalonic acid, in that the dicarboxylic acid is a product of a secondary reaction according to the equation

$$RCH_2Na \xrightarrow{CO_2} RCH_2COONa \xrightarrow{RCH_2Na} RCH(Na)COONa \xrightarrow{CO_2} RCH(COONa)_2$$

It is of particular value to this discussion because it eliminates any necessity for assuming the intermediate free radical which accounted for the supposed disodium compound.

The Quantitative Yield.—The higher the yield of organosodium compound, the more obvious the two phases of the reaction. A good yield depends on (a) presence of excess sodium in a finely divided state, (b) absence of a protective coating on the metal and (c) an unreactive carbon–halogen bond.

The first requirement is met by adding the halide to the sodium which is as finely divided as possible and is being agitated vigorously. In earlier work[1] with amyl chloride and sodium, the conversion to an organosodium compound was 95% when one-fifth equivalent of chloride was added and was 63% when an equivalent had been used. We have now raised the final yield to 72% by improved agitation using a stirrer at 10,000 r. p. m. The trend is unmistakenly toward 100% yield.

The second requirement of no protective coating is best realized with a primary alkyl chloride. As seen under a microscope, a primary alkyl chloride produces an insoluble, colloidal, jelly-like mass that usually appears to be pushed out rapidly as a broad band from the interior of a small but seemingly inexhaustible particle of sodium. Characteristic shapes are drawn in Fig. 1. Occasional

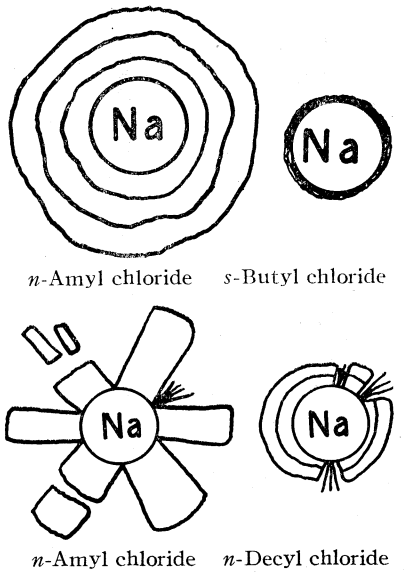
(1) Gilman and Pacevitz, THIS JOURNAL, **62**, 1301 (1940).
(2) Morton and Richardson, *ibid.*, **62**, 123 (1940).
(3) Morton, Hallowell and Richardson, *ibid.*, **63**, 327 (1941).
(4) Morton and Fallwell, *ibid.*, **60**, 1426 (1938).

eruptions give evidence of a vigorous reaction and of the ability of the chloride to penetrate the colloidal mass rapidly and sustain the rate. In contrast to this ease of contact between halide and metal, the secondary chloride forms an apparently hard and impenetrable coating. No reaction is visible. This difference in the surface coatings probably explains the observations of Richards[5] who found the reaction of ethyl iodide with sodium first order with respect to ethyl iodide. He assumed the presence of a "high stationary radical concentration" and discarded a view that the rate was controlled by diffusion of the iodide to the sodium surface, because the reaction of isopropyl iodide progressed much more slowly than would have been predicted from changes in the diffusion rates. If the coating on the metal surface has not been exactly the same in each case, as indeed seems doubtful, the necessity for assuming a special concentration of free radicals would be obviated.

The third specification is that the carbon–halogen bond should be sufficiently firm that the alkyl halide will not react too rapidly with the organosodium product. Exact information on this matter is lacking because the subject of reactivity is interwoven with that of penetrability of the surface coatings. Highest yields of monosodium compounds have been obtained with primary alkyl chlorides and with chlorobenzene; moderate to poor results with secondary and tertiary chlorides, with alkyl bromides and iodides.

Our opinion is that high yields are obtained when the carbon–chlorine bond is so unreactive that the alkylsodium can be pushed some distance from the metal before undergoing any appreciable reaction; that poor yields are found when the carbon–chlorine bond is so labile that the initial alkylsodium product reacts in the immediate vicinity of the metal surface and thus forms an adhering layer of sodium chloride. This view does much to explain the long existing anomaly that halides which react most readily with water are least reactive with sodium.

Sodium Metal as a Trap.—The suggestion has been made[5] that the mode of addition and the excess metal used in these preparations serve to trap the free radical as fast as formed. If so, the trap is perfect and there is again no need for assuming a free radical. But it is difficult to believe that these ideal conditions serve merely as a trap for a



n-Amyl chloride *s*-Butyl chloride

n-Amyl chloride *n*-Decyl chloride

Fig. 1.—Sketches showing the appearance of small particles of metallic sodium when in contact with an alkyl chloride.

radical which might otherwise be free. The smallest particles we have yet prepared vary from 0.08 to 0.2 mm. in diameter.[6] One drop of alkyl chloride is more than enough to cover the surface of all such metal one molecule thick. Since addition of drops is regular, it would be no time at all before the coating would be appreciable. Certainly, there is no visual evidence that the metal surface is bright and shiny after the first few drops of alkyl chloride have been added; nor is there evidence under the microscope that any part of the metal is exposed. It seems unreasonable to suppose, therefore, that the metal surface beneath the coating on small particles is any more ideal for trapping than is that beneath the surface of very large particles. In both cases this coating must be traversed before the chloride makes contact with the metal. The rate of this diffusion is, therefore, important. The advantage of the finely divided metal reaches only to the point of affording enough surface of this type that the first phase can compete favorably with the second phase for the alkyl halide; not to the point of offering an unlimited area. This view is supported by two earlier experiments[2]; amyl chloride was added to fine sodium sand in one case, and the same sized sand was added to amyl chloride in the second. The yield of decane was approximately the same in each case.

It is, therefore, obvious that there is no phenome-

(5) Richards, *Trans. Faraday Soc.*, **36**, 956 (1940).

(6) Measurements by the courtesy of E. L. Little.

non whatever that requires or profits by assuming a free radical as a precursor of the organosodium compound. If any such radical exists the present methods of testing have not revealed it.

Experiments

Carbonation of *n*-Butylsodium (by H. N.).—The apparatus was similar to that used in previous work. Sodium sand, 35 g. (1.5 g. atoms), activated by 2 ml. of isoamyl alcohol while stirred in 200 ml. of petroleum ether, was treated with 31.5 ml. (0.3 mole) of *n*-butyl chloride added dropwise with an equal volume of petroleum ether at 18–20° over a period of one hour. After being stirred for an additional hour, the mixture was forced from the flask under pressure of nitrogen onto solid carbon dioxide. The yield of valeric acid was 42.2% (0.126 mole); that of propylmalonic acid was 3.3%.

Microscopic Examination of Coating Formed on Sodium (by J. D.).—A small quantity of fine sodium sand was placed in the cavity of a hanging-drop microscope slide which contained *n*-decane. A cover glass was then placed so as to nearly close the cavity. The tip of a specially built micro-pipet was then inserted in the opening and small quantities of alkyl chloride pushed into the cavity by slowly turning a screw device on the far end of the pipet. Observations were made with *n*-propyl, *n*-butyl, *n*-amyl, *n*-octyl, *n*-decyl, cetyl, and *s*-butyl chlorides.

Improved Conditions for Isolating the First Phase (by J. D.).—The apparatus was an improved model of the high-speed stirring equipment described in an earlier paper.[7] A weighed amount (11.5 g. (0.5 atom)) of sodium metal was put in the flask and 340 ml. of *n*-octane added. The mixture was then heated to 105° at which temperature the stirrer was operated at 10,000 r. p. m. until the metal was finely dispersed, after which the stirrer was stopped and the flask allowed to cool. The powder prepared by this method settled slowly and was the finest which so far has been obtained in this work. It required no activation by amyl alcohol.

n-Amyl chloride (30.2 ml. or 0.25 mole) diluted with 30 ml. of *n*-octane was added over a period of one hour during which time a bath of kerosene and solid carbon dioxide kept the temperature at 0°. After one additional hour of stirring (all at 10,000 r. p. m.) at this temperature, the reaction mixture was forced out of the container onto solid carbon dioxide by a pressure of nitrogen. The yield in two separate experiments was 71 and 72% total acids. The best yield previously obtained, using these proportions of reagents, was 63%. This improvement was realized in spite of adverse solvent conditions shown earlier[8] in this series.

Although these conditions are far better than any so far employed, they are still insufficient to give a high yield of organosodium compound from a secondary halide. Under comparable conditions, 2-chlorobutane and 2-chloropentane yielded 1.5 and 2.2% of acids, respectively.

(7) Morton and Knott, *Ind. Eng. Chem., Anal. Ed.*, **13**, 649 (1941).

Summary

The first phase of the Wurtz reaction is reasonably interpreted as the formation of an organosodium intermediate.

Conditions necessary for preparing this intermediate in quantitative yield are described.

Primary halides form a loose porous coating in the surface of sodium. Secondary halides form a comparatively impenetrable coating.

The difficulties in separating the first from the second phases of the Wurtz reaction are discussed.

The function of finely divided sodium sand does not appear to be that of a trap for a free radical.

Assumption of a free radical is unnecessary.

(8) Morton and Palmer, THIS JOURNAL, **60**, 1428 (1938).

CAMBRIDGE, MASS. RECEIVED MARCH 18, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, NO. 264]

Condensations by Sodium. XXIII. The General Theory of the Wurtz Reaction. Part II. The Second Phase

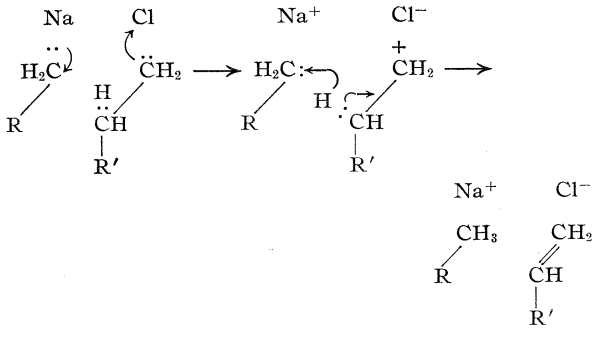
BY AVERY A. MORTON, JOHN B. DAVIDSON AND BARTON L. HAKAN

The previous paper[1] contained evidence that an organosodium compound could represent the first phase of the Wurtz reaction; this paper will show that the reactions of this intermediate with an alkyl or aryl chloride can constitute the concluding phase.

In the main the arguments for this thesis are: (1) disproportionation is a logical consequence of such a reaction; (2) polymerization proceeds according to a regular pattern and products are predictable with an organometallic theory. It is further indicated that the phenomenon of metal–halogen interchange tends to obscure primary processes. Fluctuations in the products of the Wurtz reaction are shown to have no simple explanation on a free radical basis. A critical discussion of certain analogies from which a free radical mechanism for the Wurtz reaction has been inferred is presented.

(1) Morton, Davidson and Newey, THIS JOURNAL, **64**, 2240 (1942).

Disproportionation.—Disproportionation has been so universally accepted as the criterion of a free radical that there has been no attempt to show a derivation from other molecular species.[1a] Nevertheless, a mechanism for this phenomenon by way of an organometallic intermediate appears exceptionally reasonable. If an alkylsodium meets an alkyl halide in such manner that the two alkyl chains are adjacent to each other while sodium halide is being formed, the two alkyl residues will have unlike charges and a proton will be drawn to the alkyl radical having the two unsaturated electrons. The reaction is merely the conventional prototropic change taking place between adjacent portions of two molecules whose inorganic components are effecting, or have just completed, a union.



If this view be accepted, the olefin produced must come from the alkyl halide rather than at random from both participant alkyl radicals. Though conclusions are to some extent obscured by a metal–halogen interchange (see later), all available facts unquestionably point to the correctness of this deduction. In reactions which involved octylsodium and various alkyl halides (Table I), the octane predominated over the octene in every instance.

In parallel studies with amylsodium (Table II) the quantity of pentane in all cases exceeded the amount of pentene.

TABLE I

PRODUCTS OF REACTION OF OCTYLSODIUM WITH ALKYL HALIDES

Halide	Per cent. yield of products: Octane	Octene	Hexadecane	Wurtz product
Ethyl iodide	15.2	8.8	27.9	18.8
Ethyl bromide (V)[a]	14.6	10.3	10.7	31.0
Ethyl bromide	20.1	0.4	11.1	31.4
Ethyl chloride (V)	35.1	0.2	...	10.8
Propyl iodide	16.6	5.5	15.3	13.6
Propyl bromide	20.9	11.0	...	7.8
Propyl chloride	28.6	15.3	...	...

[a] The letter V refers to the fact that the reaction mixture became very viscous.

TABLE II

PRODUCTS[a] OF REACTION OF AMYLSODIUM WITH ALKYL HALIDES

Group	Halide	Pentane, %	Pentene, %	Ratio of pentane to pentene	Decane, %	Wurtz product
1	Methyl iodide	22.3	2.0	11.1	58.4	0
2	*n*-Hexyl iodide	5.4	5.0	1.1	39.8	32.6
	Methyl bromide	7.1	4.9	1.5	44.4	13.1
	Ethyl iodide	8.2	5.7	1.4	30.9	2.1
	n-Butyl iodide	7.8	6.3	1.2	30.4	17.8
3	Ethyl bromide	12.3	8.5	1.4	15.1	24.2
	n-Butyl bromide	13.1	11.4	1.2	10.0	32.0
	n-Hexyl bromide	9.8	8.5	1.2	15.2	45.6
	n-Hexyl chloride	5.1	1.6	3.2	19.8	13.4
	n-Butyl chloride	7.4	2.8	2.7	6.4	8.8
4	Ethyl chloride	11.6	1.1	11.1	9.0	30.2
	Methyl chloride	15.2	1.0	15.2	6.3	43.7

[a] The arrangement is in the approximate order of decreasing decane content in order to illustrate an important point developed later in this discussion.

A third series (Table III) compares (a) reactions between two radicals (amyl and hexyl) in which the inorganic components were interchanged and (b) reactions of hexylsodium with amyl and octyl chlorides which represent radicals smaller and larger than hexyl. The distribution of alkanes and alkenes was again not at random.

TABLE III

PRODUCTS FROM REACTION OF AMYL, HEXYL AND OCTYL RADICALS

Reaction pair: RNa + R′Cl	Hexane, %	Hexene, %	Octane, %	Octene, %	Wurtz product, %
$C_5H_{11}Na + C_6H_{13}Cl$	9.5	11.5			24
$C_6H_{13}Na + C_5H_{11}Cl$	30.	7.7			23
$C_6H_{13}Na + C_8H_{17}Cl$	24.5	7	9.5	22.6	25

In these three series of experiments carried out under different conditions with widely different halides and various alkylsodium compounds, the products of disproportionation were uniformly proportioned according to the principle outlined above.

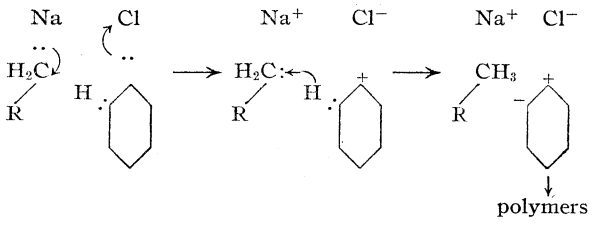
Polymerization.—A previous paper[2] recorded that the reaction of amylsodium with chlorobenzene produced more polymer than any other isolable product; that of phenylsodium with amyl chloride produced less polymer than any other

(1a) This statement was true at the time this article was submitted. Since then a paper by Whitmore and Zook has appeared (THIS JOURNAL, **64**, 1783 (1942)) in which the saturated and unsaturated products of disproportionation are credited as coming from the sodium alkyl and the alkyl chloride, respectively.

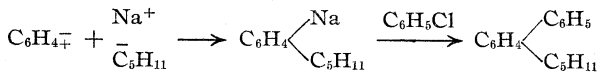
(2) Morton and Fallwell, *ibid.*, **60**, 1429 (1938).

fraction. The total quantity in the last case was about a fifth that obtained from the first pair of reactants.

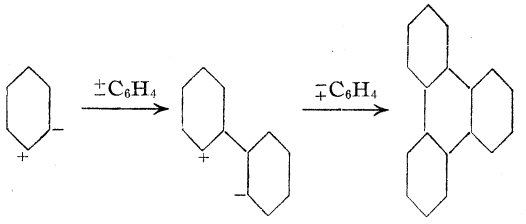
The organometallic mechanism affords an adequate explanation for this polymerization. The disproportionation process between amylsodium and chlorobenzene leads to a dipolar phenylene as shown



This intermediate dipolar compound cannot be stabilized by double bond formation and consequently undergoes further reaction with polar reagents. It may, for example, unite with more amylsodium giving a new organosodium compound which then reacts with more chlorobenzene according to a general scheme outlined



It may also condense with itself. The dimer would be a new dipolar intermediate which could react with more organosodium compound. The trimer could be the stable triphenylene. More complex products are obviously possible



In any event, ortho substituted products should predominate, and the polymer should be composed of more radical from the halide than from the organosodium reagent. These conclusions are supported by facts. In the reaction of chlorobenzene with sodium,[3] the proportion of ortho to para substituted products was more than a thousand to one; in the reaction of amylsodium with chlorobenzene[2] one fraction contained three phenyl to one amyl unit. The triphenylene produced by reaction of chlorobenzene with sodium is thus a consequence of a series of changes by polar reagents rather than an indication that free radicals[4] are at hand.

Metal–Halogen Interchange.—A metal–halogen interchange has been known for some time to occur between lithium alkyls and bromo- and iodo- compounds.[5] Since methyl iodide reacts with octyl- or amylsodium,[6] yielding hexadecane and decane, respectively, this process, too, may be associated with a preliminary formation of amyl iodide according to the equation

$$C_5H_{11}Na + CH_3I \longrightarrow C_5H_{11}I + CN_3Na$$

In agreement with this view, amyl iodide was obtained in 50% yield when amylsodium was added to methyl iodide. The comparative yields of hexadecane (Fig. 1) and of decane (Table II) suggest the extent to which this change occurs in other cases. Iodides in general appear to favor an interchange, and methyl iodide reacts preponderantly in this manner. Chlorides, on the other hand, with the possible exception of the hexyl compound seem to participate only slightly in exchange reactions.

When such an exchange occurs, the new products can then in turn undergo disproportionation or coupling. The results of such secondary reactions complicate seriously the effort to trace primary processes. Since disproportionation is then operating in the reverse order and some alkane is formed from what was originally the alkyl halide, this change is one factor which tends to lower the ratio of alkane to alkene. In any given case, a high yield of symmetrical coupling product would indicate a large amount of metal–halogen interchange and would be associated with a low ratio of alkane to alkene. Qualitatively, the results are in agreement with this view. *n*-Hexyl, *n*-butyl and ethyl iodides and methyl bromide (Table II) each formed decane in over 30% yield and gave a pentane–pentene ratio of from 1.1 to 1.5. On the other hand, the two lowest percentages of decane, *viz.*, those obtained with methyl and ethyl chlorides are associated with the highest ratios. Methyl iodide alone appears anomalous. The majority of the bromides as well as *n*-butyl and hexyl chloride occupy an intermediate position in that the large amount of decane predicted

(3) Bachmann and Clarke, THIS JOURNAL, **49**, 2092 (1927).

(4) (a) Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, pp. 452, 537; (b) Hey, *Annual Reports*, **37**, 245 (1941); (c) Richards, *Trans. Faraday Soc.*, **36**, 956 (1941); (d) Morton, Massengale and Richardson, THIS JOURNAL, **62**, 126 (1940).

(5) Marvel, Hager and Coffman, *ibid.* **49**, 2323 (1927); Wittig and Pöckels, *Ber.*, **72**, 89 (1939); Gilman and Banner, THIS JOURNAL, **62**, 344 (1940).

(6) Morton and Fallwell, *ibid.*, **59**, 2387 (1937).

by a low pentane–pentene ratio appears to have been replaced by relatively higher proportions of Wurtz coupling products. The data in Table II are divided into four groups in order to indicate these relationships.

Variation of the Products.—A radical which is really free might be expected to show a specific chemical behavior toward another reagent irrespective of its source. That is to say, methyl, derived by reaction of the chloride, bromide or iodide with octylsodium, should have one reaction only with octyl, provided, of course, that the environment was constant and the concentration of the methyl radical was always so low that it could not react with itself. Figure 1 shows that such is not the case. Data in Tables II and III do not support this view. This argument may be questioned on the ground that the rate of formation of the methyl radical is different in the three cases. If the method of adding the methyl halide as a vapor in a stream of nitrogen does not keep the concentration sufficiently low, or if other changes are possible during the different periods of formation, then we would conclude that the rate should be fastest with the iodide and slowest with the chloride, and that a rapidly formed methyl radical would promote symmetrical coupling (hexadecane); a slowly formed radical would favor unsymmetrical coupling (nonane). These deductions from the free radical view, however, contribute nothing concrete to the explanation of phenomena in the Wurtz reaction compared with that offered by the organometallic theory.

Apart from considerations of mechanism, the results with the methyl halides are interesting because they show the limits possible in control of the products of the reaction.

Analogies with Other Reactions.—Before the general theory of the Wurtz reaction can be summarized in terms of organometallic compounds, some attention should be given to analogies which have suggested the likelihood of free radicals being the active agent. Polanyi[7] found good reason for postulating the existence of free methyl in reactions of methyl iodide with sodium vapor at extremely low pressures and comparatively high temperatures. The existence of free radicals under conditions highly favorable for their occurrence and above the limit of thermal stability of the alkylsodium compound is, of course, an entirely different matter from the assumption of

(7) Horn, Polanyi and Style, *Trans. Faraday Soc.*, **30**, 189 (1934).

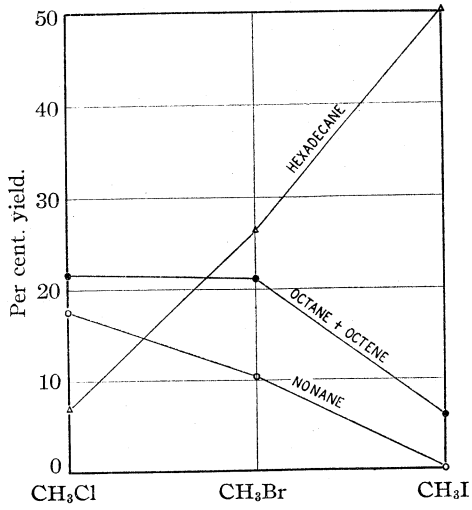


Fig. 1.—Yield of products obtained by reaction of methyl halides with octylsodium.

their existence in a liquid phase at ordinary pressures on a surface of metallic sodium. Where even such ideal conditions as those mentioned have as yet failed to demonstrate the presence of free propyl, butyl and higher members[8] of the series, the conclusion might well be drawn that free radicals, so extremely difficult to obtain in an appropriate environment, would have little chance of being present in such an unfavorable medium as a liquid phase.

Another analogy stems from the vast amount of research on triphenylmethyl and other free radicals of long life. The reasoning in this case is very logical. If there are free radicals of long life, there should be also free radicals of short life. The force of this argument is granted; the opinion that any fact so far submitted definitely indicates their occurrence in the Wurtz reaction is questioned. Assumption of presence of a free radical in a system obviously containing a large proportion of an active polar compound implies that the two-step process involving, first, a change of ion to free radical and then a combination of radicals with themselves is faster than the direct interaction of ions to give the final product. There is no evidence so far available to support the idea that the ion is not itself sufficiently reactive without the interposition of a secondary change to a second intermediate of questionably greater activity. The converse indeed might well be true and the phenomenon of disproportionation which occurs in free radicals of long life, might be itself preceded

(8) Rice and Rice, "The Aliphatic Free Radicals," The Johns Hopkins Press, Baltimore, Md., 1935, pp. 33, 64.

by conversion of the radical to an ion before a proton moves from one radical to the other.

General Summation of Reactions.—All primary and secondary products from the Wurtz reactions can be expressed by the following sets of equations

Reactants		Primary products		Secondary products
First Phase				
$RX + 2Na$	$\longrightarrow$	$RNa + NaX$		
Second Phase				
$RNa + XR''$	$\longrightarrow$	(a) $RR' + NaX$		
		(b) $R_H + R'_{-H} + NaX$	$\longrightarrow$	Polymers
		(c) $RX + R'Na$	$\longrightarrow$	RR, R'R', RR', or $(R'_H + R_{-H})$, +NaX

The relative importance of these various reactions differs with the reagents used. As far as the Wurtz coupling product, RR', is concerned, the yields decrease as the radical attached to sodium is benzyl, phenyl or alkyl. This order is the same as the relative affinities for sodium observed in metalation studies. As for the halide half of this reaction, the limited number of observations so far made suggest that bromides as a class are apt to give better results than iodides or chlorides.

The purpose of this work is not, of course, to deny all existence of a free radical in the Wurtz reaction but to point out that in the present state of knowledge on this subject the very phenomena for which the free radical interpretation has been considered essential in reality furnish excellent evidence that an organometallic agent is at work. In spite of very commendable efforts in the past, decisive evidence of any free radical phase which may be present in this common reaction is a goal yet to be reached. On the other hand, the organometallic mechanism is an adequate instrument for interpreting and predicting the reactions known to occur. It is, of course, beyond the scope of this paper to rewrite all equations of disproportionations in the Wurtz reaction which previously have been written as being in agreement with or supporting the free radical concept. It is sufficient to say that all such phenomena can be expressed satisfactorily as the normal behavior of a polar reagent, which has been proved to be present in sizable quantities.

Experiments

Octylsodium and Alkyl Halides (J. D.).—The apparatus consisted of a 500-ml. flask with four creases and an inverted bottom.[9] The usual three-necked addition tube was employed. The stirrer was operated at 1500 r. p. m. *n*-Octylsodium was prepared by adding 0.15 mole of octyl chloride to 15 g. of sodium sand over a one-hour period at −10°, as described before.[1] Methyl, ethyl and propyl halides were then admitted by vaporizing them in a current of nitrogen while the liquid was kept about 10° below its boiling point. The tube between the vaporizer and the reaction vessel was electrically heated in order to prevent condensation of the vapors. The inlet tube terminated just above the surface of the suspension of octylsodium so as to ensure as far as possible a maximum opportunity for reaction of the alkyl halide with excess organosodium compound. One-tenth of a mole of each halide was added except in the case of methyl chloride, which being a gas, was allowed to pass slowly over the surface until reaction was complete. Water was then added to remove excess sodium. The hydrocarbons, RR', were fractionated through a column of the Podbielniak type having about ten theoretical plates, and collected over a 5° range. The octene content of the octane fraction (118–125°) was measured by a bromination method.[10] The hexadecane boiled from 277 to 283°. Percentage yields (Fig. 1 and Table I) are calculated on the basis of the octyl chloride used. For some undetermined reason the reaction mixture occasionally became so viscous that stirring was nearly impossible. The letter (V) in the table indicates when this condition was present.

Amylsodium and Alkyl Halides (J. D.).—The apparatus used in this series was the one mentioned before as operating at 10,000 r. p. m. Amylsodium was prepared by adding 30.2 ml. (0.25 mole) of *n*-amyl chloride to 11.5 g. (0.5 atom) of sodium powder during one hour at 0°. After the reaction mixture had been stirred for an additional hour, 0.177 mole of the alkyl halide was added dropwise at 0° during one-half hour. The mixture was stirred for fifteen minutes longer, then poured on solid carbon dioxide, and later treated with water to remove the very small amount of unreacted sodium metal. The hydrocarbon products were separated as in the foregoing description. Results are tabulated in Table II.

Amyl-, Hexyl- and Octylsodium with Alkyl Halides (B. H.).—The apparatus in this case was, in general, similar to that employed for octylsodium except that the stirrer was operated at 4000 r. p. m. The sodium sand (17.5 g.) was suspended in olefin-free pentane and activated by addition of 1.7 ml. of amyl alcohol. The alkyl halide (1 mole equivalent to 2 g. atoms of sodium metal) dissolved in twice its volume of pentane was added at 0 to −5° over a one-hour period. The second alkyl halide (about 0.7 mole equivalent) was then added at the same rate. After stirring for a brief time longer, carbon dioxide was passed into the mixture to remove any unchanged organosodium compound which was always present in a small amount only, and water was added to remove excess sodium. The hydrocarbon layer was dried over calcium

(9) Morton and Knott, *Ind. Eng. Chem., Anal. Ed.*, **13**, 649 (1941).

(10) Uhrig and Levin, *ibid.*, **13**, 90 (1941).

chloride and then fractionated through a packed column having about twenty plates. Yields are given in Table III. Calculation is based on the quantity of alkyl halide added. The percentage yield of the Wurtz coupling product is determined on the basis of the first halide added. All results are the average of two determinations.

Amylsodium and Methyl Iodide (J. D.).—*n*-Amylsodium, prepared as in the previous experiment, was forced, during a fifteen-minute interval, into a flask containing 168 ml. of methyl iodide maintained at a temperature between −30 and 20°. After adding water to remove excess sodium, the organic layer was fractionated in the packed column at reduced pressure. The fraction boiling from 57 to 60° at 30 mm. had a specific gravity of 1.504 (recorded value[11] for amyl iodide 1.517) and weighed 23 g. (47% based on the amyl chloride used). The sodium fusion test for halogen was positive. The 3,5-dinitrobenzoate derivative, prepared from this fraction, melted at 44–45°. The recorded value[12] is 46°.

(11) Lieben and Rossi, *Ann.*, **159**, 74 (1871).
(12) Malone and Reid, THIS JOURNAL, **51**, 3426 (1929).

Summary

Complete explanations for the phenomena of disproportionation and polymerization, hitherto considered as demanding a free radical intermediate, are made on the basis of an organometallic reagent.

The saturated hydrocarbon product of disproportionation comes from the organosodium compound, the unsaturated from the halide.

Amylsodium yields amyl iodide when poured into methyl iodide.

The general basis from which a free radical theory is associated with the Wurtz reaction is critically discussed.

All products in the Wurtz reaction are interpreted on a simple basis by the organometallic mechanism.

CAMBRIDGE, MASS. RECEIVED MARCH 18, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, NO. 265]

Condensations by Sodium. XXIV. The Pyrolysis of Amylsodium

BY AVERY A. MORTON AND HERBERT A. NEWEY

The experiments reported in this paper are directed toward a careful examination of the stability of amylsodium over a wide range of temperature and toward a determination of the type of reaction involved in pyrolysis. The information was of importance to a general understanding of the behavior of amylsodium in various reactions and in particular to the studies on mechanism since an appreciable quantity of pentane or pentene formed by low temperature pyrolysis would nullify some of the conclusions drawn in the previous paper.[1] The products of pyrolysis proved clearly to be the result of metalation and dehydrogenation.

Pyrolysis required thirteen hours at 60° for completion and was fast enough at 120° and above to be observed by rapid evolution of gas. The rate of pyrolysis over a two-hour period was slight at 40°, moderate (22%) at 70°, and approximately complete at 90° (see Fig. 1). The slopes of the curve at 45, 55 and 65° are as 2.4 to 4.9 to 8.7. The logarithms of the reciprocal of these values, plotted against the temperature, give approximately a straight line. Extrapolation of this line to 20 and to 0° shows that the decomposition over a two-hour period was definitely below 1% and probably negligible. Since the time period required for the experiments on the mechanism of the Wurtz reaction was considerably less than that employed in these pyrolysis experiments, there is no danger that the comparative quantities of pentane and pentene were affected by decomposition of the organosodium compound.

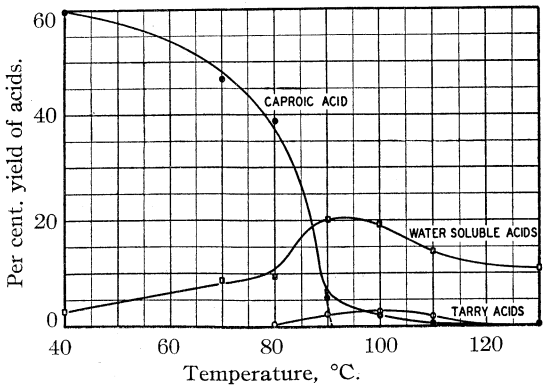


Fig. 1.—Yield of acids obtained after heating amylsodium for two hours at different temperatures.

The curve (Fig. 1) suggests that disappearance of amylsodium is related to appearance of another sodium compound which upon carbonation yields

(1) Morton, Davidson and Hakan, THIS JOURNAL, **64**, 2242 (1942).

very water-soluble carboxylic acids. At 90° the quantity of such acids was 20%. In view of the 60% yield of caproic acid before pyrolysis, it would appear that about one-third of the metal in amylsodium was present in the new compound. The remaining two-thirds had apparently reverted to sodium.

Examination of the acids, which were complex, showed more clearly the direction of the changes. Except for some tarry product, the acids which resulted from carbonation of the pyrolyzed organosodium compound had more than one carboxyl group per original amyl unit (in a preferred fraction nearly two such groups) and showed unsaturation. These changes in their elementary form are pictured by Eqs. 1 and 2.

$$C_5H_{11}Na + C_5H_{11}Na \longrightarrow NaC_5H_{10}Na + C_5H_{12} \quad (1)$$
$$NaC_5H_{10}Na + 2C_5H_{11}Na \longrightarrow NaC_5H_8Na + 2C_5H_{12} \quad (2)$$

The carboxyl groups are not attached to the same carbon atom, since tests on the preferred fraction showed no carbon dioxide evolution below 140°. Neither did the di-acid appear to form an anhydride when heated to 200°. These results suggested remote carbon atoms as points for attachment of sodium. Efforts to simplify identification of the product by hydrogenation failed to produce other than oily products. The possibility of some rearrangements occurring is not excluded, of course. The process of producing unsaturation, if continued a second time, would lead to a diene. Polymerization of such an unsaturated compound would account for the tars and other obviously large polymers produced.

No fragmentation of the carbon chain was evident since gases such as ethylene or propylene were not formed. The only gaseous product evolved was pentane with but a trace of pentene and this hydrocarbon was not evolved rapidly enough to be observed readily under the conditions employed until the temperature was above 120°, far above the point where, after longer periods of heating, the acidic products recovered showed obviously that pyrolysis had been complete.

All of the foregoing results are readily understandable as the behavior of an organosodium reagent without the necessity for assumption of any free radical. However, the mode of decomposition of all organosodium compounds under different conditions is not necessarily the same. For example, Carothers and Coffman,[2] who examined the gaseous products only of the pyrolysis of ethylsodium in absence of any solvent, found that ethylene was the first gas evolved. These investigators assumed also that sodium hydride was formed. The present study showed that this last material was produced at relatively high temperatures and then only in small quantities. Formation of an alkane instead of an alkene as the principal hydrocarbon product of pyrolysis of amylsodium may be due to the longer alkyl chain, the end portion of which can apparently be metalated.

In previous papers,[3] efforts were made to improve the yield of butylmalonic acid by heating amylsodium before carbonation. Little or no increase resulted. These results are confirmed by the present work. The idea of an amylidene disodium is, in view of recent evidence that one amyl radical exists for every combined sodium, no longer tenable.[4] The approximate constancy of the butylmalonic acid noted previously must therefore be ascribed either to a difference in size and reactivity of the solid particles, a common occurrence indeed in these reactions, and to variations in the process of carbonation, which in the light of present knowledge would certainly produce some quantities of the dicarboxylic acid.

Experimental

Amylsodium was made in a creased flask in the usual manner[5] from 19 g. (0.82 g. atom) of sodium sand, 32 g. (0.3 mole) of *n*-amyl chloride, in olefin-free pentane (b. p. 30–40°). The metal was activated as usual with 2 ml. of isoamyl alcohol prior to addition of the chloride. Preparation was carried out at 10–15°, during one hour, and the mixture stirred for one hour longer at the same temperature. The pentane was then removed by distillation and 250 ml. of synthetic *n*-decane added. The mixture was then heated and stirred at the temperature desired for pyrolysis. Carbonation was effected by cooling the mixture to room temperature and forcing it under nitrogen pressure onto lumps of solid carbon dioxide.

After carbonation was complete, water was added to remove excess sodium metal and to dissolve the sodium salts. The aqueous layer was then acidified by hydrochloric acid. Tarry acids which separated were recovered by filtration or lifted out on a stirring rod, washed with water, dried, weighed and titrated. The aqueous layer was extracted with petroleum ether to remove caproic acid, which boiled between 202 and 206° and left little residue. This acid was further identified by conversion to the *p*-bromophenacyl ester melting at 72° (recorded value 72°). The quantity of acid was determined by titration and also by weighing the distillate. The remaining water-soluble

(2) Carothers and Coffman, THIS JOURNAL, **51**, 588 (1929).

(3) Morton and Hechenbleikner, *ibid.*, **58**, 1697 (1936); Morton and Richardson, *ibid.*, **62**, 129 (1940).

(4) Morton, Davidson and Newey, *ibid.*, **64**, 2240 (1942); Gilman and Pacevitz, *ibid.*, **62**, 1301 (1940).

(5) Morton and Richardson, *ibid.*, **62**, 123 (1940).

TABLE I

PROPERTIES OF THE METHYL ESTERS OF THE ACIDS PRODUCED BY CARBONATION OF THE PRODUCT OF PYROLYSIS OF AMYLSODIUM AT TEMPERATURES FROM 80–130°

Frac.	B. p., °C.	B. p., °C. 760 mm.	Quantity, g.	S. E.[a]	Carbomethoxy groups per amyl unit	Mol. wt. Calcd.[b]	Mol. wt. Obs.[c]	Polymer in amyl units	Double bonds[d]
1[e]	80 (20 mm.)	205	0.5	112	1.32	148	196	1.3	+
2[f]	110–120 (5 microns)	285	2.5	98[g]	1.80	176	197	1.1	1.15
3	120–250 (5 microns)	...	0.3	101	1.67	168	268	1.6	+
4	Residue		6.7	135	.92	124	900	7.3	+

[a] Saponification equivalent. [b] Average molecular weight per amyl unit calculated from the saponification equivalent. [c] Determined by boiling point elevation in acetone in a Swietoslawski apparatus. [d] Each fraction showed unsaturation. One fraction analyzed by catalytic absorption of hydrogen. [e] This fraction probably consists chiefly of methyl butylmalonate. [f] This fraction was considered as a preferred one because it was the lowest boiling of the pyrolyzed products and was the nearest to having two carbomethoxy groups to one amyl chain. [g] Neutralization equivalent of the free acid was 87 as determined by the silver salt.

acids were recovered by saturating the solution with salt and extracting first with ether and then with methyl ethyl ketone. The ether occasionally removed some butylmalonic acid which crystallized, but for the most part the products were extracted only by methyl ethyl ketone and remained as oily liquids after evaporation of that solvent. The results are given in the graph (Fig. 1). All yields are based on the amount of amyl chloride originally added.

A parallel series of experiments was made in which all conditions were the same except that carbonation was effected by bubbling carbon dioxide into the reaction mixture. The results are in general identical save for the formation of larger quantities of butylmalonic acid and the initial occurrence of tar at 68° instead of 80°. The data are therefore not recorded in this paper.

Acidic Products of Pyrolysis.—In general, the water-soluble products were dark brown, viscous materials slightly soluble in ether but readily soluble in methyl ethyl ketone, acetone or alcohol. In the case of the products of pyrolysis at temperatures below 90°, the recovered water-soluble acids could again be redissolved in water readily. Where the pyrolysis had been effected at higher temperatures the dried acid would not redissolve in cold water. A quantity of these acids from pyrolysis at 80 to 100° was esterified with diazomethane. Ten grams of the ester was distilled. The properties of each fraction are recorded in Table I. Although the second fraction was the one most likely to give a single compound, no crystalline ester or derivative could be obtained, even after catalytically hydrogenating, converting to the acid, amide, or *p*-bromophenacyl ester.

The tarry acids recovered from the low temperature pyrolysis were dark brown and sticky materials. As the temperature of pyrolysis increased, they became progressively harder and eventually appeared as a dry fluffy powder. These last products did not dissolve in acetone and formed a methyl ester which was not volatile in a molecular still. Hence their molecular weight was very high. The graph indicates a decrease in the tar formed at higher temperature. Actually the weight of the tar in that range remained fairly constant, the seeming drop being due to a loss in the number of carboxyl groups.

Formic acid, suggesting the presence of sodium hydride, was present in small amounts only and then only among the products of pyrolysis at higher temperatures. Detection was difficult. The method of proving its presence was to evaporate the combined sodium salts of the acids to dryness, add them to glacial acetic acid and fractionate carefully. A sample from the first portion of distillate readily reduced alkaline permanganate. Another sample was diluted with water, the aqueous solution treated with magnesium turnings and the resulting aldehyde[6] treated with dimethyldihydroresorcinol. The dimethone derivative, after being recrystallized, melted at 188–189° and showed no depression when melted with an authentic sample. Although other tests such as steam distillation of the water-soluble acids and treatment of the distillate with potassium permanganate or mercuric chloride showed evidence of its presence, the quantity of formic acid was never more than a trace. In fact, no conclusive evidence could be found that it resulted when the temperature of pyrolysis was kept below 90°.

Hydrocarbon Products from Pyrolysis.—The amylsodium was prepared as before, petroleum ether solvent removed, and *n*-decane added. On heating rapidly, a small amount only of material distilled from the mixture below 120°. No gases were evolved. Between 120 and 130° the mixture in the flask boiled vigorously. The condensate was collected in a trap which was cooled by solid carbon dioxide. All exit gases passed through a second trap containing bromine water. No decoloration occurred. The liquid caught in the first trap boiled between 34 and 40°, most of it at 34 to 36°, suggesting that the product was chiefly *n*-pentane. It decolorized only traces of bromine. On treatment with cold concentrated sulfuric acid less than a fifteenth of the volume was lost. The total volume of liquid collected was 33 ml., which was more than the amount equivalent to the amyl chloride used. The excess might have come from occlusion of some solvent used in preparation or from a complex formation of solvent pentane with amylsodium.

The contents of the reaction vessel, after pyrolysis, were poured on solid carbon dioxide, water was added, and the hydrocarbon layer collected and distilled. This material proved to be *n*-decane which boiled from 172 to 176°, and showed no unsaturation when tested by permanganate. The residue from fractionation contained no high-boiling compounds.

Summary

The rate of decomposition of amylsodium is

(6) Fenton and Sisson, *Chem. Centr.*, **79**, 1379 (1908).

very slight at 40°, fair at 70° and rapid (two hours for completion) at 90°.

Acids, obtained by carbonation of the pyrolyzed organosodium compound, are (a) water soluble, unsaturated compounds with more than one carboxyl group to amyl unit; (b) tarry or insoluble acids which are unsaturated and of relatively high molecular weight.

The sole hydrocarbon product was pentane. The solvent, *n*-decane, was not attacked by the organosodium compound under the conditions employed.

The chemical reactions which occur during pyrolysis involve metalation (dismutation) and dehydrogenation.

CAMBRIDGE, MASS. RECEIVED MARCH 18, 1942

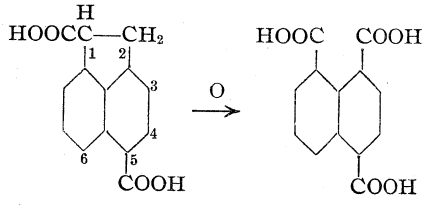
[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, NO. 266]

Condensations by Sodium. XXV. Reactions of Amylsodium with Naphthalene, Acenaphthene and Decalin

BY AVERY A. MORTON, JOHN B. DAVIDSON, T. R. P. GIBB, JR., ERNEST L. LITTLE, E. F. CLARKE AND A. G. GREEN

Nearly half of the carbonated product obtained from the reaction of amylsodium with naphthalene is di- and tri-substituted, whereas nearly all of the product in the case of benzene is monosubstituted. Octyl- is more active with naphthalene than is amylsodium and the proportion of higher substituted compounds is slightly increased. The α- and β-monoacids, and the 1,3-, 1,8-, and 2,6-dicarboxylic acids were isolated. The trisubstituted compounds were not examined.

Acenaphthene was expected to behave somewhat similarly to toluene. One sodium atom did, in fact, replace a hydrogen atom in a methylene group but a second one entered the ring, giving a dicarboxylic acid, probably the 1,5-compound, in about 50% yield. Oxidation of this diacid with permanganate gave 1,4,5-naphthalene tricarboxylic acid, showing that one carboxyl must have been attached to a methylene, *i. e.*, in the



1-position, and the second was bound to the 5- or 6-position in the aromatic nucleus. The 5-position is considered more likely because (a) in benzene[1] the directing influence of one sodium atom on a second entering one is largely meta; (b) in naphthalene the influence on substitution of another metal in the same ring is meta; and (c) even in benzylsodium[2] a second metalation, when it does occur, is exclusively in the meta position. The 5-position is also in accord with the general principle[3] that the introduction of substituents into a bicyclic system containing a meta directing group will take place in the unsubstituted ring. Metalation of acenaphthene by an organo alkali compound, butyllithium, has been observed[4a] once before but no product was isolated. Horvitz[4b] also studied the action of amylsodium on acenaphthene but was unable to obtain a product of known purity because of the difficulty in separation.

The action of amylsodium on decalin was most surprising because metalation took place with extreme ease. From a great variety of products a very small amount of a crystalline ester of a tetracarboxylic acid was eventually isolated. It readily formed a dianhydride after being saponified and acidified. The positions of the carbethoxy group are not known but the 1,4,5,8-product is suspected because these positions are reasonably remote from each other, and have the symmetrical arrangement which would increase the tendency of the compound to come out of mixtures in a crystalline form. Moreover, the corresponding acids could easily form a dianhydride of high melting point. The original hope had been that substitution would occur at the tertiary or indented position and that the process would therefore prove to be a new synthetical method in that

(1) Morton and Fallwell, THIS JOURNAL, **60**, 1924 (1938).

(2) Unpublished research.

(3) Grieve and Hey, *J. Chem. Soc.*, 968 (1933).

(4) (a) Gilman and Bebb, THIS JOURNAL, **61**, 109 (1939); (b) Horvitz, Ph.D. Thesis, Massachusetts Institute of Technology, 1938.

series. The crystalline product isolated, however, could not have had a carbomethoxy group in that location because there was no resistance to saponification under ordinary conditions. Furthermore, alkylation[5] of decalin by sodium and amyl chloride after the manner employed successfully for toluene, formed products which, though they boiled in the range expected for amyldecalin, yielded an inappreciable quantity of naphthalene and traces only of amyl mercaptan when fused with sulfur. Both of these products would have been expected had alkylation occurred on the tertiary carbon atom. Metalation of decalin is of more than passing interest because it is the first recorded instance of substitution in a hydrocarbon which does not contain an aromatic nucleus.

Experimental

Amyl- or Octyl-sodium with Naphthalene (J. D.).—*n*-Amyl chloride, 18 ml., was added dropwise to 15 g. of sodium sand suspended in a solution of 50 g. of naphthalene in 240 ml. of ligroin maintained at 72° in an atmosphere of nitrogen in the apparatus used for preparing octylsodium.[6] After carbonating and adding water, the aqueous layer was acidified yielding 4.9 g. of solid product whose neutralization equivalent was 156.2. Ether extraction of the aqueous layer yielded 0.64 g. of acidic material which had a neutralization equivalent equal to 98.5. On the reasonable assumption that the solid precipitate consisted of mono- and di- acids only and that the acids recovered by ether extraction were a mixture of di- and tri-acids, the calculated yields were 14 mono, 10 di, and 2% tri or a total of 26%. From a parallel experiment with *n*-octyl chloride, the yields were 17, 15, and 5%, respectively, or a total of 37%. Separation of pure compounds from the mixture of products was carried out by a series of steps which began with an extraction of the precipitate (4.9 g.) with 4 liters of hot water. The insoluble material was reduced by this treatment to 2.5 g. The aqueous solution, after being cooled, yielded 1.1 g. of precipitate which was fractionally crystallized from a mixture of acetic acid and water. The least soluble portion from the dilute acetic acid was converted to the methyl ester by use of the silver salt and methyl iodide. After being recrystallized from methyl alcohol and then from acetic acid, the methyl ester of the 2,6-di acid (m. p. 189 to 192°) was recovered. The portion moderately soluble (as distinguished from most soluble and least soluble) in dilute acetic acid was sublimed. The sublimate was partially soluble in sodium carbonate. Acidification of the aqueous carbonate fraction gave about 44 mg. of β-naphthoic acid melting 182–184°. The amide melted at 192°. The portion insoluble in sodium carbonate was the anhydride of the 1,8-dicarboxylic acid, melting at 272–275°. The imide melted at 299–300°; the anil at 202–203°. The four liters of aqueous solution from which the above acids had been precipitated was extracted with ether, from which about 1.2 g. of acid was recovered by evaporation of solvent. This material was fractionally crystallized from water and the moderately soluble portion consisting of 212 mg. was sublimed. The volatile product was crystallized from ligroin yielding a very small amount of α-naphthoic acid, melting 159–160°. The non-volatile portion from the sublimation was recrystallized from water, yielding the 1,3- acid which melted at 264–265°. In all cases the yields were very small because of the many steps involved in separation. The properties of the acids were compared with those recorded by Bradbrook and Linstead.[7] Examination of the hydrocarbon layer showed little, if any, evidence of alkylation. An experiment[3] exactly parallel to that between octylsodium and naphthalene but using benzene as the hydrocarbon yielded 33% of benzoic acid with scarcely any phthalic acid. No evidence of alkylation was noted.

Amylsodium and Acenaphthene (T. G.).—*n*-Amyl chloride, 75 ml., was added to 40 g. of fine sodium sand suspended in a solution of 30 g. of acenaphthene in 400 ml. of petroleum ether. The sodium metal was previously activated with 5 ml. of *n*-amyl alcohol. No evidence of any reaction between the metal and acenaphthene was observed. The apparatus was the one used formerly[8] in this series of studies. The temperature was maintained at below 15° during the forty-five minutes required for addition of the chloride. The color changed progressively from gray to blue to dark green. After four hours the temperature was allowed to rise to 30°, where it remained during the next nineteen hours while stirring was continued. The dark green paste was then heated to 40° for one and a half hours, cooled to 9° and treated with a stream of carbon dioxide. After adding water to remove excess sodium, the aqueous layer was filtered, and acidified with hydrochloric acid. The mixture of gummy yellow precipitated acids was filtered and dried, yielding 54 g. of crude material. This product proved extremely difficult to purify by extraction with organic solvents, gradual acidification of the neutralized salts, conversion to methyl ester with dimethyl sulfate and other conventional methods. Contact with air appeared to cause formation of dark brown tars. The residues, after a considerable number of extractions had been made, were finally combined, the mixture suspended in ether, and treated with diazomethane. After one hour the yellow solution was filtered to remove suspended material and allowed to evaporate. Large yellow needle-like crystals of an ester resulted in a yield of approximately 50% calculated on the original amyl chloride used. After being recrystallized from ether, these crystals were colorless and melted at 112°, were lath-shaped with square ends, had an extinction angle of 10° and showed negative elongation.

Anal. Calcd. for $C_{18}H_{14}O_4$: C, 71.2; H, 5.2; sapon. equiv., 135. Found: C, 71.1; H, 5.5; sapn. equiv., 131, 134.

This diester was very soluble in cold methanol, acetone, methyl cellosolve, and carbon tetrachloride, moderately soluble in ether, and sparingly soluble in petroleum ether.

The dicarboxylic acid recovered after saponification was

(5) Morton and Fallwell, Jr., THIS JOURNAL, **60**, 1429 (1938); Morton, Richardson and Hallowell, *ibid.*, **63**, 327 (1941).

(6) Morton, Davidson and Best, *ibid.*, **64**, 2239 (1942).

(7) Bradbrook and Linstead, *J. Chem. Soc.*, 1739 (1936).

(8) Morton, Fallwell and Palmer, THIS JOURNAL, **60**, 1426 (1938).

moderately soluble in carbitol, cellosolve, and *t*-butyl alcohol, sparingly soluble in cold acetone, dioxane, and ether, almost insoluble in chloroform, and water, and insoluble in carbon tetrachloride, benzene and xylene; melting point 292–294°.

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.4; H, 4.1. Found: C, 69.4; H, 4.3.

When heated (280°) with an equal weight of lime and copper bronze, the mixture gave acenaphthene as a sublimate; heated in the absence of these agents, it yielded two products which proved to be acenaphthene and an acid melting at 215° (acenaphthene 5-carboxylic acid melts at 217°).

One-tenth gram of the acid was oxidized by excess permanganate solution (2.2%) at 50–60° with stirring. At the end of an hour the solution was decolorized with alcohol, and filtered. A white precipitate was obtained after the filtrate was acidified. This material was redissolved in aqueous alkali, reprecipitated with acid and then crystallized from ether; m. p. 266–268°. The neutralization equivalent was 86, agreeing with the value for a naphthalene tricarboxylic acid. The acid readily changed on drying to the anhydride which melted at 273–275° (cor.).

Anal. Calcd. for $C_{13}H_6O_5$: C, 64.4; H, 2.48. Found: C, 64.3; H, 2.58.

When mixed with an authentic sample[9] of naphthalene-1,4,5-tricarboxylic acid anhydride, no depression of the melting point was obtained.

The mono methyl ester anhydride was also prepared according to the directions of Fieser and Peters[7] and had the properties described by these workers.

Amylsodium and Decalin (E. L., E. C., and A. G.).—Numerous experiments were made in an endeavor to obtain a pure compound readily from the carbonation of the product of amylsodium and decalin. Some of these involved tests with pure *cis* and *trans* decalin but isolation of pure materials was not apparently simplified by such means. The following account is of two experiments employing the method which finally proved successful. Amylsodium was prepared in the usual manner from 100 g. of *n*-amyl chloride and 48 g. of sodium sand in 400 ml. of petroleum ether contained in a 1-liter creased flask. Two hours were required for addition of the chloride at 15 to 20°. Decalin (59.1 g. in one experiment and 119 g. in the other) was then added quickly, and the mixture heated to 49 and 53°, respectively, for two hours. The contents were then cooled to room temperature and treated with a stream of carbon dioxide. Toward the end of the two hour carbonation process the mixture was again heated to a refluxing temperature. Subsequently the excess sodium sand was removed by water and the aqueous layer acidified with hydrochloric acid. The aqueous layer was first extracted with petroleum ether, then saturated with salt and extracted with ethyl ether. The ethyl ether extract was twice esterified with methyl alcohol and hydrochloric acid. This method of esterification was expected to effect a separation of those acids in which the carboxyl group was sterically hindered by being in the indented position. The ester from this step was freed from all acid by washing with aqueous sodium carbonate. The combined esters from both experiments were then fractionated through an 8-plate Podbielniak type column at 2 mm. About 5 ml. of methyl butylmalonate was collected at 64–89°, and 15 cc. of another liquid at 84 to 112°. Crystals then clogged the condenser system. The viscous red oily residue, after standing a week, also formed a mass of crystalline material which had the appearance of a fine mold-like growth over the surface. The crystals from both sources were identical with each other. After being recrystallized from methyl alcohol and water, they melted at 61–62°. The saponification value of 92 was that calculated for the methyl ester of a decalyl tetracarboxylic acid. The molecular weight (Rast) was 374 as compared with a calculated value of 368. The compound proved difficult to burn for analysis.

The product recovered after being saponified and acidified was a white solid which melted near 300° with sublimation. The neutralization equivalent of this material agreed with that calculated for a dianhydride.

Anal. Calcd. for $C_{14}H_{10}O_6$: C, 60.87; H, 4.35. Found: C, 60.8; H, 4.58.

The remaining acids and esters were liquids whose neutralization and saponification equivalents did not agree with any calculated for a mono-, di- or tri-acid, although the scheme of separation by solvent extraction, methylation by both methyl alcohol and acid and by diazomethane (of the difficultly esterified portion) and fractionation was carried to completion. Out of 87.9 g. of total ester (all of the acids were eventually esterified) from both experiments, only 0.15 g. of the methyl decalyltetracarboxylate was obtained. One of the fractions from a methylation by diazomethane had an unusually low saponification equivalent, indicating the presence of even more than four carboxyl groups per decalin unit.

Alkylation of Decalin (E. L.).—*n*-Amyl chloride (200 g.) in 100 ml. of decalin was added gradually to 300 ml. of decalin in which was suspended 96 g. of sodium sand which had been activated by addition of 8.4 ml. of *n*-amyl alcohol. The temperature was maintained at 72 to 80° in expectation that decalin would be converted to amyldecalin in the same manner as toluene was changed to hexylbenzene.[5] The reaction proceeded smoothly at first but after all but 60 ml. of the diluted amyl chloride had been added, the mixture became too solid to stir. The material was allowed to stand overnight under nitrogen, and then treated with a stream of carbon dioxide and reheated for about an hour and a half. The mixture was then allowed to cool. Water was added as usual to remove excess sodium. Much of the metal had agglomerated together in large lumps which were eventually lifted from the mixture with forceps. This agglomeration of sodium particles had been noticed only in the case of some of the experiments with decalin. The hydrocarbon fraction was dried over calcium chloride and fractionated carefully through a packed column of about fourteen plates, in order to remove low-boiling compounds, decane, and decalin. The residue boiling above 194° consisted of about 60 ml. which was then fractionated at 10 mm. through a Podbielniak type column of about eight plates. A portion (2.3 g.) of the fraction (6 cc.) boiling from 124–137° at 10 mm. was mixed with 1.9 g. of sulfur and heated for three hours at 230°. The product was then extracted with small portions

(9) The authors are greatly indebted to Professor L. F. Fieser of Harvard University for his courtesy in furnishing this sample. See Fieser and Peters, THIS JOURNAL, **54**, 4352 (1932).

(200 ml. in all) of ethyl ether. The combined ether extracts were fractionated (final temperature 230°). Since no principal fraction boiling at 126°, the boiling point of *n*-amyl mercaptan, was found, the combined distillate was extracted with sodium hydroxide, the alkali solution then acidified and extracted with ether. The ether was evaporated and the residual foul-smelling liquid treated with 2,4-dinitrochlorobenzene, which produced a few crystals of the *n*-amyl 2,4-dinitrophenyl thioether melting at 80–81° (recorded[10] value 80°). The material left after extraction with alkali was treated with picric acid in hot alcoholic solution. A few yellow crystals melting from 268–273° were obtained. Had the amyl group been substituted in the indented position, the product should have been naphthalene picrate, melting at 149–150°. Several experiments using decalin showed that the above process would give good yields of naphthalene and naphthalene picrate.

Summary

A series of studies on the reaction of amyl-sodium with bicyclic compounds showed that metalation occurred readily in a considerable number of places. The positions of attack were shown by examination of the products of carbonation.

The end-products from naphthalene were both mono-carboxylic acids, at least three dicarboxylic acids, and some tricarboxylic acid.

Acenaphthene was attacked readily; the only product which could be isolated was a dicarboxylic acid, either 1,6- or probably 1,5.

Decalin was attacked very easily and a considerable variety of products was formed. A small amount of the dianhydride of a tetracarboxylic acid was separated. The tertiary hydrogen atom in decalin may be attacked but does not appear to be a favored position.

(10) Bost, Turner and Norton, THIS JOURNAL, **54**, 1986 (1932).

CAMBRIDGE, MASS. RECEIVED MARCH 18, 1942

[CONTRIBUTION FROM THE OIL AND PROTEIN DIVISION, NORTHERN REGIONAL RESEARCH LABORATORY[1]]

The Diastereoisomerism of the 9,10,12-Trihydroxystearic Acids and the Geometric Configurations of Ricinoleic and Ricinelaidic Acids

BY J. P. KASS AND S. B. RADLOVE

In the course of an investigation of the dehydration of ricinoleic and ricinelaidic acids to isomeric linoleic acids, it became necessary to identify the parent 12-hydroxy-9,10-octadecenoic acids by means of their partial oxidation to the 9,10,12-trihydroxystearic acids. Theoretical considerations[2,3,4] indicate that each of the geometrically isomeric, dextrorotatory monohydroxy acids should yield two diastereoisomeric trihydroxystearic acids, with the following configurations of the initially dextrorotatory twelfth carbon atom and the newly asymmetric ninth and tenth carbon atoms

$$\begin{array}{lll} \text{I} & a & (12) + (10) + (9) + \\ & b & (12) + (10) - (9) - \\ \text{II} & c & (12) + (10) + (9) - \\ & d & (12) + (10) - (9) + \end{array}$$

Moreover, assuming that no inversion occurs during oxidation, the pairs of the derivatives should be related in such a manner that the products of the *cis*-hydroxylation of one of the unsaturated acids must correspond to the products of the *trans*-addition to its geometric isomer; specifically, the mild alkaline permanganate oxidation of ricinoleic acid should yield two trihydroxystearic acids identical with the pair resulting from the oxidation of ricinelaidic acid with acid hydrogen peroxide, and *vice versa*. This relationship has been shown to obtain uniformly in the monoethenoid[5,6] and linoleic acid[7] series.

The older literature[8] reports the preparation of three of the trihydroxystearic acids under consideration, and intimates the existence of the fourth isomer. The oxidation of ricinoleic acid with cold alkaline permanganate was first shown by Hazura and Grüssner[9] to produce two trihydroxystearic acids, m. p. 110–111° and 140–142°, for which Dieff[10] later reported m. p. of 100–114° and 137–140°. From similarly treated ricinelaidic

(1) The Northern Regional Research Laboratory is one of four regional laboratories authorized by Congress in the Agricultural Adjustment Act of 1938 for the purpose of conducting research to develop new uses and outlets for agricultural commodities. These laboratories are administered by the Bureau of Agricultural Chemistry and Engineering of the U. S. Department of Agriculture. (Not subject to copyright.)

(2) Mangold, *Monatsh.*, **13**, 326 (1892).

(3) Walden, *Ber.*, **27**, 3471 (1894).

(4) Smit, *Rec. trav. chim.*, **49**, 675 (1930).

(5) Hilditch, *J. Chem. Soc.*, 1828 (1926).

(6) Braun, THIS JOURNAL, **51**, 228 (1929).

(7) Kass and Burr, *ibid.*, **61**, 1062 (1939).

(8) *Cf.* Lewkowitch and Warburton, "The Chemical Technology and Analysis of Oils, Fats and Waxes," 6th ed., Vol. I, The Macmillan Co., London, 1938, p. 236.

(9) Hazura and Grüssner, *Monatsh.*, **9**, 475 (1888).

(10) Dieff, *J. prakt. Chem.*, [2] **39**, 339 (1889).

acid, Grüssner and Hazura[11] and Dieff[10] succeeded in isolating only one trihydroxystearic acid, m. p. 114–115°, although Mangold[2] claimed that he obtained two substances, m. p. 113–116° and 117–120°, in amounts too small for further identification. The optical activity of only the first isomer, m. p. 110–111°, has been determined by Walden,[3] who found $[\alpha]_D$ −6.25 to −6.0° (c = 10–15 in glacial acetic acid).

However, Dean[12] apparently assumed the identity of the two possible pairs of derivatives, while Brady[13] recently repeated the earlier work and stated that the mild alkaline permanganate oxidation of both ricinoleic and ricinelaidic acids produced the same two trihydroxystearic acids, m. p. 110 and 141°, albeit in different proportions. His statement has been accepted by Henshall and Smith.[14] Furthermore, Scanlan and Swern[15] implied that the single trihydroxystearic acid, m. p. 108–109°, which they obtained through the oxidation of the ricinoleic acid of castor oil with hydrogen peroxide in acetic acid, was presumably identical with Hazura and Grüssner's[9] product, m. p. 110–111°, of the alkaline permanganate oxidation of ricinoleic acid, rather than of ricinelaidic acid. Previously, Smit[4] had shown that the oxidation of ricinelaidic acid with perbenzoic acid yielded two trihydroxystearic acids, m. p. 112 and 137°, presumably identical with the compounds formed by the alkaline permanganate oxidation of ricinoleic acid. The latter did not, however, yield any identifiable trihydroxystearic acids with the perbenzoic acid.

In view of the unsatisfactory state of the experimental data and the apparent contradiction between some of the more recent work and the theoretical expectations, it was considered desirable to characterize more fully the trihydroxystearic acids derived from the oxidation of ricinoleic and ricinelaidic acids with both alkaline permanganate and acid hydrogen peroxide. Contrary to the findings of Brady,[13] four distinct diastereoisomers were obtained, the behavior of which was in complete agreement with the theoretical considerations outlined in the introductory section, as shown in the accompanying table. In line with a previous suggestion,[7] each acid has been designated with a Greek letter prefix, the lower-melting isomer in each pair having the lower designation. It is probable that the hitherto unreported γ-trihydroxystearic acid, m. p. 86.8–87.4°, has been overlooked by previous workers because of its relatively pronounced solubility in organic solvents, while the failure of the recent workers[13,15] to recognize the distinction between the α- and δ-trihydroxystearic acids may have been due to the close similarity of the melting points of these substances.

Correlation of the specific rotations of the individual trihydroxystearic acids with their possible stereochemical configurations indicated in the introductory discussion offers corroborative evidence for the *cis*-configuration of ricinoleic acid and the *trans*-configuration of ricinelaidic acid; at least, it presents an analogy between the fatty acids and maleic and fumaric acids, respectively. Where fumaric acid on oxidation with alkaline permanganate yields racemic tartaric acid, ricinelaidic acid similarly produces the strongly dextrorotatory γ-trihydroxystearic and the even more strongly levorotatory δ-trihydroxystearic acid, which are diastereoisomeric because of the presence of the already asymmetric dextrorotatory twelfth carbon atom (structures *a* and *b*, respectively). Conversely, where maleic acid forms *meso*-tartaric acid, ricinoleic acid yields the two weakly levorotatory α- and β-trihydroxystearic acids, the comparatively slight levorotations of these diastereoisomers being due to the partial internal compensation of the strong levorotation of either the ninth or tenth carbon atoms by the other newly asymmetric carbon atom possessing a relatively weaker dextrorotation (either of structures *c* and *d*).

Experimental

Preparation of Ricinoleic and Ricinelaidic Acids.—Castor oil (900 g.) was extracted five times with 500-cc. portions of petroleum ether (b. p. 30–60°). The residue, freed from solvent on the water-bath *in vacuo*, was saponified by boiling for one-half hour with a solution of 360 g. of potassium hydroxide in 243 cc. of water and 1800 cc. of alcohol. The acids were liberated in the usual manner, washed three times with hot water, and dried over sodium sulfate in diethyl ether solution. After filtration and evaporation of the solvent *in vacuo*, the residual acids, which did not solidify completely in the refrigerator at 3°, were extracted four times with large volumes of cold petroleum ether. Evaporation (*in vacuo*) of the solvent from the insoluble acids left 623 g. of an amber oil; I. V. 86.3 (theory for ricinoleic acid, I. V. 85.1). This crystallized completely in the refrigerator.

(11) Grüssner and Hazura, *Monatsh.*, **10**, 196 (1889).

(12) Dean, "The Utilization of Fats," A. Harvey, London, Eng., 1938, p. 18.

(13) Brady, THIS JOURNAL, **61**, 3464 (1939).

(14) Henshall and Smith, "Annual Reports of the Chemical Society of London for 1940," **37**, 213 (1941).

(15) Scanlan and Swern, THIS JOURNAL, **62**, 2309 (1940).

CONSTANTS OF THE 9,10,12-TRIHYDROXYSTEARIC ACIDS

Parent acid	M. p., °C. from literature[a]	M. p., °C. from present work	Trihydroxystearic acids produced by oxidation with alkaline permanganate $[\alpha]^{23}D$ in ethanol	$[\alpha]^{23}D$ in acetic acid	with hydrogen peroxide in acetic acid M. p., °C. from present work	$[\alpha]^{23}D$ in ethanol	$[\alpha]^{23}D$ in acetic acid
Ricinoleic	α112[4] α111[3,9] α100–114[10] α110[13]	112	− 2.9 (c = 5)	− 6.6 (c = 4)	δ110	−26.6	−38.7
	β137[4] β140–142[9] β137–140[10] β141[13]	138	− 3.9 (c = 2)	−11.6 (c = 2)	γ87	+19.1	+21.8
Ricinelaidic	γ	87	+19.1 (c = 4)	+21.8 (c = 2)	β138	− 3.9	−11.6
	δ113–116[2] δ115[11] δ110[13] δ109[15]	110	−26.6 (c = 2)	−38.7 (c = 4)	α112	− 2.9	− 6.6

[a] To avoid confusion arising from the multiplicity of melting points cited and the similarity of the m. p. of the α and δ acids, the previously published m. p. are recorded here with regard to the correct isomeric relationships of the trihydroxystearic acids, rather than their source as reported by the original investigators.

Further purification was effected by treating an alcoholic solution of the potassium salt of the crude ricinoleic acid with an equivalent aqueous solution of barium chloride and recrystallizing the precipitated and washed barium salt three times from 95% alcohol. The barium ricinoleate was then extracted with diethyl ether and the dried, finely powdered salt was suspended in the ether and decomposed by vigorous shaking with successive small portions of dilute hydrochloric acid. Evaporation (*in vacuo*) of the washed and dried ether solution left a colorless oil which solidified in the refrigerator to a crystalline mass, m. p. about 5°. (The crude acid polymerizes very rapidly, for the addition of aqueous barium chloride to the alcoholic solution of the potassium soap of a portion of the acid which was left at room temperature for several weeks produced only a gummy precipitate. However, preliminary saponification of the estolide with an excess of alcoholic alkali and the subsequent isolation of the free acid permitted the recovery of the crystallizable barium salt.)

The ricinelaidic acid was prepared by the action of nitric acid and sodium nitrite on the crude ricinoleic acid which was obtained by the saponification of castor oil previously extracted with petroleum ether as described above. The acids from 1000 g. of castor oil were warmed without preliminary drying to 60° and mixed during vigorous mechanical stirring with 400 cc. of 50% nitric acid at the same temperature. A solution of 30 g. of sodium nitrite in 200 cc. of water was added at once through a delivery tube reaching to the bottom of the reaction flask, and the mixture was vigorously stirred for ten minutes at 60°. The flask was then transferred to an ice-bath and the stirring continued for several hours until the supernatant layer solidified. The product was washed several times with hot water and taken up in five volumes of diethyl ether. The solution was washed with water, dried with sodium sulfate, filtered and chilled. To facilitate the filtration of the voluminous material which separated on chilling, the cooling and filtrations were performed at 10° intervals to −30°. Two recrystallizations of the combined material from diethyl ether yielded 220 g. of white ricinelaidic acid, m. p. 50–51°.

The combined mother liquors from the recrystallizations of the ricinelaidic acid were completely freed from solvent, and the liquid residue was again treated with nitric acid and nitrite exactly as before. An additional 185 g. of ricinelaidic acid was thereby obtained, having a m. p. of 50–51° after a single recrystallization from diethyl ether.

The 405 g. of the crude ricinelaidic acid was taken up in a large volume of boiling petroleum ether, which left undissolved 5 g. of a white crystalline solid, m. p. 134–136°, presumably the natural dihydroxystearic acid.[16] This residue was reserved for future study. Recrystallization of the ricinelaidic acid from petroleum ether raised the m. p. of the main product to 51–52°.[17]

(1) Oxidation with Alkaline Potassium Permanganate

(a) Ricinoleic Acid.—The procedure followed was that of Lapworth and Mottram[18] exactly as employed by Brady.[13] A solution of 5 g. of ricinoleic acid in 2500 cc. of water containing 1.6 g. of potassium hydroxide was stirred for ten minutes at 0° with 5.3 g. of potassium permanganate dissolved in 250 cc. of water. Decolorization was effected with 15 g. of sodium sulfite and an excess of dilute sulfuric acid. The flocculent precipitate was permitted to settle for several hours in the cold, when it was filtered, washed thoroughly with cold water, and finally dried in a vacuum desiccator. After exhaustion with petroleum ether, it was extracted with boiling chloroform. The chloroform-soluble fraction (α-trihydroxystearic acid) was recrystallized from alcohol, then aqueous acetic acid, and again from alcohol; m. p. 109–111.5°; yield, 1.1 g. as a micro-crystalline powder.

The chloroform insoluble fraction (β-trihydroxystearic acid) was similarly recrystallized to yield 1.2 g. of a white powder, m. p. 136–138°.

(16) Ref. 8, p. 226.

(17) Subsequent work in this Laboratory has shown that pure methyl ricinoleate may be very simply prepared by the fractional distillation of the crude mixed methyl esters of castor oil fatty acids through a packed, electrically heated fractionating column. The final purification of ricinelaidic acid is also greatly facilitated by a preliminary fractional distillation of its crude methyl ester. Details of the separations will be described in a forthcoming publication.

(18) Lapworth and Mottram, *J. Chem. Soc.*, **127**, 1628 (1925).

(b) **Ricinelaidic Acid.**—The identical procedure was applied to ricinelaidic acid, 15 g. of which was dissolved with slight warming in a solution of 4.8 g. of potassium hydroxide in 100 cc. of water. (The solid acid is not easily wet and care must be taken to ensure complete solution.) The soap solution was diluted with 2.5 l. of cold water and treated with 16 g. of potassium permanganate in 1 l. of water. After decolorization with 50 g. of sodium sulfite and 250 cc. of 1:4 sulfuric acid, the washed and dried white precipitate was extracted with ligroin. The mixture of crude acids obtained weighed 10.5 g. and melted indefinitely above 70°. The entire product dissolved easily and completely in 100 cc. of warm chloroform. Cooling to approximately 0° precipitated 6 g. of a partially crystalline solid, melting indefinitely above 86° after removal of the stubbornly adhering chloroform with petroleum ether. The chloroform mother liquor was chilled to −40°, at which temperature it deposited about 1 g. of a powder having a m. p. of 83–86° after thorough drying in the vacuum desiccator. The substance remaining in the chloroform was precipitated with ligroin as a waxy solid which melted on rubbing. This was discarded after futile attempts to crystallize it from ether and alcohol.

The main fraction, melting above 86°, was recrystallized twice from chloroform at 0° to yield 3.5 g. of large lustrous plates having a m. p. of 109–110° after washing with ligroin. This compound (δ-trihydroxystearic acid) differed markedly in appearance from the microcrystalline α-trihydroxystearic acid (m. p. 109–111.5°); the m. p. of a mixture of the two was 97–104°.

The solid obtained at −40° was combined with the residue left by the evaporation of the chloroform mother liquors of the δ-trihydroxystearic acid, and the crude product (2.5 g.), m. p. 82–86°, was recrystallized several times from chloroform, aqueous alcohol, and finally from ether, when its m. p. became constant at 86.8–87.4°; the neut. equivalent was 336 (calcd. for trihydroxystearic acid, 332).

Anal.[19] Calcd. for $C_{18}H_{36}O_5$: C, 65.06; H, 10.84. Found: C, 65.20; H, 10.94.

The new acid (γ-trihydroxystearic acid) precipitated on cooling its solutions as a micro-crystalline powder, but slow evaporation left clusters of feathery crystals.

(2) **Oxidation with Hydrogen Peroxide in Acetic Acid.** (a) **Ricinoleic Acid.**—As already pointed out by Scanlan and Swern,[15] whose procedure was used, free ricinoleic acid reacted very sluggishly with the reagent in comparison with its glyceride, despite the purification of the acid immediately before use. Nevertheless, significant amounts of γ- and δ-trihydroxystearic acids were obtained. However, the proportions were different from those obtained with the parent castor oil, which readily produced good yields of the δ-isomer but only small amounts of the γ-acid.

Forty-five grams of pure ricinoleic acid was stirred with a solution of 36 g. of 30% hydrogen peroxide in 50 cc. of glacial acetic acid which had previously been heated for one hour at 80–85° and then cooled to room temperature. The temperature of the mixture rose slowly and spontaneously to 42° in the course of several hours and then dropped without causing the mixture to become homogeneous. The viscous mixture was poured into 400 cc. of hot water. The aqueous layer was siphoned off, and the residue was then refluxed for one hour with 400 cc. of a normal solution of sodium hydroxide. Acidification precipitated the trihydroxystearic acids, which were taken up in chloroform, filtered through decolorizing charcoal and crystallized in the ice-bath to yield 3.35 g. of a crystalline solid having a m. p. of 108.5–110° after one crystallization from alcohol. The m. p. of a mixture of this product with α-trihydroxystearic acid produced by the permanganate oxidation of ricinoleic acid (m. p. 109–111.5°) was 97–100°; that of a mixture with δ-trihydroxystearic acid (m. p. 109–110°) obtained by the permanganate oxidation of ricinelaidic acid was 109–110°.

After evaporation of the mother liquor under vacuum, the residue was extracted with ligroin and finally taken up in diethyl ether. On cooling to below 0°, the ether solution deposited 1.5 g. of a white solid, m. p. 78.5–82.5°. This was dissolved in 50 cc. of ether and cooled to 0°, when a small amount of the δ-acid precipitated. At −40°, the remainder crystallized with a m. p. of 83–87°; this was recrystallized from aqueous alcohol and ether to a m. p. of 86–87°, showing no depression with the γ-trihydroxystearic acid obtained by the permanganate oxidation of ricinelaidic acid.

Equally poor yields of the γ- and δ-trihydroxystearic acids were similarly obtained from ricinoleic acid oxidized with hydrogen peroxide in glacial acetic acid at 0° in the course of one week, according to the method of Hilditch.[5]

The oxidation of about 300 g. of castor oil with 225 g. of 30% hydrogen peroxide in 820 cc. of glacial acetic, previously warmed and cooled as before, duplicated all the observations of Scanlan and Swern,[15] the temperature of the reaction mixture rising quickly to 70°, at which point the mixture became homogeneous. The crude trihydroxystearic acids, obtained after saponification of the reaction product with dilute alkali and subsequent acidification, were recrystallized from alcohol and then toluene to yield about 90 g. of a beautifully crystalline solid, m. p. 109–110°, which was identical with the higher-melting compound produced in the similar oxidation of the free ricinoleic acid and in the permanganate oxidation of ricinelaidic acid. It caused a marked depression in m. p. when mixed with α-trihydroxystearic acid. The mother liquors of the above crystallization were combined and evaporated to a small volume from which about 5 g. of solid material precipitated on cooling. This product was recrystallized from aqueous alcohol, exhaustively extracted with boiling water in which the δ-acid is somewhat soluble, and finally fractionally crystallized from diethyl ether. The first crop, obtained at 0°, melted at 108–110°; the residue melted at 81–85°. Further fractionation of this residue narrowed the m. p. to 85–87°, which was unaffected by admixture with γ-trihydroxystearic acid.

(b) **Ricinelaidic Acid.**—The *trans*-isomeride reacted with the acid hydrogen peroxide as sluggishly as did ricinoleic acid but produced relatively better yields of α- and β-trihydroxystearic acids, which were easily purified. Thirty grams of ricinelaidic acid was stirred into a solution of 22.7 g. of 30% hydrogen peroxide in 32 cc. of glacial acetic which had been warmed for one hour at 80° and

(19) Micro analyses by C. H. Van Etten, Division of Analytical and Physical Chemistry, Northern Regional Research Laboratory.

cooled to room temperature. An additional 18 cc. of the acetic acid was added to facilitate the solution of the solid acid. The temperature of the mixture rose only to 43°. After standing at room temperature for two days, the substantially homogeneous solution was filtered to remove a slight amount of waxy solid and the free acids were recovered from the filtrate by dilution with water, saponification with 100 cc. of 1 *N* sodium hydroxide and acidification as in the procedure followed with ricinoleic acid. The dried crude acids were separated with boiling chloroform, which left undissolved about 4 g. of a white powder, m. p. 137–138.5° without further purification. This proved to be β-trihydroxystearic acid, identical with the corresponding product of the permanganate oxidation of ricinoleic acid.

The chloroform solution readily deposited 4 g. of a white solid, m. p. 110–111°. The mixed m. p. showed no depression with α-trihydroxystearic acid (obtained by the permanganate oxidation of ricinoleic acid) and a wide range in m. p., beginning below 100°, with the δ-trihydroxystearic acid (m. p. 109–110°, derived from the permanganate oxidation of ricinelaidic acid or the peracetic acid oxidation of ricinoleic acid).

Further Purification of the Trihydroxystearic Acids and the Determination of their Specific Rotations.—Prior to the determination of their optical activities, the corresponding lots of trihydroxystearic acids were combined and purified as follows, the m. p. being determined with calibrated Anschütz thermometers: the α-acid was recrystallized from aqueous alcohol and then fractionated from successively smaller volumes of ether, which left undissolved small residues, m. p. 110–124° and 110–114°. The fractionation of the more soluble portion was continued from diminishing volumes of ether until both the insoluble and soluble portions melted at 109.6–112.4°. This substance was readily soluble in chloroform and benzene, which, however, were found to be unsuitable for recrystallization because the substance separated from such solutions carried much solvent and was difficult to filter off. A 95% alcoholic solution containing 5.562 g./100 cc. at 23° showed a rotation in a 2-dm. tube of −0.32°, $[\alpha]^{23}D$ −2.87°; for a glacial acetic acid solution containing 4.497 g./100 cc., the angle of rotation was −0.60°; $[\alpha]^{23}D$ −6.67°. Considering the difference in concentrations, the latter value agrees well with Walden's[3] figure of $[\alpha]D$ −6.25°.

The β-acid was thoroughly extracted with boiling toluene, and then with ether; it was recrystallized from alcohol, 50% acetic acid, again from alcohol, and was finally dried with diethyl and petroleum ethers. The purified acid was a microcrystalline powder which was poorly soluble in acetone, from which it precipitated in a form difficult to filter. The m. p. was 137.6–138.2°. Three additional crystallizations from alcohol followed by another from a large volume of water failed to change its m. p. or appearance. The rotation in a 4-dm. tube of an alcoholic solution containing 1.992 g./100 cc. was −0.31°, $[\alpha]^{23}D$ −3.89°; for the acetic acid solution of 2.152 g./100 cc. it was −1.0°, $[\alpha]^{23}D$ −11.62°.

The combined portions of the γ-acid were treated as before by exhaustion with boiling water and recrystallization from aqueous alcohol and finally from ether. It was the most soluble of the four isomers described; m. p. 86.8–87.4°. The rotation in a 2-dm. tube of an alcoholic solution containing 3.581 g./100 cc. was +0.37°, $[\alpha]^{23}D$ +19.13; for glacial acetic acid (c = 2.039), the rotation was +0.89°, $[\alpha]^{23}D$ +21.82°.

The δ-isomer is readily distinguished from the α-trihydroxystearic acid by its relatively poorer solubility in organic solvents, and by the fact that it is the only one of the four diastereoisomers which readily forms large crystals. It is best recrystallized from toluene. Its m. p. was 109.4–110.4°. The rotation in a 4-dm. tube of a 95% alcoholic solution containing 2.440 g./100 cc. was −2.60°, $[\alpha]^{23}D$ −26.63°; in a 2-dm. tube, for an acetic acid solution containing 4.311 g./100 cc. the angle was −3.34°, $[\alpha]^{23}D$ −38.85°.

Summary

1. The partial oxidation of ricinoleic and ricinelaidic acids with alkaline permanganate and with peracetic acid has been shown to result in four distinct diastereoisomeric 9,10,12-trihydroxystearic acids formed in two inter-related pairs, as expected from theoretical considerations but contrary to statements in the recent literature.

2. The α- and β-trihydroxystearic acids, m. p. 112 and 138°, and $[\alpha]^{23}D$ −6.6 and −11.6° in acetic acid (or −2.9 and −3.9° in ethanol), respectively, were obtained by the oxidation of ricinoleic acid with alkaline permanganate or of ricinelaidic acid with hydrogen peroxide in acetic acid. The γ-trihydroxystearic acid, previously unreported, and the δ-isomer, m. p. 87 and 110°, and $[\alpha]^{23}D$ +21.8 and −38.7° in acetic acid (or +19.1 and −26.6° in ethanol), respectively, were obtained by the oxidation of ricinelaidic acid with alkaline permanganate or of ricinoleic acid with hydrogen peroxide in acetic acid.

3. The optical activities of the four trihydroxystearic acids, previously unreported for three of them, were related to the *cis*- and *trans*-structures of the parent ricinoleic and ricinelaidic acids, respectively.

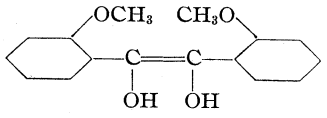
PEORIA, ILLINOIS RECEIVED APRIL 16, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HOWARD UNIVERSITY, WASHINGTON, D. C.]

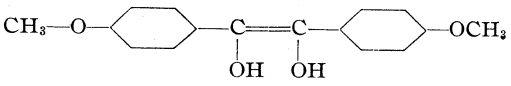
The Effect of Methoxyl toward Stabilizing Ene-diols

BY R. P. BARNES AND WENDELL M. LUCAS[1]

In keeping with a mechanism recently presented in connection with the effect of the *p*-methoxyl group on the rearrangement of anisbenzoin into benzanisoin,[2] the authors set out to investigate the stability of 2,2′-dimethoxydiphenylacetyleneglycol (I) and 4,4′-dimethoxydiphenylacetyleneglycol (II).

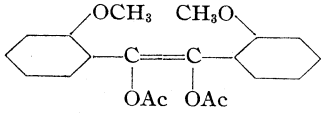


I

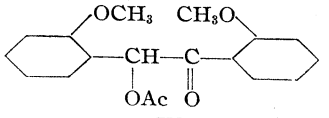


II

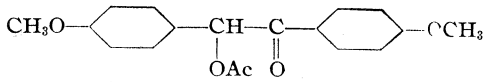
The 2,2′- and 4,4′-dimethoxybenzoins were prepared and acetylated.[3] In cases previously reported,[2,3,4] this method of acetylation has served admirably to convert α-hydroxy ketones into diacetates of ene-diols. In the case of these two substituted benzoins the presence of the methoxyl groups similarly placed in the aromatic nuclei seems to stabilize the benzoins by repressing enolization, with the result that no diacetate is obtained in either case. The monoacetates (IV and V) are obtained in excellent yield in both cases. Further acetylation of the monoacetate (IV) yields a small amount of the diacetate (III); under similar treatment, the monoacetate (V) does not yield any of the diacetate (VIII). Thus



III



IV

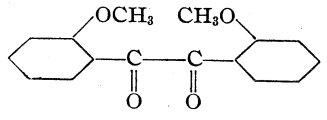


V

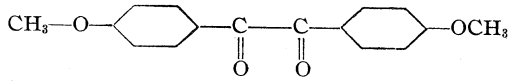
the methoxyl effect is real. The strong electron release tendency of one methoxyl group is offset by the same tendency of the similarly placed methoxyl group from the opposite direction. The para substituents are more powerful than the ortho

The original conception of the effect of similarly placed methoxyl groups was that it would serve to stabilize the ene-diols—or at least prevent ketonization.

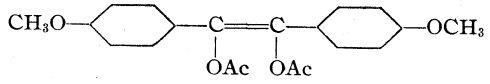
Not being able to obtain the ene-diol diacetates by direct acetylation, we prepared the 2,2′- and 4,4′-dimethoxybenzils, (VI) and (VII), and reduced them catalytically in the presence of acetic anhydride, according to the method of Thompson,[5] producing the diacetates (III) and (VIII),



VI

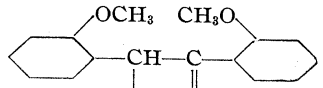


VII



VIII

respectively. These diacetates cannot be hydrolyzed to the monoacetates in acetic acid solution in the presence of potassium acetate.[3] Hydrolysis of the diacetates (III) and (VIII) by means of sulfuric acid resulted in the 2,2′-dimethoxybenzoin (IX) and the 4,4′-dimethoxybenzil (VII), respectively.



IX

Thus the 2,2′-dimethoxydiphenylacetylene glycol (I) shows a tendency toward ketonization, whereas the 4,4′-dimethoxydiphenylacetyleneglycol (II) is autoxidized. These results indicate conclusively that methoxyl groups in the para positions have a greater stabilizing effect on both the

(1) In partial fulfillment of the requirements for the Master's degree.

(2) R. P. Barnes and V. J. Tulane, THIS JOURNAL, **63**, 867 (1941).

(3) R. P. Barnes and V. J. Tulane, *ibid.*, **62**, 894 (1940).

(4) Dauben, Evans and Meltzer, *ibid.*, **63**, 1883 (1941).

(5) R. B. Thompson, *ibid.*, **61**, 1281 (1939).

benzoin and the ene-diol, which is the intermediate in the hydrolysis of the diacetate, than do methoxyl groups in the ortho positions.

Experimental

2,2′-Dimethoxylbenzoin Monoacetate (IV).—To a solution of 17 g. of 2,2′-dimethoxybenzoin in 90 cc. of acetic anhydride was added 8.5 g. of freshly fused potassium acetate, and the mixture refluxed on the steam-bath for thirty minutes. After cooling thoroughly, the solution was poured into 500 cc. of cold water and stirred vigorously to decompose the excess acetic anhydride. A yellow oil separated and solidified. It was filtered, washed thoroughly with water and dried. The crude yield was 21 g. This solid was crystallized from ether and melted at 102°.

Anal. Calcd. for $C_{18}H_{18}O_5$: OCH_3, 19.73. Found: OCH_3, 19.66.

4,4′-Dimethoxybenzoin Monoacetate (V).—This monoacetate was prepared from 17 g. of the 4,4′-dimethoxybenzoin under the same conditions as above. The crude yield was 20 g. Recrystallized from ether, it melted at 93.5°.

Anal. Calcd. for $C_{18}H_{18}O_5$: OCH_3, 19.73. Found: OCH_3, 19.76.

Acetylation of the Monoacetates (IV) and (V).—A solution of 5 g. of the 2,2′-dimethoxybenzoin monoacetate in 30 cc. of acetic anhydride was refluxed gently for three and one-half hours with 10 g. of freshly fused potassium acetate. The reaction mixture darkened after one and one-half hours. It was thoroughly chilled and poured with rapid stirring into 500 cc. of cold water. A brown oil separated, which, after several washings with cold water, solidified. The solid was crystallized from 40 cc. of dilute alcohol (3:2), yielding 4 g. of a light brown crystalline solid which melted from 99–101°. This solid was warmed for a few minutes with 75 cc. of ether. A small portion of the solid was insoluble in ether. The ether-soluble portion gave the pure unchanged monoacetate, melting and mix-melting at 102°. Three and one-half grams of unchanged monoacetate was recovered. The ether-insoluble fraction (0.8 g.) was recrystallized from the least amount of alcohol in which it is extremely soluble. The practically colorless crystals melted at 149°.

Anal. Calcd. for $C_{20}H_{20}O_6$: OCH_3, 17.41. Found: OCH_3, 17.34.

A 5-g. sample of the 4,4′-dimethoxybenzoin monoacetate was treated similarly. There resulted 3.5 g. of an oil from which 2.5 g. of the starting material was recovered.

Reduction of 2,2′-Dimethoxybenzil.—To a solution of 5 g. of the benzil in 75 cc. of acetic anhydride was added 1 g. of freshly fused zinc chloride and 0.08 g. of Adams catalyst. The solution was treated for seven and one-half hours in the Burgess–Parr hydrogenation apparatus. At the end of this treatment the product was poured into a liter of ice and water. A solid separated. It was filtered, washed with water, and crystallized from an alcohol-acetone solution. The yield was 2.5 g., melting at 150°, giving no depression in melting point with the 149°-melting substance obtained by way of acetylation of the 2,2′-dimethoxybenzoin monoacetate.

Reduction of 4,4′-Dimethoxybenzil.—A solution of 5 g. of the benzil with 1 g. of freshly fused zinc chloride in 150 cc. of acetic anhydride to which was added 0.1 g. of Adams catalyst, was subjected to hydrogenation for a period of twelve hours. The product was worked up as above. The colorless solid obtained was crystallized from methanol, yielding 3.5 g. of material melting from 118–123°. After repeated recrystallizations, the substance melted from 121–124°.

Anal. Calcd. for $C_{20}H_{20}O_6$: OCH_3, 17.41. Found: OCH_3, 17.49.

A small amount (0.1 g.) of colorless material insoluble in methanol was recrystallized from acetone and melted at 215°. This material failed to give a test for acetic acid.

Treatment of the Diacetates with Acetic Acid and Potassium Acetate.—Both diacetates were subjected to the following treatment: Four-tenths of a gram of the diacetate was dissolved in 10 cc. of acetic acid with 0.7 g. of potassium acetate and refluxed for seven hours. In each case the diacetate was recovered.

Hydrolysis of 2,2′-Dimethoxydiphenylacetyleneglycol Diacetate.—A solution of 0.85 g. of the diacetate in 20 cc. of cold concentrated sulfuric acid is green. This solution was put in an atmosphere of nitrogen and allowed to stand overnight. The green solution was poured onto finely cracked ice. A colorless solid separated. It was filtered, washed and dried and crystallized from alcohol. It melted and mix-melted with the original material at 150°. To a suspension of 0.7 g. of the diacetate in 10 cc. of alcohol was added 30 cc. of 20% sulfuric acid. The mixture was refluxed for one hour. The solid dissolved in about fifteen minutes. The solution was chilled, and a colorless crystalline solid separated. This solid melted from 94–97°. It mix-melted with the monoacetate from 80–85°; it gave no depression when mix-melted with the 2,2′-dimethoxybenzoin.

Hydrolysis of 4,4′-Dimethoxydiphenylacetyleneglycol Diacetate.—One gram of the diacetate was dissolved in 30 cc. of cold concentrated sulfuric acid. The green solution was allowed to stand at room temperature for thirty minutes, and was then poured onto finely cracked ice. A cream colored solid separated. It was filtered, washed and dried, and recrystallized from alcohol. It melted at 133°. The mix-melt with anisil was unchanged.

Summary

1. 2,2′- and 4,4′-dimethoxybenzoins can be effectively acetylated to the corresponding monoacetates, but not to the corresponding acetyleneglycol diacetates.

2. 2,2′- and 4,4′-dimethoxydiphenylacetyleneglycol diacetates can be obtained by catalytic hydrogenation in acetic anhydride solution.

3. The diacetates are not hydrolyzable to the monoacetates in acetic acid solution.

4. When completely hydrolyzed, the intermediate 2,2′-dimethoxydiphenylacetyleneglycol ketonizes to the benzoin, while the intermediate 4,4′-dimethoxydiphenylacetyleneglycol, being more resistant toward ketonization, is autoxidized to the corresponding benzil.

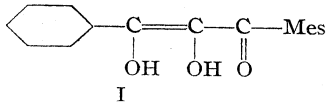
WASHINGTON, D. C. RECEIVED JULY 6, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, HOWARD UNIVERSITY]

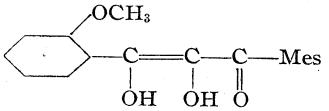
The Preparation and Properties of an Ene-diol. α-*o*-Methoxyphenyl-β-mesitoylacetylene Glycol

BY R. P. BARNES AND WENDELL M. LUCAS[1]

The effect of 2,2′-dimethoxyl substitution on the stability of benzoin and its ene-diolic modification has already been pointed out.[2] This work was undertaken to determine the effect of introducing the methoxyl group in the ortho position of the phenyl group in α-phenyl-β-mesitoylacetyleneglycol[3] (I). It has been found that the methoxyl-substituted compound (II) is more stable than the unsubstituted compound (I).



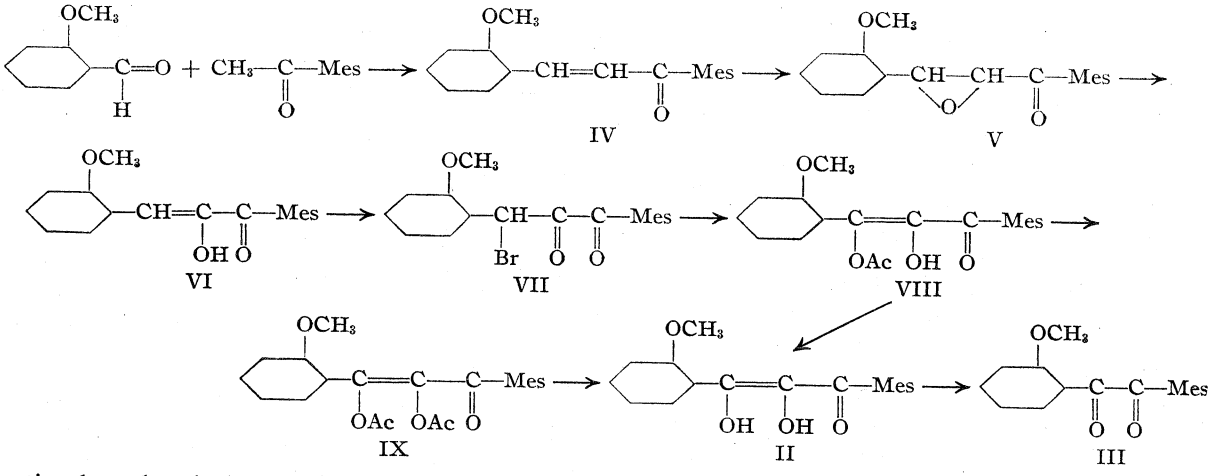
I



II

The ene-diol (II) is a colorless needle-like crystalline solid, extremely soluble in alcohol, very appreciably soluble in water and only sparingly soluble in ether and petroleum ether. It gives a deep greenish-blue color with alcoholic ferric chloride, which color fades gradually to yellow. It bleaches iodine and 2,6-dichlorobenzeneoneindophenol. It is slowly oxidized by atmospheric oxygen. The end-product of these reactions is *o*-methoxyphenylmesityl diketone (III).

The following schematic representation indicates the manner in which the ene-diol (II) is obtained



Experimental

***o*-Methoxybenzalacetomesitylene (IV).**—A solution of 15 g. of sodium hydroxide in 40 cc. of water was diluted with 100 cc. of alcohol. To this alkaline alcoholic solution was added 23 g. of acetylmesitylene with stirring and chilling. To this cold solution was added slowly and with stirring 28 g. of *o*-methoxybenzaldehyde. At the end of twenty minutes considerable solid material had separated. Stirring was continued for one hour. The product was filtered, washed, dried and recrystallized from alcohol. The yield was 36 g. of a pale yellow solid, melting at 95°.

Anal. Calcd. for $C_{19}H_{20}O_2$: OCH_3, 11.07. Found: OCH_3, 11.06.

α-*o*-Methoxyphenyl-β-mesitoylethylene Oxide (V).—To a solution of 31 g. of *o*-methoxybenzalacetomesitylene in 200 cc. of alcohol was added 14 cc. of 30% hydrogen peroxide. This solution was made alkaline with 25 cc. of 20% sodium hydroxide. It was warmed gently with stirring. As the reaction proceeded considerable heat was evolved. The reaction mixture was maintained at room temperature by cooling. On standing in the cold a cream-colored solid separated. The solution was diluted with water and the product was filtered, washed and dried. Recrystallized from alcohol, the yield was 26 g. of colorless solid, melting at 73–74°.

Anal. Calcd. for $C_{19}H_{20}O_3$: OCH_3, 10.47. Found: OCH_3, 10.29.

The Enolic Modification of Mesityl-*o*-methoxybenzylglyoxal (VI).—To a solution of 23 g. of the ethylene oxide, dissolved in 125 cc. of alcohol, was added a solution of 15 g. of sodium hydroxide in 30 cc. of water. The mixture was boiled gently for ten minutes. The solution became deep yellow in color. It was cooled and poured into a cold dilute solution of hydrochloric acid. A pale yellow solid

(1) In partial fulfillment of the requirements for the Master's degree.

(2) R. P. Barnes and W. M. Lucas, THIS JOURNAL, **64**, 2258 (1942).

(3) R. P. Barnes and Leila S. Green, *ibid.*, **60**, 1549 (1938).

separated. The solid was filtered, washed, dried and recrystallized from alcohol. The yield was 16 g., melting at 137°.

Anal. Calcd. for $C_{19}H_{20}O_3$: OCH_3, 10.47. Found: OCH_3, 10.60.

An alcoholic solution of this substance gives a cherry-red color with ferric chloride. Kurt Meyer titrations[4] indicate that it is 98% enolic.

α-Bromo-*o*-methoxybenzylmesitylglyoxal (VII).—To a solution of 8 g. of the enol in 75 cc. of carbon tetrachloride was added 8 g. of precipitated calcium carbonate. A solution of 4.4 g. of bromine in 30 cc. of carbon tetrachloride was added dropwise with stirring to the solution containing the calcium carbonate in suspension. Hydrogen bromide was evolved. The enol in solution decolorized the bromine solution instantaneously with the addition of each drop. The resulting orange-colored solution was filtered from the suspended material, and evaporated in a stream of dry air. Final traces of carbon tetrachloride and moisture were removed *in vacuo*. Eleven grams of a deep yellow oil resulted. This oil was crystallized from methanol in golden-yellow needles, melting at 84°.

Anal. Calcd. for $C_{19}H_{19}O_3Br$: OCH_3, 8.2. Found: OCH_3, 8.3.

The bromo compound is non-enolic.

The Acetate of α-Oxy-*o*-methoxybenzylmesityl-α-diketone (VIII).—To a solution of 5.5 g. of the bromo compound in 50 cc. of acetic acid was added 11 g. of freshly fused potassium acetate. The solution was refluxed gently for four hours. It turned cherry-red. The solution was cooled thoroughly and poured into a large volume of cold water and stirred vigorously. A yellow oil separated and solidified. It was filtered, washed and dissolved in alcohol. On chilling a cream colored solid separated, melting from 84–86°. On recrystallization from alcohol, it melted at 94°. The yield was 3 g.

Anal. Calcd. for $C_{21}H_{22}O_5$: OCH_3, 8.75. Found: OCH_3, 8.84.

This compound in alcoholic solution gives a cherry-red color with alcoholic ferric chloride. It is enolic[4] to the extent of 80%.

The Diacetate of α-*o*-Methoxyphenyl-β-mesitoylacetylene Glycol (IX).—One gram of the monoacetate was dissolved in 10 cc. of acetyl chloride and refluxed for one hour. The excess acetyl chloride was pumped off and the oily residue taken up in alcohol, from which solution a colorless solid, melting at 103–104°, was obtained. The yield was 0.8 g.

Seven grams of the bromo compound was dissolved in 66 g. of acetic anhydride, to which solution 10 g. of freshly fused potassium acetate was added. The mixture was refluxed gently for one and one-half hours. It became light yellow and potassium bromide separated. The thoroughly chilled mixture was poured into a large volume of cold water and stirred An orange-red oil separated. It was washed several times with cold water and finally taken up in alcohol, from which solution a colorless solid melting and mix-melting with the above substance at 103–104°, was obtained.

Anal. Calcd. for $C_{23}H_{24}O_6$: OCH_3, 7.83. Found: OCH_3, 7.84.

This substance gives no color with alcoholic ferric chloride.

α-*o*-Methoxyphenyl-β-mesitoylacetylene Glycol (II).—Four grams of the monoacetate was dissolved with stirring in 50 cc. of cold concd. sulfuric acid. The solution was orange colored. It was allowed to stand for thirty minutes at 0°. It was then poured onto finely cracked ice in a g. s. flask. The air in the flask was displaced by nitrogen, the flask was stoppered and shaken vigorously. A fine needle-like colorless solid separated. It was allowed to stand overnight at 0°. It was filtered, washed with a little iced water, then with ether. It was recrystallized from dilute alcohol, yielding 3 g., melting at 105°.

Four grams of the diacetate was treated similarly. The result was about 2 g. of colorless needles, melting and mix-melting with the above substance at 105°.

Anal. Calcd. for $C_{19}H_{20}O_4$: OCH_3, 9.9. Found: OCH_3, 9.8.

This substance is extremely soluble in alcohol and quite soluble in water. It is rather insoluble in ether and insoluble in petroleum ether. It produces a bluish-green color with alcoholic ferric chloride, which color fades gradually to yellow. It decolorizes iodine solution and bleaches 2,6-dichlorobenzeneoneindophenol instantaneously.

The Diketone (III).—Alcoholic test solutions of the ene-diol with ferric chloride, iodine and indophenol blue all resulted in yellow solutions from which a yellow solid, melting at 132°, was obtained. Atmospheric oxidation goes on slowly producing a more highly colored solid, which upon crystallization results in the same light yellow solid, melting at 132°.

Anal. Calcd. for $C_{18}H_{18}O_3$: OCH_3, 10.89. Found: OCH_3, 10.90.

The diketone is cleaved by alkaline hydrogen peroxide, yielding mesitoic and *o*-methoxybenzoic acids, identified by comparison with known samples.

Summary

A new ene-diol, α-*o*-methoxyphenyl-β-mesitoylacetylene glycol, has been synthesized and its properties listed.

The *o*-methoxyl in the phenyl group has rendered the ene-diol more stable than the unsubstituted α-phenyl-β-mesitoylacetylene glycol.

The only product which is obtainable from oxidation reactions is the diketone.

WASHINGTON, D. C. RECEIVED JULY 6, 1942

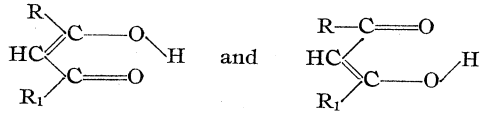
(4) S. R. Cooper and R. P. Barnes, *Ind. Eng. Chem., Anal. Ed.*, **10**, 379 (1938).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, HOWARD UNIVERSITY]

The Properties of *o*-Methoxybenzoylmesitoylmethane

BY R. P. BARNES AND CHAPPELLE C. COCHRANE

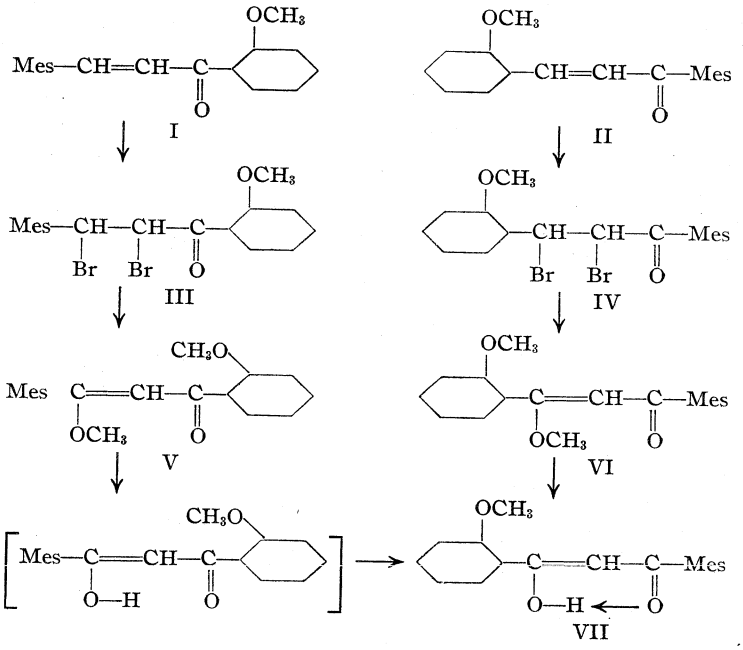
In an earlier paper[1] we reported two series of reactions which gave a single enol, although, according to the mechanism, one would expect two isomeric enols. Sidgwick[2] states that coördination of hydrogen occurs in ordinary chelation in keto-enols



He states further that the strain in the 6-ring with two double links is very small and that the same position of the atoms fits either structure. Thus the fact that two isomeric enols of this type have never been isolated is accounted for.

Steric hindrance is also a very important factor, contributing to the non-existence of two isomeric enols. In this communication we are reporting two parallel series of reactions which give rise to a single enol. The effect of the mesityl nucleus in offering hindrance to 1,2-addition reactions to adjacent carbonyls is well known, and one would predict a single enol on this basis alone in this case. This enol is obviously chelated, being a beta-diketone,[3] and this is evidenced by the fact that it is neither acetylated by the ordinary reactions of acetylation, nor does it yield to O-methylation.

The following series of reactions indicates the manner in which the enol is obtained.



Experimental

The α,β-unsaturated ketone (I) and the dibromides (III) and (IV) were prepared according to standard methods as given in "Organic Syntheses."[4a,b]

The methyl ethers (V) and (VI) were obtained by refluxing 1 g. of each of the respective dibromides for one and one-half hours in methyl alcoholic sodium methylate made by dissolving 0.2 g. of metallic sodium in 20 cc. of the alcohol. Sodium bromide separated. The cooled mixture was poured into a large volume of cold water. The oils which separated in each case were crystallized from methyl alcohol as colorless solids, producing no color with alcoholic ferric chloride.

One gram of each of the methyl ethers (V) and (VI) was dissolved in 50 cc. of methyl alcohol and refluxed for one hour with 10 cc. of concd. hydrochloric acid. On cooling, colorless solids separated, which upon filtering and recrystallizing from methanol melted and mix-melted at 105°. This enol gives a deep red color with alcoholic ferric chloride and is 100% enolic.[5] Repeated treatments with diazomethane always resulted in a recovery of unchanged enol. In like manner treatment with acetic anhydride and sulfuric acid or with acetyl chloride did not effect acetylation of the enol.

TABLE I

Compound	Melting point, °C.	Formula	OCH_3 Analyses, % Calcd.	Found
I	118	$C_{19}H_{20}O_2$	11.07	11.00
III	135	$C_{19}H_{20}O_2Br_2$	7.04	7.01
IV	86	$C_{19}H_{20}O_2Br_2$	7.04	7.00
V	87	$C_{20}H_{22}O_3$	20.00	20.20
VI	85	$C_{20}H_{22}O_3$	20.00	19.93
VII	105	$C_{19}H_{20}O_3$	10.47	10.50

Summary

Herein are reported two parallel series of reactions which give rise to a single enol, for which there is given some chemical evidence of hydrogen bonding.

WASHINGTON, D. C. RECEIVED JULY 6, 1942

(1) R. P. Barnes, Charles I. Pierce and Chappelle C. Cochrane, THIS JOURNAL, **62**, 1084 (1940).

(2) Sidgwick, *Annual Reports of the Chemical Society*, **XXXI**, 41 (1934).

(3) Hilbert, Wulf, Hendricks and Liddel, THIS JOURNAL, **58**, 548 (1936).

(4)(a) "Org. Syn.," Col. Vol. I, p. 71; (b) p. 200.

(5) S. R. Cooper and R. P. Barnes, *Ind. Eng. Chem., Anal. Ed.*, **10**, 379 (1938).

[CONTRIBUTION FROM THE BURROUGHS WELLCOME & CO. U. S. A. EXPERIMENTAL RESEARCH LABORATORIES]

Esters of Secondary Hydroxyaralkylalkylamines[1]

BY JOHANNES S. BUCK AND RICHARD BALTZLY

The preparation of esters of phenolic secondary amines of the type of 4-hydroxyphenethylmethylamine, wherein the amino group is not also acylated, presents difficulties. No compounds of this type have been found in the literature. The sensitiveness of phenolic esters precludes their use as starting materials for building up the amine, and the reactivity of the amino group of the hydroxyamines prevents preferential acylation of the hydroxy groups.[2] Furthermore, it is not possible to remove only the N-acyl group from the completely acylated hydroxy amine.[3] Protection by the carbobenzoxy group was not found to be feasible as the group did not survive the reactions used.

By extending the method previously described[4] for preparing secondary amines, the authors have succeeded in obtaining the desired O-acyl compounds by a series of smooth reactions of general applicability. In the cases described below, a methoxy- or dimethoxyphenethylbenzylmethylamine was O-demethylated, the phenolic group or groups acylated, and the protecting benzyl group then removed by catalytic hydrogenation. From homoanisylamine were prepared 4-acetoxy-, 4-benzoyloxy- and 4-ethylcarbonatophenethylmethylamines. Similarly N-methylhomoveratrylamine was converted into 3,4-diacetoxy-, 3,4-dibenzoyloxy- and 3,4-diethylcarbonatophenethylmethylamines.

The compounds in question, being stabilized or protected forms of pressors and the like, are of considerable pharmacological interest, and they are being investigated from this point of view.

Experimental

4-Methoxyphenethylbenzylmethylamine Hydrochloride.—4-Methoxyphenethylbenzylamine[5] was methylated by the Eschweiler–Clarke[6] method, using 1.1 mol of formaldehyde and 5 mols of absolute formic acid, and the product was isolated as the hydrochloride. The yield approached the theoretical.

3,4-Dimethoxyphenethylbenzylmethylamine Hydrochloride.—Attempts to prepare this compound from benzylhomoveratrylamine[7] by the foregoing method, gave unsatisfactory results, probably owing to partial cyclization.[8] It was therefore prepared as follows: one mol of 3,4-dimethoxyphenethylmethylamine[9] dissolved in three volumes of ethanol, was treated with one mol of benzyl chloride. After three days the alcohol was evaporated off, water added, and the whole made acid; 0.8 mol of sodium nitrite, in solution, was added, and the whole extracted with ether. The aqueous layer, after making alkaline, was extracted with ether. After evaporation of the ether, the residue was converted into the hydrochloride; the yield was mediocre (30%).

4-Hydroxy- and 3,4-Dihydroxyphenethylbenzylmethylamines.—The corresponding 4-methoxy and 3,4-dimethoxyphenethylbenzylmethylamine hydrochlorides were demethylated with concentrated hydrochloric acid, in a carbon dioxide atmosphere, for two hours at 170°. The colorless solutions were evaporated to dryness *in vacuo*. The yields approached the theoretical.

Acylation of the Phenolic Amines.—Acetylation was accomplished by refluxing the amine hydrochlorides in a mixture of acetic anhydride and acetyl chloride, in which they gradually dissolved. After about two hours, the solvent was removed in an air stream. The residues were ground with acetone and filtered off prior to recrystallization. Use of alcohols in crystallizing the acetoxy derivatives is inadvisable. With the benzoyloxy and ethylcarbonato compounds alcohols are probably permissible but were avoided.[10]

Benzoylation of the phenolic amines was carried out by the Schotten–Baumann method. The oils resulting from the reaction were taken into ether and dried over potassium carbonate before being converted to the hydrochlorides.

The carbethoxylations required a modified Schotten–Baumann technique of which the following is an example. One mol of 4-hydroxyphenethylbenzylmethylamine hydrochloride was dissolved in water and stirred in an atmosphere of nitrogen, with ice-cooling. A solution of sodium hydroxide (3 mols), was run in slowly, 2 mols of ethyl chlorocarbonate being admitted simultaneously, keeping the alkali a little ahead of the chlorocarbonate (any considerable excess of chlorocarbonate could be detected in the stream of escaping nitrogen). The resulting oil was extracted with ether, dried over anhydrous potassium carbonate and the hydrochloride precipitated by gaseous hydrogen chloride.

In the preparation of 3,4-diethylcarbonatophenethylbenzylmethylamine hydrochloride an additional mol of sodium hydroxide and of ethyl chlorocarbonate was used. This compound, however, was not obtained crystalline,

(1) This work is part of a joint research started in collaboration with a pharmacological group then under Dr. A. M. Hjort, at the above laboratories.

(2) *Cf.* Barger, *J. Chem. Soc.*, **95**, 1128 (1909).

(3) *Cf.* Tutin, Caton and Hann, *ibid.*, **95**, 2123 (1909).

(4) Buck and Baltzly, THIS JOURNAL, **63**, 1964 (1941).

(5) By reduction of benzylidene homoanisylamine, method of ref. 7.

(6) Clarke, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

(7) Buck, *ibid.*, **53**, 2192 (1931).

(8) *Cf.* Buck, *ibid.*, **56**, 1769 (1934).

(9) Buck, *ibid.*, **52**, 4119 (1930).

(10) *Cf.* Baltzly and Buck, *ibid.*, **63**, 2022 (1941).

TABLE I

DERIVATIVES OF PHENETHYLBENZYLMETHYLAMINE HYDROCHLORIDE, 4-R($C_{16}H_{19}NCl$) AND 3,4-R_2($C_{16}H_{18}NCl$)

4-R or 3,4-R_2	Recrystn. solvent + ether	Crystal form	M. p., °C.	Formula	Percentages: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3O	E. Al.,[c] E. Ac.[c]	Needles	170	$C_{17}H_{22}ONCl$	69.96	69.95	7.61	7.82
$(CH_3O)_2$	E. Al., E. Ac.	Leaves	205	$C_{18}H_{24}O_2NCl$	67.17	67.34	7.52	7.70
OH	M. Al.,[c] E. Ac.	Prisms	198	$C_{16}H_{20}ONCl$	69.16	69.26	7.26	7.48
$(OH)_2$	E. Al., E. Ac.[a]	Prisms	153	$C_{16}H_{20}O_2NCl$	65.40	65.50	6.87	7.05
CH_3COO	E. Al., H_2O	Spindles	211	$C_{18}H_{22}O_2NCl$	67.59	67.73	6.94	7.07
$(CH_3COO)_2$	Ac.,[a] E. Ac.	Needle prisms	174–5	$C_{20}H_{24}O_4NCl$	63.55	63.58	6.41	6.64
C_6H_5COO	Ac.[b]	Prisms	191	$C_{23}H_{24}O_2NCl$	72.33	72.37	6.34	6.67
$(C_6H_5COO)_2$	Ac.	Prisms	131–2	$C_{30}H_{28}O_4NCl$	71.76	71.93	5.62	5.87
$C_2H_5CO_3$	Ac.	Prisms	128–9	$C_{19}H_{24}O_3NCl$	65.20	65.20	6.92	7.23

DERIVATIVES OF PHENETHYLMETHYLAMINE HYDROCHLORIDE, 4-R($C_9H_{13}NCl$) AND 3,4-R_2($C_9H_{12}NCl$)

CH_3COO	Ac.,[b] E. Ac.	Leaves	194	$C_{11}H_{16}O_2NCl$	57.49	57.71	7.02	7.20
$(CH_3COO)_2$	Ac., E. Ac.	Leaves	142–3	$C_{13}H_{18}O_4NCl$	54.24	54.16	6.31	6.64
C_6H_5COO	Ac.[b]	Leaves	198	$C_{16}H_{18}O_2NCl$	65.84	65.80	6.22	6.30
$(C_6H_5COO)_2$	Ac.[b]	Needles	163–4	$C_{23}H_{22}O_4NCl$	67.05	66.87	5.39	5.55
$C_2H_5CO_3$	Ac.	Leaves	138.5–139	$C_{12}H_{18}O_3NCl$	55.47	55.65	6.99	7.06
$(C_2H_5CO_3)_2$	Ac., E. Ac.	Leaves	115	$C_{15}H_{22}O_6NCl$	51.78	51.99	6.38	6.68

[a] No ether. [b] Moist acetone. [c] Ac. = acetone, E. Al. = ethyl alcohol, M. Al. = methyl alcohol and E. Ac. = ethy acetate.

and was debenzylated directly. The yields of both substances are improved somewhat by using greater excesses of alkali and of acylating agent.

Debenzylations.—These were performed by catalytic hydrogenation of the hydrochlorides in 80% acetic acid solution, using a Burgess–Parr apparatus, at room temperature and three atmospheres pressure. Palladized charcoal (from 1.2 g. of palladium chloride and 6 g. of Darco G60) was used as catalyst. The theoretical amount of hydrogen was taken up in two to three hours (from 10 g. of starting material). The solutions were filtered and evaporated to dryness *in vacuo* before recrystallization. The yields were excellent. The secondary amine hydrochlorides are colorless solids, soluble in water and alcohol, moderately soluble in acetone, sparingly soluble in ethyl acetate and insoluble in ether and non-polar solvents.

The authors are indebted to Mr. W. S. Ide for the many microanalyses performed, including some chlorine and nitrogen analyses not recorded here.

Descriptive and analytical data are presented in the table.

Summary

A method has been developed for preparing phenolic esters wherein an unacylated secondary amino group is required on a side chain. The method involves N-debenzylation.

TUCKAHOE, NEW YORK RECEIVED JUNE 6, 1942

[CONTRIBUTION FROM THE LABORATORY OF HIGH MOLECULAR CHEMISTRY, THE HEBREW UNIVERSITY]

Poly-condensation of α-Amino Acid Esters. I. Poly-condensation of Glycine Esters[1]

BY MAX FRANKEL AND EPHRAIM KATCHALSKI

This paper deals with the poly-condensation of methyl, ethyl and isobutyl esters of glycine and with the further condensation of isolated primary reaction products.

Curtius[2] has shown that under certain conditions glycine ethyl ester yields, besides glycine anhydride, a tetraglycine ethyl ester, the so-called "Biuret Base." This tetrapeptide ester is the highest condensation product which hitherto has been obtained directly from the glycine ethyl ester. No clear results are reported in the literature concerning the formation of the corresponding tetrapeptide ester from glycine methyl ester.[3] In any case it is clear that the tetrapeptide esters were regarded as the highest peptide esters formed by condensation from the glycine ester. Nothing definite seems to be known about the condensation to chains of glycine esters other than those of methanol and ethanol.

(1) Certain minor errors in the manuscript as originally submitted were noted by the Editorial Board. Ordinarily these would have been brought to the attention of the authors prior to publication. International conditions at present are such that it appears impossible to follow this procedure except at the risk of indefinite postponement. The Editor has therefore taken the responsibility to make any corrections which appeared to be unquestionably required.—THE EDITOR.

(2) Curtius, *Ber.*, **37**, 1284 (1904).

(3) Curtius and Goebel, *J. prakt. Chem.*, [2] **37**, 159 (1888).

In a preliminary report[4] we have described some of our results obtained by C-polymerization of glycine ethyl ester. In our experiments we were able to isolate directly polypeptide esters with an average chain length of ten to thirty-five glycine units. These isolated products, when allowed to undergo additional condensation by heating, yield higher linear polymers. In the present paper we describe polymers thus obtained with an average chain length of 48–110 units.

The poly-condensations were carried out (a) with the pure liquid esters and (b) with their solutions in organic, water-free solvents. In a number of experiments in series (a) a stream of gas (nitrogen, hydrogen or oxygen) was passed through the liquid. In the experiments of series (b) solvent and temperature were varied.

The reaction mixtures contained, in addition to the higher condensation products, glycine anhydride and lower peptide esters. The separation was based mainly on the different solubility of the compounds concerned, which permitted the quantitative removal of all lower condensation products by extraction with hot water. A modified sensitive picric acid test, worked out for this purpose, was used in order to follow the complete removal of glycine anhydride. The quantitative removal of the water-soluble lower peptide esters was ascertained by the negative biuret reaction of the washings.

As is usual with products obtained by polymerization, mixtures containing polymer homologs are to be expected. The average chain length of the peptide ester form was ascertained by the determination of the terminal alkoxy group (*cf.* discussion). To avoid circumlocution, the polymerized products discussed in this paper are referred to as, *e. g.*, 20-glycine ethyl ester. It is to be understood that the specific names applied to the preparations merely indicate the average composition which corresponds most closely to the analytical results. They are not to be taken as implying that the preparations are homogeneous specimens of the substance named.

Experimental

I. Poly-condensation of Glycine Ethyl Ester.—The free glycine ethyl ester was liberated from its hydrochloride according to the method of Fischer[5] immediately before carrying out the condensation.

(a) **Poly-condensation of the Free Liquid Ester.**—These experiments were carried out by passing an indifferent gas through the liquid amino acid ester.

1. A stream of dried nitrogen was passed through 4 g. of freshly distilled glycine ethyl ester for twenty-four hours. Access of carbon dioxide and moisture was prevented. The liquid solidifies gradually and after twenty-four hours the passage of gas had to be discontinued. The reaction mixture which was soluble in water and gave a positive biuret reaction and a positive picric acid test was kept for five months in a desiccator over soda-lime. After this time a part of the product was found to be insoluble in hot water. Traces of unchanged ethyl ester were removed by extraction with ether. The fraction insoluble in hot water was separated from the lower condensation products by repeated washing with hot water and centrifuging till the biuret reaction and the picric acid test in the washings became negative. The amount of the vacuum dried fraction insoluble in hot water was about 250 mg.

Properties.—The substance is practically insoluble in the usual organic solvents and even in hot water. In the latter characteristic swelling occurs. In concentrated alkalies and acids the substance dissolves gradually apparently by undergoing hydrolysis. It is horn-like in appearance; no melting point, decomposition at about 280–300°. On heating a suspension with ninhydrin solution the particles gradually become blue-violet in color, the fluid remaining colorless. On allowing a suspension of the substance to stand with a 30% solution of sodium hydroxide and a few drops of a dilute solution of copper sulfate, a positive biuret reaction appears within some hours. This is obviously due to the hydrolysis of the high peptide ester (which owing to its insolubility does not give a positive biuret reaction) to a lower soluble peptide chain showing the biuret reaction. Calcd. for 20-glycine ethyl ester: C_2H_5O, 3.79; N, 23.59. Found: C_2H_5O, 3.87; N, 23.24.

In order to show that during the process of separation, which consists of repeated treatment with hot water, no hydrolysis of the terminal ester group occurs, 50 mg. of the analyzed substance no. 1 was washed repeatedly with hot water and afterward reanalyzed. No change in ethoxy content was found.

Thirty mg. of the 20-glycine ethyl ester was totally hydrolyzed by refluxing with 2 ml. of 10% sulfuric acid for five hours. After quantitative removal of the sulfate by barium hydroxide solution, and boiling with cupric oxide, 54 mg. of the copper salt of glycine was obtained (calcd. amount of $Cu(NH_2CH_2COO)_2 \cdot H_2O$, 56.3 mg.).

Anal. Calcd. for $Cu(NH_2CH_2COO)_2 \cdot H_2O$: Cu, 27.68. Found: Cu, 27.38.

2. Four grams of glycine ethyl ester was treated as in 1 except that hydrogen instead of nitrogen was bubbled through the ester. The experimental details were similar to those of the previous experiment. 200 mg. of a horn-like fraction was obtained. Calcd. for 20-glycine ethyl ester: C_2H_5O, 3.79; N, 23.59. Found: C_2H_5O, 3.99; N, 23.38.

3. On repeating experiment 2 and allowing the reaction mixture to stand in contact with air after the treatment with gas, the water-insoluble fractions which were finally obtained (200 mg.) corresponded in analysis with a 25-glycine ethyl ester. Calcd. for 25-glycine ethyl ester: C_2H_5O, 3.05; N, 23.79. Found: C_2H_5O, 3.09; N, 23.40.

4. When oxygen was used, solidification of the liquid, unlike that in the above experiments, was accompanied

(4) Frankel and Katchalski, *Nature*, **144**, 330 (1939).
(5) Fischer, *Ber.*, **34**, 433 (1901).

by the gradual appearance of a pink color. After keeping the primary reaction mixture in a desiccator for three months, the water-insoluble fraction obtained (160 mg.) corresponded to the 16-glycine ethyl ester. Calcd. for 16-glycine ethyl ester: C_2H_5O, 4.69; N, 23.37. Found: C_2H_5O, 4.66; N, 22.78.

5. Control experiments carried out without passing gas through the esters showed that under otherwise similar conditions no high chain products insoluble in hot water were formed.

(b) Poly-condensation of the Free Ester in Solution.—1. In xylene at room temperature: 3 g. of freshly distilled glycine ethyl ester was dissolved in 12 ml. of pure, water-free xylene and kept for three months at room temperature. The precipitate which developed during this time was filtered, carefully washed with ether and dried *in vacuo* (1.7 g.). It was fractionated as before; 300 mg. of a water insoluble fraction was obtained corresponding to a 12-glycine ethyl ester. This product shows the general behavior of the higher polypeptides mentioned above, including the property of swelling in hot water, except that it is amorphous and not horn-like. Calcd. for 12-glycine ester: C_2H_5O, 6.15; N, 23.00. Found: C_2H_5O, 6.12; N, 22.81.

2. In xylene at boiling temperature: The solution as in (b)1 was refluxed for eight hours and then allowed to stand for two months at room temperature. After the usual treatment, there was obtained 240 mg. of a product similar in properties to that isolated in (b)1. Its analysis indicated an average chain length of 13 units. Calcd. for 13-glycine ethyl ester: C_2H_5O, 5.72; N, 23.11. Found: C_2H_5O, 5.52; N, 23.44.

3. In benzene at room temperature: 4 g. of glycine ethyl ester in 12 ml. of water-free benzene was kept for seventy days at room temperature. The 0.5 g. of precipitate was entirely soluble in hot water and gave both the biuret reaction and the picric acid test. The analytical data correspond to an equimolecular mixture of glycine tetrapeptide ethyl ester and glycine anhydride. *Anal.* Calcd. for this mixture: N, 21.62; C_2H_5O, 11.59; amino N, 3.60. Found: N, 21.47; C_2H_5O, 11.40; amino N, 3.55.

4. In boiling benzene: A solution of the same composition as that of (b)3 was refluxed for seven hours and then kept for seventy days at room temperature. The precipitate was treated as above with hot water and 150 mg. of material corresponding to a 17-glycine ethyl ester was obtained. Calcd. for 17-glycine ethyl ester: C_2H_5O, 4.43; N, 23.44. Found: C_2H_5O, 4.47; N, 23.67.

Total hydrolysis: 30 mg. of 17-glycine ethyl ester was refluxed with 2 ml. of 25% hydrochloric acid for six hours. After approximate neutralization with concentrated alkali, the *p*H of the solution was adjusted to 6.1 with 0.1 *N* sodium hydroxide. The amount of the amino nitrogen after hydrolysis was determined by titration according to Linderstrøm-Lang.[6] *Anal.* Calcd. for total hydrolysis of 17-glycine ester: amino N, 23.43. Found: N, 22.14.

5. No high condensation products have as yet been obtained under our experimental conditions from ether, dioxane and ethanol solutions. From the ethanol solution a precipitate was obtained which, on boiling with absolute alcohol, filtering, and cooling, gave a small number of colorless needle-like crystals. Analysis indicated a mixture of one molecule of glycine anhydride for every two molecules of "biuret base." *Anal.* Calcd. for this mixture: glycine anhydride, 17.2; N, 21.13; C_2H_5O, 13.58; amino N, 4.25. Found: glycine anhydride, 20.6; N, 21.19; C_2H_5O, 13.23; amino N, 4.23. Here, as well as in experiment (b)3, the products isolated may represent molecular compounds between the two components (*cf.* Pfeiffer).[7]

II. Poly-condensation of Glycine Methyl Ester.[8]—Glycine methyl ester hydrochloride was prepared by the method Johnson and Rinehart[9] used for obtaining glycine ethyl ester hydrochloride from methyleneaminoacetonitrile and methanol saturated with gaseous hydrogen chloride. As hot methanol dissolves considerable quantities of ammonium chloride, a recrystallization of the crude glycine methyl ester hydrochloride from ethanol is required to free it from the inorganic salt. The yield from 100 g. of methyleneaminoacetonitrile was 164.5 g. of pure glycine methyl ester hydrochloride.

The liberation of the free ester from its hydrochloride by the methods used for other glycine esters is not satisfactory; poor yields result. A more satisfactory method was worked out in collaboration with Dr. F. Stern using dry ammonia gas in place of sodium hydroxide: 10 g. of glycine methyl ester hydrochloride was suspended in 60 ml. of pure, water-free ether and a stream of carefully dried ammonia was passed with constant shaking at 0° through the suspension. Moisture was excluded. One to two hours later the solution of glycine methyl ester in ether was filtered from the suspended ammonium chloride, the latter washed with ether and the solution carefully dried over anhydrous sodium sulfate. The ether distillation was carried out with an effective column, to avoid loss of the ester. The free ester was then distilled *in vacuo* at 20 mm. and 45°; yield 4.8–5.0 g. of free ester.

(a) Poly-condensation of the Free Liquid Ester.—1. 0.5 g. of freshly prepared glycine methyl ester was kept in a closed vessel for a month at room temperature. The fraction insoluble in hot water corresponded on analysis to 18-glycine methyl ester. Calcd. for 18-glycine methyl ester: CH_3O, 2.93; N, 23.81. Found: CH_3O, 2.96; N, 23.42.

2. Nitrogen was passed through 1.5 g. of glycine methyl ester for twelve hours and the semi-solid reaction mixture allowed to stand at room temperature for one month. After fractionating in the way previously mentioned, about 50 mg. of material averaging 30 units was obtained. Calcd. for 30-glycine methyl ester: CH_3O, 1.78; N, 24.11. Found: CH_3O, 1.77; N, 23.85.

(b) Poly-condensation of the Free Ester in Solution.—1. In ether at room temperature: 1 g. of glycine methyl ester in 3 ml. of water-free ether was allowed to stand for three months; 250 mg. of a 27-glycine methyl ester was isolated by the usual procedure. Calcd. for 27-glycine methyl ester: CH_3O, 1.97; N, 24.06. Found: CH_3O, 1.90; N, 23.89.

2. In boiling xylene: 1.5 g. of glycine methyl ester in 4 ml. of water-free xylene was refluxed for four hours and

(6) Linderstrøm-Lang, *Z. physiol. Chem.*, **173**, 32 (1928).

(7) Pfeiffer, "Organische Molekülverbindungen," second edition, 1927, p. 319.

(8) The authors are indebted to Miss A. Saperstein for collaboration in this series of experiments.

(9) Johnson and Rinehart, THIS JOURNAL, **46**, 768, 1653 (1924).

then allowed to stand for three months at room temperature. About 200 mg. of 35-glycine methyl ester was obtained. Calcd. for 35-glycine methyl ester: CH_3O, 1.52; N, 24.17. Found: CH_3O, 1.54; N, 24.00.

In general the high glycine peptide methyl esters resemble the analogous ethyl esters but they seem to be slightly more soluble in hot water.[10]

III. Poly-condensation of Glycine Isobutyl Ester.—Glycine isobutyl ester hydrochloride was prepared by the method of Johnson and Rinehart[9]; 20 g. of aminoacetonitrile was refluxed for three hours with a mixture of 183 g. of dry isobutanol saturated with gaseous hydrogen chloride and 380 g. of isobutanol. The alcohol was distilled *in vacuo* from the filtered solution and the residue dried in a desiccator over sulfuric acid. The glycine isobutyl ester hydrochloride crystallizes after long standing as small, hygroscopic crystals; yield 40 g.

The free ester was liberated according to the method of Glenn and Skinner.[11] Dried nitrogen was passed through 5 g. of glycine isobutyl ester for thirty hours. The biuret reaction soon became positive. The cloudy liquid was allowed to stand at room temperature for about one and a half years, during which it became solid. By the usual treatment, 300 mg. of horny, water-insoluble product, free from anhydride, was obtained. It corresponded to a 10-glycine isobutyl ester. *Anal.* Calcd. for 10-glycine isobutyl ester: N, 21.74; C_4H_9O, 11.34. Found: N, 21.83; C_4H_9O, 10.81.

IV. Further Condensation of the Primary Condensation Products of Glycine Esters.—The linear polymers obtained in the above experiments were finely ground and kept at a temperature of about 130° for varying periods of time. They underwent further condensation which was demonstrated by a decrease in the alkoxy percentage. No glycine anhydride was formed during the operation (see Table I).

TABLE I

POLY-CONDENSATION OF 20-GLYCINE ETHYL ESTER AT 130°				
Time, days	0	4	9	34
C_2H_5O, %	3.99	3.26	2.51	1.86
Calcd. av. chain length	20	24	30	42
POLY-CONDENSATION OF 16-GLYCINE ETHYL ESTER AT 130°				
C_2H_5O, %	4.66	4.10	3.77	2.65
Calcd. av. chain length	16	18	20	30
POLY-CONDENSATION OF 30-GLYCINE METHYL ESTER AT 130°				
CH_3O, %	1.77		0.49	
Calcd. av. chain length	30		110	

V. Analytical Methods.—Qualitative tests were made on micro and semi-micro scales. All quantitative determinations were by micro methods. Methoxy and ethoxy determinations were made according to Vieböck[12] using hydrogen iodide of d. 1.96; the determination of isobutoxy groups was carried out as in the preliminary experiments of Furter.[13] It has been found that quantitative results are obtained by extending the heating of the substance in Furter's apparatus for four hours, with hydrogen iodide of d. 1.96, and with a stream of carbon dioxide of five bubbles per second.

Amino nitrogen determinations were made by a micro modification of Linderstrøm–Lang's titration.

The picric acid tests for glycine anhydride were carried out according to a modification of the usual procedure[14] by which the sensitivity was considerably increased. It may be mentioned here that this modification served also as a basis for the quantitative determination of the anhydride in the presence of amino acids, peptides or their esters. This method will be described in detail elsewhere.

Two ml. of a saturated solution of picric acid and 0.2 ml. of 0.1 *N* sodium hydroxide solution were added to 1 ml. of the solution to be tested and the mixture boiled for thirty seconds; a brownish-red color indicates the presence of anhydride. If amino acids, peptides or their esters are present, an equivalent amount of sodium hydroxide has to be added before carrying out the determination. The quantitative determination is carried out colorimetrically.

Discussion

The well-known stability of the free amino acids, which is explicable by their zwitterionic nature, induced us to choose their esters as the starting material.

From the above experiments we conclude that the following factors favor the formation of long-chain peptide esters: elevated temperatures, use of a solvent and the passing of indifferent gases through the esters. In a later paper we shall give an explanation for certain indications (not mentioned here) that carbon dioxide promotes the condensation.

According to the general conception of poly-condensation as formulated by Carothers[15] in particular, a linear chain structure is to be attributed to the products described here. This view is supported by the following experimental indications.

(1) It is possible to prove the presence of alkoxy and amino end-groups in the glycine condensation products, although they are insoluble in water and the usual solvents. The alkoxy group can be detected according to Zeisel,[16] while the presence of the amino group is indicated by the blue coloring of the suspended particles on boiling with ninhydrin.

(2) The results of quantitative hydrolysis as

(10) Pacsu, *Nature*, **144**, 551 (1939).
(11) Glenn and Skinner, THIS JOURNAL, **46**, 731 (1924).
(12) Vieböck and Brecher, *Ber.*, **63**, 3207 (1930).
(13) Furter, *Helv. Chim. Acta*, **21**, 1144 (1938), and private communication.
(14) Abderhalden and Komm, *Z. physiol. Chem.*, **139**, 180 (1924).
(15) Carothers, *Chem. Rev.*, **8**, 353 (1931).
(16) Zeisel, *Monatsh.*, **6**, 989 (1885); **7**, 406 (1886).

carried out on substance no. 1 and no. 7, prove that the high poly-condensation products are quantitatively built up of glycine units linked by peptide bonds. The presence of the latter is also indicated by the positive biuret reaction.

(3) The average chain length of the glycine polymers was ascertained by quantitative alkoxy determinations, as in the series of polymer homologs the alkoxy content varies distinctly with growing chain length. NH_2 determinations, although also indicative of the chain length, could not be carried out here owing to the insolubility of the glycine polymers.

(4) The results of alkoxy determinations were throughout in agreement with total nitrogen determinations (Kjeldahl). Moreover, as will be shown in the following paper, in the case of similar alanine poly-condensation products, soluble in water, the results of additional amino group determinations were throughout in very satisfactory agreement with those of alkoxy determinations and fully confirmed the conclusions drawn from the latter as regards the chain length.

Carbon and hydrogen determinations are not suitable means to assess the chain length; the differences in their values for the higher homologs lie within the experimental error.

It appears that high polymers can be obtained more easily and in better yields from the methyl ester than from isobutyl or the ethyl ester of glycine.

Our linear synthetic glycine products resemble in some properties the poly-amides obtained by Carothers[15] by the poly-condensation of di-amines and di-carboxylic acids.

Summary

On condensation under various conditions, glycine ethyl ester yielded a series of water insoluble polymers. The preparations were amorphous and contained ethoxyl in amounts corresponding, respectively, to 12-, 13-, 16-, 17- and 20-glycine peptide ethyl esters. From glycine methyl ester analogous preparations were obtained that contained methoxyl corresponding to 18-, 27- and 30-glycine methyl esters, respectively. Glycine isobutyl ester yielded a product of which the isobutoxy content corresponded to 16-glycine isobutyl ester.

On being heated to 130°, several of these products underwent further polymerization as indicated by decrease in alkoxy content. Preparations that corresponded in composition to 42-glycine ethyl ester and 110-glycine methyl ester were thus secured.

On being subjected to hydrolysis with acid, several of these polymers gave high yields of glycine suggesting that the polymers are in fact polypeptide esters. It appears that high polymers are more easily obtained from glycine methyl ester than from glycine ethyl and isobutyl esters.

The poly-condensation products described are (except the amorphous 12- and 13-glycine ethyl esters) horn-like, practically insoluble in water, in which they show characteristic swelling. They give positive ninhydrin and biuret reactions.

JERUSALEM, PALESTINE RECEIVED DECEMBER 19, 1941

[CONTRIBUTION FROM THE LABORATORY OF HIGH MOLECULAR CHEMISTRY, THE HEBREW UNIVERSITY]

Poly-condensation of α-Amino Acid Esters. II. Poly-condensation of Alanine Ethyl Ester[1]

BY MAX FRANKEL AND EPHRAIM KATCHALSKI

Alanine ethyl ester is a stable compound as compared with glycine ethyl ester. According to Fischer[2] and more recent literature, condensation to a peptide ester giving the biuret reaction has never been observed; moreover, even the formation of alanine anhydride, the so-called lactimide, takes place slowly.

Thus it seemed less probable that alanine ethyl ester would give polymers. We tried therefore to establish experimental conditions specially favorable to intermolecular reaction. Thus, although we obtained clear indications for poly-condensation of alanine ethyl ester on using experimental conditions similar to those described

(1) Certain minor errors in the manuscript as originally submitted were noted by the Editorial Board. Ordinarily these would have been brought to the attention of the authors prior to publication. International conditions at present are such that it appears impossible to follow this procedure except at the risk of indefinite postponement. The Editor has therefore taken the responsibility to make any corrections which appeared to be unquestionably required.—THE EDITOR.

(2) Fischer, *Ber.*, **34**, 433 (1901).

for glycine ester,[3] it was found advantageous to carry out the poly-condensations with the liquid ester under reduced pressure in order to facilitate the splitting off of the ethanol formed during the poly-condensation.

In these experiments various high alanine peptide esters along with alanine anhydride were obtained. The lowest peptide ester hitherto isolated from the condensation mixtures was the alanine tetrapeptide ethyl ester. This hitherto unknown compound represents the alanine analog of the Curtius biuret base—the glycine tetrapeptide ethyl ester. Like the latter it gives a positive biuret reaction with pink-red color. It is soluble in cold water, ether and other organic solvents in which the corresponding glycine peptide ester does not dissolve. As will become clear later, the solubility of alanine peptide esters is in general greater than that of the corresponding glycine polypeptide esters.

The higher alanine peptide esters obtained from alanine ethyl ester corresponded in average chain length with 10, 14 and 16 units, respectively.

These compounds were isolated by molecular distillation from the reaction mixture, from which the ether soluble part, containing unchanged alanine ethyl ester and the alanine tetrapeptide ethyl ester, was previously removed. During the molecular distillation the alanine anhydride was distilled and the remaining fraction consisted only of the high alanine peptide esters. The separation of the latter had to be effected by this technique as the reaction mixtures were entirely soluble in water and could not be fractionated by differences in the solubility of the various condensation products.

The isolated high alanine peptide ethyl esters are insoluble in ether but soluble in water. Their solutions give a positive ninhydrin reaction and an immediate positive biuret reaction with violet color.

As the carrying out of NH_2-determinations was rendered possible by the solubility of the high alanine peptide esters in water, both the alkoxy- and the amino nitrogen groups were determined. The values for chain length calculated in every case from each of these two independent determinations were identical. Total nitrogen content was also in agreement with the formulas derived from the other data.

The determination of the molecular weight of one representative polypeptide ester, the 10-alanine ethyl ester, by the micro method of Barger[4] showed very satisfactory agreement between the molecular weight found (750) and calculated (756).

Another proof for the structure of the poly-condensation products is furnished by hydrolysis and subsequent quantitative determination of the free alanine formed. The results obtained show that the poly-condensates are built up quantitatively from alanine units linked by —CONH— bonds.

It has been found that the primary polymerization products isolated from the reaction mixtures undergo further poly-condensation at 150°. In this way from 14-alanine ethyl ester, polypeptide esters averaging 17, 19 and 23 units were obtained.

Experimental

Alanine ethyl ester was prepared according to Fischer.[2] Freshly distilled ester was used throughout. For reasons explained in the theoretical part the condensations were carried out in closed vessels at reduced pressure. The temperature was varied between room temperature to about 80°.

Poly-condensation at Room Temperature.—Three grams of freshly distilled alanine ethyl ester was kept in a sealed test-tube under reduced pressure (15 mm.) at room temperature for five months. During standing a precipitate formed which finally filled the whole liquid. After opening the test-tube the mixture gave a strong picric acid test and a positive biuret reaction. The mixture dissolved entirely in water. It was repeatedly treated with ether till the latter gave no positive biuret reaction. The ether solution was in each case separated by centrifuging from the insoluble part and finally the ether extracts combined.

1. Separation of Alanine Tetrapeptide Ethyl Ester from Lower Products.—The ether from the combined extracts was evaporated in a desiccator *in vacuo* at room temperature with rigid exclusion of water, the residue dissolved in 1 ml. of dry ethyl acetate and to the clear solution 2 ml. of petroleum ether was added. The oily precipitate formed was separated from the liquid by decantation, washed with petroleum ether and dried in a desiccator *in vacuo* over sulfuric acid and soda-lime.

The dried semisolid oil (150 mg.) shows positive ninhydrin and biuret reactions, the latter with a pink-red color. On analysis it agreed with alanine tetrapeptide ethyl ester. *Anal.* Calcd. for $C_{14}H_{26}O_5N_4$: N, 16.95; amino N, 4.24; C_2H_5O, 13.64. Found: N, 16.62; amino N, 4.20; C_2H_5O, 13.76.

In order to convert the free tetrapeptide ester into its hydrochloride, it was treated with 2 ml. of absolute ethanol previously saturated with gaseous hydrogen chloride. The residue obtained after drying *in vacuo* was treated once more in the same way. Finally a very hygroscopic semisolid product was obtained which by its chlorine content proved to be alanine tetrapeptide ethyl ester hydro-

(3) Frankel and Katchalski, THIS JOURNAL, **64**, 2264 (1942).

(4) Barger, *J. Chem. Soc.*, **85**, 286 (1904); Barger, *Ber.*, **37**, 1754 (1904).

chloride. *Anal.* Calcd. for $C_{14}H_{26}O_5N_4 \cdot HCl$: Cl, 9.68. Found: Cl, 9.53.

From the solution in petroleum ether only alanine ethyl ester could be isolated.

Alanine tetrapeptide ethyl ester hydrochloride prepared from alanine tetrapeptide synthesized in the usual way was found to be identical with the hydrochloride described above. The free alanine tetrapeptide ethyl ester liberated from this ester hydrochloride was identical with the corresponding product obtained by condensation. It dissolves in ether, alcohol and ethyl acetate. From the latter it is precipitated by addition of petroleum ether.

2. Separation of the Higher Alanine Condensation Products from Alanine Anhydride.—The residue remaining after treatment of the primary reaction mixture with ether dissolved in water, showing a slight alkaline reaction. It gave a strong color reaction with picric acid, indicating the presence of anhydride, and blue-violet biuret reaction, indicating the presence of higher peptide esters. Separation between the anhydride and the higher linear poly-condensation products was carried out by molecular distillation. Alanine anhydride distilled over at an external bath temperature of 140° and a pressure of about 10^{-3} mm.; 1.0 g. of alanine anhydride was obtained; melting point 270°. *Anal.* Calcd. for $C_6H_{10}O_2N_2$: N, 19.70; amino N, 0. Found: N, 19.92; amino N, 0.

The amorphous residue from the molecular distillation was free from alanine anhydride; it gave a negative picric acid test and a blue-violet biuret reaction. It was soluble in water and in 80% alcohol; it showed a distinct alkaline reaction. According to analysis it is 10-alanine ethyl ester. *Anal.* Calcd. for 10-alanine ester: N, 18.52; amino N, 1.85; C_2H_5O, 5.95. Found: N, 18.75; amino N, 1.41; C_2H_5O, 5.67.[5]

The molecular weight of this compound was determined by the micro method of Barger[4] using 80% alcohol as solvent and azobenzene as a standard. By this method it has been determined that the molar concentration of a solution containing 10.5 mg. of 10-alanine ethyl ester in 1.5 ml. of solvent is 0.00933; the molecular weight found from these data is 750, the molecular weight calcd. for the 10-alanine ester $C_{32}H_{56}O_{11}N_{10}$, 756; for the 13-alanine ester, 970.

Poly-condensation at 40°.—Three grams of freshly distilled alanine ethyl ester was allowed to undergo condensation as described above except that the temperature was kept at 40°. The separation of the different fractions was carried out as above. 1.1 g. of alanine anhydride, 120 mg. of alanine tetrapeptide ethyl ester and 200 mg. of high poly-condensation product, which proved on analysis to correspond with 16-alanine ethyl ester, were obtained. *Anal.* Calcd. for $C_{50}H_{86}O_{17}N_{16}$: N, 18.95; amino N, 1.18; C_2H_5O, 3.81. Found: N, 18.90; amino N, 1.32; C_2H_5O, 3.84. In its properties the 16-alanine ethyl ester resembled the 10-alanine ethyl ester.

Poly-condensation at 80°.—Three grams of freshly distilled alanine ethyl ester was kept *in vacuo* at a temperature of 80° for one month and then left for about four months at room temperature. The semi-solid substance thus formed was treated as above: 0.8 g. of alanine anhydride; 100 mg. of alanine tetrapeptide ethyl ester and 300 mg. of the higher poly-condensation product were obtained. The latter is according to analysis 14-alanine ethyl ester. *Anal.* Calcd. for $C_{44}H_{76}O_{15}N_{14}$: N, 18.85; amino N, 1.31; C_2H_5O, 4.32. Found: N, 18.47; amino N, 1.29; C_2H_5O, 4.20. The 14-alanine ethyl ester resembles its linear ester homologs mentioned above.

Quantitative Hydrolysis of 14-Alanine Ethyl Ester.—6.450 mg. of the substance, which according to analysis was 14-alanine peptide ethyl ester, was dissolved in 1 ml. of hydrochloric acid (0.2 ml. of concd. HCl in 0.8 ml. of water) and refluxed for eight hours in a flask with ground-in condenser of 2 ml. content. In order to avoid bumping a few platinum tetrahedra were added.

The determination of the free alanine formed by hydrolysis was carried out according to Friedemann and Kendall.[6] The hydrolyzate was diluted in a 50-ml. flask to 17.5 ml. The flask was kept on a boiling water-bath, and within twenty minutes 3 ml. of sodium nitrite (2.5 g. in 100 ml. of water) was added, and within an additional twenty minutes 3 ml. of urea (7.5 g. in 100 ml. of water). The total solution was brought to 50 ml. and the amount of lactic acid determined according to Friedemann and Kendall using 0.005 *N* iodine solution. *Anal.* Calcd. amount of alanine formed after hydrolysis of 6.45 mg. of 14-alanine ethyl ester: 7.72 mg. Found: 7.20 mg. From the results the conclusion may be drawn that the substance which underwent hydrolysis is built up quantitatively of alanine units held together by —CONH— links. The hydrolysis confirms therefore the other analytical results.

Further Poly-condensation of 14-Alanine Ethyl Ester.—14-Alanine ethyl ester was finely ground and kept at a temperature of about 150° for various periods of time. The progress of condensation was demonstrated by the decrease in alkoxy percentage. No anhydride was found during the operation.

TABLE I

POLY-CONDENSATION OF 14-ALANINE ETHYL ESTER ON KEEPING AT 150°

Time, days	0	5	15	30
C_2H_5O, %	4.20	3.67	3.30	2.66
Calcd. chain length	14	17	19	23

Enzymatic Experiment.—The action of pancreatin was tried on the 16-alanine polymer but the results indicated none or very little enzymatic hydrolysis. These peptides are, however, so far removed from the type of structure to be found in naturally occurring proteins that this failure to observe enzyme action has little bearing on the question of the type of linkage present in the polymer.

Summary

Alanine ethyl ester kept in sealed tubes at reduced pressure and at various temperatures polymerized to compounds whose average size corresponded to 10, 14 and 16 alanine ethyl ester units.

(5) Note by the Editor: These analytical data for nitrogen and amino nitrogen agree better with the formula for a 13-alanine ethyl ester ($C_{41}H_{71}N_{13}O_{14}$). This formula would require N, 18.78 and N in NH_2, 1.44. Similarly, the data for the ethoxy group would agree more closely with an 11-alanine ethyl ester ($C_{35}H_{55}N_{11}O_{12}$) which would require C_2H_5O, 5.44.

(6) Friedemann and Kendall, *J. Biol. Chem.*, **82**, 23 (1929); Friedemann, *J. Inf. Diseases*, **47**, 171 (1930).

14-Alanine ethyl ester underwent further polycondensation at 150° to compounds corresponding to 17, 19 and 23 alanine ethyl ester units.

These alanine peptide esters are, unlike their glycine analogs, soluble in water.

JERUSALEM, PALESTINE RECEIVED DECEMBER 19, 1941

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Condensations. XVII. The Acylation of the Anions of Certain Alkyl Esters with Phenyl Esters. A New Method for the Preparation of Ethyl Propionylacetate and Certain Related β-Keto Esters[1,2]

BY B. ABRAMOVITCH AND CHARLES R. HAUSER

The difficulty in effecting satisfactorily the Claisen condensation between two different alkyl esters both of which have α-hydrogen is well known. Even when the ester to be acylated is first converted largely into its anion (or sodium enolate) by means of sodium triphenylmethyl and the anion then treated with the acylating ester, a mixture of β-keto esters is generally obtained.[3] Evidently, the ester anion reacts with the α-hydrogen of the second ester more readily than with its carbonyl group, resulting in a hydrogen exchange to yield a mixture of two different ester anions and two different esters from which four β-keto esters might be formed.

Ester anions are acylated by acid chlorides without first undergoing the hydrogen exchange but with the anion of ethyl acetate (or other ester having two α-hydrogens) the β-keto ester first formed is further acylated by the acid chloride yielding mainly the diacylacetate.[4] Although the latter can be satisfactorily ammonolyzed back to the monoacylacetate the over-all yield is generally low. Thus, when the anion of ethyl acetate was treated with propionyl chloride and the resulting dipropionylacetate ammonolyzed, the over-all yield of ethyl propionylacetate was only 16%.

Obviously a suitable reagent for the direct preparation of monoacylacetates, $RCOCH_2CO_2C_2H_5$, should be one which would acylate the anion of ethyl acetate without first undergoing the hydrogen exchange, but one which would not acylate the monoacylacetate. Such an acylating reagent should presumably have a carbonyl group which is more reactive than that of an alkyl ester but one not as reactive as that of an acid chloride. It seemed possible that phenyl esters (or substituted phenyl esters) might serve as suitable acylating reagents, since, as measured by the rates of alkaline hydrolyses, the carbonyl group of phenyl acetate is approximately thirteen times as reactive as that of ethyl acetate,[5] yet phenyl acetate does not appear to be sufficiently reactive to acylate the anion of ethyl acetoacetate.[6] In agreement with these considerations, treatment of the anion of ethyl acetate with phenyl propionate apparently yielded ethyl propionylacetate,[6] but unfortunately the β-keto ester could not be separated from the phenol which was also produced in the reaction. When *p*-diphenyl propionate was used as propionylating reagent, however, the ethyl propionylacetate was readily separated from the relatively high-boiling by-product, *p*-hydroxydiphenyl. The reactions, including the formation of the ester anion by means of the triphenylmethyl ion, and the conversion of the β-keto ester into its anion, may be represented as follows.

$$CH_3CO_2C_2H_5 + {}^-C(C_6H_5)_3 \longrightarrow (CH_2CO_2C_2H_5)^- + HC(C_6H_5)_3$$

$$C_2H_5CO_2C_6H_4C_6H_5 + (CH_2CO_2C_2H_5)^- \longrightarrow C_2H_5COCH_2CO_2C_2H_5 + {}^-OC_6H_4C_6H_5$$

$$C_2H_5COCH_2CO_2C_2H_5 + (CH_2CO_2C_2H_5)^- \longrightarrow (C_2H_5COCHCO_2C_2H_5)^- + CH_3CO_2C_2H_5$$

Using molecular equivalents of ethyl acetate, sodium triphenylmethyl and *p*-diphenyl propionate, the yield of practically pure ethyl propionylacetate was 44% based on the sodium triphenylmethyl. It can be seen from the equations that although the ethyl acetate first reacts with the

(1) This paper has been constructed from portions of a Thesis presented by B. Abramovitch, in partial fulfillment of the requirements for the Ph.D. degree at Duke University.

(2) This investigation was supported in part by a grant from the Duke University Research Council.

(3) Hudson and Hauser, THIS JOURNAL, **63**, 3158 (1941).

(4) It should be pointed out that the acylation of disubstituted acetic acid esters such as ethyl isobutyrate gives good yields of β-keto esters of the type $RCOC(R'R'')CO_2C_2H_5$ (ref. 3, p. 3159).

(5) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 211.

(6) Unpublished observations by B. E. Hudson in this Laboratory.

equivalent of the base to form the ester anion, one-half of the ester is regenerated when the ethyl propionylacetate is converted into its anion (third step). The equivalent of *p*-diphenyl propionate used is twice the amount theoretically required; however, this excess is desirable, since in an experiment using one-half of an equivalent, the ethyl propionylacetate obtained was contaminated with some ethyl acetoacetate. Although a relatively large amount of sodium triphenylmethyl is required, this method of preparation of ethyl propionylacetate appears to be more satisfactory than either of the two commonly used methods. In one of these, involving the reaction of ethylmagnesium bromide with ethyl cyanoacetate, yields ranging from 12[7] to 60%[8] have been reported, while, in the other, involving the ammonolysis of ethyl propionylacetoacetate,[9] a mixture of ethyl propionylacetate and ethyl acetoacetate is obtained which is difficult to separate. In their book on pyrroles, Fischer and Orth[10] regard the second method as better than the Grignard method even though the yield of ethyl propionylacetate is only 10–12%.

In a similar manner, the anion of *n*-amyl acetate has been propionylated with phenyl propionate giving a 30% yield (based on the sodium triphenylmethyl) of essentially pure *n*-amyl propionylacetate; this β-ketoester boils sufficiently high to be separated by distillation from the phenol which is also formed.

$$C_2H_5CO_2C_6H_5 + (CH_2CO_2C_5H_{11})^- \longrightarrow C_2H_5COCH_2CO_2C_5H_{11} + {}^-OC_6H_5$$

Also, in a similar manner, the anion of ethyl isovalerate has been propionylated with phenyl propionate to give ethyl α-isopropylpropionylacetate.

$$C_2H_5CO_2C_6H_5 + [(CH_3)_2CHCHCO_2C_2H_5]^- \longrightarrow C_2H_5COCHCO_2C_2H_5 + {}^-OC_6H_5$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad CH(CH_3)_2$$

The by-product, phenol, was readily separated by distillation from the ethyl α-isopropylpropionylacetate, but it was not possible to remove the excess of the phenyl propionate in this manner. The β-keto ester was freed from most of the phenyl propionate by shaking the mixture several times with alkali at room temperature. This treatment hydrolyzed the phenyl propionate to phenol (which was removed as its salt) but did not appreciably affect the β-keto ester, which was obtained somewhat impure in 58% yield. The product on ketonic hydrolysis gave ethyl isobutyl ketone in 50% yield. Ethyl α-isopropylpropionylacetate has been prepared previously by Blaise[11] employing the Reformatsky reaction between ethyl α-bromoisovalerate and propionitrile in which the yield reported is 25–50%.

In connection with the work described above, several unsuccessful attempts have been made to prepare ethyl propionylacetate and related compounds by modifications of certain of the common methods. It is not surprising that the reaction of ethylmagnesium bromide with ethyl cyanoacetate is not very satisfactory for the preparation of ethyl propionylacetate, since the Grignard reagent can attack not only the cyanide group leading to the β-keto ester, but also the ester group or the methylenic hydrogens.[7] In an experiment designed to hinder the attack of the Grignard reagent on the ester group, ethylmagnesium bromide was treated with *t*-butyl-cyanoacetate, but no appreciable amount of *t*-butyl propionylacetate was obtained; apparently the Grignard reacted mainly with the methylenic hydrogen.

The method of Wallingford and co-workers[12] for the preparation of β-keto esters from ketones and ethyl carbonate in the presence of sodium ethoxide is apparently not suitable for the synthesis of ethyl propionylacetate because the ketone, methyl ethyl ketone, undergoes self-condensation too readily. In an attempt to avoid the self-condensation of the ketone, we have converted methyl ethyl ketone into its anion by means of sodium triphenylmethyl and treated the anion immediately with ethyl carbonate; however, the ketone still self-condensed and 50% of the ethyl carbonate was recovered.

Experimental

***p*-Diphenyl Propionate.**—This ester was prepared by a modification of the method used by Chattaway[13] for the preparation of phenyl esters. *p*-Hydroxydiphenyl (Eastman Kodak Co.) (57.5 g., 0.338 mole) was dissolved in a hot solution of 20.3 g. of sodium hydroxide and 2200 cc. of water. The solution was cooled to 15° and 700 g. of crushed ice added, the temperature thus being lowered to approximately 5°. Propionic anhydride (Eastman) (55.2 g., 54.1 cc., 0.425 mole) was then rapidly added to the solution (contained in a large Pyrex bottle), and the

(7) Breckpot, *Bull. soc. chim. belg.*, **32**, 386–97 (1923).
(8) Willstätter and Clarke, *Ber.*, **47**, 298 (1914).
(9) Bouveault and Bongert, *Bull. soc. chim.*, [3] **27**, 1089 (1902).
(10) Fischer and Orth, "Die Chemie des Pyrrols," Vol. I, Akademische Verlagsgesellschaft, Leipzig, 1940, p. 404.
(11) Blaise, *Compt. rend.*, **132**, 479 (1901).
(12) Wallingford, Homeyer and Jones, THIS JOURNAL, **63**, 2252 (1941).
(13) Chattaway, *J. Chem. Soc.*, 2495 (1931).

mixture shaken vigorously for thirty seconds. The crude, pasty product was collected on an 8-inch Büchner funnel and sucked dry. The crude product was shaken in a separatory funnel with 1200 cc. of ether, the aqueous layer removed, the ether solution washed with three 200-cc. portions of 8% sodium hydroxide solution, and dried over anhydrous sodium sulfate followed by Drierite. Ether was distilled, final traces being removed by means of a water pump, leaving a fairly pure crystalline mass of *p*-diphenyl propionate, melting at 90–92°. After one recrystallization from absolute methanol (99%) there was obtained 55.5 g. (73% yield) of pure material, m. p. 92–92.5°.

Anal.[14] Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.79; H, 6.03.

Ethyl Propionylacetate.—A calibrated 4-liter Pyrex bottle was fitted with a four-hole rubber stopper provided with an inlet tube for dry nitrogen, a mechanical stirrer, a 50-cc. dropping funnel (for ethyl acetate), and a wide glass tube connected to a large dropping funnel (for an ether solution of *p*-diphenyl propionate). The air in the bottle was displaced with nitrogen and 1200 cc. (0.36 mole) of a 0.3 molar sodium triphenylmethyl solution (prepared and analyzed as described previously)[3] transferred to the bottle. To the vigorously stirred solution, chilled in an ice-bath at −5°, was added 31.7 g. (0.36 mole) of ethyl acetate (b. p. 76.9–77.0°), the color of the sodium triphenylmethyl disappearing immediately. After twenty seconds the cold (0°) ether solution (1700 cc.) of *p*-diphenylpropionate (81.4 g., 0.36 mole) was added rapidly (one minute). After the contents in the bottle were stirred in the cold for one hour and forty-five minutes, the bottle was removed from the cold bath, stoppered with a ground glass stopper, vigorously shaken and allowed to warm up to 15° (one-half hour). Glacial acetic acid (40 cc.) was then added, the mixture extracted with water followed by a 10% sodium carbonate solution. The ether solution was dried over Drierite and the solvent distilled. The residue was distilled *in vacuo*, collecting 15.0 g., b. p. up to 160° at 10 mm. Upon refractionation from a modified Claisen flask equipped with a twelve-cm. Vigreux column the distillate gave 0.8 g., b. p. 70–91° at 17 mm., and 11.5 g. (44% yield based on the sodium triphenylmethyl) of ethyl propionylacetate, b. p. 91–92° at 17 mm.[15]; a mid-fraction was taken out for analysis.

Anal.[14] Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.17; H, 8.32.

The product was also characterized by converting it into 1-phenyl-3-ethyl-pyrazolone-5, m. p. 100°,[15] and 3-ethyl-pyrazolone-5-carbamyl-1, m. p. 197°.[15]

On repeating the experiment under similar conditions but using 0.21 mole of *p*-diphenyl propionate to 0.38 mole each of sodium triphenylmethyl and ethyl acetate there was obtained a mixture of ethyl acetoacetate and ethyl propionylacetate.

Ethyl propionylacetate has also been prepared from the anion of ethyl acetate and propionyl chloride through the dipropionylacetate. Directions using a large excess of propionyl chloride have been described previously.[3] In the present investigation 38.7 g. (0.443 mole) of ethyl acetate was treated at 0° with 0.443 mole of sodium triphenylmethyl, and after twenty seconds the ester anion treated with 0.443 mole of propionyl chloride. After fifteen minutes 5 cc. of glacial acetic acid was added and the reaction mixture worked up in the usual manner. There was obtained 13.5 g. (32%) of ethyl dipropionylacetate, b. p. 98–102° at 10 mm., mainly at 100–102°. The dipropionylacetate was ammonolyzed in 50% yield to ethyl propionylacetate, b. p. 91–92° at 17 mm.; yield 50%; over-all yield, 16%; m. p. of phenylpyrazolone, 100°.[15]

***n*-Amyl Propionylacetate.**—A solution (1240 cc., 0.324 mole) of sodium triphenylmethyl was transferred to a calibrated 2-liter Pyrex bottle, fitted with a mechanical stirrer, dropping funnel, and a tube delivering a slow stream of dry nitrogen. To the vigorously stirred solution, cooled in an ice–salt-bath at −10°, was added 42.7 cc. (37.6 g., 0.324 mole) of *n*-amyl acetate (b. p. 147–148°). The color was discharged within thirty seconds and a precipitate was formed. After one minute 48.6 g. (0.324 mole) of phenyl propionate (b. p. 103–104° at 21 mm.) was added. Stirring was continued in the cold for one and one-half hours and the bottle was then stoppered and allowed to warm up to 15° (two hours). Glacial acetic acid (32 cc.) dissolved in 200 cc. of ice-water was then added. The aqueous layer was removed and the ether layer washed with 10% sodium carbonate solution, dried, and the solvent distilled. The residue was distilled *in vacuo* collecting up to 160° at 10 mm. Fractionation of the distillate through a twelve-inch Vigreux column yielded 15 g. (40%) of *n*-amyl acetate (b. p. 60–72° at 25 mm., mainly at 62–64°), 36.0 g. (b. p. 80–93° at 10 mm.) consisting of a mixture of phenol and phenyl propionate, 3.0 g. (b. p. 93–113° at 10 mm., mainly at 98–100°), and 9.0 g. (30% yield based on the sodium triphenylmethyl) of *n*-amyl propionylacetate, b. p. 113–115° at 10 mm.

Anal.[14] Calcd. for $C_{10}H_{18}O_3$: C, 64.5; H, 9.90. Found: C, 65.0; H, 9.89.

The *n*-amylpropionylacetate was converted into 1-phenyl-3-ethylpyrazolone-5, m. p. 100°.[15]

On repeating the experiment using the same proportions of reagents but allowing the reactants to stand at room temperature (28°) for seven hours there was obtained a small yield of *n*-amyl propionylacetate contaminated with some *n*-amyl acetoacetate.

Ethyl α-Isopropylpropionylacetate.—To one liter (0.327 mole) of sodium triphenylmethyl solution at room temperature (27°) was added 49 cc. (42.5 g., 0.327 mole) of ethyl isovalerate (b. p. 134–135°). After shaking the mixture for two minutes the color changed to a dark orange. Forty-nine grams (0.327 mole) of phenyl propionate was then added and the mixture allowed to stand at room temperature for twenty hours. Glacial acetic acid (33 cc.) dissolved in 200 cc. of ice water was added. The aqueous layer was washed with two 75-cc. portions of 10% sodium carbonate solution, dried, and the solvent distilled. The residue was distilled *in vacuo*, collecting 73.5 g. of distillate boiling from 50° at 60 mm. to 180° at 20 mm. The distillate on fractionation through a twelve-inch Vigreux column yielded 15.8 g. (37%) of ethyl isovalerate (b. p. 43–65° at 21 mm., mainly at 43°), 22.6 g. (b. p. 65–102° at 21 mm.) of phenol and phenyl propionate, and

(14) Analysis by S. Gottlieb, Columbia University, New York, N. Y.

(15) Blaise, *Compt. rend.*, **132**, 978 (1901).

27.2 g. (b. p. 102–118° at 21 mm., mainly at 105–110°) consisting of a mixture of phenyl propionate and ethyl α-isopropyl propionylacetate. An ether solution (150 cc.) of this mixture was shaken with ten 50-cc. portions of 10% sodium hydroxide solution, the ether solution dried, and distilled. The residue on fractionation through a twelve-inch Vigreux column yielded 18.3 g. (58% yield based on the sodium triphenylmethyl) of ethyl α-isopropyl propionylacetate, b. p. 107–109° at 21 mm. (b. p. reported in the literature, 107–108° at 21 mm.[11]). An analysis (calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 68.24; H, 8.12) indicated that the β-keto ester was still contaminated with phenyl propionate. The product (10.6 g.) was hydrolyzed by refluxing for eight hours with a mixture of 30 cc. of glacial acetic acid, 3 cc. of concentrated sulfuric acid and 3 cc. of water. There was obtained 3.3 g. (50% yield) of ethyl isobutyl ketone, b. p. 133–135°[16] (semicarbazone, m. p. 128–129°[16]).

t-Butyl Cyanoacetate with Ethylmagnesium Bromide.—t-Butyl cyanoacetate was prepared[17] in 32% yield from t-butyl α-bromoacetate and potassium cyanide in methanol solution.

Anal.[14] Calcd. for $C_7H_{11}O_2N$: N, 9.92. Found: N, 9.67.

t-Butyl α-bromoacetate was obtained in 70% yield by treating t-butyl alcohol with α-bromoacetyl bromide in the presence of dimethylaniline.[18]

Sixteen grams (0.11 mole) of t-butyl cyanoacetate (b. p. 107–108° at 23 mm.) dissolved in 25 cc. of dry ether was added, with stirring, during one hour to 0.25 mole of cold (0°) ethylmagnesium bromide solution. At first, addition of the nitrile caused the formation of a precipitate and the evolution of gas. The mixture was stirred at room temperature and then allowed to stand for twelve hours. On working up the reaction mixture, the products obtained consisted of a mixture boiling over a very wide range with considerable tarry material.

(16) Douris, *Compt. rend.*, **157**, 57 (1913).

(17) The procedure was similar to that used by Noyes for the preparation of ethyl cyanoacetate, THIS JOURNAL, **26**, 1545 (1904).

(18) For the preparation of t-butyl acetate by this method, see Norris and Rigby, THIS JOURNAL, **54**, 2097 (1932).

Methyl Ethyl Ketone with Ethyl Carbonate.—Methyl ethyl ketone (14.4 g., 0.2 mole) (b. p. 80°) was added to 0.2 mole of sodium triphenylmethyl solution cooled in a bath at −5°. The color changed immediately to a light orange. After twenty seconds 23.5 g. (0.2 mole) of ethyl carbonate (b. p. 125.5–126°) was introduced. The bottle containing the mixture was shaken vigorously and allowed to stand in the cold bath, after which it was allowed to warm up (1 hour) to room temperature (30°). The reaction mixture was worked up in the usual manner, and upon fractionation of the products, first at atmospheric pressure and then *in vacuo*, there was obtained 2.4 g. of unreacted ketone (b. p. 75–85°), 11.7 g. (50% recovery) of ethyl carbonate (b. p. 122–127°) and 3.9 g. of 3-methyl heptene-3-one-5, b. p. 60–75° at 20 mm., mainly at 65–70° (reported b. p. 66–68° at 20 mm.).[19] The ketone was converted into the semicarbazone, m. p. 113–114°; reported m. p. 114–115°.[19] The 65–70° fraction on redistillation gave a small fraction which gave a positive ferric chloride test indicating the presence of some β-keto ester.

Summary

1. A study has been made of the use of phenyl esters as reagents for the acylation of the anions of certain alkyl esters.

2. Ethyl propionylacetate has been prepared by the acylation of the anion of ethyl acetate with p-diphenylpropionate.

3. n-Amyl propionylacetate and ethyl α-isopropyl propionylacetate have been prepared from phenyl propionate and the anions of n-amyl acetate and of ethyl isovalerate, respectively.

4. Unsuccessful attempts were made to prepare t-butyl propionylacetate from t-butyl cyanoacetate and ethylmagnesium bromide, and ethyl propionylacetate from the sodium enolate of methyl ethyl ketone and ethyl carbonate.

(19) Bodroux and Taboury, *Compt. rend.*, [11] **149**, 422 (1909).

DURHAM, NORTH CAROLINA RECEIVED JUNE 26, 1942

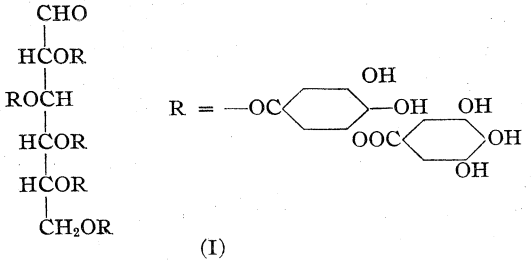
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NORTH CAROLINA]

Chemical Constitution and the Tanning Effect. I. Simple Esters and Polyesters of Gallic Acid

BY ALFRED RUSSELL AND W. G. TEBBENS, JR.

Leather is the imputrescible substance that is obtained through treatment of easily putrescible animal protein by various materials. The tanning effect of certain metallic salts (chromium, iron, zirconium, etc.), of aldehydes (chiefly formaldehyde), of various drying oils and, most important of all, natural organic tanning materials, is well established. However, up to the present, no serious attempt has been made to relate the characteristic leather forming properties of any of these with their chemical constitution. It is now proposed to investigate the relation between chemical constitution and the tanning effect of the natural organic tannins through the preparation of relatively simple compounds of known constitution that have tanning properties and produce leather similar to "vegetable" leather in quality. "Vegetable" leather is very distinctive in charac-

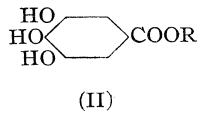
ter and in the present work leather made with pure gallotannin (tannic acid) will be used as a standard for comparison. Emil Fischer[1] proposed that pure gallotannin was penta-*m*-digalloyl glucose (represented in the aldehyde form I).



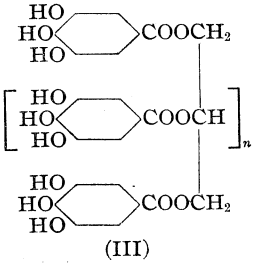
(I)

Incidentally, most natural tannins do not have this structure[2] but are related to the natural plant pigments—chalcones, flavones, anthocyanins, etc.

Using the gallotannin molecule as a model, it is proposed to prepare various phenolic materials of definite constitution and, through actual tanning tests, to measure their tanning properties. The present communication describes the preparation and testing of various simple esters (type formula II) and polyesters (type formula III) of gallic acid.



(II)



(III)

The simple esters of gallic acid were prepared from gallic acid and an excess of the appropriate alcohol using anhydrous hydrogen chloride according to the accepted procedure.[3,4,5]

The polyesters were prepared by condensation of triacetylgalloyl chloride with the appropriate polyhydric alcohol in the presence of quinoline and chloroform, followed by cautious deacetylation with dilute sodium hydroxide.[1] The preparation of such compounds tested as are already known is not included.

The results of tanning tests are as follows: *Very good tannage.* Gallotannin. *No tannage.* Gallic acid, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *n*-amyl, *n*-hexyl gallates, ethylene glycol, glycerol, *d,l*-erythritol, *d*-arabitol sorbitol. *Poor tannage.* Ethylene glycoldigallate, glycerol trigallate. *Fair tannage.* *d,l*-Erythritol tetragallate, *d*-arabitol pentagallate, mannitol hexagallate, sorbitol hexagallate.

Experimental

The simple esters of gallic acid were made by passing anhydrous hydrogen chloride into a solution of gallic acid in an excess of the appropriate alcohol until saturated. The mixture was then refluxed for four hours, after which time the excess alcohol was removed under reduced pressure. The residue was then extracted with anhydrous benzene and the product recrystallized from the same solvent.[3-7] An alternative recrystallization procedure for the lower esters was extraction of the residue with hot acetone and addition, with mechanical stirring, of the acetone extract to a large excess of ice-water. The crystalline product so formed contained water of hydration.

n-Amyl Gallate.—Prepared in 58% yield from 100 g. of pure anhydrous gallic acid and 466 g. of redistilled *n*-amyl alcohol. The ester formed fine, white plates after being recrystallized twice from anhydrous benzene, m. p. 127°. It was soluble in benzene, chloroform, acetone, alcohol and ether, and very slightly soluble in water. A blue-black color was given with ferric alum solution. *Anal.* Calcd. for $C_{12}H_{16}O_5$: C, 60.0; H, 6.71. Found: C, 59.9; H, 6.77.

n-Hexyl Gallate.—Prepared in 48% yield from 94 g. of pure anhydrous gallic acid and 511 g. of redistilled *n*-hexyl alcohol. The compound gave white plates from anhydrous benzene after two recrystallizations, m. p. 92°. The ester was soluble in benzene, chloroform, acetone, alcohol and ether and was insoluble in petroleum ether. The ester gave a blue-black coloration with ferric alum solution. *Anal.* Calcd. for $C_{13}H_{18}O_5$: C, 61.4; H, 7.14. Found: C, 60.8; H, 7.21.

The polyesters were prepared by the method developed by Fischer[1] from the appropriate anhydrous, finely powdered polyhydric alcohol and triacetylgalloyl chloride in chloroform and quinoline. The acetyl derivatives paralleled those of Fischer in all cases.

Triacetylgalloyl Chloride.—The method used for the preparation of triacetylgallic acid paralleled that of Fischer.[1] The acid chloride was made in 90% yield by reaction of the anhydrous acid with a 10% excess of freshly distilled thionyl chloride. The product, after removal of the excess thionyl chloride by distillation, was recrystallized twice from carbon tetrachloride, m. p. 104°.

Penta-(triacetylgalloyl)-*d*-arabitol.—6.08 g. of anhydrous, finely powdered *d*-arabitol was taken up in 28.4 g. of freshly distilled anhydrous quinoline and 75 cc. of freshly distilled anhydrous chloroform. 69.0 g. of triacetylgalloyl chloride was added with cooling and the whole shaken for two days at room temperature. The reaction mixture was washed in succession with water, cold 1% sulfuric acid and then with water until neutral to litmus. The chloroform solution was dried over anhydrous sodium

(1) Emil Fischer, "Untersuchungen über Depside und Gerbstoffe," Julius Springer, Berlin, 1919.
(2) Russell, *Chem. Rev.*, **17**, 155 (1935).
(3) McKenzie and Muller, *J. Chem. Soc.*, **95**, 547 (1909).
(4) Sabalitschka and Tietz, *Arch. Pharm.*, **269**, 563 (1931).
(5) Christiansen, THIS JOURNAL, **48**, 1385 (1926).
(6) Hamburg, *Monatsh.*, **19**, 594 (1898).
(7) Biddle, THIS JOURNAL, **35**, 96 (1913).

sulfate. After filtering, the solution was taken to dryness on a steam-bath under reduced pressure and the residue was taken up in anhydrous acetone, filtered, and again reduced to dryness. The tan friable solid which weighed 57.4 g. (93%) was finally dried in an Abderhalden pistol at 57° over phosphorus pentoxide and paraffin at 1 mm. pressure for five days, m. p. 72° (sintered). The acetyl compound was tasteless and odorless. It gave no color with ferric alum solution and was insoluble in water. *Anal.* Calcd. for $C_{70}H_{62}O_{40}$: C, 54.5; H, 4.05. Found: C, 54.4; H, 4.08.

***d*-Arabitol Pentagallate.**—30.8 g. of penta-(triacetylgalloyl)-*d*-arabitol was taken up in 60 cc. of acetone and an oxygen-free stream of nitrogen passed into the solution while 330 cc. of 1 *N* sodium hydroxide solution was added with mechanical stirring at such a rate that the reaction temperature was maintained at 0° (ice–salt-bath). The gummy mass which separated was brought into solution by the addition of 100 cc. of acetone. Stirring was continued under a nitrogen atmosphere for two and one-half hours at 0°, 330 cc. of cold 1 *N* sulfuric acid was added, and the acetone was removed from the solution under reduced pressure. The residual solution was extracted with neutral ethyl acetate and the solvent layer dried over sodium sulfate, filtered, and concentrated to dryness under reduced pressure. The golden colored, friable hygroscopic glass produced was suspended in chloroform and then filtered. Repetition of this suspension gave 20 g. of a water soluble product. After drying at 57° over phosphorus pentoxide and paraffin at 1 mm. pressure for five days the color was a very pale tan, m. p. 83° (sintered). This product gave a blue-black color with dilute ferric alum solution. *Anal.* Calcd. for $C_{40}H_{32}O_{25}$: C, 52.6; H, 3.53. Found: C, 52.5; H, 3.52.

Hexa-(triacetylgalloyl)-sorbitol.—The method employed by Fischer[1] for the corresponding mannitol derivative was applied to sorbitol. The white, odorless tasteless product gave no coloration with ferric alum, m. p. 106° (sintered). After drying in an Abderhalden pistol as described for the derivative of *d*-arabitol it was converted to the gallic ester.

Sorbitol Hexagallate.—18.5 g. of hexa-(triacetylgalloyl)-sorbitol was treated by the method employed by Fischer[1] for the production of mannitol hexagallate to give 8.6 g. of gritty, white solid which was dried in a pistol as indicated above (m. p. 76° sint.). It has an astringent taste, was soluble in water and in neutral ethyl acetate, but was insoluble in petroleum ether. It gave a blue color with ferric alum. *Anal.* Calcd. for $C_{48}H_{38}O_{30}$: C, 52.5; H, 3.49. Found: C, 52.6; H, 3.51.

The experimental tannages were carried out on pickled calf-skin using the following standard procedure. A piece of selected pickled calfskin (8″ × 4″, wt. 25–35 g.), covered with three times its weight of 4% aqueous sodium chloride was treated with 25% of its weight of the material to be tested and the whole was rotated slowly in a bottle for from twenty-four to forty-eight hours. The piece of skin was now washed with water to a *p*H of 4.5, dried and compared as to color, feel, texture, flexibility and fullness with a similar piece tanned with gallotannin.

Summary

A number of simple esters and polyesters of gallic acid have been prepared and tested for leather forming properties. None of the simple esters showed any such properties. However, leather forming properties were shown by the polyesters of gallic acid with various polyhydric alcohols. The leather forming properties of the members of the latter series were poor but definite, and seemed to improve on ascending the series.

CHAPEL HILL, N. C. RECEIVED JUNE 19, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ST. PETER'S COLLEGE]

The Catalytic Properties of Charcoal. IV. Factors Influencing the Indophenol Reaction[1,2]

BY CLAUDE SCHWOB, WITH JOHN E. BIEGNER, KENNETH J. CARSON AND GEORGE V. SCOTT

The indophenol reaction has been used in this Laboratory to investigate the oxidase and peroxidase action of charcoal.[3,4] In this reaction indophenol is formed by the oxidation of a mixture of *p*-phenylenediamine and α-naphthol by oxygen or hydrogen peroxide in the presence of charcoal. It was found that when equimolar amounts of *p*-phenylenediamine and α-naphthol are used, the yield of indophenol diminishes after the first minute. Moreover, in later work, considerable difficulty was encountered in duplicating results.

In an attempt to clear up these points, and in order to gain further knowledge of the mechanism of the reaction, four modes of attack were employed: (a) variation in the concentrations of the individual reagents, (b) study of the *p*H during the course of the reaction, (c) effect of catalyst poisons and (d) study of the factors affecting the recovery of indophenol.

1. Reagent Concentrations.—Previous evidence[4] indicated that excess reagents are responsible for the drop in the yield of indophenol after

(1) Paper III, THIS JOURNAL, **60**, 2483 (1938).

(2) Presented in part at the 102nd meeting of the American Chemical Society, Atlantic City, N. J., September, 1941.

(3) Schwob, THIS JOURNAL, **58**, 1115 (1936).

(4) O'Brien, Tkac and Schwob, *ibid.*, **60**, 2480 (1938).

the first minute. Figure 1 summarizes the results obtained when the amounts of the reagents are varied individually. The concentrations are expressed as multiples of the "normal" amount, the reaction mixture normally containing equimolar amounts of *p*-phenylenediamine and α-naphthol, with a 20-fold excess of hydrogen peroxide, in the presence of sucrose charcoal, the whole being buffered to *p*H 4.5.[4]

Charcoal (curve 1): As expected, the ten-minute yield of indophenol is proportional to the amount of charcoal used, from one-half to twice the normal amount.

α-Naphthol (curve 2): Increasing concentrations of α-naphthol diminish the yield in a very marked manner, indicating that this substance is the chief culprit in the observed destruction of the indophenol. Due to the low over-all yield of indophenol (less than 6% in all cases) only a small amount of α-naphthol is needed for the actual formation of the dye. The excess "destroys" the indophenol in a manner not yet investigated in this Laboratory.

p-Phenylenediamine (curve 3): Excess amine does not affect the yield of indophenol very much. The yield diminishes in the expected manner when the concentration is below "normal."

Hydrogen Peroxide: Experiments involving variation in peroxide concentration were inconclusive. This is very probably due to the fact that charcoal has definite oxidase properties.[4] As the concentration of peroxide is lowered, the oxidase action predominates and obscures the role of the peroxide. However, at high concentrations of peroxide the yield of indophenol is somewhat lower (0.32 mg. of indophenol for 2.5 times normal concentration of hydrogen peroxide). Attempts to investigate the role of the peroxide anaerobically are futile due to the unavoidable decomposition of peroxide by the charcoal, providing an ample supply of oxygen.

2. Hydrogen-ion Concentration.—In addition to the change in the shape of the time–yield curve previously observed with *p*H variation, there is a definite increase in yield as the hydrogen-ion concentration decreases.[4] In the present investigation it was observed that during the course of the indophenol reaction relatively large quantities of an acid substance are formed, leading to a decrease in *p*H in spite of the presence of the buffer. For the "normal" reaction mixture the *p*H drop, measured by means of a glass electrode, was from 4.5 to 2.8 in seven minutes. A large increase in conductivity was observed also as the reaction progressed. It is likely that these effects are due to the liberation of hydrochloric acid as the *p*-phenylenediamine dihydrochloride is consumed, either in the formation of indophenol, or by being independently oxidized to unknown products by the peroxide under the influence of the charcoal.[5]

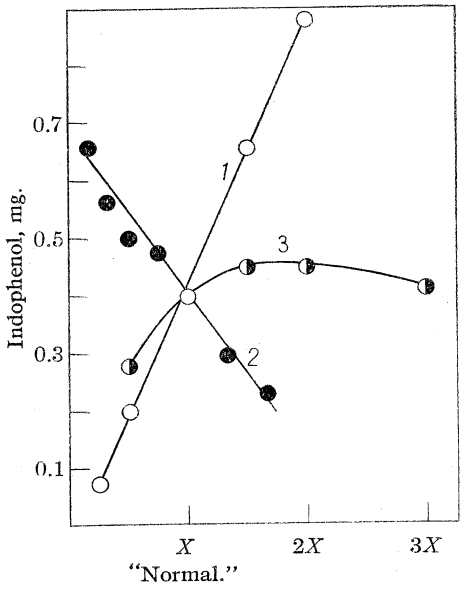


Fig. 1.—Ten-minute yield of indophenol in the presence of varying amounts of: charcoal (curve 1), α-naphthol (curve 2), and *p*-phenylenediamine (curve 3).

3. Catalyst Poisons.—The effects of potassium cyanide and amyl alcohol on the indophenol reaction have already been described.[4] The cyanide inhibits the formation as well as the destruction of the dye, but permits the uncatalyzed formation of indophenol to proceed at the same rate as in the absence of charcoal. The amyl alcohol stops all processes, so that the yield does not change with time after its addition. These different and characteristic effects were reinvestigated by means of conductivity measurements. Using a Fisher Titrimeter, the resistance of the normal reaction mixture, in the absence of poisons, drops with time, reaching a constant value of about one-half the original resistance after thirty minutes. This points to the liberation of hydrochloric acid for thirty minutes. Since indophenol is not being formed throughout

(5) Preliminary observations point to the feasibility of using a conductance method, involving this catalyzed oxidation of *p*-phenylenediamine dihydrochloride, for the rapid estimation of certain enzymes.

this period, the *p*-phenylenediamine must be losing some of its basic character by being oxidized independently.

In the presence of potassium cyanide (0.005 *N*) no drop in resistance can be observed. This indicates that not only does the cyanide poison the charcoal surfaces responsible for the formation and destruction of indophenol, but it also inhibits the independent oxidation of *p*-phenylenediamine.

On the contrary, in the presence of amyl alcohol the usual drop in resistance takes place, showing that the charcoal-catalyzed oxidation of the *p*-phenylenediamine is not affected by the amyl alcohol. Hence it is probable that there are at least two distinct surfaces of charcoal active in the indophenol reaction: (a) the portion of the surface which catalyzes the formation and destruction of indophenol, inhibited by both cyanide and amyl alcohol, and (b) the portion which catalyzes the oxidation of *p*-phenylenediamine, inhibited by cyanide but not by amyl alcohol.

4. Recovery of Indophenol.—It has been observed throughout this investigation that the indophenol-bearing charcoal must not be dried at too elevated a temperature or the indophenol will be destroyed. Another recurring source of annoyance in determining yield has been the varying shades of red which toluene solutions of indophenol exhibit, making colorimetric comparisons difficult and sometimes impossible.

The solid phase destruction of indophenol has been investigated by preparing indophenol-bearing charcoal, analyzing a portion and submitting other portions of the same batch to various treatments before analysis. The charcoal was prepared by using it to catalyze the formation of indophenol, using the "normal" concentrations. After filtering, the charcoal was washed with water and with 70% alcohol in an endeavor to remove most of the reagents and by-products. Alternately pure indophenol was adsorbed on charcoal from alcoholic solution.

The effect of heat was investigated first. Heating the charcoal in the dry state for progressively longer periods at the same temperature, or for the same time at increasing temperatures, causes a gradual destruction of the indophenol. For example, heating at 80° for sixty minutes decreased the indophenol content of a sample from 0.9 mg. per g. of charcoal to 0.5 mg. per g. In an attempt to find the lowest temperature at which indophenol is still destroyed at a significant rate, it was observed that a good deal of destruction takes place at room temperature. A sample of charcoal decreased in indophenol content from 0.6 mg. per g. to 0.3 mg. on exposure to air at room temperature for seventy-two hours.

The effect of excess reagents on this dry destruction of indophenol was studied by allowing the dye-bearing charcoal to adsorb one or another of the reagents from suitable solutions. As expected, the results are generally consistent with the findings described in the first part of this paper. Excess α-naphthol considerably increases the rate of destruction, while excess *p*-phenylenediamine actually increases the indophenol content of the charcoal after heating for one hour at 80°. This seems to be due to α-naphthol on the charcoal carried over from the reaction mixture and reacting with the added diamine. Further support for this view is furnished by the fact that if charcoal is supplied with indophenol by a reaction mixture containing only one-half the usual amount of α-naphthol, the increase in indophenol content on heating in the presence of added *p*-phenylenediamine is much less.

A study of the effect of reagents on indophenol adsorbed on charcoal from solutions of the pure dye in alcohol should be enlightening in these respects, since then none of the reaction mixture would be present to obscure the results. Unfortunately, as soon as charcoal so prepared was dried thoroughly, toluene no longer extracted the indophenol, and these experiments were perforce abandoned.

The second disturbing effect in estimating indophenol yields is the color variation exhibited by different toluene solutions of the dye. It was found that the presence of a trace of ethyl alcohol shifts the color toward the blue. Acid fumes make the solutions more yellow.

5. Conclusions.—A consideration of the present findings in the light of the previous work on the charcoal catalysis of the indophenol reaction enables us to list some of the processes taking place simultaneously or concurrently: A, charcoal catalyzed (1) formation of indophenol, (2) destruction of indophenol when its concentration reaches a definite level dependent on the charcoal, the temperature, and on the *p*H, (3) oxidation of the *p*-phenylenediamine, (4) decomposition of hydrogen peroxide due to the catalase action of the charcoal; B, uncatalyzed (1) slow formation of indophenol.

Summary

The oxidation of α-naphthol and *p*-phenylenediamine in the presence of activated charcoal appears to involve several simultaneous and successive processes. The measurement of the indophenol production is not an adequate test of the charcoal activity.

JERSEY CITY, N. J. RECEIVED MAY 27, 1942

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

Cocarboxylase and Related Esters

BY JOHN WEIJLARD

In previous publications concerning synthetic cocarboxylase, a rather indefinite acid mixture prepared by dehydrating orthophosphoric acid has been employed for the phosphorylation.[1,2,3] A different method was employed by H. Weil-Malherbe,[4] who prepared cocarboxylase by interaction of bromo-thiamine with silver pyrophosphate, a reaction that does not fall within the scope of this paper.

The obvious method to prepare cocarboxylase would be the interaction of pure pyrophosphoric acid and thiamine hydrochloride (I). It was found, however, that pyrophosphoric acid itself did not form any thiamine ester whatever, but with anhydrous sodium pyrophosphate as catalyst produced thiamine orthophosphoric acid ester (IV) in fair yields instead of the expected pyrophosphoric acid ester, as shown by the fact that mild hydrolysis produced no phosphoric acid.[2] Similarly, 4-methyl-5-hydroxyethylthiazole (II) formed 4-methyl-5-hydroxyethyl thiazole orthophosphoric acid ester (VI) with pyrophosphoric acid and pyrophosphates. Concentrated sulfuric acid with anhydrous sodium pyrophosphate produced thiamine sulfuric acid ester (III) from thiamine hydrochloride in good yields, but no thiamine pyrophosphoric acid ester could be detected in the reaction mixture.

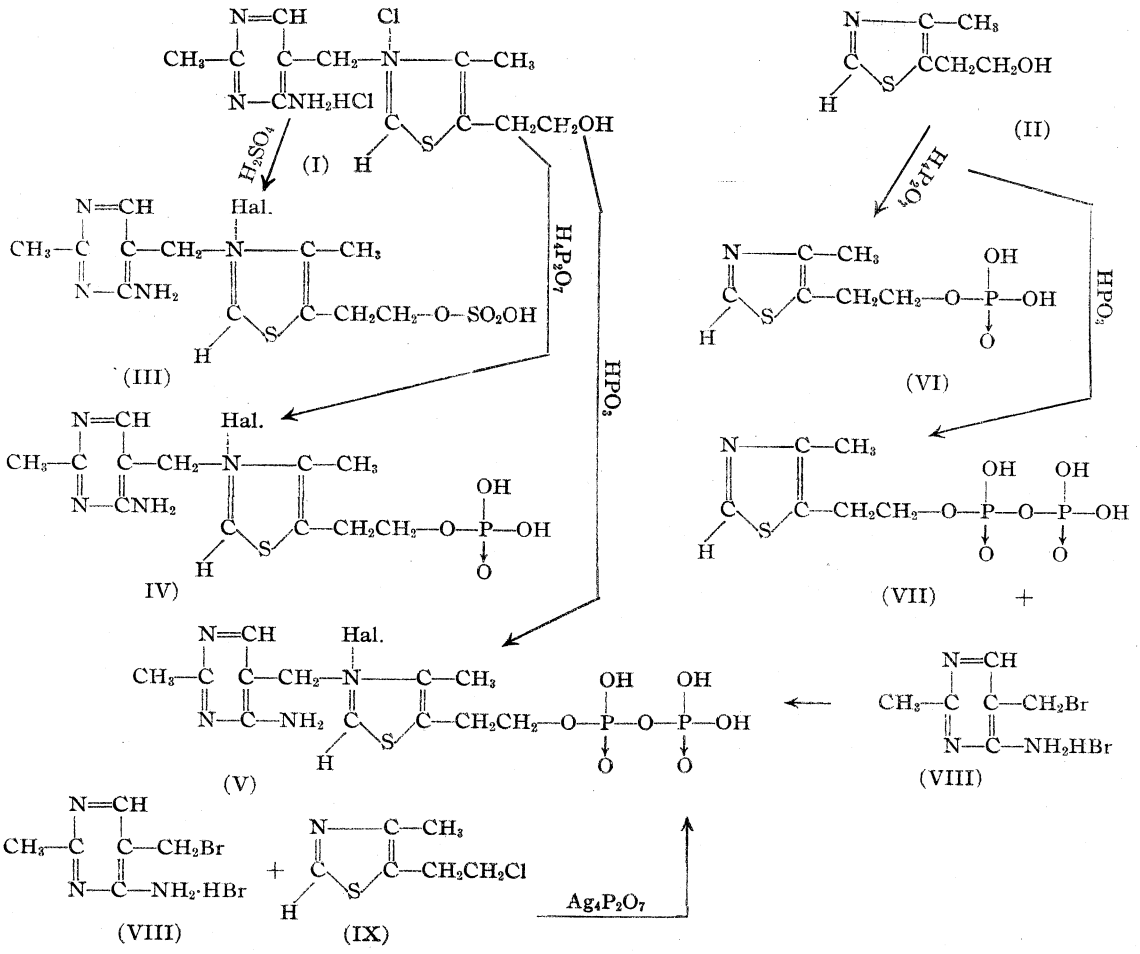
Phosphorus pentoxide was hydrated to give metaphosphoric acid,[5] and with the acid thus produced it was actually possible to esterify thiamine hydrochloride to thiamine pyrophosphoric acid ester chloride (cocarboxylase) (V). Yields similar to those previously reported[3] of thiamine pyrophosphoric acid ester were obtained when thiamine hydrochloride was esterified with a mixture of phosphorus pentoxide dissolved in pyrophosphoric acid with sodium pyrophosphate as catalyst. Such a solution should be a mixture of meta and pyro acids, with perhaps some unchanged phosphorus pentoxide, similar to the mixture obtained upon dehydrating orthophosphoric acid.[6,7] The mixture from dehydrated orthophosphoric acid gave with 4-methyl-5-hydroxyethylthiazole the compound, 4-methyl-5-hydroxyethylthiazole pyrophosphoric acid ester (VII), isolated as the silver salt,[2,8] which varies in composition according to varying *p*H and salt concentration.

2-Methyl-4-amino-5-bromomethylpyrimidine hydrobromide (VIII) was condensed with 4-methyl-5-hydroxyethylthiazole pyrophosphoric acid ester (VII) on the one hand, and with 5,β-chloroethyl-4-methylthiazole (IX) in the presence of silver pyrophosphate on the other to form cocarboxylase. Cocarboxylase was obtained in these reactions as ascertained by biological tests, but the yields were no higher than those obtained by the more simple direct phosphorylation of thiamine hydrochloride.

Experimental

Thiamine Orthophosphoric Acid Ester.—Five grams of pyrophosphoric acid was heated to faint fuming to remove any excess water, 2 g. of anhydrous sodium pyrophosphate was dissolved in the hot acid, 2 g. of thiamine hydrochloride was added and the mixture held at 150–155° for twenty minutes while stirring continuously. The cooled mass was dissolved in 100 cc. of water, and a slight excess of concentrated barium hydroxide solution was added. The precipitate was removed by centrifugation and discarded, the excess barium removed by adding a slight excess of 10% sulfuric acid and centrifuging. The solution was then concentrated to 60 cc. *in vacuo*. Sufficient one normal silver nitrate solution was added to precipitate the chloride, and the precipitate was removed by centrifuging and was discarded. The solution was neutralized with ammonia and an excess of 1 *N* silver nitrate solution added. The

(1) H. Tauber, THIS JOURNAL, **60**, 730 (1938).
(2) John Weijlard and Henry Tauber, *ibid.*, **60**, 2263 (1938).
(3) John Weijlard, *ibid.*, **63**, 1160 (1941).
(4) H. Weil-Malherbe, *Biochem. J.*, **34**, 980 (1940).
(5) E. B. R. Prideaux, *Trans. Faraday Soc.*, **5**, 37 (1909).
(6) G. Tammann, *J. prakt. Chem.*, [2] **45**, 417 (1892).
(7) Fritz Ephraim, "Inorg. Chemistry," 1939, pp. 720–722.
(8) K. Lohmann and P. Schuster, *Biochem. Z.*, **294**, 188 (1937).



mixture was centrifuged, the silver salt washed with water and suspended in 100 cc. of water and decomposed with hydrogen sulfide. The sulfide was filtered off and the solution aerated to remove excess hydrogen sulfide. Sufficient hydrochloric acid was added to make the solution eight-tenths normal. An excess of 25% phosphotungstic acid was added, the mixture was centrifuged and the solution discarded. The solid was treated with acetone to cause disintegration of the solid and precipitation of the ester. The mixture was chilled and the supernatant liquid decanted and discarded. The acetone insoluble material was dissolved in 50 cc. of 0.1 *N* hydrochloric acid and 10 volumes of acetone added. The solution was chilled at 0° overnight and filtered. The crude ester was recrystallized twice by dissolving in 0.1 *N* hydrochloric acid to form a 5% aqueous solution, adding three volumes of alcohol and seven volumes of acetone and cooling in ice; yield, 0.40 g. m. p. 200–202°. Hydrolysis with normal acid for one-half hour at 100° produced no phosphoric acid, hence no pyrophosphoric acid ester was present.

Anal. Calcd. for $C_{12}H_{18}O_4N_4ClSP\cdot 2H_2O$: C, 34.50; H, 5.31; N, 13.42; P, 7.44. Found: C, 34.59; H, 5.53; N, 13.22; P, 7.81.

Thiamine Sulfuric Acid Ester.—One gram of anhydrous sodium pyrophosphate was added to 2.5 cc. of concentrated sulfuric acid and heated to 150°. One gram of thiamine hydrochloride was added and the mixture heated at 150° for seven minutes. The mass was dissolved in 40 cc. of water and worked up essentially as above. The ester was finally recrystallized from 12 cc. of 0.1 *N* hydrochloric acid and 60 cc. of alcohol; yield 0.54 g., m. p. 258–259° with decomposition. No phosphorus was present. Its aqueous solution gave no precipitate with barium chloride, but on prolonged boiling with dilute hydrochloric acid the ester hydrolyzed slowly and the sulfate could be precipitated.

Anal. Calcd. for $C_{12}H_{17}O_4N_4ClS_2\cdot H_2O$: C, 36.10; H, 4.80; N, 14.05; S, 16.08. Found: C, 35.73; H, 4.93; N, 14.16; S, 16.26.

4-Methyl-5-hydroxyethylthiazole Orthophosphoric Acid Ester.—Four grams of pyrophosphoric acid was heated to faint fuming. One and seventy-five hundredths grams of 4-methyl-5-hydroxyethylthiazole was added and the mixture stirred and held at 150–160° for one hour. The cooled mass was dissolved in 50 cc. of water and the phosphoric acids removed by adding a slight excess of barium hydroxide solution and centrifuging. The excess barium was removed by adding a slight excess of sulfuric acid and centrifuging. The solution was made neutral with ammonia and an excess of normal silver nitrate solution was added. The precipitate was collected by centrifugation, washed with water several times, then suspended in 50 cc. of water and decomposed with hydrogen sulfide. The

silver sulfide was removed by filtration and the solution concentrated to dryness *in vacuo* at 30°. The residue, a thick oil, was dissolved in absolute alcohol and precipitated with ether. The flocculent white precipitate which resulted was collected on a filter and dried *in vacuo;* yield, 0.45 g., m. p. 162°.

Anal. Calcd. for $C_6H_{10}O_4NSP \cdot H_2O$: C, 29.85; H, 5.01; N, 5.80; P, 12.86. Found: C, 30.00; H, 4.87; N, 5.67; P, 12.98.

4-Methyl-5-hydroxyethylthiazole Pyrophosphoric Acid Ester Isolated as the Silver Salt.[2,8]—Four cc. of 85% orthophosphoric acid was heated until heavy fumes were produced and the hot acid appeared milky (290–310°). Two grams of anhydrous sodium pyrophosphate was dissolved in the hot acid and the mixture cooled down to 150°. One gram of 4-methyl-5-hydroxyethylthiazole was added and the mixture was stirred for one-half hour at 150–155°. The mixture was cooled and dissolved in 40 cc. water and a slight excess of barium hydroxide solution was added. The precipitate was centrifuged off and washed with water. The filtrate and washings were made slightly acid to congo red with 10% nitric acid, then concentrated *in vacuo* at 35° to 30 cc. The solution was made neutral to congo with ammonia, but was still acid to litmus. A few drops of normal silver nitrate solution was added and a small amount of silver chloride filtered off. Fifteen cc. of 50% silver nitrate solution was added and the mixture concentrated at room temperature *in vacuo* to one-half volume. The silver salt crystallized out slowly in the form of needles. The mother liquor was decanted off after three days of standing and the crystals washed first with 50% alcohol, then 90% alcohol, finally 100% alcohol followed by an ether washing; yield 0.40 g.

Anal. Calcd. for $C_6H_8O_7NSP_2Ag_3 \cdot 3/10AgNO_3 \cdot 6/10\text{-}HNO_3 \cdot 3H_2O$ (mol. wt., 766.6): C, 9.39; H, 1.92; N total, 3.47; N nitrate, 1.64; P, 8.09; Ag, 46.4. Found: C, 9.48; H, 1.89; N total, 3.82; N nitrate, 1.75; P, 8.00; Ag, 48.2. Hydrolysis under mild conditions (normal nitric acid for one-half hour at 100°): found 4.45% P which is 55.6% of the total phosphorus.

Thiamine Pyrophosphoric Acid Ester from Phosphorus Pentoxide Hydrated to Give Metaphosphoric Acid.—To 5 grams of phosphorus pentoxide, 0.65 g. of water was added in a closed vessel, and the mixture held at 150° until the mass was nearly transparent. Two grams of thiamine hydrochloride was added and the mixture held at 150° for one-half hour with stirring. The mass was cooled and dissolved in 100 cc. of water, then worked up as outlined in a previous paper[3]; m. p. 238–240°.

Anal. Calcd. for $C_{12}H_{19}O_7N_4ClSP_2 \cdot H_2O$: C, 30.08; H, 4.42; N, 11.71; P, 12.96. Found: C, 30.01; H, 4.35; N, 11.43; P, 13.43.

Thiamine Pyrophosphoric Acid Ester from Pyrophosphoric Acid with Added Phosphorus Pentoxide.—Five grams of pyrophosphoric acid was mixed with 1.5 g. of phosphorus pentoxide and heated until clear. A mixture of 0.5 g. of anhydrous sodium metaphosphate and 0.5 g. of anhydrous sodium pyrophosphate was added followed by 2 g. of thiamine hydrochloride. The mixture was held at 150–155° for fifteen minutes and worked up according to standard procedure[3]; yield 0.23 g. of cocarboxylase, which is the approximate yield obtained using the indefinite mixture resulting from dehydrating orthophosphoric acid.[2,3]

Anal. Calcd. for $C_{12}H_{19}O_7N_4ClSP_2 \cdot 3/4H_2O$: C, 30.41; H, 4.36; N, 11.80; P, 13.08; H_2O, 2.84. Found: C, 30.45; H, 4.39; N, 11.40; P, 12.80; H_2O, 2.75.

Condensation of 4-Methyl-5-hydroxyethylthiazole Pyrophosphoric Acid Ester and 2-Methyl-4-amino-5-bromomethylpyrimidine Hydrobromide.—A suspension of 0.33 g. of silver salt of 4-methyl-5-hydroxyethylthiazole pyrophosphoric acid ester in water was decomposed with hydrogen sulfide, the sulfide was filtered off, the filtrate concentrated *in vacuo* at room temperature to dryness and the residue dried *in vacuo;* yield, 140 mg. of 4-methyl-5-hydroxyethyl thiazole pyrophosphoric acid ester, a glass that did not readily crystallize. This ester was mixed with 150 mg. of 2-methyl-4-amino-5-bromomethylpyrimidine hydrobromide. Three cc. of liquid petrolatum was added and the mixture held at 110° for five minutes with continuous stirring. The mixture was cooled and the oil washed out with ether. The residue was dissolved in 10 cc. of water and the bromide ion removed by the addition of a slight excess of normal silver nitrate solution and centrifugation. The excess silver was precipitated with hydrochloric acid and the precipitate removed by centrifugation. The clear solution (acid to congo) was mixed with 10 volumes of acetone and the mixture chilled in the ice box overnight. The mother liquor was decanted and the residue crystallized by dissolving in 10 cc. of 0.1 *N* hydrochloric acid, adding 30 cc. of alcohol and 70 cc. of acetone and cooling in ice for two days. After decantation, the crystals were washed with alcohol and ether; yield, 110 mg. The cocarboxylase activity indicated a yield of about 10% cocarboxylase.

Condensation of 5,β-Chloroethyl-4-methylthiazole with 2-Methyl-4-amino-5-bromo-methylpyrimidine Hydrobromide in Presence of Silver Pyrophosphate.—One-half gram of 5,β-chloroethyl-4-methylthiazole (distilling at 82.8–83.8° at 2 mm.), 2 g. of anhydrous silver pyrophosphate and 0.9 g. of 2-methyl-4-amino-5-bromomethylpyrimidine hydrobromide were mixed rapidly with 5 cc. of liquid petrolatum and held at 110° for ten minutes with stirring. The cooled mixture was washed with ether to remove the oil, then disintegrated by shaking with 30 cc. of water and the solution made acid to congo with hydrochloric acid. The solid was centrifuged off and the clear solution mixed with 10 volumes of acetone, then chilled overnight. The crude material was recrystallized as outlined above; yield 0.15 g. The cocarboxylase activity indicated about 10% cocarboxylase.

Acknowledgments.—I wish to express my appreciation to Drs. R. T. Major and J. R. Stevens for advice and interest; to Dr. Alphonse Walti for the cocarboxylase testing; to Mr. Harold Levy for general assistance. The analytical work was carried out by Messrs. D. F. Hayman, W. Reiss, H. Clark and R. N. Boos.

Errata.—The formulas for analyses in the previous article[3] are given as $C_{12}H_{21}O_8N_4ClSP_2 \cdot {}^1/_2\, H_2O$. They should read: $C_{12}H_{19}O_7N_4ClSP_2 \cdot {}^1/_2\, H_2O$.

Summary

It has been shown that pure pyrophosphoric acid produces the orthophosphoric acid esters of thiamine as well as of 4-methyl-5-hydroxyethyl thiazole, and that metaphosphoric acid or phosphorus pentoxide calculated to give metaphosphoric acid is necessary to form the pyrophosphoric acid ester of thiamine (cocarboxylase). Thiamine sulfuric acid ester has been prepared as well as the pyrophosphoric acid ester of 4-methyl-5-hydroxyethyl thiazole. The latter ester was condensed with the pyrimidine portion of cocarboxylase to give a product with cocarboxylase activity. A similar condensation was carried out with the pyrimidine portion and chlorothiazole in the presence of silver pyrophosphate, the isolated reaction product showing cocarboxylase activity.

RAHWAY, NEW JERSEY RECEIVED JULY 10, 1942

[CONTRIBUTION FROM THE DIVISIONS OF ANIMAL HUSBANDRY AND CHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF CALIFORNIA AT DAVIS]

Absorption of Oxygen by Glutathione in Alkaline Solutions. I. Kinetics of the Reaction at *p*H 9 to 11

BY M. B. YOUNG AND H. A. YOUNG

It has been shown[1] that, in the presence of a copper salt as catalyst and at a *p*H below approximately 8.5, a solution of glutathione is oxidized by oxygen from the mercaptan to the disulfide, that the rate of the reaction increases with increase in *p*H, and that the factor determining the rate is the concentration of the dissociated ion.

It has also been shown[2] that as the *p*H is increased beyond 8.5, the reaction becomes more complex both with regard to the products formed and to the interpretation of the reaction rates. From approximately *p*H 9 to 11, the volume of oxygen absorbed per mole of glutathione is slightly greater than that calculated to change the mercaptan to the disulfide. The absorption, however, comes to a definite and abrupt end and there is no indication of a further reaction involving the formation of an oxidation product higher than the disulfide. Colorimetric tests with titanium sulfate have shown this excess absorption to be caused by the production of small amounts of hydrogen peroxide, which appears to be quite stable, particularly at *p*H 9, even in the presence of the copper catalyst. As the *p*H increases beyond 11, the reaction involving the disulfide formation

$$2GS^- + {}^1/_2O_2 + H_2O = GSSG + 2OH^- \quad (a)$$

is followed by another reaction involving oxygen and the disulfide produced n (a) and indicated by a continued slow increase in oxygen absorption. This follow reaction increases in rate as hydroxide ion increases while the rate of reaction (a) remains essentially constant until finally all discontinuity in the resulting curve is lost. The volume of oxygen absorbed indicates that the principal product formed is the salt of the sulfinic acid of glutathione and that the follow reaction is

$$GSSG + {}^3/_2O_2 + 2OH^- = 2GSO_2^- + H_2O \quad (b)$$

Again the oxygen absorbed is a few per cent. high, possibly caused by the formation of more hydrogen peroxide or some sulfonic acid.

The reaction has been studied over the *p*H range 9 to 13.3 with glutathione concentration 0.00110 to 0.00880 molar, copper sulfate concentration 0 to 25 $\times$ 10^{-6} molar and oxygen pressure 0.2 to 1.0 atm. The results of three exemplary experiments are shown in Fig. 1 in which approximately equal amounts of glutathione, 5 cc. of 0.00220 molar solution in the presence of copper sulfate of approximately 5 $\times$ 10^{-6} mole per liter, were oxidized by oxygen at 1 atmosphere at hydroxide ion concentrations of 10^{-5}, 0.0431, and 0.171 mole per liter, respectively. The lines A and B indicate the calculated volumes of oxygen to change the mercaptan to the disulfide and to the sulfinic acid, respectively. There is a distinct break in curve 2 near A.

The present publication is concerned with an attempt to explain the kinetics of the simplest of the reactions, *i. e.*, the oxidation of the mercaptan to the disulfide as it occurs at *p*H 9 to 11.

Experimental

The experiments were carried out in the Warburg apparatus at 37°. Four cc. of glutathione

(1) Carl M. Lyman and E. S. G. Barron, *J. Biol. Chem.*, **121**, 275 (1937).

(2) M. B. Young, H. A. Young and Max Kleiber, THIS JOURNAL, **63**, 1488 (1941).

solution was placed in the main compartment of the reaction flask and 1 cc. of a mixture of sodium hydroxide and copper sulfate in the side arm. Oxygen at the desired pressure was used to saturate the solutions and to fill the gas space above (about 10 cc.). After the establishment of temperature equilibrium, the sodium hydroxide–copper sulfate mixture was mixed with the glutathione[3] and the rate of oxygen absorption measured at constant volume. Since the process of mixing necessitated the removal of the apparatus from the thermostat for a few seconds, readings taken during the first minute are considered to be in error.

The apparatus was shaken at a rate of 180 oscillations per minute. Increasing the rate to 320 showed no increase in the rate of oxygen absorption; decreasing it to 100 showed a slight decrease. During several test experiments, the reaction was stopped before completion by adding sufficient sulfuric acid, and the concentration of the unoxidized glutathione determined iodometrically following the procedure of Woodward and Fry.[4] Even in the faster experiments, the total reducing power of the glutathione solution checked the oxygen consumption within 3%. In view of the fact that more than enough oxygen is dissolved in the solution initially to oxidize all of the glutathione, it is assumed that these experiments indicate that equilibrium had been established throughout between the oxygen of the gas phase and that of the solution. Changing the glass surface within the reaction flask by adding glass beads had no effect upon the reaction rate.

C. P. quality chemicals were used throughout without further purification. As was to be expected in a reaction sensitive to traces of catalyst, there was some variation in going from one source of chemical to another, particularly the sodium hydroxide. A bottle of Mallinckrodt heavy metal-free product was finally obtained and used consistently. The water was doubly distilled in Pyrex glass. Various samples of glutathione obtained from different establishments (Eimer and Amend, Paul–Lewis Laboratories) were reasonably reproducible. By using the same supply of reactants, any series of experiments performed within a period of a month or so proved to be reproducible; and when going from one source of glutathione to another, while the absolute rates varied somewhat, the shapes and general form of the absorption curves were always the same.

No buffers were added to the reaction system.

(3) Under the conditions of the experiments the suspension of copper hydroxide dissolved immediately in the glutathione forming a glutathione-copper complex of some kind. For simplification Cu^{++} will refer to Σ Cu in whatever form it may be.

(4) Gladys E. Woodward and Edith G. Fry, *J. Biol. Chem.*, **97**, 465 (1932).

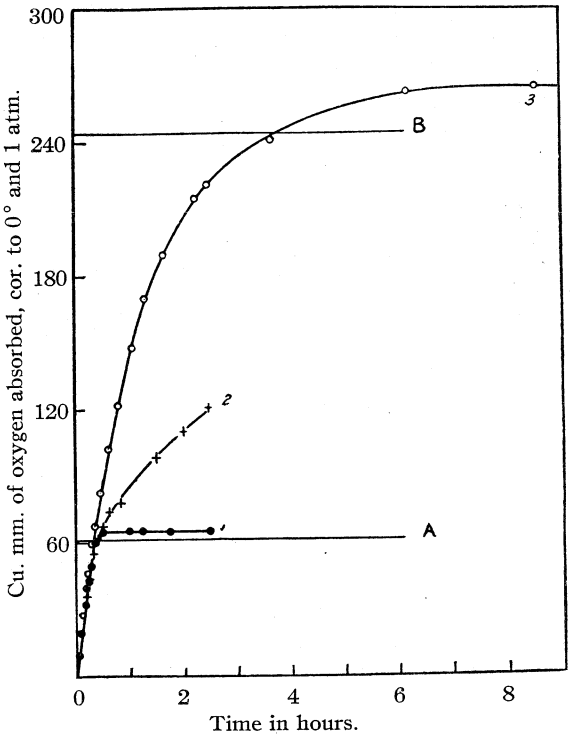


Fig. 1.—Absorption of oxygen at 37° and 1 atm. pressure by glutathione in alkaline solutions.

Experimental Results

Within the chosen *p*H ranges, two types of absorption curves were encountered. In Fig. 2, the curve represents an autocatalytic reaction with its maximum rate occurring at about 75% completion. This type of reaction is always associated with an excess absorption of oxygen. In Fig. 3, the curve represents a reaction which has its maximum rate at zero time. If excess oxygen absorption occurs at all, it is to a much slighter degree. In both figures line A represents the theoretical volume of oxygen required to convert the mercaptan to the disulfide. All kinds of intermediate curves may be obtained, depending upon experimental conditions. Factors tending to produce the first type are high values of the ratio of copper ion to glutathione, high oxygen pressure, and high *p*H. Those tending to produce the latter are conversely low values of the ratio of copper ion to glutathione, low oxygen pressure, and low *p*H.

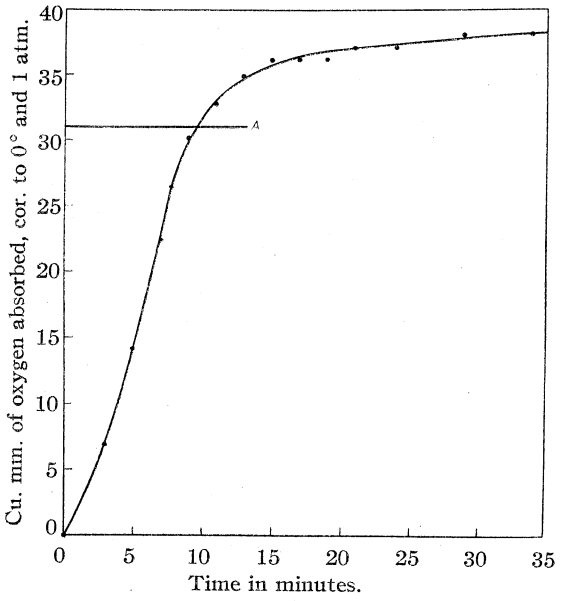


Fig. 2.—Absorption of oxygen by glutathione: GS^- = 0.00111 *M*; Cu^{++} = 4.63 × 10^{-6} *M*; initial *p*H, 10.8 (3.07 equivalents NaOH); O_2, 1 atm.

Tests with titanium sulfate indicated that hydrogen peroxide often accumulated during the course of the reaction. In several cases, the amount of hydrogen peroxide formed was determined colorimetrically by comparison with standard hydrogen peroxide solutions to which titanium sulfate had been added. The results are shown in Table I. Although the experimental error in such colorimetric determinations is high, the results indicate that the excess oxygen consumption can be satisfactorily explained by the presence of hydrogen peroxide. They also illustrate the fact that the faster the reaction, the greater the accumulation of hydrogen peroxide.

Effect of Hydroxide Ion.—The variation of reaction rate with hydroxide ion is shown in Fig. 4, where the observed maximum rates are plotted against the equivalents of sodium hydroxide in-

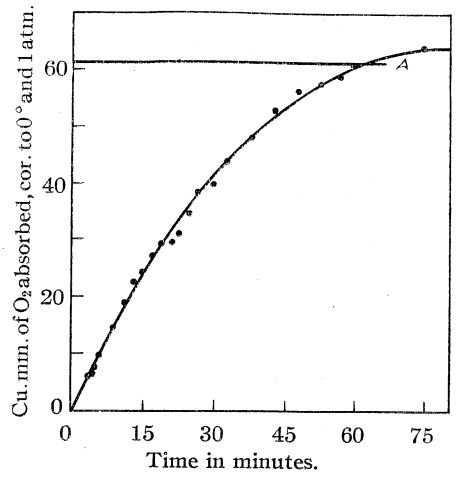


Fig. 3.—Absorption of oxygen by glutathione: GS^- = 0.00220 *M*; Cu^{++} = 4.63 × 10^{-6} *M*; initial *p*H, 9.4 (2.05 equivalents NaOH); O_2, 0.2 atm. (air).

itially added to the reaction mixture. The copper sulfate and glutathione concentrations are 5.0 × 10^{-6} and 0.00220 molar, respectively. As is shown, the rate increases with increase in base until about 3.5 equivalents are present at a *p*H of approximately 11. As more base is added, there is actually a slight decrease, accompanied, however, by the appearance of the follow reaction involving the formation of the sulfinic acid—as referred to earlier.

TABLE I

COMPARISON BETWEEN OBSERVED AND CALCULATED HYDROGEN PEROXIDE CONCENTRATION

GS^-	OH^- equiv.	Cu^{++} × 10^6	O_2	Calcd. $\frac{H_2O_2}{G_2S_2}$	Found $\frac{H_2O_2}{G_2S_2}$	Found H_2O_2	Calcd. H_2O_2
0.00223	3.35	2.52	1	0.08	0.07	0.8 × 10^{-4}	0.8 × 10^{-4}
.00223	3.35	10.08	1	.24	.18	.2 × 10^{-4}	2.4 × 10^{-4}
.00220	1.50	10.08	1	.20	.1	1 × 10^{-4}	2.6 × 10^{-4}
.00220	1.50	10.08	0.5	.20	.1	1.0 × 10^{-4}	2.0 × 10^{-4}
.00220	1.50	10.08	0.2	.16	.05	5 × 10^{-5}	18 × 10^{-5}
.00198	1.50	10.08	1	.14	.15	1.5 × 10^{-4}	1.4 × 10^{-4}
.00100	1.65	10.08	1	.16	.18	1.5 × 10^{-4}	1.6 × 10^{-4}
.00397	1.65	10.08	1	.04	.07	1.5 × 10^{-4}	0.8 × 10^{-4}

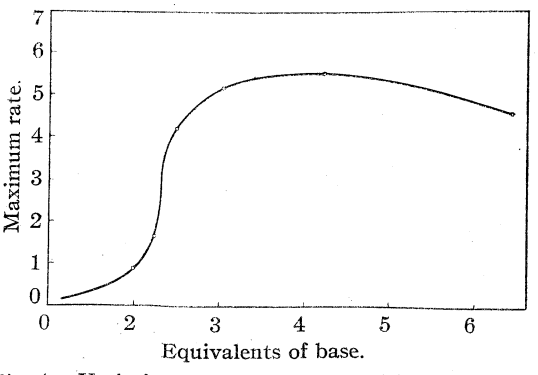


Fig. 4.—Variation of maximum rate with added base.

In 1929 Pirie and Pinhey[5] obtained a titration curve for the then recently discovered glutathione using a product obtained from yeast. For the dissociation of the —SH group, they chose a pK of 9.62. Except for a slight horizontal displacement, we have reproduced quite closely their titration curve using our commercial supply of glutathione at 0.00220 M and including copper sulfate at concentrations comparable to those in the rate experiments (see Fig. 5). The pH values were determined with a Coleman glass electrode, readings being taken immediately after mixing of the glutathione and base. The shaded points represent values obtained with Cu^{++} concentrations of 10×10^{-6} mole per liter; the open circles 5×10^{-6} mole per liter. The three circled points at high pH values have been corrected for errors resulting from glass electrode determinations at the sodium ion concentrations involved. Following the interpretation of Pirie and Pinhey, a value of 10.0 has been chosen as representing the pK of the reaction GSH = $GS^- + H^+$.

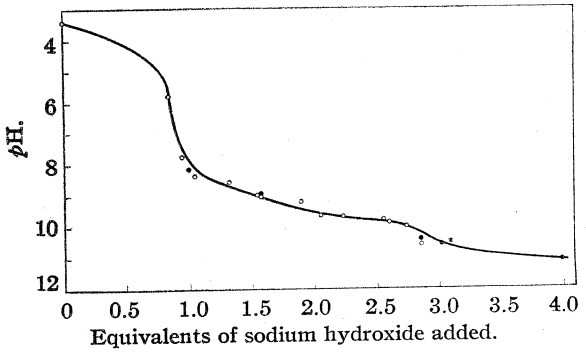


Fig. 5.—Titration curve of glutathione at 25°.

Considering the above results, it is seen that the maximum reaction rate is obtained at the pH where the transformation of GSH to GS^- becomes complete. We have therefore concluded, as did Lyman and Barron,[1] that GS^- is the primary reactant and have looked to the rate results at pH 11 for an explanation of the reaction system. Also, since at this pH, the autocatalytic nature of the absorption curve persists, the effect of the OH^- produced in (a) in transforming any GSH to GS^- as the reaction proceeds cannot be considered a complete explanation for this characteristic.

Effect of GS^- Concentration, pH 11.—Figure 6 shows four experiments in which Cu^{++} was maintained at 5×10^{-6} molar, O_2 at 1 atm., and GS^- varied from 0.00110 to 0.00884 molar. This series of experiments indicates that the effect of GS^- is very slight, since the maximum rates are largely independent of the GS^- concentration. Although not clearly seen on the small plot, the greater the GS^- concentration the nearer the origin to the maximum rates occur.

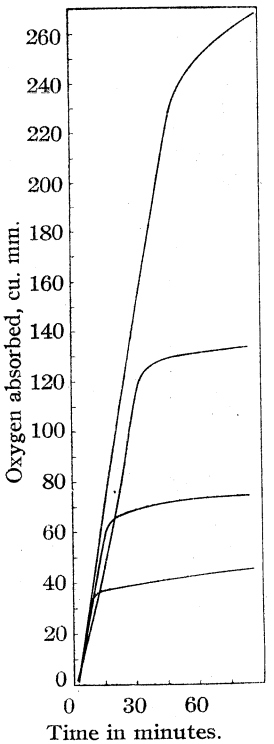


Fig. 6.—Absorption of oxygen by glutathione at various GS^- concentrations: $Cu^{++} = 5 \times 10^{-6}$ M; pH, 10.9 (3.38 equivalents NaOH); O_2, 1 atm. Beginning with lowest curve, GS^- = 0.00111, 0.00220, 0.00440, 0.00884 M, respectively.

Effect of Cu^{++} Concentration and Oxygen Pressure, pH 11.—The effect of varying Cu^{++} concentration is shown in Fig. 7. In all of these experiments GS^- was kept constant at 0.00220 mole per liter and the oxygen pressure at 1 atmosphere. It is observed that small amounts of Cu^{++} ion influence the reaction rate tremendously and that the reaction becomes more autocatalytic as Cu^{++} increases. The residual reaction in 1 is presumably caused by traces of catalyst in the reactants. Again, line A represents the theoretical oxygen consumption. When these autocatalytic curves are plotted on a large scale, it is noticeable that the maximum slope of the curve is nearly proportional to the Cu^{++} concentration. This fact is seen in Fig. 8 where maximum slopes are plotted against Cu^{++} concentration at three different oxygen pressures.

The above observation suggests that as the Cu^{++} increases, a catalyst is formed, the concentration of which controls the rate of oxygen consumption and which is determined by Cu^{++} concentration. Further, in the very rapid runs, the indication is that the steady state concentration of this intermediate is not reached until the reaction is nearly over; but when Cu^{++} is very low, the steady state is reached quite early in the experiment.

(5) Norman W. Pirie and Kathleen Goodwin Pinhey, *J. Biol. Chem.*, **84**, 321 (1929).

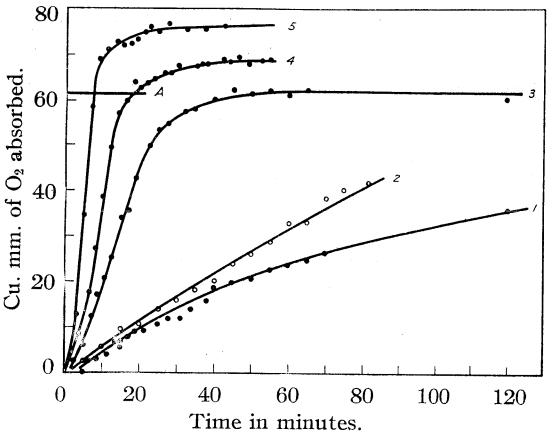


Fig. 7.—Absorption of oxygen by glutathione at various concentrations of Cu^{++}: GS^- = 0.00220 *M*; initial *p*H 10.9 (3.42 equivalents NaOH); O_2, 1 atm.; Cu × 10^6 in 1, 2, 3, 4, 5 is 0, 0.504, 2.52, 5.04, 10.08 *M*, respectively.

The effect of changes in oxygen pressure is also shown in Fig. 8. At very low Cu^{++} concentration, the reaction rate is independent of oxygen pressure but as Cu^{++} increases, this is no longer true. If the maximum rates of Fig. 8 are plotted against the square roots of the oxygen pressures for the three highest Cu^{++} concentrations, a series of lines passing through the origin is obtained. These indicate that, neglecting any effects of absorption or diffusion, the maximum reaction rate at high Cu^{++} concentration varies as the one-half power of the oxygen pressure. During the course of any experiment the oxygen pressure remains essentially constant as less than 1% of the total oxygen available is used.

Rate Law and Mechanism

The foregoing observations that GS^- is the reactive species, that the rate of the autocatalytic reaction is independent of GS^- concentration and dependent upon Cu^{++} concentration together with what is known about the usual role of cupric ion as a catalyst in oxygen reactions suggest the following series of reactions

$$Cu^{++} + GS^- \xrightarrow{(O_2)} X \qquad (1)$$

$$X + O_2 \xrightarrow{(GS^-)} G_2S_2 + X \qquad (2)$$

$$X + GS^- \xrightarrow{(O_2)} G_2S_2, \text{ with destruction of X} \qquad (3)$$

Parentheses indicate that the substances are used in the reaction but do not enter into the rate law. In other words, each of the above incomplete equations indicates the substances entering into the rate-determining step of a series of two or more reactions.

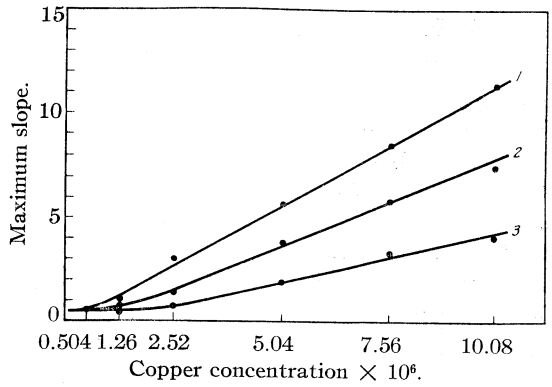


Fig. 8.—Variation of maximum slope with Cu^{++} concentration at *p*H 11.0: O_2 pressures in 1, 2, 3 are 1, 0.5, 0.2 (air) atm., respectively.

Proceeding in the usual manner, and remembering the experimental facts regarding oxygen pressure, the following rate expressions are obtained

$$-\frac{d[GS]}{dt} = k_1(Cu^{++})(GS^-) + k_2(X)(O_2)^{1/2} + k_3(GS^-)(X) \qquad (4)$$

$$-\frac{d[X]}{dt} = k_1(Cu^{++})(GS^-) - k_3(X)(GS^-) \qquad (5)$$

$$-\frac{d[O_2]}{dt} = -\frac{d(GS^-)}{dt}(2.8 \times 10^4) \qquad (6)$$

Equation 6 is obtained assuming that the only reduction product of oxygen is hydroxide ion.

When the catalyst, X, is in a steady state, then

$$X = k_1(Cu^{++})/k_3 \qquad (7)$$

When the concentration of Cu^{++}, and consequently X, is relatively high, the maximum rates occur near the end of the experiment, after the concentration of GS^- has been greatly decreased. Under these conditions, the contributions of reactions 1 and 3 to the rate of absorption of oxygen are negligible, and the rate expression may be written

$$-\frac{d[GS^-]}{dt} = k_2(X)(O_2)^{1/2} = k_2\frac{k_1}{k_3}(Cu^{++})(O_2)^{1/2} \qquad (8)$$

and

$$-\frac{d[O_2]}{dt} = k_1\frac{k_2}{k_3}(Cu^{++})(O_2)^{1/2}(2.8 \times 10^4) \qquad (9)$$

Using the values of maximum rates and Cu^{++} concentration of Fig. 8, a value of 40 is obtained for the function k_1k_2/k_3 at an oxygen pressure of one atmosphere.

The solution to the system of differential equations (4), (5), (6) is elusive. However, by using the method of successive approximations, it is possible to approximate the oxygen consumption as a function of time. By assuming $k_1 = k_3 = 200$ and k_2 between 30 and 40, it was possible to repro-

duce reasonably well the experimental data so far obtained at *p*H 11. The variation of k_2 is considered to be within the range of experimental error. Figure 9 shows the comparison between observed and calculated curves for three cases. Although the agreement is not perfect, it seems sufficiently good to encourage the view that the main features of the autocatalytic reaction are represented by equations (1), (2) and (3). The results of varying the oxygen pressure indicate, however, that the catalytic reaction is probably more complicated than as represented in equation (2). A possible explanation of the one-half power for the oxygen pressure would be the establishment of a rapid reversible equilibrium involving oxygen.

It will be observed from reactions (1), (2) and (3) that, when the concentration of X is low or when oxygen pressure is low, reaction (2) becomes less important, and a departure from the catalytic rate law would be expected. This condition is clearly realized at low oxygen pressures, Fig. 8, where the reaction rate becomes independent of oxygen pressure. Further, if undissociated glutathione can function in the destruction of the catalyst X, but not in its production, the rate law would be expected to fail at hydroxide ion concentration at which the concentration of GS^- was small compared to that of GSH. This assumption is borne out by the experiments at *p*H 9 (Table II) where the reaction rates become dependent upon the concentration of $\Sigma GSH = GSH + GS^-$. Column 6 in Table II represents the approximate per cent. of the reaction completed when the maximum rate occurs.

TABLE II

VARIATION OF MAXIMUM RATE WITH ΣGSH AT *p*H 9

GSH, moles per liter	$Cu^{++}(10^6)$, moles per liter	O_2 pressure, atm.	$H_2O_2(10^4)$ produced, moles per liter	Maximum slope, cu. mm./minutes	% completion at maximum rate
0.00397	10.08	1	1.5	12.30	5
.00198	10.08	1	1.5	5.22	75
.00100	10.08	1	1.5	5.20	77
.00442	4.63	1		5.64	30
.00220	4.70	1		4.00	75

Hydrogen peroxide has been eliminated as the catalytic agent on the basis of experiments in which hydrogen peroxide, added to the reactants in molar concentrations varying from 1 to 20% of that of the glutathione, did not change the reaction rate. In this respect, the autoöxidation of glutathione differs from that of ascorbic acid in which hydrogen peroxide in the presence of copper ion has been shown to be a definite catalyst.[6]

(6) Dekker and Dickinson, THIS JOURNAL, **62**, 2165 (1940).

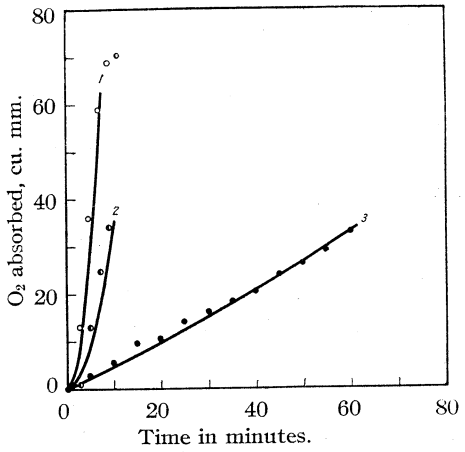


Fig. 9.—Comparison between experimental and calculated curves. The points are experimental; the lines are calculated. Initial *p*H is 10.9 (3.4 equivalents NaOH); O_2, 1 atm. In curves 1, 2, and 3 the concentrations of Cu^{++} (10^6) are 10.1, 5.0, and 0.50 and of GS^- are 0.00220, 0.00110, and 0.00220 *M*, respectively.

Also we have concluded that HO is not the catalyst since, in the *p*H range considered, chloride ion in concentrations varying from 1 to 500% of that of the glutathione does not inhibit the reaction rate.[7]

In view of the widely recognized evidence that peroxy radicals often function as catalysts in the autoöxidation of organic substances, it seems reasonable to identify X as a radical of GS, probably GSO_2, and to write the following reactions as the initiators of the catalysis.

$Cu^{++} + GS^- \rightleftharpoons Cu^{++}GS^-$	rapid, reversible
$Cu^{++}GS^- \longrightarrow Cu^+ + GS$	relatively slow
$GS + O_2 \longrightarrow GSO_2$	rapid

While it is possible to write several series of reactions completing the mechanism, it seems advisable to await the interpretation of results at higher hydroxide ion concentrations before deciding upon the most probable reactions involved.

The authors are indebted to Prof. Max Kleiber for the use of the Warburg apparatus.

Summary

1. The rate of absorption of oxygen by glutathione in the *p*H range 9 to 11 and in the presence of copper sulfate catalyst has been measured. The effect of changes in copper sulfate and glutathione concentrations and oxygen pressure are presented.

2. A rate law and partial mechanism are proposed.

DAVIS, CALIFORNIA RECEIVED MAY 19, 1942

(7) Taube and Bray, *ibid.*, **62**, 335 (1940).

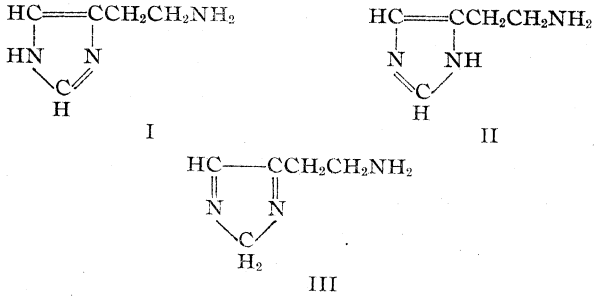
[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 893]

The Relation between Structure and Histamine-Like Activity

BY CARL NIEMANN AND JOHN T. HAYS

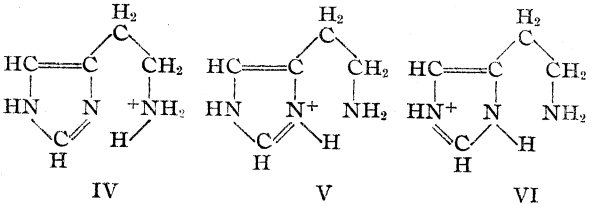
Recently Walter, Hunt and Fosbinder[1] reported that the physiological action of β-(2-pyridyl)-ethylamine is similar to that of histamine and that the action of β-(4-pyridyl)-ethylamine resembles that of epinephrine. This striking difference in the pharmacological behavior of the above two isomeric β-pyridylethylamines led us to inquire as to the physiological properties of the third and remaining isomeric β-pyridylethylamine, *i. e.*, β-(3-pyridyl)-ethylamine in the hope that information about the latter compound would lead to a more general understanding of the relation between structure and histamine-like activity.

dl-β-(3-Pyridyl)-alanine[2] was decarboxylated using the method of Abderhalden and Gebelein[3] to give β-(3-pyridyl)-ethylamine. A comparative study of the physiological properties of the three isomeric β-pyridylethylamines was undertaken by Dr. G. A. Alles of this Institute and it has been found that β-(3-pyridyl)-ethylamine resembles β-(4-pyridyl)-ethylamine in its pharmacological properties and does not show any notable histamine-like activity, which characterizes the pharmacological action of β-(2-pyridyl)-ethylamine.[4] For histamine we may write the three tautomeric structures I, II and III. However, it is clear from



I II III

a consideration of the possible resonance forms of each tautomer[5] and from the bond energies[6,7] that at equilibrium we need consider only structures I and II. Under physiological conditions tautomers I and II will add a proton and exist in the form of cations. If we ignore interaction between the side-chain and the nucleus, we must assign equal weight to each cation, but if we assume that side chain–nucleus interaction does take place through the medium of an intramolecular hydrogen bond, it follows that the cation has the structure (IV, V, VI). This ion with respect to



IV V VI

bond distances and chelation is more nearly related to tautomer I than to tautomer II. A similar chelation is to be expected in the cation of β-(2-pyridyl)-ethylamine. Thus it appears that the characteristic pharmacological properties of histamine are associated with structures that have their origin in tautomer I and we may look upon this tautomer as containing the obligatory structural requirements requisite for histamine-like activity.

The similarity of the physiological action of histamine and β-(2-pyridyl)-ethylamine led Walter, Hunt and Fosbinder[1] to conclude that the molecular fragment —CH=N—C($CH_2CH_2NH_2$)=CH—, which they consider as being present in both histamine (tautomer I) and β-(2-pyridyl)-ethylamine, is primarily responsible for the histamine-like activity of these compounds. Taking advantage of the studies of Hill and Branch[5] and of Schomaker and Pauling,[8] we can give greater precision to the above conclusion of Walter, Hunt and Fosbinder[1] by defining the obligatory structural fragment requisite for histamine-like activity as —CH—*a*—N—*b*—C($CH_2CH_2NH_2$)—*c*—CH— where $a = 1.36 \pm 0.01$ Å., $b = 1.38 \pm 0.02$ Å., and $c = 1.40 \pm 0.01$ Å., and when chelation between the nitrogen atoms occurs in the cation.

A comparison of the structures that can be written for β-(3-pyridyl)-ethylamine and for

(1) L. A. Walter, W. H. Hunt and R. J. Fosbinder, THIS JOURNAL, **63**, 2771 (1941).

(2) C. Niemann, R. N. Lewis and J. T. Hays, *ibid.*, **64**, 1678 (1942).

(3) E. Abderhalden and F. Gebelein, *Z. physiol. Chem.*, **152**, 125 (1926).

(4) The authors wish to express their indebtedness to Dr. Alles for this information.

(5) T. H. Hill and G. E. K. Branch, *Science*, **91**, 145 (1940).

(6) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940.

(7) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, New York, N. Y., 1941.

(8) V. Schomaker and L. Pauling, THIS JOURNAL, **61**, 1769 (1939).

tautomer II reveals that each of these substances contains the molecular fragment —CH—*a*—N—*b*—CH—*c*—C($CH_2CH_2NH_2$)—. As β-(3-pyridyl)-ethylamine is devoid of any histamine-like activity, we conclude, on the basis of the preceding argument, that tautomer II is likewise devoid of any histamine-like activity. This conclusion is in accord with and supports the previous contention that tautomer I is the structure responsible for the histamine-like activity of histamine and that the principle obligatory structural requirement for histamine-like activity is the molecular fragment —CH—*a*—N—*b*—C($CH_2CH_2NH_2$)—*c*—CH—.

Experimental[9]

β-(3-Pyridyl)-ethylamine Dihydrochloride.—A mixture of 1 g. of *dl*-β-(3-pyridyl)-alanine[2] and 20 g. of diphenylamine was heated to 245–250° and maintained at that temperature for two hours.[3] The reaction mixture was digested with 40 ml. of 3 *N* hydrochloric acid and the digest allowed to cool to 25° with vigorous stirring. The diphenylamine was removed by extraction with ether, an excess of aqueous sodium hydroxide added to the aqueous phase and the latter extracted with ether. The ethereal solution was dried over sodium sulfate and then acidified with dry hydrogen chloride. The amine dihydrochloride separated as an oil, which was collected and crystallized from 20–25 ml. of hot absolute ethanol. This product (0.4 g.) was recrystallized from a mixture of absolute ethanol and ether to give β-(3-pyridyl)-ethylamine dihydrochloride, m. p. 195–205° with decomposition.

(9) Microanalyses by Dr. G. Oppenheimer and G. A. Swinehart.

Anal. Calcd. for $C_7H_{12}N_2Cl_2$ (195.1): C, 43.1; H, 6.2; N, 14.4; Cl, 36.4. Found: C, 43.3; H, 6.3; N, 14.4; Cl, 36.4.

Preliminary Pharmacological Report.[10]—In the cat both β-(3-pyridyl)-ethylamine and β-(4-pyridyl)-ethylamine are pressor in minimally active and higher doses, being about one-fifth to one-tenth as active as β-phenylethylamine. In the rabbit the pressor responses are not great with minimally active doses and with higher doses an initial depressor effect may be noted that is, however, unlike that of histamine, and is shown in similar degree by both β-(3-pyridyl)-ethylamine and β-(4-pyridyl)-ethylamine. In sufficient concentration both β-(3-pyridyl)-ethylamine and β-(4-pyridyl)-ethylamine decrease movement and tone of isolated rabbit jejunum preparations. This resembles the activity of more than minimally active concentrations of β-phenylethylamine, and is the reverse of the effect of histamine. No stimulant effect in concentrations up to 10^{-3} molar was noted upon isolated guinea-pig ileum preparations though this same concentration of β-phenylethylamine causes some increase in tone and concentrations of but 10^{-6} molar histamine are very active upon such preparations.

Summary

β-(3-Pyridyl)-ethylamine has been prepared and it has been found that this amine, in common with β-(4-pyridyl)-ethylamine and in contrast to β-(2-pyridyl)-ethylamine, has pressor activity. The relation between structure and histamine-like activity is discussed.

(10) The authors are indebted to Dr. G. A. Alles for this report and to Dr. L. A. Walter for samples of β-(2-pyridyl)-ethylamine and β-(4-pyridyl)-ethylamine.

PASADENA, CALIFORNIA RECEIVED MAY 22, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UNIVERSAL OIL PRODUCTS COMPANY]

The Addition of Hydrogen Fluoride to the Triple Bond[1]

BY ARISTID V. GROSSE[1a] AND CARL B. LINN

We have recently demonstrated[2] that olefins will add hydrogen fluoride, even in the complete absence of catalysts, to give good yields of alkyl fluorides. Likewise the cyclopropane ring is opened by hydrogen fluoride to give *n*-propyl fluoride. The chemical literature contains no reference to a similar addition of hydrogen fluoride to the triple bond. In view of the ease of addition to the double bond, a similar behavior was expected of the *triple bond*. This proved to be the case and we found that unsaturates of this type readily *add hydrogen fluoride* in the *absence of catalysts*, according to the equations

$$R—C{\equiv}C—R' + HF \longrightarrow R—CF{=}CH—R' \quad (1)$$
$$R—CF{=}CH—R' + HF \longrightarrow R—CF_2—CH_2—R' \quad (2)$$

giving *difluorinated hydrocarbons* of the type

$$R—CF_2—CH_2—R'$$

Previous to our investigation only the two simplest[3] members of this series were known, namely, 1,1-difluoroethane[4] and 2,2-difluoropropane.[5] Subsequently A. L. Henne, in his well known studies of aliphatic fluorine compounds, has extended the reaction of antimony or mercuric

(1) Presented before the Organic Section of the American Chemical Society at its Baltimore meeting, April, 1939 (see Abstracts, Section M., p. 27).

(1a) Present address: Department of Chemistry, Columbia University, New York, N. Y.

(2) A. V. Grosse and C. B. Linn, *J. Org. Chem.*, **3**, 26 (1938).

(3) For CH_2F_2, see A. L. Henne, THIS JOURNAL, **59**, 1400 (1937).

(4) A. L. Henne and M. W. Renoll, *ibid.*, **58**, 889 (1936).

(5) A. L. Henne and M. W. Renoll, *ibid.*, **59**, 2434 (1937).

fluorides upon the corresponding dichloro compounds and recently described[6] 2,2-difluorobutane and -pentane. 1,1-Difluoroheptane has also been reported by him.[6]

We have accomplished the *addition* of *hydrogen fluoride* to *ethyne, propyne, butyne-1* and *-2, pentyne-1, hexyne-1* and *-3* and *heptyne-1.*

The formation of an unsaturated monofluoride, according to equation 1 above, was demonstrated only in the case of acetylene where *vinyl fluoride* was isolated. Each of the other alkynes studied yielded a saturated compound analyzing for two atoms of fluorine in the molecule.

The possibility is not excluded that, under appropriate conditions, the method may be developed as a means of preparing monofluorides of the formula RCF=CHR′.

The addition of *both* hydrogen fluoride molecules takes place according to Markownikoff's rule and in line with Kharasch's theory,[7] leading to the attachment of *both* fluorine atoms to the *same* carbon atom.

The structure of our difluoroparaffins was definitely established in the case of the products from ethyne, propyne, butyne-1 and -2 and pentyne-1 by the identity of their physical properties with those prepared by Henne's substitution method from dichlorides of known structure (see Table I; for ethyne see p. 2291).

Further proof of the above-mentioned reaction scheme is the fact that butyne-1 and butyne-2 hydrofluorinate to give an *identical* reaction product, as can also be seen in Table I. Butyne-2 can yield no product with a fluorine attached to a terminal carbon atom and in this case it is shown that the second atom of fluorine entering goes to the already fluorinated carbon, as would be expected.

There is no reason to assume that the entering fluorine atoms take different or abnormal positions in the higher alkynes. A rigid characterization of these compounds, however, is hindered because there is no reaction, as yet, by which a fluorine atom in such a molecule may be converted into another atom or group.[8]

Our difluorides are completely inert and do not lose hydrogen fluoride, in contrast to alphyl fluorides,[2] a point stressed by Henne and Renoll,[5] relative to 2,2-difluoropropane. They have a not unpleasant odor, somewhat like straight chain paraffins. Their indices of refraction are substantially lower than those of paraffins of equal boiling points.

(6) A. L. Henne, M. W. Renoll and H. M. Leicester, THIS JOURNAL, **61**, 939 (1939).

(7) M. S. Kharasch, Engelmann and Mayo, *J. Org. Chem.*, **2**, 298 (1937).

(8) Cyclohexyl fluoride readily can be converted into cyclohexyl chloride by the action of antimony trichloride (unpublished work of the authors).

Experimental

Source of Reagents.—The acetylene was from Prest-O-Lite welding cylinders. The propyne was prepared by us by treating methyl sulfate with sodium acetylide prepared according to the directions of G. F. Hennion.[9] The other alkynes[10] were prepared for us by Dr. Hennion at the University of Notre Dame and fractionated before use. The anhydrous hydrogen fluoride for all these preparations was supplied in cylinders by the Harshaw Chemical Company. It was over 99% pure and contained only 0.1% of water, and less than 0.04% of residue on evaporation at 100°.

The Action of Hydrogen Fluoride on Acetylene.—Preliminary experiments showed that there was *no reaction* when acetylene was passed into hydrogen fluoride at temperatures of −70 and 0°, respectively, although at the latter temperature there was some formation of a solid polymer. In another experiment a mixture of acetylene and hydrogen fluoride in molal ratio 1:3, was passed through a nickel reaction tube packed with nickel shavings, at a temperature of 300°. At a contact time of five seconds, the acetylene went through unreacted except for the formation of a black powder in the heated part of the reaction tube. The exit gas after being freed from hydrogen fluoride had a molecular weight of 26 (acetylene = 24) and contained no constituent of higher boiling point than acetylene. Pressure experiments, however, achieved hydrofluorination of acetylene.

Experiment under Pressure at Room Temperature.—Into a stainless steel autoclave of 1 liter capacity equipped with a mechanical stirrer was charged 128 g. of hydrogen fluoride. To this was connected a line supplying acetylene under pressure from a commercial cylinder. During the course of the reaction the operator was protected by a curtain of steel and remote controls were used. With the reactor at room temperature, the pressure was raised to 13 atmospheres, a temperature rise of 3° being observed. The pressure dropped slowly over a period of hours and was maintained at 8–12 atmospheres for seventy-two hours, during which time the autoclave contents was stirred continuously. The autoclave was then cooled in an ice-bath and the pressure released through a line which scrubbed out the hydrogen fluoride vapors, dried the gas; and then passed through a trap cooled to −78°. 12 g. of water-white liquid condensed in the trap. The non-condensable gas was shown to be pure acetylene. Inside the autoclave was found 30 g. of a polymer, which when washed and dried was a brittle brownish-black solid burning with difficulty.

The condensable gas was distilled on a low temperature Podbielniak column and separated into two constant boil-

(9) Paper presented before the Indiana Academy of Science at Manchester College, November 5, 1937.

(10) A comparison of some physical properties of our butyne-1 and -2 samples will be given in another paper.

ing fractions. Fraction 1, corresponding to 35 mole %, boiled at −72° and had a molecular weight of 45 (Dumas), while fraction 2, equalling 65 mole %, boiled from −26 to −24° and had a molecular weight of 65. Approximately 15% of the acetylene reacting was converted into these two products.

These data check those described by Julius Söll of the I. G. Trust in a German patent[11] for physical constants of *vinyl fluoride* and *2,2-difluoroethane*. Söll prepared them by the *catalytic* hydrofluorination of acetylene in the presence of mercury salts and/or activated charcoal.

Fraction 1 thus corresponds to vinyl fluoride, CF_2=CHF, mol. wt. 46; b. p. −72.2 (760 mm.).[11]

Fraction 2 corresponds to 1,1-difluoroethane, CH_3—CHF_2, mol. wt., 66; b. p. −24.7 (760 mm.).[11]

The refractive index (n_D) of the 1,1-difluoroethane was 1.3011 at −72° or extrapolated to room temperature ≏ 1.255. As far as we know, this is the lowest index of refraction ever recorded for an organic or inorganic liquid compound.

The Action of Hydrogen Fluoride on Propyne and Higher Alkyl Acetylenes

Description of Apparatus and Procedure.—As shown in the attached drawing (Fig. 1) the reaction chamber was a nickel cylinder 5 cm. in diameter, 35 cm. high, and open at the top. Into this was fitted a rubber stopper carrying an oil-sealed nickel stirrer, a dropping funnel, a thermocouple, and a "cold-finger" reflux cooled by dry-ice and acetone. The cylinder was surrounded by a cooling bath of acetone and dry-ice. In the case of propyne the dropping funnel was replaced by a copper tube through which the gaseous alkyne was introduced directly into the liquid hydrogen fluoride.

A distinct temperature effect was noted during the addition of alkyne, the operation requiring around forty minutes. The reaction appeared to be instantaneous. Stirring was continued for an additional thirty minutes and the product worked up immediately. When alkynes above propyne were used, cracked ice was added to the reaction mixture, it was warmed to 0° and poured into a separatory funnel where the water insoluble reaction product was quickly removed from the hydrofluoric acid, washed several times with water, dried with potassium carbonate, and then carefully distilled. With propyne, the above procedure had to be modified so that no product was lost during the dilution of the hydrogen fluoride with water. Water was added slowly from a dropping funnel in a closed system and escaping gas was washed through dilute alkali, dried with soda lime and calcium chloride and condensed in a trap cooled to −78°.

Anal. The liquid difluorides were analyzed for carbon and hydrogen by the technique described by Schiemann and Pillarsky,[12] using, in addition to copper oxide, both lead chromate and silver gauze. The fluorine determination was carried out as previously described.[13]

Results

In our experiments about one-half gram mole of the lower alkynes and one-quarter gram mole of the hexynes and heptynes were charged into the reaction vessel and ten molecular equivalents of anhydrous hydrogen fluoride added. The temperature, initially −70°, was controlled by stirring, etc., so that it did not rise more than 5–15°. The time of addition varied from one to one and one-half hours.

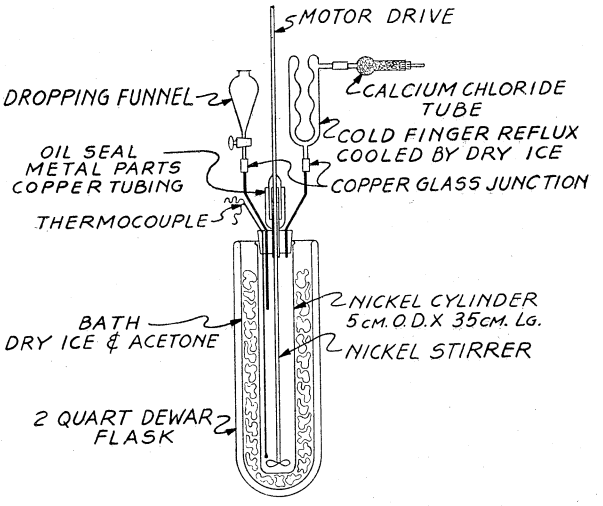


Fig. 1.

A crude liquid product, insoluble in water, was recovered which in every instance weighed 1.24 ± 0.03 times the weight of the alkyne originally charged.

The yield of difluoride based on the alkyne charged averaged 65%, but varied between the extreme limits of 46% in the butyne-1 case and 76% in the case of hexyne-3.[14]

The extreme ease of hydrofluorination of the higher alkynes, which react instantly and completely at temperatures as low as −70°, stands in contrast to the reaction of hydrogen fluoride with acetylene, where hydrofluorination was only achieved by the use of relatively high pressures and a long contact time at room temperature. This enhanced reactivity of higher alkynes contrasted to acetylene is, however, experienced in its other reactions, as recorded in the literature.

Table I gives the properties of our products as determined upon a well-fractionated and sharply boiling cut.

As can be seen from Table I the properties of difluorides formed from ethyne, propyne, butyne-1, butyne-2 and pentyne-1 are in general agreement with the predicted difluorides prepared by the method of Henne and others.

(11) German Patent 641,878.

(12) Schiemann and Pillarsky, *Ber.*, **62**, 3043 (1929).

(13) A. V. Grosse, R. C. Wackher and C. B. Linn, *J. Phys. Chem.*, **44**, 277 (1940).

(14) For additional details, see U. S. Patent 2,287,934.

TABLE I

PROPERTIES OF DIFLUORO-ALKANES FROM REACTION OF ALKYNES WITH HYDROGEN FLUORIDE

Difluoro-alkanes	B. p., °C.	Press., mm.	d^{20}_4	$n^{20}D$	$n^{-25}D$	Mol. wt. Calcd.	Found
2,2-Difluoropropane[a]	−0.1	760	0.9205[0°]	1.2904[0°]	1.3036	80.1	79
(Henne's)[b,h]	−0.6– 0.2	760	.92	..	1.3043	80.1	...
2,2-Difluoro-butane							
from butyne-1[c]	30.4–30.6	747	.9016	1.3133	..	94.1	93
from butyne-2[d]	30.4–30.6	747	.9016	1.3140	..	94.1	93
(Henne's)	30.8	760	.9012	1.3140	..	94.1	...
2,2-Difluoro-pentane	58.2– .8	749	.8904	1.3352	..	108.1	109
(Henne's)	59.8	760	.8958	1.3357	..	108.1	...
2,2-Difluoro-hexane[e]	86.0– 2	750	.8923	1.3535	1.3744	122.1	122
3,3-Difluoro-hexane[f]	86.0	742	.9024	1.3546	1.3757	122.1	120
2,2-Difluoro-heptane[g]	111.7– 9	749	.8889	1.3659	1.3866	136.1	134

[a] M. p., −104.8°. [b] M. p., −105 to −108°. [c] M. p., −116.9°. [d] M. p., −117.1°. [e] Calcd.: C, 58.97; H, 9.91; F, 31.12. Found: C, 56.4; H, 9.46; F, ≃34.1. [f] Calcd.: C, 58.97; H, 9.91; F, 31.12. Found: C, 58.76; H, 9.81; F, 31.43. [g] Calcd.: C, 61.70; H, 10.37; 29.93. Found: C, 61.51; H, 10.32; F, 28.17. We prepared about 20.8 g. of Henne's difluoride by treatment of antimony trifluoride with acetone dichloride; its mixed melting point with ours −108°.

It is important to note that the difluorides from butyne-1 and -2 were identical among themselves (see Table I; furthermore, the mixed melting point −116.9°, *i. e.*, showed no depression) and also with Henne's compound.

By-Products of the Reaction.—The hydrofluorination of propyne gave a 61% yield of the difluoride, based on the charge. The rest was accounted for in an amorphous, light brown *solid* (7 g. from 19 g. of propyne), similar to the solid encountered in the acetylene reaction. Elementary analysis of this solid showed it to have the composition: C, 79%; H, 9%; F, 12% (by difference) corresponding approximately to the formula $C_6H_{13}F$ or $3C_3H_4$, HF. In the case of alkynes above propyne the crude products on distillation yielded liquids of higher boiling point, higher refractive index and lower density than the main product, indicating alkyne *polymers* rather than fluorides.

Acknowledgment.—The authors wish to thank Mr. Willard Mann for assistance with the laboratory work pertaining to this investigation.

Summary

1. A new reaction, the direct non-catalytic, addition of hydrogen fluoride to alkynes giving a series of difluoroparaffins, of the formula R—CF_2—CH_2—R′, has been described.

2. With the exception of acetylene the alkynes studied, namely, propyne, butyne-1, butyne-2, pentyne-1, hexyne-1, hexyne-3, and heptyne-1, all reacted at temperatures around −70° to give good yields of a difluorinated paraffin.

3. The properties of 2,2-difluoro-propane, -butane, -pentane, -hexane, -heptane and 3,3-difluoro-hexane are described.

4. The hydrofluorination of acetylene was accomplished by contacting it with liquid hydrogen fluoride in an autoclave under pressure. 1,1-Difluoro-ethane and vinyl fluoride were the reaction products isolated.

NEW YORK, N. Y. RECEIVED MARCH 16, 1942

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

Tracer Studies with Radioactive Hydrogen. The Synthesis of Labelled Methyl Iodide

BY D. HARMAN, T. D. STEWART AND S. RUBEN

In connection with our work on the Menschutkin reaction[1] it was necessary to prepare methyl iodide with the methyl group labelled by the inclusion of a radioactive carbon or hydrogen atom.

There are two radioactive isotopes of carbon whose half-lives are such that they can be used as isotopic tracers, C^{11} (half-life 20.5 minutes) and C^{14} (half-life 10^3 years). Since the supply of C^{14} is limited we attempted to use the shorter lived isotope. The isotopes have already been employed in a rapid synthesis of other organic compounds.[2,3,4]

The synthesis of $C^{11}H_3I$ used may be summarized by the equations

$$C^{11}O_2 + H_2 \xrightarrow{B.\ coli} HC^{11}O_2H \quad (1)$$

$$HC^{11}O_2H + CH_3OH \longrightarrow HC^{11}O_2CH_3 + H_2O \quad (2)$$

$$HC^{11}O_2CH_3 + 2H_2 \xrightarrow[160°]{CuOCrO_3} C^{11}H_3OH + CH_3OH \quad (3)$$

$$C^{11}H_3OH + HI \longrightarrow C^{11}H_3I + H_2O \quad (4)$$

The reduction of CO_2 to formic acid was accomplished by a fresh suspension of *Bacterium coli*.[5,6]

While the above process is practicable, the time required is about three hours. It was therefore decided to label the methyl groups with radioactive hydrogen.[7] The half life of H^3 is about thirty years[8] and, moreover, samples of high specific radioactivity can be prepared. The chief difficulty in the use of H^3 is in the measurement. It emits very soft beta particles (upper energy limit 10–15 Kev)[7,8,9] and, consequently, it must be counted in gaseous form.

With radioactive hydrogen as a tracer for methyl groups there are several possible modes of preparation in addition to the one above.

$$(CH_3)NO_2 \xrightarrow{HTO} (TCH_2)NO_2 \longrightarrow (TCH_2)NH_2 \longrightarrow (TCH_2)I \quad (1)$$

$$CH_2N_2 \xrightarrow{TI} (TCH_2)I \quad (2)$$

$$CH_2N_2 \xrightarrow{TOH} (TCH_2)OH \xrightarrow{HI} (TCH_2)I \quad (3)$$

The process used here employs the apparatus developed for $C^{11}H_3I$, substituting HT for H_2.

Experimental

Preparation of $C^{11}H_3I$.—About 50 cc. of the aqueous solution of radioactive formic acid was titrated to phenolphthalein and the solution evaporated to dryness *in vacuo* at 100°. The residual sodium formate (about 0.5 g.) was placed in a semi-micro distillation apparatus and to it was added 1 cc. of a solution prepared from 25 g. of sulfuric acid and 50 g. of methanol. The first distillate of about 0.2 cc. was redistilled to give about 0.1 cc. of liquid which contained approximately 60% yield of methyl formate. This yield could be improved. The ester was converted to methanol and methyl iodide by essentially the same process as described below for the tritium derivative.

Preparation of $(TCH_2)I$.—The apparatus used, shown in Fig. 1, was designed to recover unused radioactive hydrogen which was stored in bulb I.

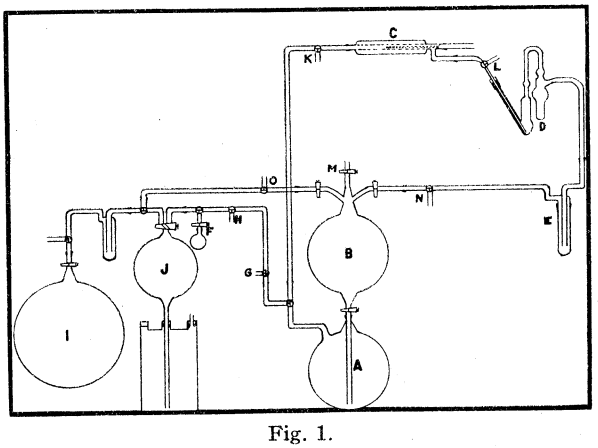


Fig. 1.

A bulb containing the methyl formate was attached at F and cooled in liquid air. The line including J, A and B was filled with hydrogen three times and evacuated. The line from K to N was swept out with a stream of hydrogen. Initially, bulb B is filled with mercury and bulb A has only enough to cover the end of the tube leading from B to A.

The reaction mixture of methyl formate and tritium (HT) was prepared in bulb A by admitting the ester to a pressure of 7.6 cm. of mercury and transferring the tritium with the help of the Toepler pump to give a total pressure of 76 cm. of mercury. This mixture was passed over the catalyst in C and through the Zeisel apparatus[10] at a rate

(1) Harman, Stewart and Ruben, THIS JOURNAL, **64**, 2294 (1942).
(2) Cramer and Kistiakowsky, *J. Biol. Chem.*, **137**, 549 (1941).
(3) Wood, Werkman, Hemingway, Nier and Stuckwisch, THIS JOURNAL, **63**, 2140 (1941).
(4) Allen and Ruben, *ibid.*, **64**, 948 (1942).
(5) Woods, *Biochem. J.*, **30**, 515 (1936).
(6) We are indebted to Professor H. A. Barker for the *B. coli* and for his helpful coöperation.
(7) Alvarez and Cornog, *Phys. Rev.*, **56**, 613 (1939).
(8) O'Neal and Goldhaber, *ibid.*, **57**, 1086 (1940).
(9) Brown, *ibid.*, **58**, 954 (1941).
(10) J. B. Niederl and V. Niederl, "Organic Quantitative Microanalysis," John Wiley and Sons, Inc., New York, N. Y., 1938, p. 187.

of about 10 cc. per minute by admitting mercury from B to A. In order to maintain atmospheric pressure mercury is added to B through M. The liquid air trap at E condensed the methyl iodide formed and unused tritium was returned through B eventually to I.

The active methyl iodide containing tritium was made in about 2 g. quantities in better than 75% yield. The crude material of d^{20}_0 1.5268 melted at about −60°. It was redistilled and the vapor passed over phosphorus pentoxide *in vacuo*.

Preparation and Use of Catalyst.—The catalyst was prepared by dissolving 120 g. of cupric nitrate in 100 cm. of water and adding a saturated solution containing 60 g. of potassium carbonate at about 50°. The precipitated basic copper carbonate was filtered off, washed well and dried; 45 g. of the pulverized material was added to 100 cc. of quartz chips (0.5 to 1 mm.) and 50 cc. of chromic acid solution containing 2 g. of CrO_3. The mixture was well stirred and dried on a steam-bath. The catalyst chamber of 3.5-cc. capacity was filled with this material and the catalyst reduced by passing about 20 cc. of hydrogen per minute over it at a temperature of 325° for six hours. Tank hydrogen was passed over the catalyst at 160°, the temperature used for the reduction of the ester, for two hours before each preparation.

Summary

Radioactive methyl iodide has been prepared by two processes, the one leading to a compound containing short-lived C^{11}, the other to a compound containing radioactive hydrogen. Each process is designed for small amounts of material.

BERKELEY, CALIFORNIA RECEIVED JUNE 8, 1942

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

A Study of the Menschutkin Reaction Using Radioactive Hydrogen as a Tracer

BY D. HARMAN, T. D. STEWART AND S. RUBEN

The reaction between amines and organic halides

$$R_3N + RX \longrightarrow R_4N^+ + I^- \qquad (1)$$

has been the subject of considerable experimentation and speculation.[1-10]

The kinetics of this reaction are of particular interest because the probability factor in the rate expression

$$\frac{d(I^-)}{dt} = k(R_3N)(RX) = PZe^{-E/RT}(R_3N)(RX) \qquad (2)$$

is unusually low, and, moreover, markedly affected by the solvent. For example, in the reaction between $C_6H_5NH_2$ and $C_6H_5COCH_2Br$ the factor P varies from 4×10^{-11} in benzene to 5×10^{-5} in benzyl alcohol.[10]

The values of log P and E in different solvents for the reaction

$$C_6H_5N(CH_3)_2 + C_6H_5CH_2Br \longrightarrow C_6H_5N^+(CH_3)_2(CH_2C_6H_5) + Br^- \qquad (3)$$

as given by V. A. Gol'tsschmidt and N. K. Vorob'ev[9] are reproduced in Table I.

TABLE I

THE ACTIVATION ENERGY AND PROBABILITY FACTOR FOR THE REACTION OF EQUATION 3

Solvent	$(CH_3)_2$-CO	C_6H_5-$COCH_3$	$C_6H_5NO_2$	C_2H_5OH
$k \times 10^4$ (30°)	80.5	84.5	118	650
E	9747	9929	11,200	13,800
$-\log P$	4.94	5.08	6.16	8.78

For other types of reaction the value of P is usually close to unity; the very low values in the Menschutkin reaction imply that very few "activated" collisions result in reaction. Many theories have been advanced to account for this abnormality and the present paper presents experimental results which offer a test of some of these explanations.

Moelwyn-Hughes and Sherman[6] have assumed that at least one of the reactants forms an unstable complex with the solvent and that the true reactant is this solvated portion. In such a case the evaluation of the product $(R_3N)(RX)$ of the rate expression is in error and the true value of P could be unity.

Hinshelwood,[5] from a consideration of Eucken's[11] work on the variation of the velocity of sound with frequency in the gas phase, and Norrish,[4] by analogy with a number of photochemical reactions, account for the apparent inefficiency of the activated collisions by assuming an intermediate collision complex which can yield the

(1) N. Menschutkin, *Z. physik. Chem.*, **6**, 41 (1890).
(2) Moelwyn-Hughes and Hinshelwood, *J. Chem. Soc.*, 239 (1932).
(3) G. E. Edwards, *Trans. Faraday Soc.*, **33**, 1294 (1937).
(4) R. G. W. Norrish, *ibid.*, **33**, 1521 (1937).
(5) C. N. Hinshelwood, *ibid.*, **33**, 970 (1937).
(6) Moelwyn-Hughes and Sherman, *J. Chem. Soc.*, 101 (1936).
(7) Stern and Eyring, *J. Chem. Phys.*, **5**, 113 (1937).
(8) Scatchard, *ibid.*, **2**, 657 (1934).
(9) V. A. Gol'tsschmidt and N. K. Vorob'ev, *J. Phys. Chem.* (U. S. S. R.), No. **4**, 473 (1939).
(10) R. G. Cox, *J. Chem. Soc.*, **119**, 142 (1921).
(11) Eucken and Jaacks, *Z. physik. Chem.*, **B30**, 85 (1935).

final products only if conditions are favorable for stabilization of the products. Otherwise the complex reverts to the reactants. Norrish, in his explanation, invoked the hypothesis of the Franck–Rabinowitch cage effect. While this hypothesis is very helpful to an understanding of what happens before highly activated intermediates (free radicals, etc.) can permanently separate, it seems doubtful if it is important in considering processes where there is very little thermodynamic tendency for recombination of the initial products of dissociation, *i. e.*, where the equilibrium state is far toward dissociation.

Edwards[3] has postulated for benzene solutions, in which the product of the Menschutkin reaction is sparingly soluble, that the reaction is primarily rapid and reversible. He presumes that the rate of the over-all reaction is governed by the rate of formation of the solid product.

$$R_3N + RX \rightleftarrows R_4N^+ + X^- \longrightarrow \text{Solid}$$

The equilibrium in solution favors the original reactants. This hypothesis takes the form of those above, in that a reversibly formed intermediate is involved in the net process.

Experimental Results and Discussion

It is possible to test the theory of a reversibly formed intermediate in the Menschutkin reaction by allowing an amine to react with an alkyl halide which contains a radioactive hydrogen or carbon atom. If the nature of the intermediate is such that the alkyl groups become spatially equivalent with respect to the halide ion before reversion to the initial reactants occurs, radioactivity should be found in the experimentally unreacted amine as well as in the alkyl halide salt. With this in mind, methyl iodide containing radioactive hydrogen or tritium (H^3) was allowed to react with trimethylamine and dimethylaniline, respectively, in both alcohol and benzene solutions.

Two equivalents of trimethylamine stood for three hours in 95% ethanol solution, with one equivalent of methyl iodide containing tritium. The reaction went to completion and the excess amine was examined for tritium content. Less than 1% of the activity to be expected on the basis of random distribution of the methyl groups between the amine and methyl iodide was obtained. An increase of amine concentration to a five-fold excess did not produce detectable interchange. The expected radioactivity appeared in the tetramethylammonium salt formed in the reaction.

Since the reaction between $C_6H_5N(CH_3)_2$ and CH_3I is very slow, the equivalent quantities of the reactants were allowed to stand for three hours at 25°, and then the unchanged $C_6H_5N(CH_3)_2$ was isolated and examined for radioactivity. No activity was found.

Ethanol as a solvent could have promoted ion separation and stabilized the initial reaction product, and, therefore, the reactions were carried out in benzene. The procedures used were the same as those employed when the reactions were carried out in ethanol except that the reaction between C_6H_5—$N(CH_3)_2$ and CH_3I was stopped after thirty minutes, which from previous experience is just prior to separation of crystals. No activity appeared in the unreacted amine in either case.

The sparingly soluble active tetramethylammonium iodide does not exchange methyl groups, at room temperature, with trimethylamine upon standing for eight hours in alcohol or for three days in benzene. The alcohol soluble tetramethylammonium chloride was prepared from the active iodide; it did not exchange with the amine in alcohol solution in eight hours.

It is evident that for the cases studied, no intermediate exists which is rapidly and reversibly formed and in which the iodide ion loses its identity with the methyl group originally present in the active methyl iodide.

Experimental

The following procedure was used for both benzene and alcohol solutions. Five cc. of 0.2 *M* radioactive CH_3I[12] solution was added to 10 cc. of 0.2 *M* trimethylamine solution contained in a 25-cc. flask. After shaking, the mixture was placed in a bath at 25°. When the reaction was carried out in alcohol, crystals began to form in about ten minutes, but with benzene as a solvent an immediate turbidity was observed. At the end of about three hours, by which time the reaction had gone to completion, the excess of amine and the solvent were removed from the salt by first freezing the contents of the flask in liquid air, connecting the latter by a wide bore tube to another flask, evacuating the system, placing the liquid air-bath around the second flask and gently warming the reaction mixture. A quantity of concentrated hydrochloric acid sufficient to convert all of the amine to the hydrochloride was then added to the distillate and the water and solvent removed at 100° under vacuum. When benzene was used as the solvent, 10 cc. of alcohol was added so that upon addition of the hydrochloric acid a homogeneous solution resulted. The flask was then equipped with a dropping funnel, an air inlet and a tube leading to a combustion furnace.

(12) D. Harman, T. D. Stewart and S. Ruben, THIS JOURNAL, **64**, 2293 (1942).

Two cc. of 50% potassium hydroxide was added to the dry salt and the amine generated was swept through a drying tube to the combustion tube by a slow stream of air. Explosions resulted from the use of pure oxygen or of too rich an air mixture. The water formed was collected in a small liquid air trap and converted to hydrogen as follows, by a procedure worked out by Mr. T. H. Norris of this Laboratory. The water was transferred to the bottom of a test-tube (29 × 300 mm.) which was then filled with magnesium turnings and connected, in a vertical position, to a glass coil which in turn was attached to a high vacuum line. After placing the lower end of the tube in liquid air the system was evacuated, the glass coil also immersed in liquid air, and an electric heater placed around the top portion of the tube. When the temperature of the heater was constant, at approximately 625°, the liquid air was removed from the bottom of the test-tube which was then gently heated to vaporize the water. The hydrogen formed was collected in a 3-liter flask on the vacuum line from which it was transferred to a Geiger counter. The counting mixture was composed of about 15 mm. mercury pressure of alcohol and 20.0 cm. mercury pressure of hydrogen. This procedure required about thirty minutes.

The data on a typical experiment are

Original reactants	
Moles methyl iodide	1.02×10^{-3}
Moles trimethylamine	2.00×10^{-3}
Equiv. of methyl group	7.02×10^{-3}
Specific radioactivity of hydrogen (counts/min./g. atom)	
From initial methyl iodide	1.85×10^{7}
From excess trimethylamine	$<1.46 \times 10^{4}$
Calcd. for random distribution	$<1.58 \times 10^{7}$

The last figure in the above calculation gives the activity to be expected in the excess amine if, during the reaction, random distribution ($6.00 \times 1.85 \times 10^{7}/7.02$) were achieved; the activity found corresponds to less than 0.1% of that predicted on the assumption. Two experiments were made in alcohol and one in benzene, as described above. One was made in alcohol in which the concentration of the amine was five times as great as that of the methyl iodide. In all cases there was no exchange within experimental error.

In order to determine whether the excess amine reacts with the quaternary salt

$$(CH_3)_4NI + (CH_3)_3N \longrightarrow (CH_3)_3N + (CH_3)_4NI$$

the amine solution was added to some of the salt formed from active methyl iodide in a previous experiment and whose activity was known. After standing for eight hours in alcohol as a solvent, or for forty-eight hours in benzene, the amine was removed and its activity, determined as above, found to be negligible.

Since tetramethylammonium iodide is not very soluble in alcohol or benzene, the experiment was repeated in alcohol using the corresponding chloride which was prepared from the same sample of iodide. No exchange was evident.

To test the possibility that, in the conversion of the amine to its hydrochloride and regeneration back to the amine, the H of the methyl groups exchanged with those of water, a 50% solution was prepared using very active water which was then used to regenerate amine from inactive trimethylamine hydrochloride. The activity of the amine was determined in the usual manner and no exchange was found.

The procedure for the reaction between dimethylaniline and methyl iodide was the same in both benzene and alcohol. Ten cc. of 0.2 *M* CH_3I was added to 10 cc. of 0.2 *M* $C_6H_5N(CH_3)_2$ and the resulting solution allowed to stand for three hours. A very few small crystals formed in this time, the quantity being greater in alcohol. The solvent and unreacted methyl iodide were separated from the quaternary salt and unreacted amine under vacuum as described above. The amount of methyl iodide in the distillate was determined as a measure of the extent of quaternization; about 1% reaction occurred. The amine was separated from the quaternary salt by treating the mixture with benzene and filtering through a fine sintered glass filter. Most of the benzene in the filtrate was removed by distillation, finally at 100° and 2-mm. pressure, and from a tube which could be placed in the combustion tube to burn the residual amine. The activity in the water was determined as above, and found to be zero within experimental error. While little net reaction had occurred, no exchange of the methyl groups was found.

Summary

Excess trimethylamine was quaternized by methyl iodide in which the hydrogen atoms were in part replaced by radioactive hydrogen or tritium. All the radioactivity was found in the quaternary salt, none in the excess amine. The solvents used were alcohol and benzene. Incomplete quaternization of dimethylaniline in alcohol or benzene produced no radioactivity in the unreacted base. It is concluded that for these cases there is no reaction intermediate which is reversibly formed and in which iodide ion loses its identity with the methyl group to which it was originally attached. Tetramethylammonium iodide or chloride does not methylate trimethylamine in alcohol solution at room temperature in eight hours; suspended in benzene no reaction occurs in three days.

BERKELEY, CALIF. RECEIVED JUNE 8, 1942

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

Some Exchange Experiments with Radioactive Tracers

BY S. RUBEN, M. D. KAMEN, M. B. ALLEN AND P. NAHINSKY

In connection with some experiments on photosynthesis in these Laboratories it was found that the centrally bound magnesium of chlorophylls *a* or *b* does not interchange[1] with Mg^{++} at room temperature in 80% acetone–water solution. This rather surprising result induced us to study various other metallo-organic exchange reactions. In this paper we report the results of the following exchange experiments: (1) Fe^{+++} and ferriheme, (2) Fe^{+++} and ferrihemoglobin, (3) Fe^{+++} and ferric pheophytin, (4) Fe^{+++} and ferric tetraphenylporphyrin, (5) Cu^{++} and cupric pheophytin, (6) Fe^{++} and ferrous ortho phenanthroline, (7) Fe^{++} and ferrous α,α'-dipyridyl, (8) Mg^{++} and magnesium 8-hydroxyquinolate.

The first 5 pairs (*i. e.*, the metallo porphyrins) showed no measurable exchange even after long periods. The remaining combinations exchanged at a slow but easily measurable rate. These results seem to indicate that structural factors are more important than covalent-ionic bond character in determining the readiness of a metallic ion (in a metallo-organic compound) to undergo exchange.

Exchange between Magnesium 8-Hydroxyquinolate and Mg^{*++}.—Since the magnesium in chlorophyll did not exchange with Mg^{++}, it was considered of interest to try the exchange with the magnesium salt of 8-hydroxyquinoline. This compound is similar in behavior to the magnesium porphyrins in that they are the only known magnesium compounds which do not form magnesium hydroxide when boiled with concentrated alkali.[2]

Radioactive magnesium, Mg^{27} (10.2 min. half life) was prepared by bombardment[3] of metallic magnesium with 8 m. e. v. deuterons for ten minutes in the 37″ cyclotron. The magnesium was dissolved in concentrated hydrochloric acid, and excess sodium hydroxide added to precipitate magnesium hydroxide. The precipitate was filtered, washed, dissolved and reprecipitated three times in order to remove the last traces of radioactive sodium (Na^{24}) which is also produced by the deuteron bombardment. The final magnesium hydroxide, rid of Na^{24}, was converted into aqueous magnesium chloride and used in this form.

A fresh precipitate of magnesium 8-hydroxyquinolate (carefully freed of excess 8-hydroxyquinoline) was shaken with Mg^{*++} for thirty minutes at room temperature. The quinolate was filtered off, thoroughly washed and found to be strongly radioactive. Indeed, although the exchange took place in a two-phase system, the quinolate contained ~60% of the radio-Mg calculated for complete interchange.

Fe^{+++}–Ferriheme and Fe^{+++}–Ferrihemoglobin.—Because of the above result it seemed pertinent to investigate metalloporphyrins other than chlorophyll. As a result of their investigations of the magnetic properties of hemoglobin and its many derivatives, Pauling and Coryell[4] have concluded that the forces holding Fe^{+++} in ferriprotoporphyrin and ferrihemoglobin are ionic. These compounds readily lend themselves for investigation, particularly since a radioactive isotope of iron, Fe^{59}, of forty-seven days' half-life[5] is known. 1.5×10^{-4} mole of Fe^*Cl_3 in 0.001 molal hydrochloric acid was added to 3×10^{-4} moles of ferriprotoporphyrin dissolved in 95% ethanol. After standing for about two months at room temperature the alcohol was evaporated off. The Fe^*Cl_3 was removed from the solid residue with 0.001 molal hydrochloric acid solution, the insoluble porphyrin being filtered off. The heme was only slightly active, containing ~2% of the Fe*. This small activity could be due to incomplete removal of Fe^*Cl_3.

In a separate experiment, 10^{-5} mole of Fe^*Cl_3 was added to an aqueous solution containing 10^{-5} mole of ferrihemoglobin[6] in a slightly acid solution. After thirty hours at room temperature the hemoglobin was precipitated with excess trichloroacetic acid and filtered off. The bulky precipitate was carefully washed and ignited to yield mainly ferric oxide. This preparation was found to be inactive, containing less than 1% of the radio-iron used. This is in agreement with the findings of Hahn, *et al.*[7]

Iron and Copper Pheophytins.—The magnesium of chlorophyll can be replaced by other metallic ions under suitable conditions without removal of the phytol or methanol. Such compounds are called pheophytins. We have found no exchange between Fe^{*+++} and iron pheophytin or between Cu^{*++} and copper pheophytin, even after two days in 80% acetone solution.

Fe^{+++}–Ferric Tetraphenylporphyrin.—This experiment was carried out in a 0.02 *N* $HClO_4$–water–ethanol–benzene solution in which both ferric and the ferric tetraphenylporphyrin[8] salts are soluble. No exchange of iron (<3%) was found after five days at room temperature.

Fe^{++}–Ferrous Ortho Phenanthroline.—The (presumably) octahedral arrangement of the six nitrogens in the orthophenanthroline complex forms a rather stable configuration around the central iron ion. It was of considerable interest to compare the lability of the metallic ion in this compound with the various organo-metallo com-

(1) Ruben, Frenkel and Kamen, *J. Phys. Chem.*, **46**, 710 (1942).

(2) B. J. Miller, Dissertation, University of Chicago, 1931.

(3) The nuclear reactions are $D^2 + Mg^{26} \longrightarrow Mg^{27} + H^1$ and $Mg^{27} \longrightarrow Al^{27} + e^-$.

(4) Pauling and Coryell, *Proc. Nat. Acad. Sci.*, **22**, 159, 210 (1936).

(5) Livingood and Seaborg, *Rev. Mod. Phys.*, **12**, 30 (1940).

(6) We are indebted to Professor C. D. Coryell for the ferrihemoglobin and for helpful advice regarding its use.

(7) Hahn, Bale, Ross, Hettig and Whipple, *Science*, **92**, 131 (1940).

(8) This compound was synthesized by Dr. S. Aronoff, and we are indebted to him for his coöperation and generosty.

pounds reported above. The results are summarized in Table I.

TABLE I

Expt. no.	Molality of $FeSO_4$	Molality of $(C_{12}H_8N_2)_3$-$FeSO_4$	Molality of H^+	Time allowed for exchange	Per cent.[a] of random distribution of Fe^{*++}
1	0.05	0.05	0.2	5 days	100 ± 5
2	.026	.022	.05	4 minutes	7 ± 2
3	.022	.012	.05	60 minutes	35 ± 5

[a] NH_4OH was used to separate ferrous ion and the ferrous phenanthroline.

From Table I it is apparent that in aqueous solution at room temperature iron is exchanged at a slow but easily measurable rate.

Fe^{++}–Ferrous α,α'-Dipyridyl Sulfate.—Ferrous α,α'-dipyridyl is somewhat similar to the phenanthroline complex in regard to structure and stability. It was of interest to study this exchange because ferrous α,α'-dipyridyl sulfate is known to be diamagnetic and Pauling has concluded[9] that the iron–nitrogen bonds are therefore mainly covalent. Thus one might be inclined to predict no exchange of iron atoms. However, this complex does exchange with Fe^{++} in aqueous solution. The results are summarized in Table II.

TABLE II

Molality of $FeSO_4$	Molality of $(C_{10}H_8N_2)_3FeSO_4$	Molality of H^+	Time allowed for exchange	Per cent. of random distribution of Fe^{*+++}
0.016	0.008	0.04	2 hours	23 ± 5

Discussion

It is interesting to note that in ferriprotoporphyrin where the iron is held by electrostatic forces, no exchange was observed even after two months. On the other hand, the α,α'-dipyridyl complex, in which the iron–nitrogen bonds are mainly covalent,[9] undergoes comparatively rapid exchange of iron. Apparently structural relations are more important than bond type.

The compounds discussed above may be separated into two classes: (1) the central metallic ion is surrounded by a fused "ring" and (2) the "ring" consists of two or more separate molecules. The magnesium, copper, and iron compounds of class (1) show extraordinary inertness toward metallic exchange, while the members of class (2) are far more labile in this respect. This difference may be due to the fact that for exchange to occur in the fused ring structures the four[10] metal–nitrogen bonds must be broken *simultaneously*[11] while for compounds of class (2) stepwise dissociation may occur so that in equilibrium with the complex there may be present in varying amounts molecular species in which the metal is held by 4, 2 or fewer bonds.

It would seem that the symmetrical planar electrostatic porphyrin ring is sufficiently strong at room temperature and moderate *p*H to prevent any reversible equilibrium involving the central metal ion. Indeed, we are tempted to generalize and say that at room temperature all metallic-fused "rings" (porphyrins, porphyrazines, phorbins, phthalocyanines, etc.) will not exchange with metallic ions in slightly acid solution. Accordingly, we would predict that disodium phthalocyanine[12] will not exchange with Na^+.

The inertness of metal porphyrins (and similar pyrrole condensed ring structures) toward exchange should be of much help in the study of certain problems in nuclear physics, namely, the search for genetic relations between nuclear isomers,[13,14] where it is imperative to find a compound that will not exchange with the daughter (lower state) isomer.

Acknowledgments.—We are indebted to Professors K. S. Pitzer and G. Mackinney for helpful discussions, and to Dr. S. Aronoff for his cooperation. We wish to thank Professor E. O. Lawrence and the members of the Radiation Laboratory for making these experiments possible.

Summary

1. Magnesium 8-hydroxyquinolate exchanges quite readily with Mg^{++}.

2. Neither ferriheme nor ferrihemoglobin, both of which are paramagnetic, exchanges with Fe^{+++}.

3. Copper and iron pheophytins also do not exchange with Cu^{++} and Fe^{+++}.

4. Ferric tetraphenylporphyrin does not exchange with Fe^{+++} over a period of five days.

5. Ferrous orthophenanthroline exchanges slowly with Fe^{++}.

6. Ferrous α,α'-dipyridyl, which is diamagnetic, also exchanges slowly with Fe^{++}.

7. It appears that the rate of exchange depends more on structure than on bond type (*i. e.*, covalent or ionic).

8. It is suggested that metallo porphyrin compounds may be of help in the search for nuclear isomers among the metallic elements.

BERKELEY, CALIFORNIA RECEIVED JUNE 9, 1942

(9) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, p. 109.

(10) Because of resonance.

(11) We are indebted to Professor K. S. Pitzer for this suggestion.

(12) Barrett, Dent and Linstead, *J. Chem. Soc.*, 1719 (1936).

(13) Segre, Halford and Seaborg, *Phys. Rev.*, **55**, 321 (1939).

(14) De Vault and Libby, *ibid.*, **55**, 322 (1939).

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

Tracer Studies with Radioactive Carbon. The Synthesis and Oxidation of Several Three Carbon Acids

BY P. NAHINSKY, C. N. RICE, S. RUBEN AND M. D. KAMEN

Many three carbon acids, when oxidized with alkaline permanganate, yield one mole each of oxalate and carbonate. Interest in the mechanism of these reactions was aroused when it was discovered[1,2] that with propionate the carbonate is derived mainly from the beta carbon rather than the carboxyl group. In an attempt to learn more about the mechanism, labelled propionate, α- and β-hydroxypropionates have been synthesized and oxidized in the presence of varying concentrations of sodium hydroxide.

Oxidation of Oxalate.—It was found by Wood, *et al.*,[1] that in 0.1 *N* sodium hydroxide the oxalate to carbonate ratio was not one, as found by McNair,[3] but considerably less. This low ratio could be due to further oxidation of the oxalate since it is well-known that permanganate in acid solution oxidizes oxalic acid. Accordingly, the oxidation of oxalate by alkaline permanganate at 100° was investigated. 0.05 *M* sodium oxalate was heated with excess saturated potassium permanganate in varying concentrations of base. After reduction of the excess MnO_4^- by hydrogen peroxide at 0° the manganese dioxide was removed and washed with distilled water. The filtrate and washings were acidified to liberate carbon dioxide, which was swept out with nitrogen and absorbed in 0.3 *N* sodium hydroxide. The $CO_3^=$ was precipitated as calcium carbonate, filtered, dried and weighed. The data are summarized in Table I.

TABLE I

OXIDATION OF OXALATE BY ALKALINE PERMANGANATE

NaOH concn. (moles/l.)	Time for heating, minutes	% Oxalate oxidized
10^{-4}[a]	60	19
0.1	80	3
2	60	0 (<0.4)

[a] Buffered solution.

It is apparent from Table I that only at low hydroxide concentrations is oxalate oxidized at an appreciable rate. Thus, in 2 *N* sodium hydroxide <0.4% of the oxalate was oxidized. This is indeed interesting since it can be estimated[4] that the standard free energy change for the reaction

$$3C_2O_4^= + 2MnO_4^- + 4OH^- = 6CO_3^= + 2MnO_2 + 2H_2O \quad (1)$$

is ~ -250 kilocalories. The oxidation of oxalate cannot be the cause of its low recovery from the propionate oxidation. We have found, because of the low solubility of sodium oxalate in sodium hydroxide solutions, that an appreciable fraction is included or otherwise carried down with the manganese dioxide precipitate. The oxalate is easily extracted from the precipitate by thoroughly washing with distilled water at 100°. If this precaution is observed, and care is taken to exclude carbon dioxide from all external sources, the carbonate to oxalate ratio for propionate, lactate and β-hydroxypropionate is 1.00 ± 0.03 for hydroxide concentrations of 2 *N* and greater.

Synthesis and Oxidation of Propionate.—For the experiments described in this paper the short-lived radioactive isotope of carbon, C^{11} (20.5 minute half life) was used as a tracer. The C^{11} was prepared by bombardment of boron with 8 mev. deuterons. The yield for the nuclear reaction

$$_1D^2 + {}_5B^{10} \longrightarrow {}_6C^{11} + {}_0n^1$$

is appreciable at bombarding energies of ~2 mev. Although elementary boron gives the highest yield of C^{11}, boric oxide or boric acid are more satisfactory targets since the newly formed C* is expelled under bombardment almost completely as volatile oxides of carbon.[5,6] Thus the extraction of the radioactivity was achieved with minimum loss of time. The type of target chamber described by Kurie[7] was used in this work. The active gas, (to which ~10 cc. of tank carbon dioxide was added as carrier) from the target chamber was passed into a heated combustion tube containing cupric oxide and oxidized to carbon dioxide. The carbon dioxide was trapped in a glass spiral immersed in liquid air.

(1) Wood, Werkman, Hemingway, Nier and Stuckwisch, THIS JOURNAL, **63**, 2140 (1941).

(2) Nahinsky and Ruben, *ibid.*, **63**, 2275 (1941).

(3) McNair, *ibid.*, **54**, 3249 (1932).

(4) Latimer, "The Oxidation States of the Elements and Their Potentials in Aqueous Solutions," Prentice-Hall, New York, N. Y., 1938.

(5) Ruben, Kamen and Hassid, THIS JOURNAL, **62**, 3443 (1940).

(6) Yost, Ridenour and Shinohara (*J. Chem. Phys.*, **3**, 133 (1935)) found this to be the case to a lesser extent when bombarding at lower energies and intensity than those employed in our experiments.

(7) Kurie, *Rev. Sci. Instruments*, **10**, 199 (1939).

The propionate* was prepared by treating CH_3CH_2MgBr (in ether) with C^*O_2 for a few minutes at room temperature. The excess Grignard was hydrolyzed with dilute sulfuric acid and the small amount of unreacted C^*O_2 along with the ether was removed by boiling. Propionic acid was rapidly distilled (at low pressure) from this mixture, excess solid silver sulfate being added to prevent the distillation of hydrobromic acid. Trial experiments showed no hydrobromic or sulfuric acid in the distillate and, moreover, the yield of labelled propionic acid to be ~95%.

After purification of the labelled propionic acid and addition of carrier propionic acid, it was treated with a slight excess of potassium permanganate in varying concentrations of sodium hydroxide at 100° for periods ranging from one-half to two hours. The C^{11} content of weighed aliquots was determined with a thin-wall (0.1 mm. Al) Geiger counter. The weighed precipitates (~0.05 g.) were firmly and evenly distributed on a 5 × 7 cm. rectangle of blotting paper and held in position with a thin film of Duco cement and covered with cellophane. These samples were wrapped around the counter so that the most favorable geometrical conditions for detection of the emitted particles were obtained. The oxalate* was precipitated as $CaC_2O_4 \cdot H_2O$, and counted in the same manner. The results are summarized in Table II.

TABLE II

PERMANGANATE OXIDATION OF LABELLED PROPIONATE

Expt.	Concentration of NaOH, moles/liter	Per cent. of C* in $CO_3^=$		Per cent. of C* in $C_2O_4^=$		$\frac{\alpha C\text{-}\beta C \text{ rupture}}{\alpha C\text{-}COO^- \text{ rupture}}$
1	10^{-4}–10^{-5} (HCO_3^- Buffer)	28.2		71.8		
2	10^{-4}–10^{-5} (HCO_3^- Buffer)	27.6	28.9	72.4	71.1	2.5
3	0.1	30.7		69.3		
4	2	27.8		72.2		
5	2	30.4		69.6		
6	6	16.5		83.5		5.1
7	11	14.2	13.1	85.8	86.9	
8	11	12.1		87.9		6.6

If the carbonate were derived only from the carboxyl group of the propionic acid, the oxalate, of course, would be devoid of labelled carbon. From the results shown in Table II it is evident that *not only does alpha–beta rupture occur two to six times as often as alpha-carboxyl scission, but that the former process, moreover, is favored significantly by increase of OH^- concentration.*

In addition to the effect of hydroxide ion concentration on the splitting ratio, there is a marked effect upon the rate of the propionate oxidation. The oxidation rate is increased by hydroxyl ion, the rate varying approximately linearly with OH^- concentrations above 2 *N*. This fact should be contrasted with the effect of base upon the oxidation of oxalate by permanganate, where it is found that increasing hydroxyl ion concentration decreases the rate of oxidation so that at 2 *N* concentration there is no observable oxidation. In one hour permanganate in 2 *N* sodium hydroxide at 100° oxidizes ~80% of the propionate in a 0.2 *M* solution. Under the same conditions α- and β-hydroxypropionate are completely oxidized within a few minutes. It was of interest to observe the very large increase in oxidation rate brought about by the presence of a hydroxyl group in either the α or β carbons. If lactate or β-hydroxypropionate are intermediates[8] in the alkaline oxidation of propionate, it follows that the attack upon the ethyl group is the slowest step in the process.

It is desirable to point out that any possible exchange reactions between labelled carbonate ions and any of the possible "active" intermediates, or oxalate, are excluded by the following experiments: (1) Inactive propionate was oxidized in the presence of radioactive carbonate. The oxalate formed during the reaction, as well as the remaining unoxidized propionate, was completely inactive (<0.01% exchanged). (2) Inactive oxalate and radioactive carbonate in 2 *N* sodium hydroxide, and in contact with freshly precipitated manganese dioxide for one hour at 100° did not exchange (<0.01%).

Synthesis and Oxidation of Lactate.—Radioactive lactic acid was synthesized from $C^{11}O_2$ and CH_3CHO by the method described by Cramer and Kistiakowsky.[9] The reactions are

$$C^*O_2 + 4K + NH_3 \xrightarrow{525°} KC^*N + 2KOH + KH \quad (2)$$

$$C^*N^- + CH_3CHO + H_2O \rightleftharpoons CH_3CHOHC^*N + OH^- \quad (3)$$

$$CH_3CHOHC^*N + 2H_2O \xrightarrow{H^+} CH_3CHOHC^*OO^- + NH_4^+ \quad (4)$$

After addition of carrier lactic acid the labelled acid was purified by treating the cyanohydrin hydrolysate with decolorizing carbon which contained no acid-soluble impurities. Trial experiments showed that <5% of the lactic acid was

(8) The formation of volatile acids (acetic, etc.) other than carbon dioxide during the propionate oxidation could not be detected.

(9) Cramer and Kistiakowsky, *J. Biol. Chem.*, **137**, 549 (1941).

absorbed. The radioactive acid was separated from the volatile impurities by distillation of the clarified solution *in vacuo*. Cyanide was shown to be absent from the high boiling material (any cyanide present would be oxidized by permanganate to carbonate, and thereby not only raise the carbonate/oxalate ratio but also introduce extraneous C* in the carbonate fraction). Having been made alkaline, the high boiling solution was extracted with several portions of ether, and was freed of dissolved ether by bubbling nitrogen through it for ~ ten minutes. The lactate was oxidized under the conditions described for propionate, only a few minutes being required in this case. A carbonate to oxalate ratio of 1.00 ± 0.03 was obtained when care was taken to exclude carbonate from external sources and the purification described used.

The results are summarized in Table III.

TABLE III

PERMANGANATE OXIDATION OF LABELLED LACTATE

Expt.	NaOH concn. moles/l.	Per cent. of C* in CO_3^-		Per cent. of C* in $C_2O_4^-$		$\frac{\alpha C\text{-}\beta C \text{ rupture}}{\alpha C\text{-}COO^- \text{ rupture}}$
1	2	35.1	31.9	64.9	68.1	2.1
2	2	28.8		71.2		
3	12	34.8	32.2	65.2	67.8	2.1
4	12	37.8		62.2		
5	12	29.0		71.0		
6	12	27.4		72.6		

It seems, within the experimental limits of error, that hydroxide ion has little or no effect on the αC-βC rupture to αC-COO^- rupture ratio. A comparison of Tables II and III shows that although the ratios for propionate and lactate in 2 *N* sodium hydroxide are about the same, the propionate oxidation alone exhibits a marked response to concentrations of OH^- greater than 2 *N*.

Synthesis and Oxidation of β-Hydroxypropionate.—β-Hydroxypropionate[10] marked with C^{11} in the carboxyl position was prepared from C^*N^- and CH_2ClCH_2OH by the reactions

$$CH_2OHCH_2Cl + C^*N^- \longrightarrow CH_2OHCH_2C^*N + Cl^- \quad (5)$$

$$CH_2OHCH_2C^*N + OH^- + H_2O \longrightarrow CH_2OHCH_2C^*OO^- + NH_3 \quad (6)$$

The alkaline solution of KC^*N prepared by Cramer and Kistiakowsky's method[9] (equation 4) was evaporated almost to dryness, and the residue taken up with a small volume of absolute alcohol containing 2-chloroethanol.[11] After being refluxed at 100° for forty minutes, the solution was cooled to 0°, and β-hydroxypropionitrile was added as carrier for the labelled nitrile. The solids separating out on cooling were removed, and alcohol, water and some 2-chloroethanol were distilled from the clear solution *in vacuo*. Next, the remainder of the 2-chloroethanol and the β-hydroxypropionitrile were vacuum distilled off, and a second distillation of this mixture was made to separate the two. Carbonate–bicarbonate buffer solution was added to the alcoholic solution prior to the first distillation in order to prevent distillation of any formate* formed by hydrolysis of cyanide* ion. In the final distillate no HC*N could be detected using the sensitive Prussian blue test. In order to obtain β-hydroxypropionate*, the pure nitrile* was hydrolyzed in concentrated sodium hydroxide solution for ten minutes at 100°. As in the case of the other acid anions, the carbonate to oxalate ratio obtained on oxidation was found to be 1.00 ± 0.03 when precautions were taken to exclude carbon dioxide from external sources. The results are given in Table IV.

TABLE IV

OXIDATION OF LABELLED β-HYDROXYPROPIONATE

Expt.	NaOH concn., moles/l.	Per cent. of C* in CO_3^-		Per cent. of C* in $C_2O_4^-$		$\frac{\alpha C\text{-}\beta C \text{ rupture}}{\beta C\text{-}COO^- \text{ rupture}}$
1	2	28.7	28.9	71.3	71.1	2.5
2	2	29.1		70.9		
3	12	30.0	26.8	70.0	73.2	2.7
4	12	23.6		76.4		

Discussion

Aside from the fact that the α-β carbon bond is broken about two and one-half times as often as the α-carbon–carboxyl bond, it is surprising that at moderate hydroxide ion concentrations all three acid anions yield the same result. This suggests that under these conditions lactate or β-hydroxypropionate are intermediates in the oxidation of propionate. The finding that at concentrations of OH^- above 2 *N*, propionate undergoes even greater preferential α-β rupture while lactate and β-hydroxypropionate exhibit no such effect indicates that *in highly alkaline solution the α-β bond in propionate is broken before either of these positions is hydroxylated.*

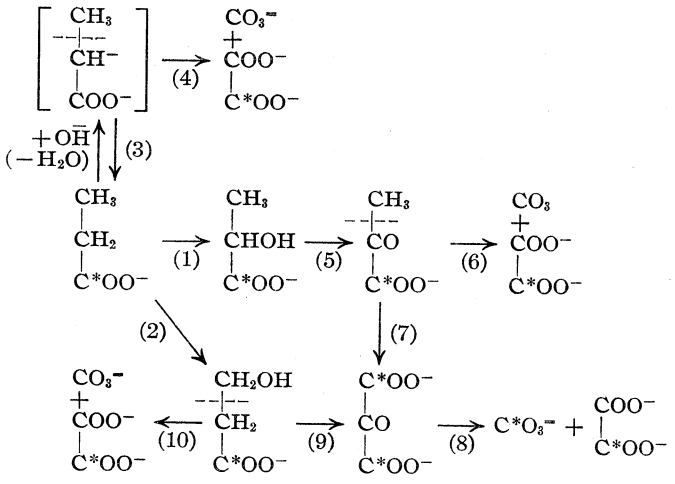
Although the oxidation of propionate, lactate and β-hydroxypropionate is quite complicated, it may be profitable to formulate a sequence of possible intermediates. The outline suggested below correlates the results obtained thus far, and also

(10) Jacobs and Heidelberger, THIS JOURNAL, **39**, 1469 (1917).

(11) Eastman Kodak Co. product redistilled, and having a boiling point of 128–129°.

leads to further predictions and suggests future experiments.

TENTATIVE FORMULATION OF PROPIONATE OXIDATION BY ALKALINE PERMANGANATE



The mesoxalate formed from pyruvate by step (7) is "symmetrical" and therefore the C* content of the carbonate and oxalate formed in (8) will be equal. It is evident from Tables II, III and IV that the rate of (6) is almost equal to the rate of (7), and (10) proceeds at approximately the same rate as (9). In other words *the α-β link is often ruptured before mesoxalate is produced.* While the ratios of (6)/(7) and (9)/(10) are independent of the hydroxide concentration, step (3) is favored over (1) and (2) by increasing alkalinity. The primary step in (3) is the reversible removal of hydrogen ion by OH^- resulting in the formation of $H_3C-\overset{\cdot\cdot}{\underset{H}{C}}-COO^-$ which due to the unshared electron pair may be more susceptible to oxidation.

Summary

1. Methods for the rapid synthesis of $CH_3CH_2C^*OOH$, CH_3CHOHC^*OOH, and $CH_2OHCH_2C^*OOH$ using $C^{11}O_2$ are described.

2. Oxidation of these acid anions by alkaline permanganate yields one mole of carbonate and oxalate each.

3. Oxalate is remarkably inert to alkaline permanganate (2 *N* in sodium hydroxide) even at 100°.

4. For propionate in hydroxide solutions of from 10^{-4} to 2 *N* concentration ~71% of the carbonate is derived from the β-carbon. At higher hydroxyl ion concentration the α-β carbon bond is broken even more preferentially.

5. No exchange between $C^*O_3^=$ and $C_2O_4^=$ could be detected.

6. With lactate and β-hydroxypropionate, ~70% of the carbonate originates from the β-carbon, and this value, within the experimental error, is unchanged by altering the hydroxide ion concentration from 2 to 12 *N*.

7. The results indicate that with propionate the α-β carbon bond is broken in strongly basic solutions before either α- or β-hydroxypropionate can be formed as an intermediate in the oxidation.

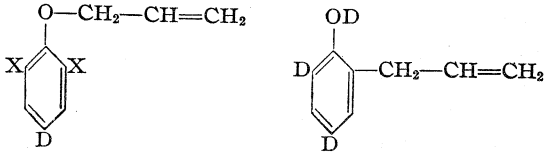
BERKELEY, CALIFORNIA RECEIVED JULY 6, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

Use of Deuterium as a Tracer in the Claisen Rearrangement

BY G. B. KISTIAKOWSKY AND ROBERT L. TICHENOR

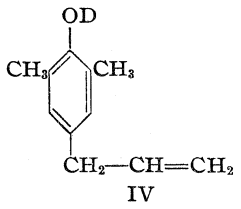
In the mechanisms proposed for the Claisen rearrangement[1] the assumption is made that the hydrogen atom displaced by the migrating allyl group moves to the oxygen atom of the resulting phenol. It was thought that definite evidence of the movement of the displaced hydrogen atom could be obtained by using deuterium as a tracer. We have, therefore, carried out the rearrangement of the allyl ethers of 2,4,6-trideutero-phenol (I) and 4-deutero-2,6-dimethyl-phenol (III). Our results are summarized in Table I.



I(X = D) ⟶ II II

III(X = CH_3) ⟶ IV

(1) D. Stanley Tarbell, *Chem. Rev.*, **27**, 495 (1940).



IV

The acetate of IV formed during the analysis for phenolic deuterium showed no detectable deuterium content (analysis by combustion and infrared absorption, estimated << 0.25% deuterium in the resulting water).

TABLE I

Expt. No.	Compound	% D in indicated positions Calcd.[a]	Found[b]	% D on oxygen after rearrangement Calcd.	Found
1	Allyl 2,4,6-trideuterophenyl ether	51	51	51	15[e]
2		77	70	70	52
3		77	70	70	52
4	2-Allyl-4,6-dideuterophenol	50			2.5[e]
5	Allyl 4-deutero-2,6-dimethylphenyl ether	72.3	< 20[d]	< 20	15
6		72	< 20[d]	< 20	13

[a] Assuming equilibrium between the indicated positions, the phenolic hydrogen (the phenol was deuterated before the ether was made) and the heavy water. Losses in alkylation were neglected. [b] Calcd. from total analyses (combustion) and assumption all the deuterium was on the indicated positions. [e] After heating the phenol, not after a rearrangement; see text. [d] These are upper limits assuming all the deuterium in the 4-position. If the methyl groups had been deuterated a far higher value (factor of 21) should have been found. [e] This low value can be attributed to poor technique in this first experiment.

This result together with 5 and 6 of Table I allow us to conclude that in the rearrangement of III all the displaced hydrogen goes to the oxygen; none is to be found elsewhere in the molecule. We may also conclude that the structure of III is correct, *i. e.*, that deuteration of the methyl groups and the meta positions was negligible.

From results 2 and 3 of Table I we see that 74% of the displaced hydrogen of I moves to the oxygen, but some 26% is unaccounted for. The low figure may be due to (1) loss of deuterium by exchange during evolution of hydrogen chloride (see analysis) or (2) to some exchange with other hydrogen of the molecule subsequent to rearrangement. Reason (2) is partly excluded by result 4 of Table I. (1) is reasonable in view of the known exchanges of esters.[2]

(2) Hsü, Ingold and Wilson, *J. Chem. Soc.*, 79 (1938).

Kincaid and Tarbell[3] have found that the rate of ortho rearrangement is first order. It is unlikely that a unimolecular reaction proceeds by two paths of nearly equal free energies of activation. Our results with III indicate that its rearrangement proceeds by a single path. In view of these two facts we are rather inclined to say that the rearrangement of I goes by a single path and that our low results can be attributed to experimental errors.

Result 4 of Table I shows that negligible exchange occurs between the phenolic hydrogen and deuterium in the ortho and para positions of 2-allyl phenol when the phenol is subjected to a heat treatment equal to that employed in the rearrangement of I.

Our picture of the movement of the hydrogen atom in the para rearrangement is not that of a directed jump, but rather that the proton is displaced by the migrating allyl group and subsequently finds its way to some oxygen anion.

Experimental

Deuteration of Phenols.—Ordinary phenol was deuterated by exchange with heavy water in the presence of hydrogen chloride for the time (two hours) and temperature (100°) shown by Koizumi[4] to be necessary for attaining equilibrium. Best and Wilson[5] have shown that only the ortho and para positions of phenol are deuterated under these conditions. 2,6-Dimethylphenol was deuterated by allowing it to exchange with heavy water for thirty hours at 100° in the presence of hydrogen chloride. No previous work has been done on its deuteration and we made no direct determination of the amount of substitution, but subsequent analyses of the ethers showed that the methyl groups and the meta positions did not exchange. We can explain the very low amount of deuterium in the 4 position (< 20% instead of a calculated 72%) by an increased rate of loss during the formation of the ether or by a failure to attain equilibrium in the initial exchange. These analyses of III (Table I) are an upper limit and thus prove that the methyl groups and the meta positions are not deuterated.

Preparation of Ethers.—13.5 g. (0.34 mole) of sodium hydroxide, 25 cc. of water, 15 cc. of freshly distilled allyl bromide, 25 cc. of acetone and 10 g. (0.106 mole) of 2,4,6-deuterophenol (or 13 g. of 2,6-dimethyl-4-deuterophenol)[6] were added quickly in this order to a 3-neck, 250-cc. flask equipped with a wire stirrer, reflux condenser and dropping funnel. The mixture was stirred and refluxed for two hours, cooled, extracted with petroleum ether, and the extract washed with sodium hydroxide, then with water and finally dried over magnesium sulfate (neutral drying

(3) Kincaid and Tarbell, THIS JOURNAL, **61**, 3085 (1939).
(4) Masao Koizumi, *Bull. Chem. Soc., Japan*, **14**, 353 (1939).
(5) A. P. Best and C. L. Wilson, *J. Chem. Soc.*, 28 (1938).
(6) We wish to thank Dr. W. E. Vaughan and the Shell Development Co. for the gift of 2,6-dimethylphenol.

agent to slow exchange). After concentration on the steam-bath the allyl phenyl ether was distilled at a pressure of 10 mm. (2 mm. for allyl 2,6-dimethylphenyl ether) through a small Podbielniak column. A faint yellow color persisted in all our preparations of allyl 2,6-dimethylphenyl ether. All the other compounds were colorless and all of them had boiling points and refractive indices in agreement with those in the literature.

Rearrangement.—The purified ether was placed in a clean Pyrex tube, cooled, evacuated, frozen and melted under vacuum to remove dissolved gases and then sealed off. The tube was heated in a Wood's metal bath until samples of the non-deuterated phenyl ether, rearranging simultaneously, were found to be almost entirely soluble in 20% sodium hydroxide solution. Bath temperatures and times: allyl phenyl ether, 230–240°, five to six hours; allyl 2,6-dimethylphenyl ether, 190–200°, four to five hours.

Analysis of Phenolic Hydrogen.—Three to four grams of the product of rearrangement, 3 cc. of acetyl chloride and a boiling chip were placed in the reaction bulb of a gas train, and the hydrogen chloride which evolved was swept through a dry ice–acetone-cooled trap to remove acetyl chloride, and was collected in a liquid air trap. The liquid air trap was then cut off from the gas train, evacuated and the gas allowed to evaporate into the evacuated infrared absorption cell. A reservoir of ordinary hydrogen chloride was connected to the filling system so that the pressure in the cell could be increased if insufficient gas was obtained from the phenol. When hydrogen chloride was added from the reservoir, the gases were mixed by freezing down in a liquid-air trap.

The infrared absorption of the resulting mixture of hydrogen and deuterium chlorides was measured over the absorption region for both components (3.46 and 4.8 μ).[7] The measurements were made at a total pressure of 368 mm. with a cell 20 cm. long. From the infrared absorption plates a curve of absorption percentage *vs.* wave length was obtained, and by measuring the area of the bands we can estimate the concentration of deuterium by comparing the area with the areas observed when known concentrations of deuterium were present. In determining the area of an absorption band there is considerable uncertainty in determining the base line (the blank). It was found that this base line apparently varied as the cell was used, and, therefore, in all measurements the edges of the absorption curve on either side of the absorption region were used as a base line. This was probably the greatest source of error in the analyses. The accuracy of analysis of a deuterium chloride–hydrogen chloride mixture was not better than ±5% but was sufficient for the present purpose.

Hydrogen Chloride and Deuterium Chloride.—Hydrogen chloride was obtained by dropping hydrochloric acid onto sulfuric acid. Deuterium chloride was made by the method of Langseth and Klit.[8] The resulting gas probably contained traces of sulfur dioxide. The thionyl chloride which we used was purified as recommended by Fieser.[9]

Analysis for Deuterium on Carbon.—Nuclear deuterium was determined by combustion and the density of the resulting water found by the falling drop method or by use of the interferometer.[10]

Acetate of 4-Allyl-2,6-dimethylphenol.—As a check on the course of the reactions used to produce hydrogen chloride, the resulting acetates were purified and identified by their physical constants or by analysis. The acetate of 4-allyl-2,6-dimethylphenol is a new compound, a colorless oil, b. p. (2 mm.) 105–110°, bath temperature 146–160°, $n^{25}D$ 1.5050. *Anal.* Calcd. for $C_{13}H_{16}O_2$: C, 76.42; H, 7.90. Found: C, 76.81; H, 8.33. The phenol from which this acetate was prepared was carefully purified and found to melt at 26–27°, $n^{25}D$ 1.5356. The phenylurethan of this phenol melted at 137–139° (uncor.) after two recrystallizations from ligroin.

Polymerization During Rearrangement.—We were troubled at first by a polymerization of allyl phenyl ether similar to that described by Hurd.[11] Occasionally, some would polymerize during the rearrangement, whereas much of our material gave 95% yields of the expected phenol. It was found that the addition of one drop of allyl bromide to 2 g. of the ether (which was known to rearrange normally) produced polymerization. None of the other reactants or products acted in this manner. Careful removal of allyl bromide during distillation (prevention of diffusion of allyl bromide from first fraction into later fractions in the multiple receiver of the still by removal of first fraction before completing the distillation) gave, in all cases, an ether which rearranged without darkening or polymerization.

Summary

1. The deuterium atom displaced by the migrating allyl group in the Claisen rearrangement of allyl 4-deutero-2,6-dimethylphenyl ether becomes the phenolic deuterium of the product.

2. It has been shown that the bulk of the deuterium displaced by the migrating allyl group in the rearrangement of allyl 2,4,6-trideuterophenyl ether becomes the phenolic deuterium of the product. It is likely that all the displaced deuterium becomes phenolic deuterium.

3. Phenolic tautomerism of 2-allylphenol was not observed to occur to an appreciable extent on heating for the time and temperature necessary to rearrange allyl phenyl ether (six hours at 210–230°).

4. A new method for estimating the deuterium content of hydrogen chloride–deuterium chloride mixtures has been outlined. It has been used in estimating the deuterium content of phenolic hydrogen.

CAMBRIDGE, MASS. RECEIVED JUNE 6, 1942

(7) We used the instrument described by Gershinowitz and Wilson, *J. Chem. Phys.*, **6**, 197 (1938). We wish to thank Professor E. Bright Wilson, Jr., for advice and help in operation of the spectrograph.

(8) A. Langseth and A. Klit, *Kgl. Danske Videnskab. Selskab. Math.-fys. Medd.*, **15**, No. 13, 22 (1937); *Chem. Abs.*, **32**, 2515 (1938).

(9) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, 1935, p. 339.

(10) We thank Edward S. Lewis for the use of his apparatus and for the analysis of several samples. The apparatus is described by Keston, Rittenberg and Schoenheimer, *J. Biol. Chem.*, **122**, 227 (1937).

(11) Charles D. Hurd and Louis Schmerling, THIS JOURNAL, **59**, 107 (1937).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY]

Solubility of Potassium Iodate and Zinc Iodate in Dioxane–Water Mixtures; Effect of Sorting of Solvent Molecules

BY J. E. RICCI AND G. J. NESSE

In the further study of the relationship between the solubility of electrolytes and the dielectric constant of the medium, measurements have been made of the solubilities of potassium iodate and zinc iodate in dioxane–water mixtures at 25° over the complete range of concentrations from 0 to 100% dioxane at intervals of 10% by weight; the measurements thus extend over a dielectric range from 2.10 to 78.55. The results have been used to test the empirical relation between the solubility of slightly soluble electrolytes and the dielectric constant of the solvent, previously reported by Ricci and Davis.[1] An attempt has also been made to estimate the mean ionic radius of these salts by using the Debye expression for the distribution of solvent molecules in a dielectric mixture around ions,[2] in conjunction with the fundamental Born equation relating electrolyte solubility, ionic radius and dielectric constant.[3]

Materials.—A C. P. grade of potassium iodate was used both for the solubility determinations and for the standardization of the silver nitrate solution used in the analyses.

The zinc iodate was prepared by mixing dilute solutions of sodium iodate and zinc nitrate in stoichiometric proportions. The solutions were poured slowly into a large beaker with constant mechanical stirring. The zinc iodate was obtained by evaporating some of the liquid, filtering, washing and drying at 100°. Volumetric analysis by the method described below gave a value of 99.3% $Zn(IO_3)_2$; the additional 0.7% probably represented water not readily driven off by heat without decomposition of the salt.

The dioxane was purified and its purity verified as described in similar investigations.[4]

Solubility Determinations and Analysis.—Mixtures of dioxane and water, prepared in the desired proportions by direct weighing, were stirred with excess of the salt, in 250-ml. glass-stoppered Pyrex bottles. To avoid the introduction of foreign matter into the solutions, vaseline was omitted entirely in stoppering the tubes containing solvents of high dioxane ratio. Sufficient time (two to seven days) was allowed for the attainment of equilibrium, which was verified by determining every solubility from both under- and super-saturation.

For the analysis of the saturated solutions, gravimetric methods were first tried, but discarded. Precipitation and weighing of the iodate as the silver or lead salt from solutions containing zinc ion, gave low results, possibly because of co-precipitation of zinc iodate. Iodometric titration also was discarded because of the difficulty involved in removing the interfering dioxane. Precipitation of barium iodate followed by iodometric titration of the washed precipitate also gave low results. The method finally used involved reduction of iodate to iodide by sodium bisulfite, the excess of reagent being removed by acidification and boiling with dilute sulfuric acid. Except in high dioxane solvents (> 77% for potassium iodate, > 40% for zinc iodate), in which the solubilities are very low, the resulting iodide solution was then analyzed volumetrically, at a *p*H of 9–10, by titration with standard silver nitrate, with eosin as indicator. An appropriate blank was calculated from a series of standardizations against pure potassium iodate similarly treated. For the very low solubilities the iodide was determined gravimetrically as silver iodide; the relative precision of some of these results is very low compared to the volumetric determinations.

Although the literature reports a di-hydrate of zinc iodate,[5] the solid phase in the present experiments was apparently the anhydrous salt. The solid residue from several of the solubility determinations was analyzed after filtration and centrifuging, giving an average of 99.3% $Zn(IO_3)_2$, ranging between 99.0 and 99.5%. KIO_3 is known to form no hydrates, and no analysis was made of this salt as solid phase.

The results of the solubility determinations are given in Table I[6]; each value is the average of at least one determination from each direction of approach to equilibrium. In the iodometric determinations the agreement between such values was about 2/1000 for potassium iodate and 6–7/1000 for zinc iodate. The gravimetric determinations were less precise. The necessary densities required for the calculation of molarities from weight percentages were

TABLE I

SOLUBILITY OF POTASSIUM IODATE AND ZINC IODATE IN DIOXANE–WATER MIXTURES, AT 25°

Wt. % dioxane	Dielectric constant	KIO_3		$Zn(IO_3)_2$	
		Wt. %	Moles/l.	Wt. %	Moles/l.
0	78.55	8.472	0.4238	0.6410	0.01548
10	69.71	5.300	.2598	.3746	.00910
20	60.81	3.172	.1531	.2301	.00562
30	51.91	1.815	.08770	.1158	.00285
40	43.00	0.8855	.04273	.0572	.00142
50	34.28	.4712	.02277	.0244	.000605
60	25.86	.1350	.00653	.0090	.00022
70	17.70	.0384	.00186	.0030	.000075
80	10.72	.0060	.00029	.0017	.000042
90	5.61	.0012	.000059	.0008	.000019
100	2.101	.0000	.00000	.0000	.00000.

(1) J. E. Ricci and T. W. Davis, THIS JOURNAL, **62**, 407 (1940).

(2) P. Debye, *Z. physik. Chem.*, Cohen Festband, 56 (1927).

(3) M. Born, *Z. Physik*, **1**, 45 (1920).

(4) T. W. Davis and J. E. Ricci with C. G. Sauter, THIS JOURNAL, **61**, 3274 (1939).

(5) Mylius and Funk, *Ber.*, **30**, 1723 (1897).

(6) All information concerning the dielectric constant of dioxane–water mixtures is taken from the measurements of G. Akerlof and O. A. Short, THIS JOURNAL, **58**, 1241 (1936).

determined by weighing appropriate filtered samples of the solutions delivered from calibrated pipets.

On the Rule of Constant Activity Coefficient.—The results have first of all been used in testing further the empirical rule of constant activity coefficient for the calculation of solubilities.[1] It has been noted in many cases that the activity coefficient of a slightly soluble electrolyte in its pure saturated solution is practically constant, independent of the dielectric constant of the medium. Hogge and Garrett[7] have recently reported such behavior for thallous chloride in alcohol–water mixtures up to 60% alcohol, and the same has also been observed for silver acetate in dioxane–water mixtures up to 50% dioxane.[8] This rule of constant activity coefficient for an electrolyte at saturation, which is here being tested again, is still purely empirical. Although an analogy with the behavior of weakly solvated sols has been pointed out by W. Ostwald,[9] a theoretical explanation of this rough constancy has not yet been found. Ostwald had noted, for weakly lyophilic sols such as arsenous sulfide, that the activity coefficient of electrolytes at concentrations causing coagulation is independent of the type of electrolyte and of the dielectric constant of the solvent.[10]

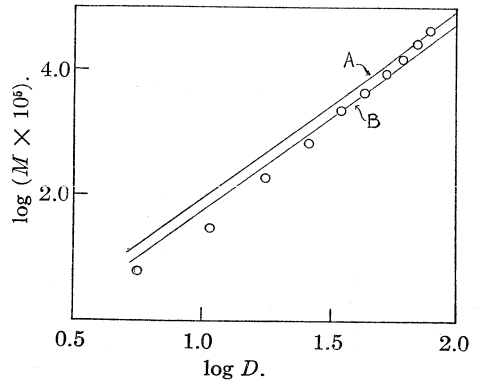


Fig. 1.—Solubility of potassium iodate in dioxane–water mixtures at 25°: A represents eq. 1, with 0% dioxane as reference; B, with 50% dioxane as reference.

As has already been shown,[1] the assumption of such constancy of the activity coefficient offers a simple way of predicting at least approximately the solubility, S_2, in any medium of dielectric constant D_2, from the solubility, S_1, in a reference medium of dielectric constant D_1, inasmuch as by the application of the Debye–Hückel limiting law, it follows that

$$\log S_2 = \log S_1 + 3 (\log D_2 - \log D_1) \qquad (1)$$

According to this equation the solubility in a series of media of varying dielectric will be given, on a plot of log M *vs.* log D, by a straight line with a slope of +3 and passing through whichever point is taken as the reference solubility. Figure 1 represents the observed solubilities for potassium iodate in the dioxane–water mixtures as compared with the straight line expected according to equation (1): A, with the solubility in pure water as reference; B, with that in 50% dioxane as reference. On either basis, solubilities in the various media may be calculated and compared with the observed, the ratios of calculated to observed solubilities being summarized for both salts in Table II. The agreement is satisfactory at least as to the order of magnitude, and is about the same for both the valence types involved and despite a great difference in the actual solubilities of the two salts; the calculation furthermore is independent of any knowledge of ionic diameters necessary for the application of the theoretical equation of Born. The largest deviations in Table II are for zinc iodate in very high dioxane solvents, where, it must be pointed out, the experimental error is probably great. The best straight line drawn through the data for potassium iodate has a slope of about 3.5 as compared to 3 as required by the equation; the zinc iodate points likewise best fit a straight line with a slope of ~ 3.5.

TABLE II

TEST OF EQ. (1): RATIO OF CALCULATED TO OBSERVED SOLUBILITIES; A WITH PURE WATER, B WITH 50% DIOXANE, AS REFERENCE

Wt. % dioxane	KIO_3		$Zn(IO_3)_2$	
	A	B	A	B
0	..	0.7	..	0.5
10	1.1	.7	1.2	.6
20	1.3	.8	1.3	.6
30	1.4	.9	1.6	.7
40	1.6	1.1	1.8	.8
50	1.5	..	2.1	..
60	2.3	1.6	2.5	1.2
70	2.6	1.4	2.4	1.1
80	3.6	2.3	0.9	0.4
90	2.6	1.7	.3	.1

This at least approximate linearity between log M and log D indicates at once that the usual Born equation, requiring a linear relation between log M and $1/D$, must fail. Furthermore, it is interesting to note that because of a substantially

(7) E. Hogge and A. B. Garrett, THIS JOURNAL, **63**, 1089 (1941).
(8) J. E. Ricci and A. R. Leo, *J. Phys. Chem.*, **45**, 1096 (1941).
(9) W. Ostwald, *Koll. Z.*, **94**, 169 (1941).
(10) W. Ostwald, *J. Phys. Chem.*, **42**, 981 (1938); *cf.* refs. 8 and 9 for other references.

linear relation between log D and mole fraction of water in the solvents, the solubilities as log M are also related roughly linearly to mole fraction of water. These relations are shown simultaneously in Fig. 2, where the linearity is seen quite clearly if the points in almost pure dioxane, in which the determinations are themselves somewhat doubtful, are disregarded. The slopes of these curves (~ -7) are again the same for the two salts.

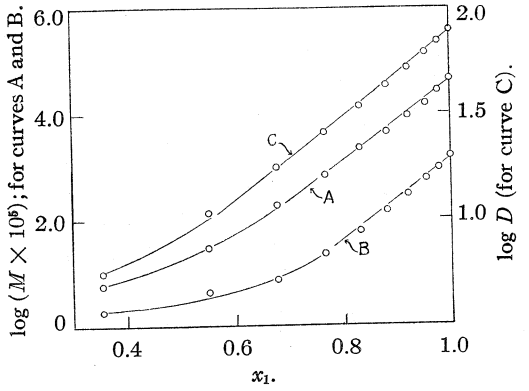


Fig. 2.—Relation between log M, log D, and x_1, mole fraction of water in dioxane–water solvents: A, KIO_3; B, $Zn(IO_3)_2$.

The Born Equation.—In Fig. 3 the results are plotted in accordance with the usual Born equation

$$\log S_1/S_2 = \frac{0.4343\ Ne^2\ z_+ z_-}{aRT}\left(\frac{1}{D_2} - \frac{1}{D_1}\right) \qquad (2)$$

in which the change of solubility depends upon the ionic diameter, a; the symbols N, e, z, R, T have their usual meaning. The theoretical limiting slopes have been calculated with 2.5 Å. as a probable value of a for both salts, by analogy with similar electrolytes such as barium iodate[4] and iodic acid,[11] giving slopes of 97 and 194 for potassium iodate and zinc iodate, respectively. It is again seen that except in very low dioxane solvents, the Born formula predicts solubilities in general far too low. Actually, the limiting slope for the potassium iodate data, as plotted on Fig. 3, corresponds to a value of only ~1.9 Å. for the diameter a.

Correction for Solvent Segregation around Ions.—Since the simple Born equation as just used assumes media of uniform dielectric constant, it should be possible to explain part of the discrepancy between observed and calculated solubilities in these cases by taking into account the non-uniformity of the dielectric constant in the

(11) S. Naidich and J. E. Ricci, THIS JOURNAL, **61**, 3268 (1939).

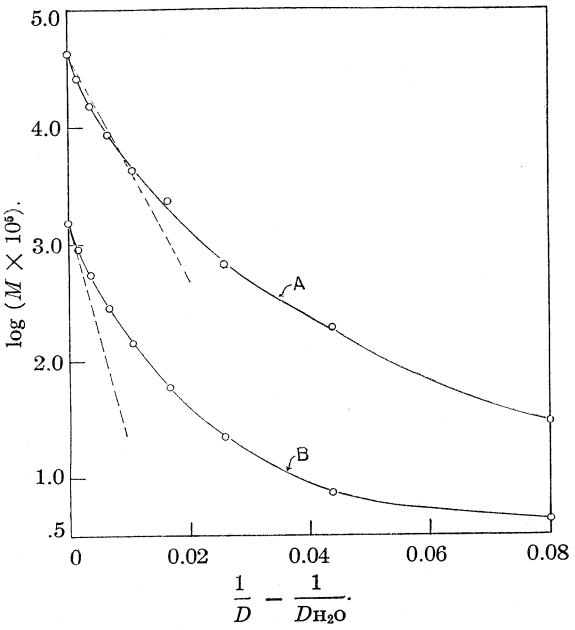


Fig. 3.—Observed solubilities compared with predictions of eq. 2: A, KIO_3; B, $Zn(IO_3)$.

vicinity of charged ions in media consisting of two solvents. We have, therefore, attempted to apply Debye's original treatment[2] for the calculation of this sorting or selective concentration of the more polar solvent by ions in mixed solvents, in order to see to what extent this factor might account for the deviation from the simple Born equation, and in order to derive, if possible, by means of this treatment, following the suggestion of Dunning and Shutt,[12] a value for the mean ionic radius of the electrolytes involved, since Debye's equation requires the sorting of the solvent molecules to be a function of the radial distance from the center of the ion.

According to Debye, this distribution of the two components of a mixed solvent (component 1 having the higher dielectric constant) is given as a function of the ionic charge, the distance from the ion and certain properties of the binary mixture, by the following equation, which we shall call the Debye equation

$$r^4\left(\frac{\bar{v}_2}{\bar{v}_1}\ln\frac{x_1}{x_1^0} - \ln\frac{x_2}{x_2^0}\right) = \frac{e^2 z_i^2}{8\pi RTD^2}\left(\frac{\bar{v}_2}{\bar{v}_1}\frac{dD}{\delta c_1} - \frac{\delta D}{\delta c_2}\right) \qquad (3)$$

The subscripts refer to the two components of the mixed solvent; the quantities x_1, x_2, $\bar{v}_1$, $\bar{v}_2$ and D are values of mole fraction, partial molal volumes and dielectric constant, at the distance r from the center of the ion of valence z_i; x_1^0 and x_2^0 are the

(12) W. J. Dunning and W. J. Shutt, *Trans. Faraday Soc.*, **34**, 1192 (1938).

over-all mole fractions, or x at $r = \infty$; c_1 and c_2, moles of each component per cc. of the mixture.

Since the distribution of dielectric will not be the same in two different mixtures of two solvents, it will be necessary to calculate this distribution and from it to calculate the corresponding value of the free energy change between a solvent of uniform dielectric (H_2O as reference, for example) and a mixed solvent of varying dielectric (or with D as $f(r)$), and if necessary, for each separate ion, inasmuch as this distribution varies with the valence of the ion.

A simplified form of this equation is suggested by Scatchard,[13] for cases in which $d(1/D)/dc_2 = a$ constant, K, when it follows that

$$r^4\left(\frac{\bar{v}_2}{\bar{v}_1}\ln\frac{x_1}{x_1^0} - \ln\frac{x_2}{x_2^0}\right) = \frac{e^2 z_i^2 \bar{v}_1 K}{8\pi RT} \qquad (4)$$

As seen in Fig. 4, this constancy holds only very roughly and for low concentrations of dioxane, in the present system.

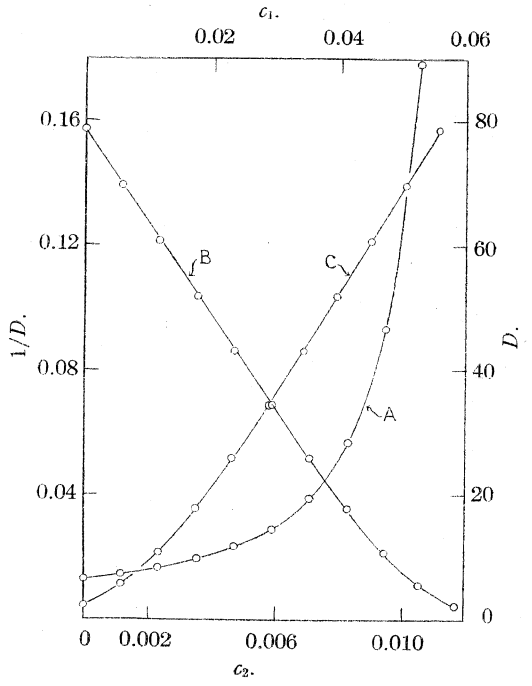


Fig. 4.—Variation of D and of $1/D$ with respect to moles of component per cc., in dioxane–water system: A, $1/D$ with c_2, moles of dioxane per cc.; B, D with c_2; C, D with c_1, moles of water per cc.

It is, therefore, necessary to use the original Debye equation, for which, fortunately, it is found that the derivatives dD/dc_1, and dD/dc_2 are quite constant, up to 60% dioxane, as seen in Fig. 4; they have the values + 1656 and −7550, respectively, for mixtures from 0 to 60% dioxane.

The data for the physical properties of the system water–dioxane required for Fig. 4 and for the use of eq. (3) were taken from the literature.[14] The distribution (r for various values of x_1 and x_2 and hence D as a function of r) was calculated for a univalent ion ($z_i = 1$), in three chosen mixtures of dioxane and water, namely, the 20, 50 and 80% dioxane mixtures (see Table III).

The curve for the distribution around a univalent ion in 50% dioxane is shown in Fig. 5 (curve A), together, for comparison, with the curves, B, for the value of $(1/Dr^2)$ around such an ion in pure water, *i. e.*, a uniform medium with a constant value of $D = 78.55$, and C, for that in a uniform medium with $D = 34.28$, the over-all limiting value of the dielectric constant in the 50% mixture.

TABLE III

SOLVENT SEGREGATION IN WATER–DIOXANE MIXTURES AROUND UNIVALENT IONS, CALCULATED THROUGH EQ. (3)

% Dioxane	20		50		80	
x_2	r, Å.	$10^4/Dr^2$	r, Å.	$10^4/Dr^2$	r, Å.	$10^4/Dr^2$
0.00001	1.79	39.7	1.70	43.8	1.63	49.6
.0001	1.94	34.0	1.81	38.8	1.68	45.1
.001	2.17	27.1	1.97	32.9	1.79	40.1
.005	2.50	21.0	2.16	28.0		
.01	2.76	17.6	2.29	25.6	1.98	34.3
.02	3.27	13.3				
.03	3.93	9.69				
.04	5.19	5.79				
.0425	6.05	4.38				
.0450	9.77	1.71				
.04667	∞	0				
(= x_2^0, 20% D)						
.05			3.02	18.2	2.38	29.1
.10			4.08	12.7	2.78	26.1
.15			6.44	6.43		
.16			7.86	4.52		
.165			9.49	3.17		
.169			14.60	1.36		
.1699			∞	0		
(= x_2^0, 50% D)						
.2					3.94	21.4
.3					5.54	16.6
.4					8.81	9.79
.42					10.40	7.61
.44					14.23	4.41
.45					∞	0
(= x_2^0, 80% D)						

Considering separate ions (z_+ and z_-) and separate media (D_1 and D_2), the Born equation may be written as follows

(13) G. Scatchard, *J. Chem. Phys.*, **9**, 34 (1941).

(14) Dielectric constant from ref. 6; densities and partial molal volumes from H. Hovorka, R. A. Schaefer and D. Dreisbach, THIS JOURNAL, **58**, 2264 (1936); **59**, 2753 (1937).

$$\ln\left(\frac{S_1}{S_2}\right) = \frac{Ne^2}{(\nu_+ + \nu_-)2RT}\left(\int_{r_i}^{\infty}\frac{\nu_+z_+^2dr}{D_2r^2} + \int_{r_i}^{\infty}\frac{\nu_-z_-^2dr}{D_2r^2} - \int_{r_i}^{\infty}\frac{\nu_+z_+^2dr}{D_1r^2} - \int_{r_i}^{\infty}\frac{\nu_-z_-^2dr}{D_1r^2}\right) \quad (5)$$

Here ν_+ and ν_- are the number of positive and negative ions formed from the molecule of the electrolyte and r_i is the effective ionic radius of each ion in each medium.

If $D_2 = f(r)$ from r_i to r_0 and is practically equal to the over-all D_2 at $r = r_0$, and if D_1 is independent of r, as is assumed to be the case with water as the reference medium, we then have, for a 1:1 electrolyte, in which the distribution of D in a mixture is the same for both ions

$$\ln(S_1/S_2) = \frac{Ne^2}{2RT}\left(\int_{r_i}^{r_0}\frac{dr}{D_2r^2} + \int_{r_0}^{\infty}\frac{dr}{D_2r^2} - \int_{r_i}^{\infty}\frac{dr}{D_1r^2}\right) \quad (6)$$

and for a 2:1 or 1:2 electrolyte

$$\ln(S_1/S_2) = \frac{Ne^2}{2RT}\left[\frac{4}{3}\left(\int_{r_{i(\pm 2)}}^{r_0}\frac{dr}{D_2r^2} + \int_{r_{0(\pm 2)}}^{\infty}\frac{dr}{D_2r^2} - \int_{r_{i(\pm 2)}}^{\infty}\frac{dr}{D_1r^2}\right) + \frac{2}{3}\left(\int_{r_{i(\pm 1)}}^{r_0}\frac{dr}{D_2r^2} + \int_{r_{0(\pm 1)}}^{\infty}\frac{dr}{D_2r^2} - \int_{r_{i(\pm 1)}}^{\infty}\frac{dr}{D_1r^2}\right)\right] \quad (7)$$

In equations (6) and (7), the integrals $\int_{r_i}^{r_0}\frac{dr}{Dr^2}$ are to be evaluated graphically in each case from the area below the curve of $1/Dr^2$ against r, as plotted in Fig. 5. The limits, r_i and r_0, are taken in each case as those values of r where $1/Dr^2$ approaches the limit of the corresponding value for H_2O, at the same r, (r_i), and where $1/Dr^2$ approaches the limit of the corresponding value for 20% or 50% dioxane (r_0). The values of these integrals together with the limits used in their graphical evaluation, are shown in Table IV.

TABLE IV

VALUES REQUIRED IN EQS. (6) AND (7)

Mixture, %	z_i	r_i	r_0	$10^4\int_{r_i}^{r_0}\frac{dr}{Dr^2}$
20	1	2	9	55.7
	2	3	7.5	27.9
50	1	2	8	70.3
	2	2.5	10	52.2
80	1	1.75	14	167.2
	2	2.5	20	119.0

The calculations for the case of $z_i = 2$ are simplified by noting that for fixed values of x_1 and x_2, and hence of D, in a given solvent mixture, the corresponding radial distances, $r_{(2)}$ and $r_{(1)}$, from the centers of divalent and univalent ions, respectively, are related as follows

$$r_{(2)} = 2r_{(1)}; \text{ whence} \quad (8a)$$

$$1/Dr^2_{(2)} = (1/2)\ 1/Dr^2_{(1)}; \text{ and} \quad (8b)$$

$$\int\frac{dr}{Dr^2_{(2)}} = \frac{1}{2}\int\frac{dr}{Dr^2_{(1)}} \quad (8c)$$

in which the integration is performed up to the same value of x_2 or of D.

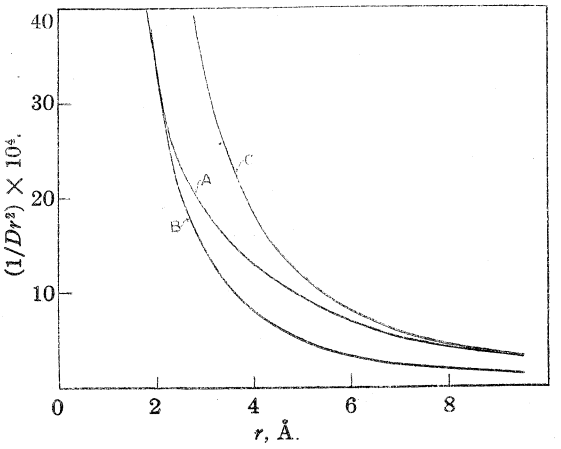


Fig. 5.—Solvent distribution in 50% dioxane–water, around univalent ions: Curve A, calculated from Table III; B, for uniform $D = 78.55$, as in pure water; C, for uniform $D = 34.28$, as in 50% dioxane–water.

The values of log S_1/S_2 then calculated through equations (6) and (7) are shown in Table V. These values refer to 25°, with water as the first medium, ($D_1 = 78.55$ and assumed uniform throughout).

TABLE V

RESULTS CALCULATED BY EQS. (6) AND (7)

Mixture, %	Electrolyte type	Log (S_1/S_2)
20	1/1	0.125
	1/2	.203
50	1/1	.521
	1/2	.839
80	1/1	1.95
	1/2	3.15

Before testing these calculated ratios on the observed solubilities, it must be pointed out that the Born equation refers theoretically to solubilities in zero ionic strength, μ; comparisons of actual solubilities simply neglect inter-ionic effects. The solubilities have therefore all been corrected to $\mu = 0$, by means of the usual Debye–Hückel expression

$$\log S_{\mu=0} = \log S - \frac{(352.6/D^{3/2})\mu^{1/2}}{1 + (2.914\ a/D^{1/2})\mu^{1/2}} \quad (9)$$

and using the values of a cited above in connection with equation (2). The results of these corrections and of the application of the ratios of Table V, are shown in Table VI. The solubilities of the salts silver acetate, silver sulfate and barium

iodate, in dioxane–water mixtures, are taken from ref. 4. The third column in this table, "Obs." $S_{\mu=0}$, lists the actual solubilities as corrected to $\mu = 0$ through eq. (9). Column 4 lists the corresponding solubilities, also at $\mu = 0$, calculated in each case from the limiting aqueous solubility through the ratios of Table V. Column 5 shows that with the exception of the 1:2 electrolytes in very high dioxane solvents, the solubilities thus calculated are distinctly too high, whereas (column 6) solubilities calculated through the uncorrected Born equation (equation 2) are in better agreement with observation in the 20% mixture, but distinctly low in higher dioxane ratios, as may be seen of course from Fig. 3.

TABLE VI

TEST OF THE CALCULATED RATIOS OF TABLE V

Salt	Solvent, % dioxane	"Obs." $S_{\mu=0}$ moles/l.	Calcd. $S_{\mu=0}$	Ratio Calcd./ "Obs."	Ratio, Born − Calcd./ "Obs."
KIO_3	0	0.2590			
	20	.0937	0.194	2.1	1.2
	50	.0136	.0780	5.7	0.48
	80	.00020	.0029	14.5	.042
$AgC_2H_3O_2$	0	.0531			
	20	.0282	.0398	1.4	1.1
	50	.00623	.0160	2.6	.76
	80	.00036	.00060	1.7	.0011
Ag_2SO_4	0	.0157			
	20	.00516	.00984	1.9	.54
	50	.000433	.00228	5.2	.017
	80	.000016	.000011	0.7	$.0_136$
$Zn(IO_3)_2$	0	.01010			
	20	.00378	.00634	1.7	.51
	50	.000436	.00147	3.4	.014
	80	.000025	$.0_2571$	0.3	$.0_131$
$Ba(IO_3)_2 \cdot H_2O$	0	$.0_3729$			
	20	$.0_3230$	.000457	2.0	.60
	50	$.0_4258$	.000106	4.1	.018
	80	$.0_560$	$.0_652$	0.1	$.0_137$

The value of log (S_1/S_2) according to the simple Born equation, without taking into consideration the dielectric distribution resulting from solvent segregation, is proportional to the area in Fig. 5 between curves B and C, while according to the modified equation (6 and 7) log S_1/S_2 is measured by the smaller area between the water-curve B and the curve A for the actual mixture. The correction is therefore seen to be in the right direction, increasing the calculated solubilities in low dielectric mixtures. But it was expected that this correction would account for only part of the discrepancy noted in the last column of Table VI and Fig. 3, inasmuch as it seems that still another factor would tend to increase the solubility over that calculated on the ionic basis, namely, the association of ions in low dielectric solvents. The present calculations, however, show a distinct and rather large over-correction. The apparent agreement obtained in the case of the 1:2 electrolytes in very high (80%) dioxane solvents, resulting from the lower and hence "better" calculated solubilities for these cases, must evidently be attributed to the strong influence here of ion association, because of which the observed total or analytical solubilities should always be greater than the ionic concentrations calculated theoretically.

This general over-correction means that the area between curves A and B of Fig. 5 is too small. One purpose of these calculations was to estimate if possible the effective value of r_i required to change this area in order to reproduce the observed value of log S_1/S_2 between 0 and 20% dioxane, and, furthermore, by repeating the process for the ratio between 0 and 50% dioxane, to test the constancy of such a radius in media of varying dielectric. Such an application of the Debye equation, no. 3, was in fact made by Dunning and Shutt[12] to the solubility of silver chloride in water and in 1 M aqueous urea. Although they were able to derive thereby a value for the mean ionic radius of silver chloride in good agreement with crystallographic data, the applicability of the equation to the case of a mixture consisting of two solvents in which the second component (urea) has the higher dielectric constant, has been questioned by Scatchard.[13] In the present case, however, it is obviously impossible to find a value of r_i satisfying the observed ratio of solubilities. At r = 2–2.5 Å. (the limit from which the integration is made), the curve for the mixture (curve A, Fig. 5) is already indistinguishable from that for pure water, both for the 20 and for the 50% solvents, so that the area between the curves cannot be extended by assuming smaller values of r_i; any larger value for r_i of course increases the over-correction by decreasing this area.

We thus meet with two unexpected results: (1) the application of the Debye equation for the distribution of molecules of a mixed solvent around charged particles leads to calculated effects distinctly greater than the observed excess of solubility above the simple Born equation; (2) it is apparently impossible to estimate the "ionic radius" by this method, inasmuch as the actual ion appears to be so intensively selectively solvated by the more polar solvent, that it may be said that the concept of effective ionic radius here loses its meaning.

The first of these results is somewhat surprising inasmuch as it had been believed that the correction would account for only part of the actual discrepancy. The most probable defect in the Debye treatment is the neglect of the discrete structure of the mixed solvent.[13,15] The corpuscular or discontinuous nature of the mixture probably demands a statistical treatment taking into account the actual size, shape and polar properties of the solvent molecules. The other factor explicitly neglected by Debye is the electrostriction or dielectric saturation of the solvent molecules attached to ions. The magnitude of this effect is difficult to estimate[13] but may be appreciable.[16] It would seem, however, that such an effect, like the Debye segregation effect itself, would contribute further to the similarity in the dielectric properties of the medium immediately surrounding the ions, in a series of mixtures of two solvents. It would consequently lead, probably, as does the present calculation of the Debye effect, to the prediction of still smaller changes in solubility between one mixture and another, and thus increase rather than cancel the over-correction.

Concerning the second result, it is of interest to note a similarity between the results of the Born equation when corrected for the non-uniformity of mixed solvents and the empirical relation of Ricci and Davis.[1] In both cases the solubility in other media may be predicted from the solubility in water or in some reference medium without previous knowledge of the always uncertain quantity, ionic diameter. It is obvious that variation of r_i between 1 and 2.5 Å. will hardly change the value of the integrals involved in the examples discussed. While this does not suggest a theoretical reason for the useful empirical equation, it does suggest that there is very possibly a fundamental reason why the effect of the ionic diameter may disappear when the solubilities are compared in different media of mixed solvents.

(15) O. Halpern and P. Gross, *J. Chem. Phys.*, **2**, 184 (1934).
(16) H. S. Frank, THIS JOURNAL, **63**, 1789 (1941).

Summary

1. The solubilities of potassium iodate and zinc iodate have been determined at 25° in mixtures of water and dioxane, up to 100% dioxane.

2. The results are used to test further the empirical rule of the constancy of the activity coefficient of electrolytes at saturation. The agreement between observed and calculated solubilities is satisfactory, at least as to the order of magnitude for both salts.

3. The results are also used to test the applicability of the Born equation when modified for the segregation of solvent molecules by ions in mixed solvents, in an attempt to account at least in part for the generally large negative error in the calculated solubilities in low dielectric media. When this distribution of dielectric is calculated according to the original Debye treatment, the solubilities now predicted for mixtures of low dielectric constant are higher than the observed, indicating an over-correction from the application of the distribution equation.

4. A similarity between the results of the corrected Born equation and the empirical relation of Ricci and Davis is pointed out, in that in both cases the solubilities calculated seem to be independent of the value attributed to the "ionic radius."

NEW YORK, N. Y. RECEIVED JUNE 16, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Kinetics and Equilibria of the Carbinol Formation of Phenolphthalein

BY MARION D. BARNES AND VICTOR K. LAMER

Introduction

That phenolphthalein fades in concentrated alkali was first observed by A. von Baeyer.[1] The rate of fading and the position of equilibrium were investigated colorimetrically by Kober and Marshall.[2] They attributed the fading process to the reaction of equimolecular proportions of alkali and the red form to yield a tribasic salt of phenolphthalic acid and formulated the process as

$$R^{=} + OH^{-} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ROH^{\equiv} \qquad (1)$$

$R^{=}$ is the colored form, k_1 is the molar rate constant for the formation of the carbinol $ROH^{\equiv}$, and k_2 is the corresponding constant for the reverse reaction. Biddle and Porter[3] observed that the molar rate constant, k_1, increased with increasing concentration of alkali but did not account for this behavior. Thiel and Jungfer[4] concluded from a spectrophotometric study of the reaction that hydroxyl ion reacts with both the colored phenolphthalein ion and a colorless lactoid phenolphthalein ion to produce the triply charged carbinol.

Lund[5] measured the rate of fading of phenolphthalein at various sodium hydroxide and sodium chloride concentrations, and properly ascribed the increase in molar rate constant with increasing sodium hydroxide to a Brönsted primary salt effect.[6] He employed the Brönsted–Debye Limiting Law (B. D. L. L.) as a means of determining the number of charges on the reactant phenolphthalein ion from the quantitative dependence of the rate of reaction upon the concentration.

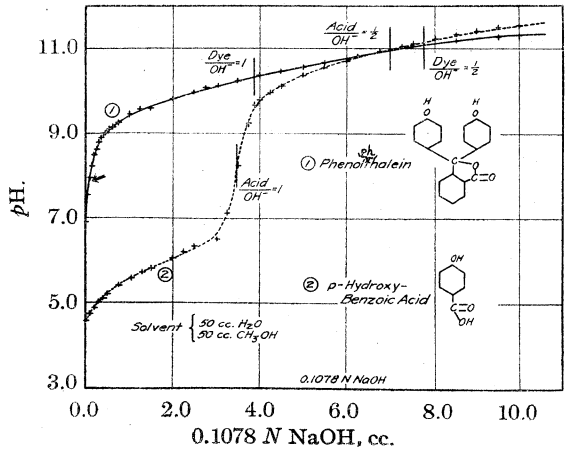


Fig. 1.

However, on plotting his data for log k_1, against the square root of the ionic strength, $\sqrt{\mu}$, he obtained the surprising result that the limiting slope was unity. This slope is one-half that required by the B. D. L. L. for a reaction between an ion of charge -2 and a hydroxyl ion. Since the B. D. L. L. has been abundantly confirmed in all cases where the charge type is definitely known, one would be forced to conclude that the reactant ion of phenolphthalein has a charge of -1 instead of -2.

This behavior became even more anomalous when LaMer and Amis[7] demonstrated that the B. D. L. L. was obeyed precisely for the rate of carbinol formation of Brom Phenol Blue (B. P. B.). The theoretical limiting slope of two (2.02) which was obtained shows that the reactant B. P. B. ion possesses a charge of -2. Phenolphthalein and B. P. B. are structurally similar. Aside from bromine substitution in the phenolic rings and the presence of a sulfonic acid instead of a carboxylic acid radical they possess identical triphenylmethane structures.

The two dyes differ, however, in color and acidic properties. B. P. B. is a relatively strong acid which dissociates hydrogen ions in a dilute or weakly acid solution whereas phenolphthalein is a much weaker acid which dissociates hydrogen ions only in alkaline solution as shown by the titration curve in Fig. 1. The estimated value of $K_1/K_2 \backsimeq 4$ from the titration curve is in accord with the colorimetric determinations of the ratio.[8] We also find that a red color appears on the addition of less than 0.10 mole of hydroxyl ion per mole of phenolphthalein. At first sight this observation might be taken as indicating a charge of less than 2 for the red ion.

(1) A. von Baeyer, *Ann.*, **202**, 36 (1880).
(2) Kober and Marshall, THIS JOURNAL, **33**, 59 (1911).
(3) Biddle and Porter, *ibid.*, **37**, 1571 (1915).
(4) Thiel and Jungfer, *Z. anorg. Chem.*, **178**, 62 (1929).
(5) Lund, *J. Chem. Soc.* (London), 1844 (1930).
(6) Brönsted, *Z. physik. Chem.*, **102**, 169 (1922); **115**, 337 (1925); LaMer, *Chem. Rev.*, **10**, 179 (1932); *J. Franklin Institute*, **225**, 709 (1938).
(7) LaMer and Amis, THIS JOURNAL, **61**, 905 (1939).
(8) Rosenstein, *ibid.*, **34**, 1117 (1912).

Bury's resonance theory,[9] however, requires that the colored form of phenolphthalein should have a charge of −2. This is clearly inconsistent with Lund's data which we have been unable to reconcile with the requirements of the theory by recalculation. The data of Lund are inadequate to establish the mechanism of carbinol formation for phenolphthalein since the equilibrium constant was not measured in order to obtain k_1 from $k_1' + k_2$ by a rigorous mathematical method. The present investigation has been undertaken to determine the charge of the reacting ion from the Brönsted–Debye limiting law and to establish experimentally a mechanism for this carbinol formation which is consistent with well established electrostatic and kinetic principles.

Experimental

A Coleman Double Monochromator Photoelectric Spectrophotometer (Model 10-S) was used to measure the transmittances of the colored solutions. The transmittance measurements are accurate to ±0.1%. The instrument was equipped with specially designed water-jacketed absorption cells (cuvettes) for accurate temperature control. The wave-length scale was calibrated against a didymium glass filter using a slit of 30 mμ width.

Phenolphthalein was twice recrystallized from absolute methanol, m. p. 261–262° (cor.). The absorption maximum was 550 mμ. The stock solution for the fading runs consisted of 0.1721 g. of phenolphthalein in 100 cc. of 50% aqueous ethanol solution. For the regeneration reactions 0.1721 g. of phenolphthalein was dissolved in 100 cc. of 1 *M* NaOH and used after at least one hour and not more than eight hours. This carbinol solution was pale pink initially, due to traces of unfaded phenolphthalein, but after about twelve hours showed an increasing absorption at 425 mμ, indicating some further reaction. All regeneration experiments were accordingly made on freshly prepared solutions.

Sodium hydroxide solutions were prepared by the method of Sörensen[10] and stored in paraffin-lined bottles protected from carbon dioxide. They were standardized against B. of S. potassium acid phthalate and showed 0.4% residual carbonate by a differential titration.

Neutral sodium chloride solutions were employed.

The temperature was maintained constant to ±0.005° and standardized against a B. of S. platinum resistance thermometer.

Calibrated hypodermic syringes[11] were used to deliver small quantities of reagents accurately.

In a typical fading experiment 1 cc. of phenolphthalein stock solution was added to approximately 499 cc. of sodium hydroxide solution of such a strength that a concentration of 0.006 to 0.02 *M* sodium hydroxide was obtained on making up to volume. The solution was mixed rapidly and an absorption cell filled therewith. The remaining solution was placed in a paraffin-lined paper milk container in the thermostat. The measurements of the transmittance of the solution which required approximately one and one-half minutes each, were made every fifteen minutes over a period of about three hours. The cuvette with water circulating around it continuously was replaced in the thermostat between observations.

The regeneration runs were made by diluting 1 cc. of stock solution with dilute sodium hydroxide of such strength that concentrations of 0.006 to 0.020 *M* were obtained on making up to volume.

A Beckmann *p*H meter was used to measure *p*H's. No correction for sodium ion was made. The glass electrode yielded stable readings in the alcohol–water solution.[12]

Calculation of Rate and Equilibrium Constants.—The differential expression describing the rate of fading formulated in (1) is

$$-\mathrm{d}[R^{=}]/\mathrm{d}t = k_1[OH^-][R^{=}] - k_2\,[\text{carbinols}] \quad (2)$$

where "carbinols" is written instead of $ROH^{=}$ to indicate the possibility of a mixture of carbinols in solution. The concentration of hydroxyl ion, $[OH^-]$, being sensibly constant during the course of a run, the reaction follows a first order course. For convenience in treating the data, k_1' was set equal to $k_1\,[OH^-]$. The concentration (C) of dye at any moment is related to the transmittance (T) by Beer's law

$$C = k_B \log T \quad (3)$$

For a reversible pseudo-unimolecular reaction, integration of (2) gives

$$k_1' + k_2 = \frac{2.303}{t} \log\left(\frac{c_e}{c_e - c}\right) \quad (4)$$

where c_e is concentration of carbinols at equilibrium and c is concentration of carbinols at time t. Substitution of equation (3) in (4) gives

$$k_1' + k_2 = \frac{2.303}{t} \log\left[\frac{\log T_{t=0} - \log T_e}{\log T_t - \log T_e}\right] \quad (4a)$$

where $T_{t=0}$, T_t, T_e are, respectively, the transmittance for time zero, time t and equilibrium. The complex reaction velocity constant $k_1' + k_2$ is given by the slope of the curve obtained by plotting time in minutes against log (log T_t − log T_e) and was proven to be independent of the direction from which equilibrium is approached.

The equilibrium constant is calculated from

$$K_C = \frac{[\text{Carbinols}]}{[R^-][OH^-]} = \frac{[\log T_{t=0} - \log T_e]}{[\log T_e][OH^-]} \quad (5)$$

The concentration of carbinols is the difference in concentration of colored ion initially (when none has faded) and at equilibrium. This value is the ordinate obtained by extrapolating the plot of equation (4) to zero time.

(9) Bury, THIS JOURNAL, **57**, 2115 (1935).
(10) Sörensen, *Biochem. Z.*, **21**, 168 (1909).
(11) Chaney, *Ind. Eng. Chem., Anal. Ed.*, **10**, 326 (1938).
(12) S. T. Schicktanz and A. D. Etienne, *Ind. Eng. Chem.*, **29**, 157 (1937).

Values of the molar rate constant are calculated from

$$k_1 = \frac{k_1 + k_2}{[OH^-] + 1/K_C} \qquad (6)$$

Results

The colored form of phenolphthalein obeys Beer's law over the range of concentrations considered in this investigation: namely, up to 1.34×10^{-5} m./l. (Table I). The values of $T_t = 0$ are extrapolated values since concentrations of hydroxyl ion, insufficient to convert all phenolphthalein to the colored ion, are sufficient to cause appreciable fading of the latter during the time of observation. The value of $k_B = -1.63 \times 10^{-5}$ m./l. is considered the most accurate, being measured from a specially purified sample of phenolphthalein. The molar extinction coefficient ($E = \frac{1}{Cl}\log(I_0/I)$) is 0.3057×10^{-5} (l = length) (7).

TABLE I

MOLAR EXTINCTION COEFFICIENTS (E) AND CONSTANTS FOR BEER'S LAW (k_B) FOR ALKALINE PHENOLPHTHALEIN SOLUTIONS

NaOH = 0.014 M, λ = 550 mμ, temp. = 25°, layer thickness = 20.054 mm.

Concn. dye, $\times 10^5$ m./l.	$k_1' + k_2$, min.$^{-1}$	$T_{t=0}$, %	E, (m./l.)$^{-1}$ cm.$^{-1} \times 10^{-5}$	$k_B \times 10^5$ m./l.
0.670	0.01209	39.60	0.2992	1.664
1.102	.01195	21.10	.3057	1.630
1.340	.01207	15.75	.2987	1.668

A typical run is given in Table II and plotted in Fig. 2. Equilibrium transmittances measured after twenty-four hours were stable and no irreversible fading[13] was observed. Extrapolated values of $T_{t=0}$ are shown in Table III. The constancy of these extrapolated values over the pH range employed in this study shows that no secondary salt effect is detectable.

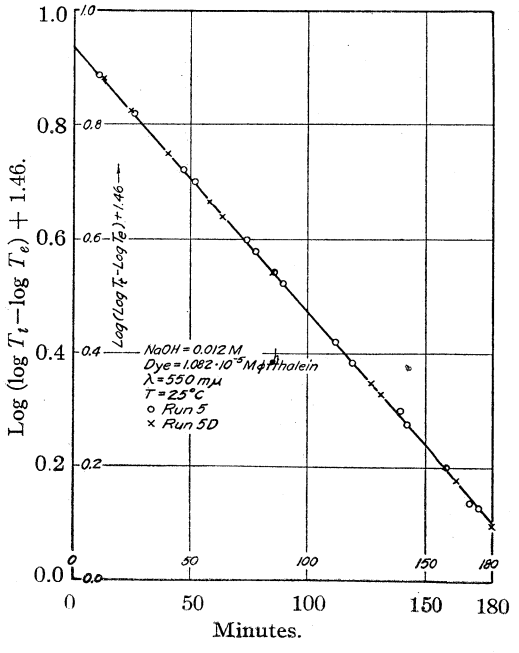


Fig. 2.

TABLE II

TYPICAL RUN

NaOH = 0.012 M, λ = 550 mμ, dye = 1.102×10^{-5} M, thickness of layer 20.054 mm.

Min.	% T	$k' + k_2 \times 10^2$ min.$^{-1}$	$k_1 \times 10^2$ min.$^{-1}$	$k_2 \times 10^2$ min.$^{-1}$
0	(21.2)			
11.17	22.9	1.069	39.5	0.5943
25.58	25.0	1.071	39.6	.5956
46.83	27.8	1.069	39.5	.5943
52.00	28.4	1.064	39.4	.5916
73.93	30.8	1.059	39.2	.5889
78.00	31.25	1.065	39.4	.5919
85.58	32.0	1.065	39.4	.5923
89.83	32.4	1.066	39.4	.5926
112.58	34.2	1.054	39.0	.5862
119.33	34.8	1.067	39.5	.5935
139.58	36.0	1.051	38.9	.5845
142.33	36.3	1.068	39.5	.5938
159.67	37.1	1.051	38.9	.5840
170.08	37.8	1.078	39.9	.5994
174.33	37.95	1.073	39.7	.5964
	42.2			
	Mean	1.065	39.40	.5920
		a.d. = 0.46%		
		A.D. = 0.14%		

TABLE III

THE INDEPENDENCE OF TRANSMITTANCES EXTRAPOLATED TO ZERO TIME UPON THE CONCENTRATION OF NaOH

Dye = 1.102×10^{-5} M; λ = 550 mμ; layer thickness = 20.054 mm.

NaOH $\times 10^3$	$T_{t=0}$, %	$k_B \times 10^5$
6	21.38	1.64
8	21.32	1.64
10	21.27	1.64
12	21.21	1.64
14	21.10	1.63
16	21.24	1.63
20	21.16	1.64

TABLE IV

RATE AND EQUILIBRIUM CONSTANTS FOR THE SIMPLE FORMULATION $R^- + OH^- \underset{k_2}{\overset{k_1}{\rightleftarrows}} ROH^=$

λ = 550 mμ, T = 25°

NaOH $\times 10^3$	$k' + k_2$, min.$^{-1} \times 10^2$	K	k_1, min.$^{-1} \times 10^2$	k_2, min.$^{-1} \times 10^2$
6	0.7568	61.78	34.12	0.5522
8	.856	63.60	36.09	.5674
10	.9638	65.25	38.06	.5832
12	1.067	66.52	39.47	.5951
14	1.195	67.86	41.59	.6128
16	1.331	69.06	43.66	.6322
20	1.622	71.00	47.59	.6702

(13) Thiel and Coch, *Z. anorg. allgem. Chem.*, **217**, 254–256 (1934)

Table IV summarizes the molar rate and equilibrium constants, which are reliable to better than 1%. The increase in these constants with concentration is shown in Table V to be due to a primary salt effect.[14]

Discussion

The theory assumes that the kinetics of the reaction may be formulated as $R^{=} + OH^{=} \rightleftarrows X^{\equiv} \rightarrow ROH^{\equiv}$ where $X^{\equiv}$ is the activated complex sensibly in equilibrium with the reactants but not with the product. The influence of the charges of the reactant species and the ionic strength of the solution is given by the Brönsted–Debye limiting law equation (B. D. L. L.)

$$\log k_1 = \log k_0 + 1.02\, Z_R\text{-}Z_{OH^-}\, \sqrt{\mu} \qquad (8)$$

where k_0 is the extrapolated molar rate constant for zero ionic strength.

The equilibrium constant is given by the expression

$$K_a = \frac{a_R\text{-}a_{OH^-}}{a_{ROH^{=}}} = \frac{C_R\text{-}C_{OH^-}}{C_{ROH^{=}}} \frac{f_R\text{-}f_{OH^-}}{f_{ROH^{=}}} \qquad (9)$$

where a is activity and c is concentration. Introducing the Debye–Hückel limiting equation for the activity coefficient (f), yields for the measured stoichiometric constant K_C

$$\log K_C = \log K_a + 1.02\, Z_R\text{-}Z_{OH^-}\, \sqrt{\mu} \qquad (10)$$

Figure (3) shows a plot of log k_1 against $\sqrt{\mu}$. The ionic strength is varied in one series of runs (circles) by increasing the concentration of sodium hydroxide, in the other (crosses) by increasing the concentrations of sodium chloride. A limiting slope of +2 is obtained in accord with formulation (1) and Eq. (8) showing conclusively that carbinol formation in phenolphthalein involves the reaction of an ion of charge −2 with the hydroxyl ion. The forward rate exhibits no anomalous behavior.

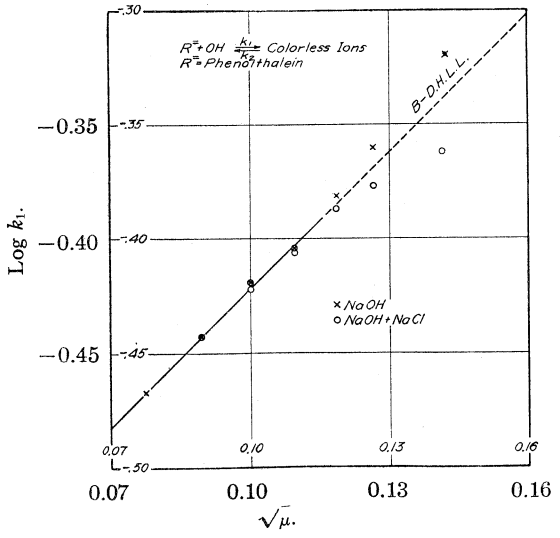


Fig. 3.

The upper curve in Fig. 4 shows the plot of log K_C against $\sqrt{\mu}$. The slope is unity or one-half the value required by the theory for an equilibrium involving doubly charged phenolphthalein, hydroxyl and triply charged carbinol ions. This abnormal behavior has been attributed erroneously by Lund to the variation of the forward rate constant with ionic strength. Failure to measure the equilibrium constant in sufficiently dilute solutions is responsible for this misunderstanding.

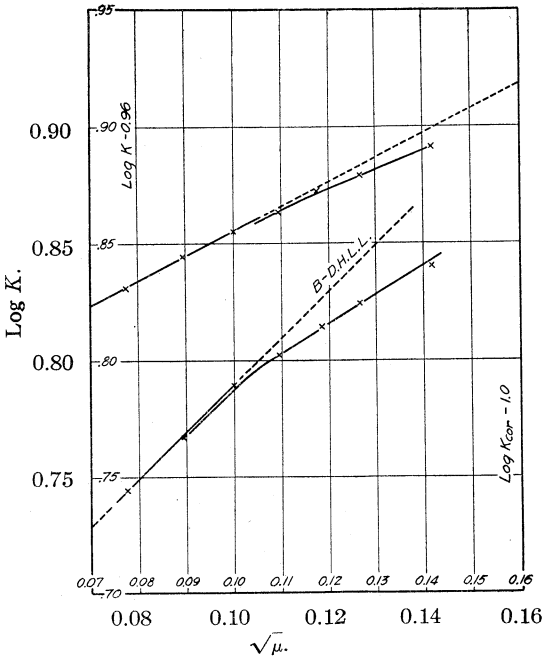


Fig. 4.

The abnormal behavior arises from the fact that the concentration of the triply charged carbinol assumed in (1) cannot be measured directly as is assumed in formulation (1). Over the pH range covered in these experiments (11.8 to 12.3) and particularly at the lower concentration of alkali the triply charged carbinol should be partially hydrolyzed. The equilibrium relationships under such conditions may be formulated

$$R^- + OH^- + H_2O \begin{cases} \xrightarrow{K_1} ROH^{=} + H_2O \\ \xrightarrow[K_2]{} \uparrow\downarrow K_3 \\ \xrightarrow{} RHOH^{-} + OH^- \end{cases} \qquad (11)$$

(14) For review see V. K. LaMer, *Chem. Rev.*, **10**, 179 (1932).

where $RHOH^{=}$ is also a colorless carbinol. The equilibrium described by K_1 considers the triply charged carbinol as the product in equilibrium with reactants $R^{=}$ and OH^{-}. This equilibrium constant is shown by (10) to be affected by the ionic strength. K_2, however, which considers the doubly charged carbinol and hydroxyl ion in equilibrium with the reactants, is not affected by the ionic strength. K_3 describes the mobile equilibrium existing between these carbinols and is defined as

$$K_3 = \frac{[ROH^{=}][H_2O]}{[RHOH^{-}][OH^{-}]} \qquad (12)$$

On the basis of this equilibrium formulation, K_c calculated from the data may be separated into K_{1a} and K_2 ($K_{2a} = K_{2c}$). Consideration of (5) and (6) shows that this operation does not affect the calculated values of k_1 which have been shown to obey precisely the predictions of the Brönsted–Debye equation. The separation of K_C into K_{1a} and K_2 is shown by the equations

$$K_C = \frac{[ROH^{=}] + [RHOH^{-}]}{[R^{=}][H_2O][OH^{-}]} = \frac{[ROH^{=}]}{[R^{=}][H_2O][OH^{-}]} + \frac{[RHOH^{-}]}{[R^{=}][H_2O][OH^{-}]} \qquad (13)$$

$$K_C = K_{1a}10^{2\sqrt{\mu}} + K_2/[OH^{-}] \qquad (14)$$

TABLE V

RATE AND EQUILIBRIUM CONSTANTS ($R^{=} + OH^{-} \underset{k_2}{\overset{k_1}{\rightleftarrows}} ROH^{=}$) IN NaOH AND NaCl SOLUTIONS

$T = 25°$

NaOH × 10³	NaCl × 10³	μ × 10³	$k_1' + k_2$, min.$^{-1}$ × 10²	K_C	k_1, min.$^{-1}$ × 10²	k_2, min.$^{-1}$ × 10²
6	0	6	0.7568	61.78	34.12	0.5522
6	2	8	.7794	63.99	36.05	.5634
8	0	8	.8560	63.60	36.09	.5674
8	2	10	.8819	65.20	37.80	.5800
8	4	12	.9065	66.41	39.33	.5944
8	6	14	.9242	68.36	40.86	.5977
8	8	16	.9359	70.27	42.10	.5991
8	12	20	.9411	73.43	43.55	.5930

A test of equation (14) is made by selecting values for K_{1a} and K_2 and calculating K_C at different hydroxyl ion concentrations. Comparison of K_C calculated from experimental data and K_C calculated from equation (14), employing $K_{1a} = 40.25$ and $K_2 = 0.038$, is shown in Table VI. The agreement is within experimental error over the range where the Debye–Hückel limiting equation is valid.

Graphically the behavior of K_{1c} expressed in concentrations is shown in the lower curve in Fig. 4. K_{1c} is obtained by solving equation (14) employing experimental values of K_C and hydroxyl ion and the value of 0.038 for K_2. The Brönsted–Debye equation is obeyed over the range of dilute solution up to $\sqrt{\mu} = 0.11$. The close agreement of the experimental K_C with the K_C calculated from (14) confirms the postulated equilibria.

TABLE VI

EQUILIBRIUM CONSTANTS (EQS. (13) AND (14)): K_c = EXPERIMENTAL EQUILIBRIUM CONSTANT; $(K_c)_{14}$ = EQUILIBRIUM CONSTANT CALCULATED FROM (14)

NaOH × 10³	K_c	$(K_c)_{14}$	ΔK_c, %
6	61.78	62.40	1.0
8	63.60	63.52	0.13
10	65.25	64.98	.43
12	66.52	66.56	.06
14	67.86	68.24	.56
16	69.06	69.87	1.2
20	71.00	73.10	2.8

The ionization constant of $RHOH^{=}$ may be calculated from (12) and the values of K_{1a} and K_2. Using $K_{1a} = 40.25$, $K_2 = 0.038$ and the ion constant for water $K_W = 1 \times 10^{-14}$ (at 25°) the value of the ionization constant is 1.1×10^{-11}.

Summary and Conclusions

1. The kinetics of the reaction of phenolphthalein with hydroxyl ion to produce a colorless carbinol have been investigated spectrophotometrically at 25° for sodium hydroxide solutions (0.006 to 0.020 M) with and without the addition of sodium chloride.

2. Precise values of the transmittances of phenolphthalein solution at 550 mμ have been obtained by extrapolating to zero time. The extinction coefficient is independent of the concentration of alkali showing that no perceptible secondary salt effect exists at these concentrations.

3. The limiting slope of the log k_1 (forward rate constant) *vs.* the square root of ionic strength, $\sqrt{\mu}$ establishes that carbinol formation involves the reaction of a doubly charged negative phenolphthalein ion with a hydroxyl. $R^{=} + OH^{-} \rightarrow$ carbinol.

4. The limiting slope of log K (equilibrium constant) *vs.* $\sqrt{\mu}$ is one-half that predicted for the simple formulation $R^{=} + OH^{-} \rightleftarrows ROH^{=}$. An interpretation consistent with established electrostatic principles is obtained on the assumption that the carbinol is partially hydrolyzed, *viz.*, $ROH^{=} + H_2O \rightleftarrows RHOH^{-} + OH^{-}$.

NEW YORK, N. Y. RECEIVED MAY 26, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN]

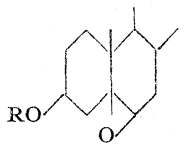
Studies on Cholesteryl Oxides[1]

BY PURNENDU N. CHAKRAVORTY AND ROBERT H. LEVIN

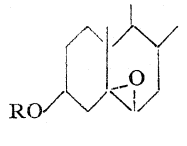
In connection with work in progress, it became necessary to study the properties of the oxide ring in cholesteryl-5,6-oxides. Previous investigators have used perbenzoic acid to prepare the various oxido derivatives of cholesterol, and from their results the nature of the substituent at C_3 appeared to influence the ratio of stereoisomeric products formed. Thus from cholesterol Westphalen and Windaus[2] obtained α-cholesterol oxide (I, R = H) in 50% yield, with some of the β-isomer (II, R = H) being isolable from the crystallization mother liquors. Ruzicka and Bosshard[3] found that treatment of cholesteryl acetate with perbenzoic acid produced largely β-cholesteryl oxide acetate. Spring and Swain[4] reported that cholesteryl benzoate, under the same conditions, formed almost equal amounts of α- and β-cholesteryl oxide benzoates in excellent yield.

In this Laboratory, preparation of oxides has been simplified by the use of monoperphthalic acid.[5] This reagent is readily prepared and is more stable than perbenzoic acid. Further, the phthalic acid which is formed from the perphthalic acid during the reaction can be separated easily from the sterol oxides because of its insolubility in chloroform. Such ease of separation is particularly useful in the preparation of bile acid oxides because it eliminates the need for washing with alkali. However, when using perphthalic acid several precautions are necessary. The chloroform should be freshly distilled over potassium carbonate, since the sterol oxides will react with even traces of hydrogen chloride. In some of our experiments, the perphthalic acid–cholesteryl compound reaction mixture was not worked up immediately but allowed to stand overnight or longer. In these instances the reaction product was quite sticky and uncrystallizable, and the yield was small. This was presumably due to a secondary reaction of the cholesteryl oxide with phthalic acid, giving, very probably, a half phthalic ester as was indicated by the solubility of the product in alkali.

When cholesteryl acetate was treated with perphthalic acid, β-cholesteryl oxide acetate (II, R = Ac) was isolated in 50% yield and the α



I[6]

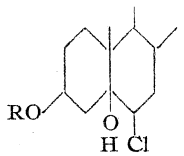


II[6]

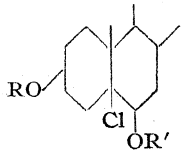
R = H, Ac, Bz

isomer (I, R = Ac) in 20% yield. A similar reaction using cholesteryl benzoate gave α-cholesteryl oxide benzoate (I, R = Bz) in 50 to 70% yield, but no β-oxide benzoate could be obtained. With cholesterol, the same reagent produced α-cholesterol oxide (I, R = H) in 60% yield, and a small amount of the β-isomer.

Several partially successful attempts to rearrange cholesteryl oxides to ketocholestane compounds have been reported. Chinaeva and Ushakov[7] used a Grignard reagent. Spring and Swain[4] employed heat and vigorous dehydrating reagents. In neither instance was the yield of 6-ketocholestanol satisfactory. It was thought that any tendency of the oxido group to isomerize into a ketone might be accelerated through a mass action effect by removing the product from the sphere of reaction as a ketone derivative. Accordingly, β-cholesteryl oxide acetate was heated with semicarbazide hydrochloride in pyridine. The product of this reaction was a halogen containing substance, m. p. 188–190°, which could be recovered unchanged after refluxing with acetic anhydride, and was therefore identified as a 3-acetoxy-5-hydroxy-6-chlorocholestane (III, R = Ac) instead of 3-acetoxy-5-chloro-6-hydroxycholestane (IV, R = Ac, R′ = H). A rational explanation of this reaction became possible when it was found



III



IV

(1) Presented in part before the Organic Division of the American Chemical Society, Memphis, April 20–24, 1942.

(2) Westphalen and Windaus, *Ber.*, **48**, 1064 (1915).

(3) Ruzicka and Bosshard, *Helv. Chim. Acta*, **20**, 244 (1937).

(4) Spring and Swain, *J. Chem. Soc.*, 1356 (1939).

(5) For preparation of the reagent see Böhme, *Ber.*, **70**, 379 (1937); "Organic Syntheses," **20**, 70 (1940).

(6) Throughout this paper the steric configurations assigned at C_3 and C_5 are purely arbitrary.

(7) Chinaeva and Ushakov, *J. Gen. Chem.* (U. S. S. R.), **11**, 335 (1941); *C. A.*, **35**, 5903.

that a solution of semicarbazide hydrochloride in pyridine has a *p*H of 6.2 and will turn blue litmus red. Since ethylene oxides are, in general, stable to alkaline reagents, but susceptible to acidic substances, this transformation is not surprising.

It has been known for some time that ethylene oxide rings in aliphatic molecules are also opened by heavy metal and even alkaline earth metal halides.[8] In an extension of this reaction to cholesteryl oxides, ferric chloride, zinc chloride and magnesium bromide[9] were found to react with β-cholesteryl oxide acetate to give compounds containing halogen. The ferric chloride reaction product was identified as 3-acetoxy-5-hydroxy-6-chlorocholestane (III, R = Ac). The zinc chloride and magnesium bromide products were not completely characterized.

As indicated above, cleavage of the cholesteryl oxide bond can produce two position isomers (III, IV). Recently some conflicting reports have been published concerning the orientation of products obtained by the action of certain acidic reagents on various cholesteryl oxide derivatives. Ruzicka and Bosshard[3] treated the β-oxide acetate with dry hydrogen chloride in pyridine and obtained 3-acetoxy-5-hydroxy-6-chlorocholestane (III, R = Ac). Hattori[10] reported this same compound resulting from the action of hydrogen chloride on α-cholesteryl oxide acetate, and claimed that very pure β-oxide acetate[11] gave a 5-chloro-6-hydroxycholestane derivative (IV, R = Ac, R′ = H). Spring and Swain[4] have found that α-cholesterol oxide and its benzoate react with benzoyl chloride in pyridine or with hydrogen chloride to give 5-hydroxy-6-chlorocholestane compounds (III), whereas β-cholesterol oxide and its benzoate form 5-chloro-6-hydroxy derivatives (IV, R = Bz, R′ = Bz, H). We treated β-cholesteryl oxide acetate, m. p. 113°, with benzoyl chloride in pyridine and obtained 3-acetoxy-5-hydroxy-6-chlorocholestane (III, R = Ac), which was characterized by mixed melting point, analysis, and its non-reactivity toward acetic anhydride. If the action of benzoyl chloride involves simply a cleavage of the cholesteryl oxide linkage followed by addition of fragments of the benzoyl chloride molecule, then in our reaction, as well as Spring and Swain's reaction with the α-oxide and its benzoate, the 5-benzoxy compound would be expected to form.[12] Since the 5-hydroxy derivative was obtained, it seems that the benzoyl chloride acts like the semicarbazide hydrochloride, that is, merely as a donor of hydrogen chloride. Formation of 6-benzoxy compounds can be explained on the assumption that the primary reaction is fission by hydrogen chloride, followed by benzoylation of the newly formed 6-hydroxy group with excess of the reagent.

It was thought that pyridine might function as a carrier of hydrogen chloride in these experiments. Therefore, the reaction of "pyridine hydrochloride" with β-cholesteryl oxide acetate was undertaken. This reagent was obtained as a hygroscopic white solid by passing dry hydrogen chloride into a solution of pyridine in ether. In petroleum ether there was no reaction, "pyridine hydrochloride" being insoluble in this solvent. In absolute ethanol a reaction readily took place, with the formation of the same 3-acetoxychlorohydrin (III) previously obtained with semicarbazide hydrochloride, ferric chloride and benzoyl chloride.

The reaction of β-cholesteryl oxide acetate with benzoyl chloride was also carried out under anhydrous conditions using carbon tetrachloride as a solvent. The substitution of a completely chlorinated solvent for pyridine, which contains hydrogen, did not alter the course of the reaction, and the same 5-hydroxy-6-chlorocholestane derivative was isolated from the reaction mixture although in a poorer yield. Apparently the elements of hydrogen chloride are obtained from the benzoyl chloride, but the mechanism of the transformation remains quite obscure.

The reaction with "pyridine hydrochloride" was extended to α-cholesterol oxide, its acetate, and benzoate; and β-cholesterol oxide. These substances, to our surprise, uniformly gave 5-hydroxy-6-chlorocholestane derivatives (III) in good yields. "Pyridine hydrochloride" is a convenient reagent to use. It is easily prepared, may be kept indefinitely in a desiccator, reacts smoothly, and any excess is readily disposed of. In the case of α- and β-cholesterol oxides, some trouble was experienced in purifying the reaction products be-

(8) Bodforss, "Die Äthylenoxyde," *Sammlung chem. u. chem. techn. Vortrage*, Ferdinand Enke, Stuttgart, 1920.

(9) Ushakov and Madaeva, *J. Gen. Chem.* (U. S. S. R.), **9**, 1690 (1939), treated α-cholesterol oxide with magnesium bromide, but did not isolate any compound containing halogen.

(10) Hattori, *J. Pharm. Soc. Japan*, **60**, 334 (1940).

(11) Hattori's value for the m. p. of β-cholesterol oxide, 136°, is at variance with all other published values and our own findings which give a m. p. of 106–107° for the pure substance. However, his oxide acetate has the accepted m. p., 112–113°.

(12) See for example Ehrenstein's acetolysis of the stereoisomeric 5,6-oxides of dehydroandrosterone acetate, *J. Org. Chem.*, **6**, 626 (1941); also Hattori, ref. 10.

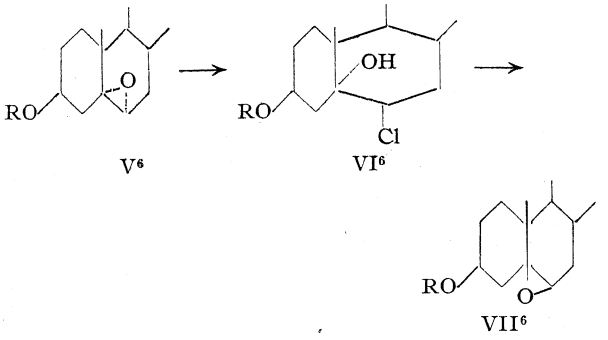
cause of dehalogenation occurring during recrystallization. The difficulty was obviated by benzoylating the crude dry reaction product and then crystallizing. Apparently the presence of a free hydroxyl group at C_3 labilizes the halogen at C_6, forming possibly a 3,6-oxide.

From the results of previous investigators it appeared that the configuration of the oxide and the nature of the substituent at C_3 affected the orientation of the chlorohydrin produced by fission of the oxide ring. Our experiments, however, indicated that the reagent might become a dominant factor in determining the course of the reaction. It became desirable to check Spring and Swain's experiments with benzoyl chloride in pyridine. Using α-cholesterol oxide, its acetate and benzoate, and β-cholesterol oxide, the products again were derivatives of 5-hydroxy-6-chlorocholestane (III). In the reaction of β-cholesterol oxide, a new substance was obtained together with 3-benzoxy-5-hydroxy-6-chlorocholestane. The new product has a m. p. of 197–198° and gave a sharp depression with the 3-benzoxy chlorohydrin obtained above. It was not, however, the expected dibenzoate of 3,6-dihydroxy-5-chlorocholestane, since that compound has a melting point of 184°. Work is in progress to elucidate its structure.

Thus Spring and Swain obtained 5-hydroxy-6-chloro compounds from the α-oxide series and 5-chloro-6-hydroxy derivatives from the β-oxides, while we could isolate only one type, regardless of which oxide we used. Since the experimental procedures were basically similar, this discrepancy, at the moment, seems difficult to explain.

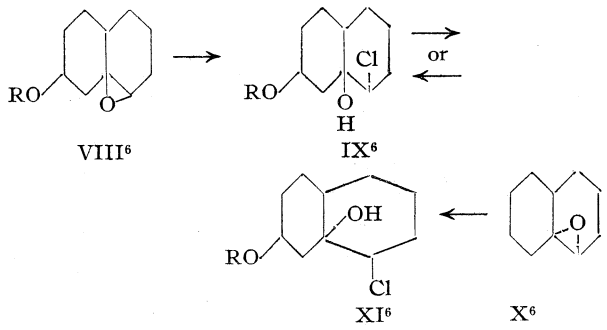
Mild saponification of 3-acetoxy-5-hydroxy-6-chlorocholestane (III, R = Ac) with sodium carbonate gave α-cholesterol oxide, m. p. 141°. This is in accordance with the work of Spring and Swain,[13] who obtained α-cholesteryl oxide benzoate by heating 3-benzoxy-5-hydroxy-6-chlorocholestane (III, R = Bz) with quinoline. Previously Windaus[14] had reported that the 5-chloro compound, 3,6-dihydroxy-5-chlorocholestane, forms β-cholesterol oxide when treated with alkali.

The stereochemical aspects of these reactions should be pointed out. In the above case, for example, an oxide with a β-configuration (V) combined with the elements of hydrogen chloride to form a 5-hydroxy-6-chloro compound (VI),



V[6] VI[6] VII[6]

which, on losing hydrogen chloride, gave an oxide of the opposite configuration (VII). Windaus[14] started with an α-oxide and obtained a 5-chloro-6-hydroxycholestane derivative which lost halogen acid and formed a β-oxide. Furthermore, we have obtained the same chlorohydrin from oxides of different configuration. The current theory states that in the cleavage of an oxide linkage a *trans*-compound is formed.[15] However, if an α-oxide (VIII) forms a *trans*-5-hydroxychlorohydrin (IX), and a β-oxide (X) similarly produces a *trans*-5-hydroxy compound (XI), then the two will neces-



VIII[6] IX[6] XI[6] X[6]

sarily be of opposite configuration at C_5,C_6. Even assuming that the α-oxide may give a 5-hydroxy-6-chloro derivative of a geometrical configuration different from IX, then the β-oxide, following the same route, would still give the opposite stereoisomer. Thus, it is necessary to postulate additional Walden inversions in one case but not in the other or an entirely different mechanism to explain how the same steric configuration is obtained by cleavage of the stereoisomeric oxides of cholesterol, or how the stereoisomers are interconverted through an intermediate chlorohydrin.

Further studies on the oxides of cholesterol will be reported in a subsequent communication.

(13) Spring and Swain, *J. Chem. Soc.*, 83 (1941).
(14) Windaus, *Z. physiol. Chem.*, **117**, 154 (1921).
(15) Lucas, Schlatter and Jones, THIS JOURNAL, **63**, 22 (1941), describe the opening of the oxide rings in the isomeric 2,3-epoxypentanes. See also Ehrenstein, *J. Org. Chem.*, **4**, 506 (1939); and Ehrenstein and Decker, *ibid.*, **5**, 544 (1940).

Experimental[16]

Monoperphthalic acid was prepared according to the method of Böhme[5] and kept in the refrigerator for as long as a month without appreciable decomposition.

β- and α-Cholesteryl Oxide Acetates.—Ten grams (0.023 mole) of cholesteryl acetate, m. p. 112–114°, dissolved in 50 cc. of ether, was mixed with 8.4 g. (0.046 mole) of monoperphthalic acid in 266 cc. of ether. The solution was allowed to reflux for six hours and the solvent removed by distillation. The residue was dried *in vacuo* and digested with 250 cc. of chloroform dried over potassium carbonate. Filtration gave a residue of 6.7 g. (87% recovery) of phthalic acid and a clear colorless solution which was taken to dryness *in vacuo*. The residue was crystallized from 30 cc. of methanol, giving 6.0 g. (58%) of β-cholesteryl oxide acetate, which on recrystallization from methanol gave the pure product, m. p. 111–112°, $[\alpha]^{25}D$ −21.8°; mixed m. p. with cholesteryl acetate, 97–101°. Concentration of the filtrate gave 1.55 g. (15%) of α-cholesteryl oxide acetate. The α-isomer was purified by crystallization from ethanol and found to have a m. p. of 101–103°, $[\alpha]^{25}D$ −44.6°. The m. p. is 5° higher than previously reported values.[2,10] However, it gave a depression (m. p. 88–104°) when mixed with pure β-oxide acetate. Saponification with methanolic potassium hydroxide and crystallization from dilute alcohol gave α-cholesterol oxide, m. p. 141–143°, $[\alpha]^{25}D$ −44.5°.[2]

In several runs the reaction mixture was left over the week-end. The yield of oxides in these instances was very poor and a considerable amount of alkali soluble substance was formed. Since this product remained dissolved in alkali after saponification, it is assumed to be a 5-halfphthalate derivative of cholestane.

α-Cholesteryl oxide benzoate was similarly prepared. Cholesteryl benzoate (16.7 g., 0.034 mole) reacting with perphthalic acid (12.7 g., 0.07 mole) gave 8.7 g. (50%) of α-cholesteryl oxide benzoate, m. p. 164–166°, $[\alpha]^{25}D$ −28.0.[4] No β-oxide benzoate could be isolated.

α-Cholesterol Oxide.—In the same manner, 5 g. (0.013 mole) of cholesterol (Wilson) and 4.7 g. (0.026 mole) of perphthalic acid gave 3.1 g. (61%) of α-cholesterol oxide, m. p. 141–143°. A small amount of the β-isomer was obtained from the mother liquors.

β-Cholesterol oxide, m. p. 105–107°, $(\alpha)^{25}D$ −12.7, was also obtained by saponification of the β-oxide acetate.

Reaction of β-Cholesteryl Oxide Acetate with Semicarbazide Hydrochloride.—A solution of 2.3 g. of β-cholesteryl oxide acetate in 10 cc. of pyridine was treated with 2.0 g. of semicarbazide hydrochloride and warmed on the steam-bath for six hours. The solution was concentrated to half its volume and poured over crushed ice. The precipitate was separated by filtration, digested with methanol, and filtered while hot to remove a small amount of disemicarbazide. Concentration and cooling gave colorless needle-like crystals, m. p. 183–186°, which gave a strong Beilstein test. These were combined with crystals recovered from the mother liquor and recrystallized twice from dilute acetone, giving 0.8 g. of cholesteryl acetate chlorohydrin, m. p. 187.5–189.5°.

Anal. Calcd. for $C_{29}H_{49}O_3Cl$: C, 72.4; H, 10.3; Cl, 7.38. Found: C, 72.2; H, 10.1; Cl, 7.31.

(16) Microanalyses by H. Emerson and W. Struck.

A portion (200 mg.) of the chlorohydrin, refluxed for fifteen minutes with acetic anhydride, was recovered unchanged, hence it was characterized as 3-acetoxy-5-hydroxy-6-chlorocholestane (III).

β-Oxide Acetate and Ferric Chloride.—β-Oxide acetate (0.40 g.) was treated with 1.0 g. of ferric chloride in alcohol. The solution was allowed to reflux for three hours, then concentrated to half its volume and water added. Ether extraction and isolation in the usual manner gave a chlorohydrin which was purified by repeated crystallization from dilute methanol and dilute acetone. The final product melted at 183–185°, and was recovered unchanged after refluxing with acetic anhydride. There was no depression of the m. p. on admixture with authentic 3-acetoxy-5-hydroxy-6-chlorocholestane.

β-Oxide Acetate and Benzoyl Chloride. 1. In Pyridine.—To a solution of 0.45 g. of β-cholesteryl oxide acetate in 5 cc. of dry pyridine was added 0.5 cc. of benzoyl chloride. The mixture was allowed to stand at room temperature for one-half hour, then heated on the steam-bath for the same period. The solution was poured into ice water and the semi-crystalline precipitate separated by decantation. Crystallization from dilute methanol gave 0.42 g. of chlorohydrin, m. p. 150–161°. Two recrystallizations from dilute acetone gave 0.25 g. of 3-acetoxy-5-hydroxy-6-chlorocholestane, m. p. 183–185°, which showed no depression of the m. p. on admixture with the product of the semicarbazide hydrochloride reaction.

Anal. Calcd. for $C_{29}H_{49}O_3Cl$: C, 72.4; H, 10.3; Cl, 7.38. Found: C, 72.3; H, 10.7, Cl, 7.26.

The compound was recovered unchanged after refluxing with acetic anhydride.

2. In Carbon Tetrachloride.—A solution of 0.60 g. of β-oxide acetate in 30 cc. of carbon tetrachloride distilled over potassium carbonate was treated with 0.50 cc. of benzoyl chloride under anhydrous conditions. The solution was allowed to reflux for three hours, then kept at room temperature for thirty-six hours. After distilling the solvent, the excess benzoyl chloride was removed *in vacuo*. Crystallization from dilute methanol gave a product which sintered at 100° and melted at 135–155°. A Beilstein test for halogen was positive. Four crystallizations from dilute acetone gave colorless needles of 3-acetoxy-5-hydroxy-6-chlorocholestane, m. p. 182–185°. There was no depression of the m. p. on admixture with an authentic sample.

Anal. Calcd. for $C_{29}H_{49}O_3Cl$: C, 72.4; H, 10.3; Cl, 7.38. Found: C, 72.3; H, 10.2; Cl, 7.17.

β-Oxide Acetate and "Pyridine Hydrochloride."—"Pyridine Hydrochloride" was prepared by passing dry hydrogen chloride into a solution of pyridine in ether and allowing the saturated solution to stand for one-half hour. The white solid was separated by filtration and found to be very hygroscopic. It is insoluble in dioxane and petroleum ether and soluble in alcohol. Crystallization from absolute alcohol–ether gave colorless platelets, m. p.: s. 81; m. 141–146°. It can be kept for months in a desiccator over calcium chloride with no evidence of decomposition.

To a solution of 1.0 g. of β-cholesteryl oxide acetate in 30 cc. of absolute ethanol was added 1.0 g. of pyridine hydrochloride. The solution was allowed to reflux for fifteen

minutes, then concentrated to half its volume and the sterol precipitated by the addition of water. Crystallization from dilute acetone gave 0.85 g. (77%) of crude 3-acetoxy-5-hydroxy-6-chlorocholestane, m. p. 148–168°. A Beilstein test was positive. After several crystallizations from dilute acetone, colorless needles, m. p. 184–186° were obtained. The product was recovered unchanged after treatment with acetic anhydride, and gave no depression in m. p. on admixture with authentic 3-acetoxy-5-hydroxy-6-chlorocholestane.

Reaction of Pyridine Hydrochloride with the Other Oxides of Cholesterol.—α-Cholesteryl oxide benzoate is sparingly soluble in alcohol, so it was necessary to dissolve it in benzene. One gram of the oxide in benzene was mixed with 2.0 g. of pyridine hydrochloride in ethanol. The solution was refluxed for fifteen minutes, the solvent evaporated, and the reaction product crystallized from methanol as a halogen containing compound, m. p. 193–196°. Recrystallization from ethyl acetate–methanol, and dilute acetone gave 0.60 g. (56%) of 3-benzoxy-5-hydroxy-6-chlorocholestane, m. p. 196–198°. It was recovered unchanged after refluxing with acetic anhydride.

Anal. Calcd. for $C_{34}H_{51}O_3Cl$: C, 75.2; H, 9.46; Cl, 6.53. Found: C, 75.0; H, 9.40; Cl, 6.33.

α-Cholesteryl oxide acetate (0.80 g.) and 1.0 g. of pyridine hydrochloride in alcohol gave 0.65 g. (74%) of 3-acetoxy-5-hydroxy-6-chlorocholestane, m. p., and mixed m. p., 185–187°. It was recovered unchanged after treatment with acetic anhydride.

α- and β-Cholesterol oxides also reacted smoothly with pyridine hydrochloride. However, the product lost halogen easily, thereby hindering its purification. Thus 0.30 g. of the **α-oxide** gave 0.25 g. of crude chlorohydrin, m. p. 154–160°; Beilstein test positive. Recrystallization from methanol–acetone gave feathery needles, m. p. 99–105°. This product no longer contained halogen.

Benzoylation of the crude product gave an easily purifiable substance. Using 0.45 g. of α-oxide and 1.0 g. of pyridine hydrochloride, a chlorohydrin was obtained. It was dried and benzoylated with 0.50 cc. of benzoyl chloride in pyridine. The product was isolated in the usual way and crystallized from ethyl acetate–methanol, giving 0.35 g. (58%) of 3-benzoxy-5-hydroxy-6-chlorocholestane, m. p. 193–196°. Recrystallization from dilute acetone, and again from ethyl acetate–methanol, gave colorless needles, m. p. 196–198°, which showed no depression on admixture with an authentic sample.

Similarly, from 0.40 g. of the **β-oxide** there was obtained 0.28 g. (52%) of 3-benzoxy-5-hydroxy-6-chlorocholestane, m. p. 192–195°. When mixed with an authentic sample the m. p. was not depressed.

Reaction of Benzoyl Chloride with the Other Oxides of Cholesterol.—Reactions with benzoyl chloride did not proceed as smoothly as the corresponding reactions with pyridine hydrochloride and the products were less pure. Treatment of 0.70 g. of **α-oxide** acetate with 0.60 cc. of benzoyl chloride gave 0.42 g. (55%) of a product, m. p. 160–170°. After heating with acetic anhydride and recrystallizing twice from dilute acetone, 3-acetoxy-5-hydroxy-6-chlorocholestane was obtained as colorless needles, m. p. 178–183°. A mixed m. p. with authentic acetoxychlorohydrin, however, was 179–184°.

Anal. Calcd. for $C_{29}H_{49}O_3Cl$: C, 72.4; H, 10.3. Found: C, 72.6; H, 10.1.

Starting with 0.50 g. of **α-oxide benzoate**[4] and 0.50 cc. of benzoyl chloride, 0.45 g. (84%) of 3-benzoxy-5-hydroxy-6-chlorocholestane, m. p. 191–195°, was obtained. Recrystallization from dilute acetone gave a pure product, m. p. 197–198.5°. A mixed m. p. with authentic benzoate chlorohydrin gave no depression.

Anal. Calcd. for $C_{34}H_{51}O_3Cl$: C, 75.2; H, 9.46; Cl, 6.53. Found: C, 75.0; H, 9.29; Cl, 6.46.

Using 0.15 g. of **α-cholesterol oxide** and 0.20 cc. of benzoyl chloride, the benzoate chlorohydrin was obtained in fair yield. After several recrystallizations its m. p. and mixed m. p. with authentic 3-benzoxy-5-hydroxy-6-chlorocholestane was 193–196°.

The reaction of **β-cholesterol oxide** with benzoyl chloride was also carried out according to Spring and Swain.[4] The results were, however, different, so the details of the experiment are given. The β-oxide (0.30 g.) in 4 cc. of dry pyridine was warmed for an hour with 0.50 cc. of benzoyl chloride. The solution was poured into ice-water and the precipitate separated by filtration. The residue was crystallized from 30 cc. of acetone–methanol, giving 0.15 g. of 3-benzoxy-5-hydroxy-6-chlorocholestane, m. p. 190–193°. Recrystallizations from acetone–methanol and dilute acetone brought the m. p. up to 195–197°.

Anal. Calcd. for $C_{34}H_{51}O_3Cl$: C, 75.2; H, 9.46; Cl, 6.53. Found: C, 74.9; H, 9.50; Cl, 6.47.

Concentration of the first mother liquor gave 0.14 g. of a crystalline compound, m. p. 176–182°. It was recrystallized twice from acetone–methanol, in which it seemed to be more soluble than the previously obtained benzoate chlorohydrin. It had a m. p. of 197–198°, and its mixed m. p. with authentic 3-benzoxy-5-hydroxy-6-chlorocholestane was 179–186°. This compound is not 3,6-dibenzoxy-5-chlorocholestane.

Anal. Calcd. for 3,6-dibenzoxy-5-chlorocholestane, m. p. 184°, $C_{41}H_{55}O_4Cl$: Cl, 5.48. Found: Cl, 7.01, 7.11.

α-Oxide from 5-Hydroxy-6-chlorocholestane Derivatives.—A solution of 0.7 g. of 3-acetoxy-5-hydroxy-6-chlorocholestane in 30 cc. of dilute alcohol was treated with 10 cc. of 2 *N* sodium carbonate and warmed on the steam-bath for thirty minutes. The addition of water gave a precipitate of 0.40 g. of **α-cholesteryl oxide** which was recrystallized twice from ethyl acetate, m. p. 141–143°. A mixed m. p. with an authentic sample of α-oxide showed no depression.

A similar reaction was carried out with 3-benzoxy-5-hydroxy-6-chlorocholestane and methanolic potassium hydroxide, again giving α-cholesterol oxide, m. p. 141–143°.

Summary

α- and β-cholesterol oxide, α- and β-cholesteryl oxide acetate and α-cholesteryl oxide benzoate have been conveniently prepared through the action of perphthalic acid on cholesterol and its derivatives.

Semicarbazide hydrochloride and ferric chloride react with β-cholesteryl oxide acetate to form 3-acetoxy-5-hydroxy-6-chlorocholestane.

All five of the cholesteryl oxides prepared react with "pyridine hydrochloride" and benzoyl chloride to give 5-hydroxy-6-chlorocholestane derivatives.

β-Cholesterol oxide, as its acetate, has been converted to α-cholesterol oxide through the 5-hydroxy-6-chloro compound.

The stereochemical implications of these reactions have been pointed out.

KALAMAZOO, MICHIGAN RECEIVED JULY 17, 1942

[CONTRIBUTION FROM THE MEDICAL-RESEARCH DIVISION, SHARP AND DOHME, INC.]

Synthesis of *p*-Hydroxyphenyl Amyl Sulfide

BY ELLIS MILLER, FRANK S. CROSSLEY AND MAURICE L. MOORE

A previous publication from these Laboratories[1] confirmed the report[2] that the hydroxyphenyl alkyl sulfides were more powerful in their bactericidal activity than the corresponding alkylphenols. These results prompted us to seek a practical method for the preparation of *p*-hydroxyphenyl *n*-amyl sulfide, which had been shown to possess maximum activity for the compounds in this series.

The hydroxydiphenyl sulfides have been prepared by Hilbert and Johnson[3] by use of the Ziegler[4] reaction between diazotized anisidine and thiophenol. The diazothio ether thus formed breaks down at 70° to give a methoxydiphenyl sulfide which is converted into the desired product by dealkylation. They reported that an attempt to prepare *p*-hydroxydiphenyl sulfide by treating diazotized *p*-aminophenol with sodium thiophenate was unsuccessful. Suter and Hansen[2] treated diazotized anisidine with potassium ethyl xanthate and decomposed the intermediate diazonium ethyl xanthate to obtain *p*-methoxythiophenol which then reacted with amyl bromide and the product was dealkylated to give *p*-hydroxyphenyl *n*-amyl sulfide. They also reported an unsuccessful attempt to combine the sodium salt of butanethiol-1 with diazotized *p*-aminophenol.

In the previous publication,[1] a more satisfactory procedure was developed which involved the synthesis of thiohydroquinone and subsequent reaction of this with amyl bromide to give the desired *p*-hydroxyphenyl *n*-amyl sulfide. The success of the thiohydroquinone synthesis suggested that diazotized *p*-aminophenol should react with the sodium salt of *n*-amyl mercaptan, even though previous workers[2,3] had been unsuccessful with similar reactions. An extensive study of possible experimental conditions for the reaction has shown that it can be used to prepare the compound in yields of 25–30%.

The diazotization was carried out at a temperature of 0–10° and the diazothio ether decomposed by heating at 60°. The resulting product was distilled and gave a yield of 50–60% of a material which solidified at room temperature. However, on crystallizing the material from solvent naphtha the yield of *p*-hydroxyphenyl *n*-amyl sulfide dropped to 25–30%. Careful fractionation of the reaction mixture disclosed that two definite products were formed during the reaction and permitted the isolation of the second product with its purification. The product was identified by preparation of derivatives and synthesis as di-*n*-amyl disulfide. The reaction has been applied to *n*- and isoamyl mercaptan with comparable results.

Experimental Part

***p*-Hydroxyphenyl *n*-Amyl Sulfide.**—*p*-Aminophenol, 21.8 g. (0.2 mole), was dissolved in 110 cc. of 4 *N* hydrochloric acid (0.44 mole) and diazotized in the usual manner by the slow addition of a solution of 15 g. (0.23 mole) of sodium nitrite in 30 cc. of water. The mixture was stirred until the diazotization was complete (starch–iodide paper test) and the deep purple solution of *p*-hydroxyphenyldiazonium chloride rapidly filtered from a small amount of insoluble material. The solution was then added slowly to a cold (10°) sludge of 24 g. (0.23 mole) of *n*-amyl mercaptan in 75 cc. of water containing 37.5 g. (0.94 mole) of sodium hydroxide. The temperature was maintained at 10° throughout the addition and frothing was controlled by the addition of small amounts of *n*-butanol. After the reaction had subsided, the cooling bath was removed and stirring continued at room temperature until the diazonium salt disappeared (R-salt test). The mixture was then heated to 60° to complete the decomposition of the diazothio ether and allowed to stand overnight at room temperature, after which it was diluted with five volumes of water, acidified with concentrated hydrochloric acid and extracted with 500 cc. of toluene. The extract was washed three times with 500-cc. portions of water, dried over anhydrous

(1) Miller and Read, THIS JOURNAL, **55**, 1224 (1933).
(2) Suter and Hansen, *ibid.*, **54**, 4100 (1932).
(3) Hilbert and Johnson, *ibid.*, **51**, 1526 (1929).
(4) Ziegler, *Ber.*, **23**, 2469 (1890).

sodium sulfate, and the toluene removed by distillation at atmospheric pressure. The residue was distilled rapidly at about 2 mm. pressure to separate the distillable portion (20 g. of orange-yellow oil which solidified on standing) from a heavy tar. A slow redistillation of this product gave 16 g. of a light yellow oil, boiling over a range of 110–140° (1 mm.), which solidified immediately.

Material (120 g.) from several of the above runs was carefully fractionated, through a 12″ indented column, insulated with a glass air-jacket, into two main fractions:

Fraction A, 45 g., b. p. 89–91° (1 mm.), $n^{20}D$ 1.4876, d^{25}_{25} 0.9224, was identified as di-*n*-amyl disulfide.[5] Reduction with metallic sodium in anhydrous ethanol[6] gave a solid sodium salt of *n*-amyl mercaptan which reacted with 2,4-dinitrochlorobenzene on refluxing in anhydrous ethanol to give 2,4-dinitrophenyl *n*-amyl sulfide, m. p. 79.5–80°, identical with the product, m. p. 80°, prepared from *n*-amyl mercaptan,[7] and by the reduction of synthetic di-*n*-amyl disulfide. The material also readily formed a crystalline derivative, m. p. 134–136°, which resolidified and did not remelt up to 250°, when treated with mercuric chloride in an alcohol solution at room temperature for seven hours which was identical with the derivative from synthetic di-*n*-amyl disulfide.

Fraction B, 45 g., b. p. 142–145° (1 mm.), was recrystallized twice from solvent naphtha and gave 37 g. of *p*-hydroxyphenyl *n*-amyl sulfide, m. p. 62–62.5°.[1]

p-Hydroxyphenyl isoamyl sulfide,[1] a red oil, b. p. 134–136° (1 mm.), $n^{25}D$ 1.5523, was prepared by the above reaction using isoamyl mercaptan and di-isoamyl disulfide, b. p. 94–96° (1 mm.), isolated as the by-product.

Di-*n*-amyl Disulfide.—(A) This compound was prepared by the method described in "Organic Syntheses" for *p,p'*-dinitrodiphenyl disulfide.[8] To 180 g. (0.75 mole) of sodium sulfide, dissolved in 750 cc. of 95% ethanol with refluxing, was added 24 g. (0.75 atom) of sulfur and the mixture stirred until dissolved. *n*-Amyl bromide, 151 g. (1 mole), dissolved in 250 cc. of 95% ethanol, was placed in a two-liter, three-necked flask, and the hot sodium disulfide solution was added at such a rate as to maintain gentle refluxing.[9] The addition was complete in about twenty minutes and the mixture refluxed on the steam-bath for three hours, after which it was allowed to stand overnight at room temperature. Alcohol was removed to about one-third volume by distilling at reduced pressure (water pump), two volumes of water added and the mixture extracted with 500 cc. of benzene. The extract was washed several times with water, dried over anhydrous sodium sulfate, and, after removing the benzene, the di-*n*-amyl disulfide distilled through the 12″ column as a colorless liquid, b. p. 90–92° (1 mm.); yield 62 g., $n^{25}D$ 1.4875; d^{25}_{25} 0.9212.

(B) *n*-Amyl mercaptan, 52 g. (0.5 mole), was dissolved in a solution of 22 g. (0.55 mole) of sodium hydroxide in 125 cc. of water and oxidized by the addition of 60.3 g. (0.475 atom) of iodine in small portions over a period of twenty minutes according to the method of Kekulé and Linnemann[10] for the preparation of diethyl disulfide. The mixture was stirred until all of the iodine dissolved and then extracted with 200 cc. of benzene. The extract was washed three times with water, dried over anhydrous sodium sulfate and the benzene removed by distillation. The yield of di-*n*-amyl disulfide was 36 g., b. p. 101–103° (2 mm.), $n^{25}D$ 1.4868.

Summary

p-Hydroxyphenyl *n*-amyl sulfide has been prepared in yields of 25–30% by the diazotization of *p*-aminophenol, coupling with sodium *n*-amyl mercaptide, and decomposition of the diazothio ether. A second product was obtained from this reaction in a yield of 25% and has been identified as di-*n*-amyl disulfide by preparation of derivatives and synthesis.

p-Hydroxyphenyl isoamyl sulfide was prepared in the same manner and di-isoamyl disulfide obtained as a second product.

GLENOLDEN, PA. RECEIVED JUNE 16, 1942

(5) (a) Rosser and Ritter, THIS JOURNAL, **59**, 2179 (1937); (b) Blackburn and Challenger, *J. Chem. Soc.*, 1872 (1938).

(6) Reid, *et al.*, THIS JOURNAL, **48**, 776 (1926).

(7) Bost, Turner and Norton, *ibid.*, **54**, 1985 (1932).

(8) "Organic Syntheses," Coll. Vol. I, p. 215.

(9) The reaction between the amyl halide and sodium disulfide was not as energetic as that between nitrochlorobenzene and sodium disulfide.

(10) Kekulé and Linnemann, *Ann.*, **123**, 277 (1862).

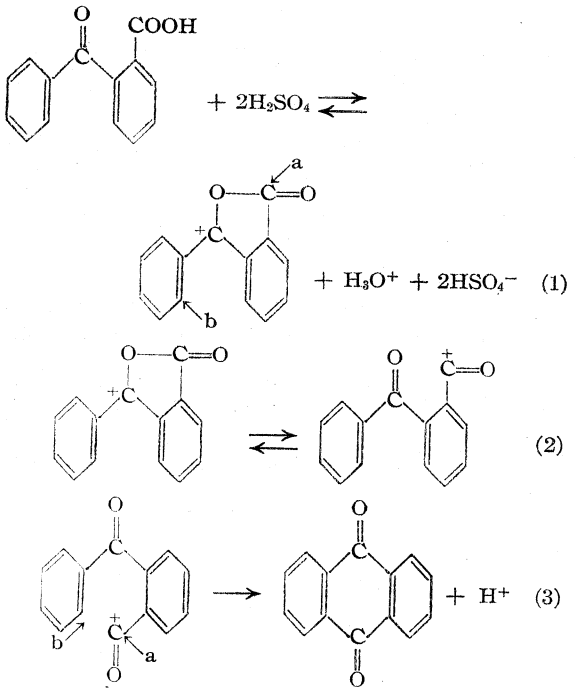
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

A Mechanism for the Formation of Anthraquinone from *o*-Benzoylbenzoic Acid

BY MELVIN S. NEWMAN

The facile ring closure of *o*-benzoylbenzoic acid to anthraquinone under the influence of sulfuric acid has never been satisfactorily explained.[1] Although ring closure condensations with acids of the *o*-benzylbenzoic and γ-arylbutyric type take place fairly readily in sulfuric acid, anthraquinone formation remains a reaction unique in organic chemistry. The ease and the high yield with which this condensation takes place ortho to a ketonic function are indeed remarkable.

It is the object of this communication to present a plausible mechanism for the formation of anthraquinone from *o*-benzoylbenzoic acid. The proposed mechanism is outlined in the following equations.



Arguments Advanced in Favor of the Proposed Mechanism

Equation 1.—The chief support for equation 1 was obtained in the following experiments.

A. A solution of 5.0 g. of *o*-benzoylbenzoic acid in 98–99% sulfuric acid was poured into 500 cc. of absolute methanol in a one-liter Claisen flask. During this addition the flask was cooled externally by ice-water and internally by dry-ice. About 300 cc. of methanol was rapidly removed under reduced pressure at low temperature and the residue was poured on ice. The organic matter was rapidly taken into ether and separated into acid and neutral fractions by sodium carbonate extraction. From the acid fraction was isolated 1.48 g. (30%) of *o*-benzoylbenzoic acid. The neutral fraction consisted of 3.17 g. (60%) of a mixture of the normal and pseudo methyl esters of *o*-benzoylbenzoic acid. This mixture was analyzed by dissolving in 32 cc. of 98–99% sulfuric acid and pouring on ice. After such treatment it is known that the normal ester is recovered unchanged while the pseudo ester is converted into *o*-benzoylbenzoic acid.[2] By this means the 3.17 g. of mixed esters was converted into 1.19 g. (40%) of *o*-benzoylbenzoic acid and 1.78 g. (56%) of methyl *o*-benzoylbenzoate, thus indicating that the ester mixture consisted of 40% of pseudo ester and 56% normal ester.

B. This experiment was carried out just as experiment A, except that instead of dissolving *o*-benzoylbenzoic acid in sulfuric acid and pouring into cooled methanol, 60 cc. of 98–99% sulfuric acid was poured into a solution of 5.0 g. of the pseudo methyl ester of *o*-benzoylbenzoic acid in 500 cc. of methanol. There was then obtained 0.18 g. (3.6%) of *o*-benzoylbenzoic acid and 4.92 g. (92.5%) of mixed esters which, by analysis as above, was shown to consist of 35% of pseudo ester and 63% of normal ester.

Before drawing any conclusions from these experiments, it is desirable to point out certain facts. From the studies cited by Hammett,[3] it seems well established that most organic acids behave as monoacid bases on ionization in solvent sulfuric acid, as follows

$$RCOOH + H_2SO_4 \rightleftharpoons RCO_2H_2^+ + HSO_4^- \quad (4)$$

When sulfuric acid solutions of such acids are poured into absolute methanol, no appreciable amount of esterification occurs other than the slow normal acid catalyzed esterification.[4] Likewise, when sulfuric acid solutions of the methyl esters of such acids are poured into water, the methyl esters are recovered almost completely unchanged.[4,5] The normal methyl ester of *o*-benzoylbenzoic acid represents such an ester.

Certain acids, chiefly 2,4,6-trialkylbenzoic acids, ionize in sulfuric acid in a more complex way,[3b] as follows

(1) Gleason and Dougherty, THIS JOURNAL, **51**, 310 (1929), and Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1935, p. 189, discuss briefly the possibility of cyclic intermediates.

(2) Newman and McCleary, *ibid.*, **63**, 1539 (1941).

(3) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, (a) pp. 45–47, (b) pp. 54–56.

(4) Newman, THIS JOURNAL, **63**, 2431 (1941).

(5) Treffers and Hammett, *ibid.*, **59**, 1708 (1937).

$$RCOOH + 2H_2SO_4 \rightleftharpoons R-C^{+}=O + H_3O^{+} + 2HSO_4^{-} \quad (5)$$

When sulfuric acid solutions of such acids are poured into methanol, almost complete esterification takes place.[4] Similarly when sulfuric acid solutions of the methyl esters of such acids are poured into water the free acid is obtained.[4,5] The pseudo methyl ester of *o*-benzoylbenzoic acid represents such an ester.

Since *o*-benzoylbenzoic acid is largely esterified by dissolving in sulfuric acid and pouring into methanol (experiment A) it seems quite likely that in sulfuric acid solution *o*-benzoylbenzoic acid ionizes according to equation 1. The cyclic form of the positive ion is the preferred structure as indicated because the pseudo methyl ester is formed on pouring the sulfuric acid solution into methanol. The fact that the ester isolated after such treatment contains a large amount of normal ester should not confuse the picture because experiment B shows that during the isolation of the reaction products considerable isomerization of pseudo ester to normal ester occurs. Furthermore, no cyclic ester could have been formed from the normal ester or from free *o*-benzoylbenzoic acid because the normal ester is stable in acid methanol and is the ester formed on acid catalyzed esterification of *o*-benzoylbenzoic acid.[2,6] To summarize briefly, then, the fact that *o*-benzoylbenzoic acid is largely esterified on pouring its sulfuric acid solution into methanol constitutes evidence that *o*-benzoylbenzoic acid undergoes a complex ionization in solvent sulfuric acid. Furthermore, the fact that the pseudo ester is first formed on pouring a sulfuric acid solution of *o*-benzoylbenzoic acid into methanol indicates that the positive ion present in the sulfuric acid solution is cyclic in nature, as shown in equation 1.

Equations 2 and 3.—Since great chemical reactivity is generally associated with positive ions in organic molecules, it would appear strange that such an ion as indicated in equation 1 did not immediately react to form anthraquinone. However, it is a fact that sulfuric acid solutions of *o*-benzoylbenzoic acid must be heated before anthraquinone is formed to any appreciable extent. Recourse to atomic models shows that in a cyclic form carbon atom *a* is far removed from carbon atom *b* with which it must join to form anthraquinone. It seems necessary, therefore, to postulate that the cyclic positive ion on heating absorbs energy and cleaves to a new open chain acyl ion of higher energy content (equation 2). This acyl ion can then rotate so that carbon atom *a* approaches carbon atom *b*. At some stage a proton is lost from carbon *b*, a new carbon–carbon link is formed between carbons *a* and *b*, and anthraquinone results (equation 3).

With the above mechanism as a working hypothesis, it is proposed to study the rate of anthraquinone formation under various conditions and to study, if possible, the effect of substituents on steps 1, 2 and 3.

Summary

A mechanism for the formation of anthraquinone from *o*-benzoylbenzoic acid in sulfuric acid is proposed. Experimental evidence in favor of the proposed mechanism is presented.

COLUMBUS, OHIO RECEIVED JULY 8, 1942

(6) Plaskuda, *Ber.*, **7**, 987 (1874); Haller and Guzot, *Bull. soc. chim.*, (3) **25**, 54 (1901); H. Meyer, *Monatsh.*, **25**, 475 (1904).

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, FACULTAD DE CIENCIAS EXACTAS, FÍSICAS Y NATURALES, UNIVERSITY OF BUENOS AIRES AND THE INSTITUTO BACTERIOLÓGICO D.N.H.]

Studies on Argentine Plants. V.[1] Identification and Characterization of Some Alkaloids in Fagara Coco (Gill) Engl.

BY V. DEULOFEU, R. LABRIOLA AND J. DE LANGHE

In 1925 Stuckert[2] and his collaborators undertook the isolation of alkaloids from the leaves and young twigs of *Fagara coco* (Gill) Engl., a tree growing in central and northern Argentina and in Bolivia, and which apparently has been used in those regions as a drug. They obtained several crystalline substances of which the three best characterized were named and described as follows: α-fagarine, $C_{18}H_{22}NO_4$, m. p. 169°; β-fagarine, $C_{12}H_{26}NO_6$, m. p. 176°; and γ-fagarine, $C_{15}H_{15}NO_3$, m. p. 139°. At Stuckert's request, Merck and Company (Darmstadt) carried out a large-scale preparation of alkaloids from *Fagara coco* and isolated: fagarine I, melting at 163°, $C_{19}H_{23}NO_5$ which is probably identical with Stuckert's α-fagarine, and fagarine II, apparently new, which melted at 202° and had a composition corresponding to $C_{18}H_{20}NO_4$.

By extraction and purification of the alkaloids from the end twigs and leaves of a sample of *Fagara coco* kindly supplied to us by Dr. Stuckert, we have obtained three well-defined substances corresponding to the α, β and γ-fagarines mentioned above. Revised formulas and melting points are given in the experimental part. In addition, small fractions of a higher-melting material which may correspond to Merck fagarine II have been obtained, but not in sufficient quantity for complete purification.

Our investigation of the properties of these alkaloids shows that two of them bear a very close relationship to substances already described in the literature. β-Fagarine is identical with skimmianine which was discovered by Honda[3] in *Skimmia japonica*, a plant belonging like *Fagara* to the family of Rutaceae. The structure of skimmianine has been established by Asahina and Inubuse[4] who showed that this alkaloid is a dimethoxy derivative of *dictamine* which was found by Thoms[5] in *Dictamus albus* and by Asahina, Ohta and Inubuse[6] in *Skimmia repens*. The identity of β-fagarine and skimmianine is proved by the close correspondence of their melting points and the melting points of a series of six derivatives and degradation products which were prepared from β-fagarine by the present authors according to the method originally described by Asahina for skimmianine.

COMPARISON OF PROPERTIES

Substance	Melting points, °C. From β-fagarine	From skimmianine[4]
Free base, $C_{14}H_{13}NO_4$	178	176
Picrate of base, $C_{14}H_{13}NO_4 \cdot C_6H_4N_3O_6$	195	195–197
Iso-skimmianine, $C_{14}H_{13}NO_4$	188–9	185
Dimethoxy-isoskimmianine	218–220	218
Skimmianic acid	248	248
Skimmianal	238	238
2,4-Dihydroxy-7,8-dimethoxyquinoline	250	250

It is recommended that the name β-fagarine be eliminated and the name skimmianine be used henceforth.

γ-Fagarine apparently has not been described under another name and the retention of the present term is therefore recommended. Nevertheless, this alkaloid is very similar to skimmianine, from which it differs by having one less methoxyl group. It forms a series of derivatives and degradation products entirely analogous to those described for skimmianine but not identical. On oxidation by permanganate, γ-fagarine yields γ-fagaric aldehyde and γ-fagaric acid. The latter, which also is derived from the aldehyde by further oxidation, on decarboxylation yields a 2,4-dihydroxymethoxyquinoline in which the position of the methoxyl group is unknown. Since none of the four isomeric dihydroxymethoxyquinolines has yet been synthesized, we have begun their synthesis in order to make these key reference compounds available for direct comparisons.

α-Fagarine is a substance quite different from these compounds and since it has not been de-

(1) Part IV, R. A. Gentile and R. Labriola, *J. Org. Chem.*, **7**, 136 (1942).

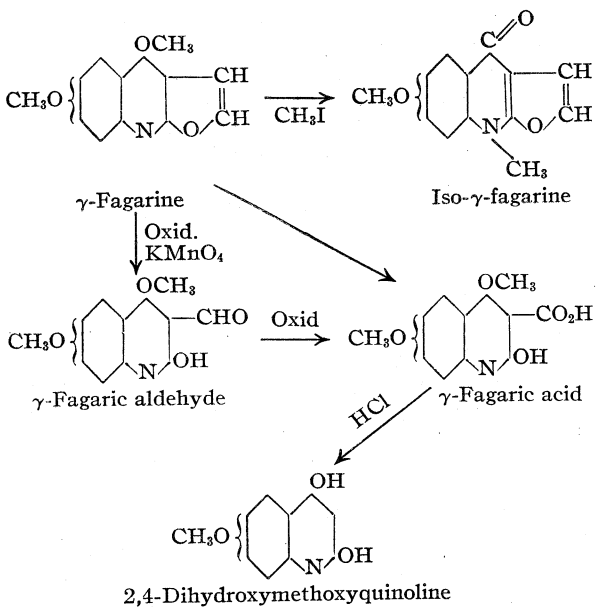
(2) "Investigaciones del Laboratorio de Química Biológica, Cordoba, Argentina," Vol. I, 1933, and Vol. II, 1938.

(3) Honda, *Arch. Exp. Path. Pharmakol.*, **52**, 83 (1904).

(4) Asahina and Inubuse, *Ber.*, **63**, 2052 (1930).

(5) Thoms, *Ber. Deut. Pharm. Ges.*, **33**, 68 (1923); Thoms and Dambergis, *Arch. Pharm.*, **268**, 39 (1930).

(6) Asahina, Ohta and Inubuse, *Ber.*, **63**, 2045 (1930).



scribed under another name as far as we know, we recommend retaining the present term. We have assigned to it the formula $C_{18}H_{21}NO_4$. Of the four oxygens, two belong to the methoxyl groups. It possesses a methylimino group and is a stronger base than skimmianine or γ-fagarine from which it may be separated easily by exploiting this difference. Preliminary experiments indicate that its behavior with methyl iodide or oxidizing agents is completely different from that of the other two bases. We are continuing its investigation.

Experimental Part

Acid Extraction.—Ten kg. of leaves and twigs of *Fagara coco* was soaked for four days in 60 liters of 10% hydrochloric acid, and this extraction was twice repeated at four-day intervals. On evaporation *in vacuo* to about 10 l., a precipitate formed which was filtered off and freed from alkaloids by repeated maceration with 20% hydrochloric acid. The combined alkaloidal extract was neutralized with dilute sodium hydroxide and extracted with trichloroethylene. The washed extract was evaporated to dryness and the residue was extracted repeatedly with 13% hydrochloric acid. The combined acid extracts were neutralized and extracted with chloroform. The residue from the washed chloroform extract was again extracted with 13% hydrochloric acid. This acid extract was treated with dilute sodium hydroxide until the weaker bases precipitated at *p*H 3.5–4.0. After twenty-four hours, the precipitate containing skimmianine and γ-fagarine was recrystallized from alcohol yielding skimmianine. Concentration of the mother liquors gave a product, 120–150°, in which γ-fagarine predominates and from which it can be crystallized in large prisms from alcoholic solution.

The alkaline mother liquor was brought to *p*H 9 with sodium hydroxide and exhaustively extracted with chloroform. Evaporation of the extract and recrystallization of the residue from alcohol yielded α-fagarine.

Acid extraction of 10 kg. of leaves gave 54 g. of impure alkaloidal residue yielding 13 g. of skimmianine, m. p. 178°; 6 g. of γ-fagarine, m. p. 139°; and 7 g. of α-fagarine, m. p. 163°.

Alcoholic Extraction.—Two kg. of leaves was boiled first with 8 l. of 96% ethanol for four hours and the extraction repeated three times with 5-l. portions of alcohol and, finally, with a 5-l. portion of alcohol to which 250 cc. of concentrated ammonium hydroxide had been added. The combined extracts from 10 kg. of leaves, after neutralizing with hydrochloric acid and drying, gave a residue of about 1.5 kg. After cooling this was extracted with 4 successive portions of cold, dilute hydrochloric acid, the combined extracts neutralized with 30% sodium hydroxide solution and then extracted exhaustively with trichloroethylene. The residue was then extracted with 2 l. of very dilute hydrochloric acid and the combined extracts were rendered alkaline, extracted with chloroform, the product washed with water, dried, and the residue again extracted with very dilute hydrochloric acid. Water was added up to 2 l., a fine suspension removed by filtration, and sodium hydroxide slowly added to *p*H 2. At this point a precipitate which did not give the alkaloidal reaction was formed and this was removed by filtration. The *p*H of the solution was brought to 3.5–4 and the procedure was continued as given for the acid extraction. The yield from the 10 kg. of leaves was 41.5 g. of skimmianine, m. p. 178°, 2.5 g. of γ-fagarine, m. p. 139°, and 5 g. of α-fagarine, m. p. 162°.

Characterization of γ-Fagarine as a Methoxy-dictamine.—When γ-fagarine of m. p. 139° was recrystallized several times from alcohol, prismatic crystals of m. p. 142° were obtained, soluble in chloroform, benzene and ether, slightly soluble in petroleum ether, and very slightly soluble in water. Alcohol was the best solvent for recrystallization.

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.12, H, 4.80; N, 6.11; two methoxyl, 27.03. Found: C, 68.14, 68.39; H, 4.99, 5.11; N, 6.22; —OCH_3, 27.12, 27.09.

γ-Fagarine Picrate.—Prepared in the usual way[4] in alcohol solution and recrystallized from the same solvent, the picrate was obtained in the form of yellow needles of m. p. 177°.

Anal. Calcd. for $C_{13}H_{11}NO_3 \cdot C_6H_3N_3O_7$: N, 12.22. Found: N, 12.50.

γ-Fagarine Picrolonate.—Prepared in the usual way,[4] and recrystallized from alcohol, the picrolonate formed yellow needles melting at 174–175°.

Anal. Calcd. for $C_{13}H_{11}NO_3 \cdot C_{10}H_8N_4O_5$: N, 14.60. Found: N, 14.84.

The Rearrangement of γ-Fagarine to Iso-γ-fagarine.—A sample of 500 mg. of γ-fagarine was treated in a closed tube at 100–105° with 3 ml. of methyl iodide for three hours. When the heating was over, the solution was filtered and evaporated to dryness. The residue thus obtained was crystallized from methanol, after decolorization by carbon. There was obtained 300 mg. of colorless needles, melting at 179°.

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.12; H, 4.80; N, 6.11. Found: C, 67.93; H, 5.18; N, 6.36.

γ-Fagaric Aldehyde.—A sample of 800 mg. was dissolved in 60 ml. of acetone heated almost to the boiling point and a hot acetone solution of 1.6 mg. of potassium permanganate was slowly added. Oxidation occurred easily. After cooling, the manganese dioxide was filtered off, and the solution was evaporated to dryness. The residue (100 mg.), recrystallized from alcohol, yielded fine, yellow needles, melting at 185°.

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.72. Found: C, 61.94; H, 5.08.

γ-Fagaric Aldehyde Phenylhydrazone.—The phenylhydrazone of the preceding aldehyde was prepared by heating the latter in alcohol solution for twenty minutes with a slight excess of phenylhydrazine and acetic acid. Upon addition of water at the end of heating, a precipitate was formed which was filtered off and, when recrystallized from alcohol, yielded yellow needles melting at 207°.

Anal. Calcd. for $C_{18}H_{17}N_3O_3$: N, 13.00. Found: N, 13.37.

γ-Fagaric Acid.—The manganese dioxide precipitate obtained during the oxidation of fagarine was digested with 10% sodium hydrate and filtered. The resultant solution was acidified with hydrochloric acid which yielded a precipitate of γ-fagaric acid. It was quite insoluble in ordinary organic solvents. It recrystallized from a large volume of boiling acetone to which carbon had been added. There was obtained 100 mg. of colorless needles, melting at 215°.

Anal. Calcd. for $C_{12}H_{11}NO_5$: N, 5.62. Found: N, 5.68.

The same acid was obtained by oxidizing with potassium permanganate a hot acetone solution of γ-fagaric aldehyde. The crystals obtained also melted at 215° and were not distinguishable from those obtained by direct oxidation of the base.

2,4-Dihydroxymethoxyquinoline.—A sample of 380 mg. of γ-fagaric acid was suspended in 40 ml. of dilute hydrochloric acid[7] and boiled until a clear solution was obtained. On cooling, a crystalline precipitate, melting at 225° and weighing 320 mg. was obtained. Recrystallized from alcohol, it yielded long prisms melting at 250°.

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.71; N, 7.33. Found: C, 63.10; H, 5.12; H, 7.59.

(7) Strong acid of density 1.19 diluted 1:2.

Nitrous Derivatives of 2,4-Dihydroxymethoxyquinoline.—An alkaline solution of the quinoline derivative mentioned, containing the necessary amount of sodium nitrite, was poured slowly into a solution of 10% sulfuric acid with stirring. There was obtained a reddish precipitate which was filtered and was recrystallized several times from acetic acid, yielding intensely red needles which melted and decomposed at 216–217°.

Anal. Calcd. for $C_{10}H_8N_2O_4$: N, 12.72. Found: N, 13.02.

α-Fagarine.—The fraction precipitating at *p*H 9 was purified by repeated recrystallization from alcohol. Two kinds of crystals have been obtained: prismatic, melting at 163°, and octahedral, melting at 169°. Recrystallized from chloroform-petroleum ether, long prisms were obtained, melting at 169°. These are the crystals which were finally analyzed. They were soluble in benzene, chloroform, ether and acetone, slightly so in petroleum ether. When pure, they were slightly soluble in water. The substance has no optical activity.

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.57; H, 6.42; N, 4.44; two methoxyls, 19.68; one $-NCH_3$ group, 9.23. Found: C, 68.58, 68.47; H, 6.36, 6.25; N, 4.33, 4.28; $-OCH_3$, 18.45; $-NCH_3$, 12.80.

α-Fagarine treated for twenty minutes with 40% sulfuric acid and phloroglucinol in a boiling water-bath yielded a red precipitate which, according to Gadamer, is characteristic of dioxymethylene groups.

Summary

The study of the alkaloids in the twigs and leaves of *Fagara coco* (Gill) Engl. has confirmed the presence of those described by Stuckert as α-, β- and γ-fagarines.

β-Fagarine has been identified with skimmianine.

γ-Fagarine has been degraded to a 2,4-dihydroxymethoxyquinoline, and it has been established that it is a methoxydictamine.

α-Fagarine is a base of a different type from the preceding ones. Some of its functional groups have been determined.

BUENOS AIRES, ARGENTINA RECEIVED APRIL 18, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

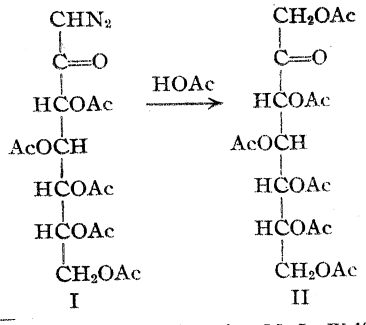
The Action of Diazomethane upon Acyclic Sugar Derivatives. III.[1] A New Synthesis of Ketoses and of their Open Chain (*keto*) Acetates

BY M. L. WOLFROM, S. W. WAISBROT AND ROBERT L. BROWN

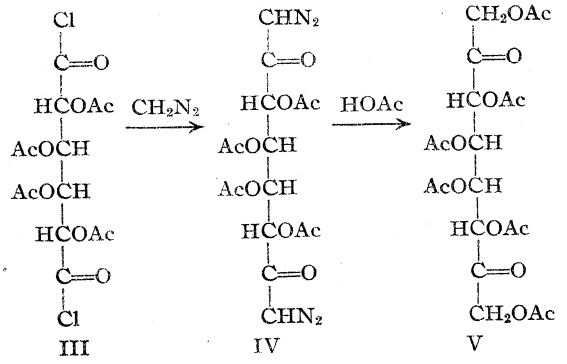
Bradley and Robinson[2] described the reaction of a diazomethyl ketone with acetic acid to produce an acetoxymethyl ketone, although analogous reactions for the acylation of diazoacetic ester had been noted earlier by Staudinger and coworkers.[3] The recent availability of the diazomethyl ketones in the sugar series[4] makes feasible the application of this reaction to the synthesis of ketoses in their open chain or *keto*-acetate structure.

The reaction was first established for the known fructose derivative and the diazomethyl ketone obtained[1] from *d*-arabonyl chloride tetraacetate and diazomethane was found to react smoothly with glacial acetic acid to produce the open chain or *keto*-form of *d*-fructose pentaacetate, a derivative that had been synthesized by Hudson and Brauns[5] by direct acetylation procedures and whose open-chain structure is established.[6] Reaction of I, designated 1-diazo-1-desoxy-*keto*-*d*-glucoheptulose pentaacetate,[4] with acetic acid produced *keto*-*d*-glucoheptulose hexaacetate (II), isomeric with and convertible (by saponification and reacetylation) to the one known cyclic hexaacetate of *d*-glucoheptulose.[7]

Utilizing the acetolysis procedure of Tambor and Du Bois,[8] 1-bromo-1-desoxy-*d*-glucoheptulose pentaacetate[1] was converted into II in somewhat lower yield than from the diazomethyl ketone I and acetic acid. This new acyclic derivative (II) exhibited no mutarotation in either chloroform or methanol solution and its ultraviolet absorption spectrum in U. S. P. chloroform revealed a pronounced absorption maximum at 2830 Å. ($\log \epsilon_{max.} = 1.60$ at 2830 Å.) which corresponds closely to the value reported by Baldwin, Wolfrom and Lowry[9] for *keto*-*d*-fructose pentaacetate ($\log \epsilon_{max.} = 1.59$ at 2830 Å.) and by Khouvine and Arragon[10] for *keto*-*l*-sorbose pentaacetate (absorption maximum at about 2800 Å.). Inasmuch as it has been shown that the cyclic acetates do not exhibit an absorption maximum in the region of that for the ketonic carbonyl group,[10] these data constitute proof that no ring closure has occurred during the series of reactions leading to the formation of the new derivatives and confirm the assignment of the acyclic or *keto* structure to our compound.



I II



III IV V

The series of reactions recorded above provide a general method for the synthesis of acyclic ketose acetates and represent a transformation of an aldose to the next higher ketose. It was then of interest to apply these reactions to a dibasic sugar acid and for this purpose the long-known mucyl dichloride tetraacetate (III)[11] was selected. From III the bisdiazomethyl ketone IV was obtained. Treatment of IV with hydrogen chloride yielded

(1) Previous publication in this series: M. L. Wolfrom, S. W. Waisbrot and Robert L. Brown, THIS JOURNAL, **64**, 1701 (1942).

(2) W. Bradley and R. Robinson, *J. Chem. Soc.*, 1310 (1928); *ibid.*, 1545.

(3) H. Staudinger and C. Mächling, *Ber.*, **49**, 1973 (1916); H. S. Staudinger, J. Becker and H. Hirzel, *ibid.*, 1978.

(4) M. L. Wolfrom, D. I. Weisblat, W. H. Zophy and S. W. Waisbrot, THIS JOURNAL, **63**, 201 (1941).

(5) C. S. Hudson and D. H. Brauns, *ibid.*, **37**, 2736 (1915).

(6) E. Pacsu and F. V. Rich, *ibid.*, **55**, 3018 (1933); M. L. Wolfrom and A. Thompson, *ibid.*, **56**, 880 (1934).

(7) W. C. Austin, *ibid.*, **54**, 1925 (1932); M. L. Wolfrom and A. Thompson, *ibid.*, **56**, 1804 (1934).

(8) J. Tambor and E. M. Du Bois, *Ber.*, **51**, 748 (1918).

(9) W. C. G. Baldwin, M. L. Wolfrom and T. M. Lowry, *J. Chem. Soc.*, 696 (1935).

(10) Yvonne Khouvine and G. Arragon, *Bull. soc. chim.*, [5] **5**, 1404 (1938).

(11) E. Jacoby, Inaugural Dissertation, Berlin, 1907; O. Diels and F. Löflund, *Ber.*, **47**, 2351 (1914); J. Müller, *ibid.*, **47**, 2654 (1914).

the dichloro derivative and treatment with acetic acid produced the well-crystallized diketose acetate V, designated 1,8-dihydroxy-mucyldimethane hexaacetate. This is an open chain acetate of a diketose, a new type of derivative in the sugar field.

Extension of this work is in progress in this Laboratory.

Experimental

***keto-d*-Fructose Pentaacetate.**—1-Diazo-1-desoxy-*keto-d*-fructose tetraacetate[1] (1 g.) was dissolved in glacial acetic acid (25 cc.) and refluxed for one hour. The dark brown solution was poured on crushed ice, and the resulting solution was extracted with three 25-cc. portions of chloroform. The combined extracts were washed free of acetic acid with water and the solution dried. Upon solvent removal under reduced pressure, a dark sirup was obtained which was dissolved in 20 cc. of absolute ethanol, decolorized repeatedly with charcoal and concentrated under reduced pressure to 8 cc. Upon standing in the ice-chest the concentrate yielded 0.5 g. of pale yellow crystals; m. p. 63–67°. Several recrystallizations from ethanol yielded a pure product identified by melting point, mixed melting point and rotation as *keto-d*-fructose pentaacetate for which Hudson and Brauns[5] record the constants; m. p. 69–70°, spec. rot.[12] +35° ($CHCl_3$).

***keto-d*-Glucoheptulose Hexaacetate (II).**—1-Diazo-1-desoxy-*keto-d*-glucoheptulose pentaacetate[4] (I, 5.0 g.) was dissolved in glacial acetic acid (100 cc.) and the solution refluxed to the cessation of nitrogen evolution (ten to fifteen minutes; delivery tube from condenser top placed in water as indicator). The hot reaction mixture was poured on crushed ice (400 g.) and the resulting solution extracted with four 50-cc. portions of chloroform. The extract was washed free of acetic acid with water, dried over Drierite and decolorized (Darco). Upon solvent removal under reduced pressure the product crystallized spontaneously as light yellow needles. The crystalline mass was dissolved in 60 cc. of hot 1:4 ethanol–water, decolorized and diluted with an equal volume of warm water. Upon cooling, the product separated as long, white prismatic needles; yield 3.7 g. (70%), m. p. 103.5–105°, spec. rot. +18° (abs. $CHCl_3$). Three additional crystallizations were effected by solution in 15 parts of hot 1:4 ethanol–water and dilution with an equal volume of water to yield pure *keto-d*-glucoheptulose hexaacetate; m. p. 104–105°, spec. rot. +18.7° (22°, *c* 2.7, U. S. P. or abs. $CHCl_3$). These constants remained unchanged on further crystallization from aqueous ethanol or acetone–petroleum ether.

The substance was soluble in ethanol, acetone, acetic acid and warm ether but was insoluble in water and petroleum ether. The compound exhibited no detectable mutarotation in either chloroform or methanol solution. An absorption spectrum analysis[13] of the substance in chloroform (U. S. P.) solution (0.0377 molar) revealed an absorption maximum at 2830 Å. ($\log \epsilon_{max.} = 1.60$ at 2830 Å.).

Anal. Calcd. for $C_7H_8O_7(CH_3CO)_6$: C, 49.35; H, 5.67; CH_3CO, 12.97 cc. 0.1 *N* NaOH per 100 mg. Found: C, 49.33; H, 5.53; CH_3CO, 12.90 cc.

keto-d-Glucoheptulose hexaacetate could also be prepared from 1-bromo-*keto-d*-glucoheptulose pentaacetate[1] by the general acetolysis procedure of Tambor and Du Bois.[8] The bromo derivative (2 g.) was dissolved in acetic anhydride (10 cc.) containing fused potassium acetate (3 g.). After shaking for five minutes the mixture was heated for thirty minutes at 70° and then allowed to stand overnight. The crystals obtained on pouring the reaction mixture into ice and water were removed by filtration and washed with a small amount of cold ether; yield 0.9 g., m. p. 102°, spec. rot. +17° ($CHCl_3$). Further purification yielded pure material identified by melting point, mixed melting point and rotation as *keto-d*-glucoheptulose hexaacetate.

The nature of the sugar portion in the above compound was verified by transformation into the one known cyclic hexaacetate of *d*-glucoheptulose.[7] *keto-d*-Glucoheptulose hexaacetate (1.0 g.) was treated for an hour at 0° with a dry methanol solution of anhydrous ammonia. The sirup obtained on solvent removal under reduced pressure was acetylated at 100° with acetic anhydride and sodium acetate, and the product obtained on pouring the cooled reaction mixture into water was recrystallized (decolorizing charcoal) from 75% ethanol; yield 0.2 g., m. p. 114.5–115.5°, spec. rot. +86° (23°, *c* 3, U. S. P. $CHCl_3$). A mixed melting point with an authentic specimen of *d*-glucoheptulose hexaacetate (m. p. 114.5–115°) was unchanged. Austin[7] recorded the following constants for *d*-glucoheptulose hexaacetate: m. p. 112°, spec. rot. +87° ($CHCl_3$). Wolfrom and Thompson[7] found the constants: m. p. 115–116°, spec. rot. +87° ($CHCl_3$). The present product is therefore identified as the *d*-glucoheptulose hexaacetate of Austin.

1,8-Bisdiazo-mucyldimethane Tetraacetate (IV).—Mucyl dichloride tetraacetate[11] (III, 4 g.) was suspended in anhydrous ether and added slowly with continuous stirring to a solution of diazomethane (4 g.) in 200 cc. of anhydrous ether, previously cooled in an ice–salt bath. The reaction was maintained at the temperature of the ice–salt bath for two hours, whereupon the product was removed by filtration and washed with ether. Pure material was obtained on further crystallization from ethanol; yield 3.5 g., m. p. 179–180° (dec.). The crystals were soluble in acetone, chloroform and dioxane.

Anal. Calcd. for $C_{16}H_{18}O_{10}N_4$: C, 45.07; H, 4.25; N, 13.14. Found: C, 45.13; H, 4.31; N, 12.82.

1,8-Dichloro-mucyldimethane Tetraacetate.—1,8-Bisdiazomucyldimethane tetraacetate (IV, 1 g.) was suspended in ether (40 cc.) and treated, under cooling, for thirty minutes with a stream of dry hydrogen chloride, whereupon the chloro compound formed was removed by filtration and purified by crystallization from ether; yield practically quantitative, m. p. 174–175°.

Anal. Calcd. for $C_{16}H_{20}O_{10}Cl_2$: C, 43.35; H, 4.55; Cl, 16.0. Found: C, 43.47; H, 4.67; Cl, 15.4.

1,8-Dihydroxy-mucyldimethane Hexaacetate (V).—1,8-Bisdiazo-mucyldimethane tetraacetate (IV, 1 g.) was refluxed for thirty minutes with glacial acetic acid (10 cc.),

(12) All rotations are recorded to the D-line of sodium light.

(13) We are indebted to Professor W. R. Brode and Mr. John Patterson of this Laboratory for this analysis.

whereupon the cooled solution was poured on ice (25 g.) and the separated solid removed by filtration and purified by crystallization from ethanol; m. p. 193–195° (dec.).

Anal. Calcd. for $C_{20}H_{26}O_{14}$: C, 48.98; H, 5.34. Found: C, 48.76; H, 5.31.

We acknowledge the assistance rendered in a portion of this work by Messrs. Ralph S. Klopper and Stephen Olin.

Summary

1. The known *keto-d*-fructose pentaacetate has been synthesized by the reaction between acetic acid and 1-diazo-1-desoxy-*keto-d*-fructose tetraacetate.

2. Acetic acid was reacted with 1-diazo-1-desoxy-*keto-d*-glucoheptulose pentaacetate (I) to produce *keto-d*-glucoheptulose hexaacetate (II), also obtainable by the acetylation of 1-bromo-*keto-d*-glucoheptulose pentaacetate.

3. Mucyl dichloride tetraacetate (III) was treated with diazomethane to produce the bisdiazomethyl ketone (IV) from which the 1,8-dichloride and the 1,8-diacetoxy (V) derivatives were formed. The latter is an acetate of a diketose, a new type of structure in the sugar field.

4. The above reactions establish a new synthesis of *keto*-acetates from aldose derivatives of lower (one or two carbon atoms) carbon content.

COLUMBUS, OHIO RECEIVED JULY 3, 1942

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

Structure of the Dextrins Isolated from Corn Sirup[1]

BY MELVIN LEVINE, JOSEPH F. FOSTER AND R. M. HIXON

The structural differences between the different starches and starch fractions, especially with regard to the questions of branching and non-reducing fractions, would appear to be somewhat clarified by a more complete study of the structure of the low molecular weight products of hydrolysis. In the older literature Brown[2] concluded that these products consist essentially of maltose and a "stable dextrin" of definite molecular size (about 40 glucose units) with a specific rotation of about 196° and a reducing power equivalent to 5.5% maltose, or about the value which would be expected for a molecule of this size if it terminated in a reducing glucose molecule. These results have been partially accepted in the corn sirup industry where "dextrin" is considered to be a definite substance having the rotation reported by Brown, but considered to be non-reducing.[3] From a theoretical standpoint these degradation products would be expected to consist of a mixture of glucose polymers of varying chain length, and with reducing power and specific rotation[4] depending on the chain length. If the original starch contains branching, as the present evidence indicates, these molecules might be expected to be further complicated.

The method which we are reporting in this paper for isolating the dextrins from corn sirup was developed primarily to make these materials available in relatively large quantities for physiological investigations. The availability of such dextrins together with the theoretical importance of a more complete knowledge of their structure has encouraged a rather detailed investigation of these materials, especially with regard to the questions of branching and the presence of any non-reducing fractions.

Experimental

Isolation of Crude Dextrins from Corn Sirup.—The conditions used for the isolation of the dextrins were selected after a study of the solubilities of glucose and maltose in aqueous alcohol (Fig. 1). Fifteen pounds of corn sirup[5] was weighed into a five-gallon container. Enough absolute methyl alcohol to bring the concentration to 80–85% was added, the mixture heated to 55° in a water-bath and stirred thoroughly until a homogeneous mixture was obtained, which was allowed to stand at approximately 45° until the supernatant alcoholic extract was clear (twenty-four to forty-eight hours) and was then decanted. The residual heavy sirup was again extracted with approximately three volumes of 80% alcohol by stirring at 55°, allowing to settle at 40°, and decanting the clear supernatant liquor. This extraction process was repeated four times.

(1) Journal Paper No. J-1007 of the Iowa Agricultural Experiment Station, Ames, Iowa; Projects No. 688 and 516. Supported in part by a grant from the Corn Industries Research Foundation.

(2) Brown and Millar, *J. Chem. Soc.*, **75**, 315 (1899).

(3) For one method of analysis and a review of the general methods in use see Fetzer, Evans and Longnecker, *Ind. Eng. Chem., Anal. Ed.*, **5**, 81 (1933).

(4) Freudenberg, Friedrich and Bumann, *Ann.*, **494**, 41 (1932).

(5) The corn sirup used was Amaizo Crystal White, 41 purity, 43° Bé., furnished by the American Maize Products Company, Roby, Ind.

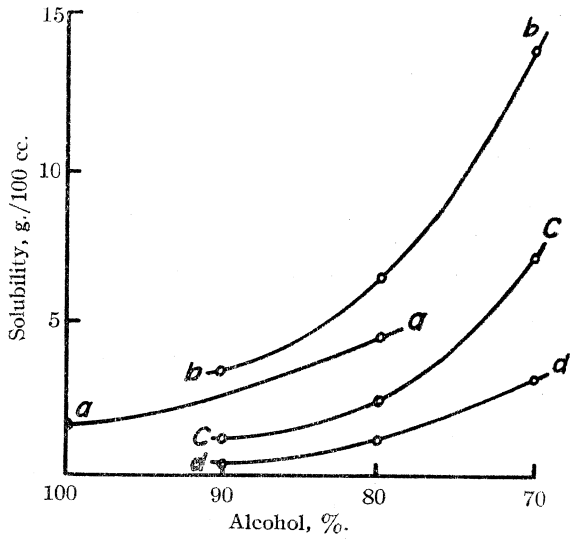


Fig. 1.—Solubility of maltose and glucose in aqueous alcohol: a, glucose in C_2H_5OH at 20°; b, maltose in CH_3OH at 40°; c, maltose in CH_3OH at 25°; d, maltose C_2H_5OH at 25°. The data for glucose are from Hudson and Yanovsky, THIS JOURNAL, **39**, 1013 (1917). The data for maltose were determined in this Laboratory by averaging the values calculated from rotation and reducing value.

The heavy, sticky residue was thinned somewhat with water, heated to 60° and filtered through a cotton filter cloth with the aid of suction. Absolute methanol was added to the filtrate to bring the concentration up to 85%, the sirup allowed to settle, then dehydrated and pulverized with absolute methanol. The powdered dextrin was recovered by filtering with the aid of suction and dried in a vacuum oven at 45° for forty-eight hours. The final products were slightly hygroscopic white powders having a slightly sweet taste, specific rotation of about 175°, and reducing value (R_{Cu}) by the alkaline ferricyanide method[6] of about 750 to 850 (maltose = 1900).

(6) Farley and Hixon, *Ind. Eng. Chem., Anal. Ed.*, **13**, 616 (1941).

Fractionation of Dextrins.—A weighed amount of crude dextrin was dissolved in twice its weight of distilled water, filtered, precipitated by the addition of four volumes of absolute methanol, allowed to stand till clear and the supernatant liquid poured off. The soluble fraction was recovered by evaporating under reduced pressure, and both soluble and insoluble fractions dried. Reducing power and rotation were run on the fractions, after which they were subjected to further fractionation by the same method. A typical fractionation is shown graphically in Fig. 2. The fractions used in the chemical studies discussed below were prepared by this method of fractionation.

To determine the completeness of removal of maltose in this method of fractionation, a mixture consisting of 3 g. of maltose and 10 g. of dextrin V (mol. wt. 1800 by iodine titration) was subjected to a single fractionation in 80% methanol. The insoluble fraction consisted of 7.2 g., mol. wt. 1950; the soluble fraction 4.5 g., mol. wt. 530. If the latter fraction be assumed to contain all of the maltose plus 1.5 g. of the dextrin, the mean molecular weight would be about 490.

Acetylation of Dextrins and Fractionation of the Acetates.—Satisfactory acetylation could be attained by any of the variations of the pyridine–acetic anhydride method.[7,8,9] A 100-g. sample of a dextrin having a reducing value of 850 was dissolved in 400 cc. of pyridine and allowed to stand for forty-eight hours. Then 500 cc. of pyridine and 500 cc. of acetic anhydride were added and the mixture shaken. After standing for forty-eight hours the solution was poured into about 10 liters of water, the precipitate collected on a filter and washed well with about 5 liters of water; yield 220 g. of white powder.

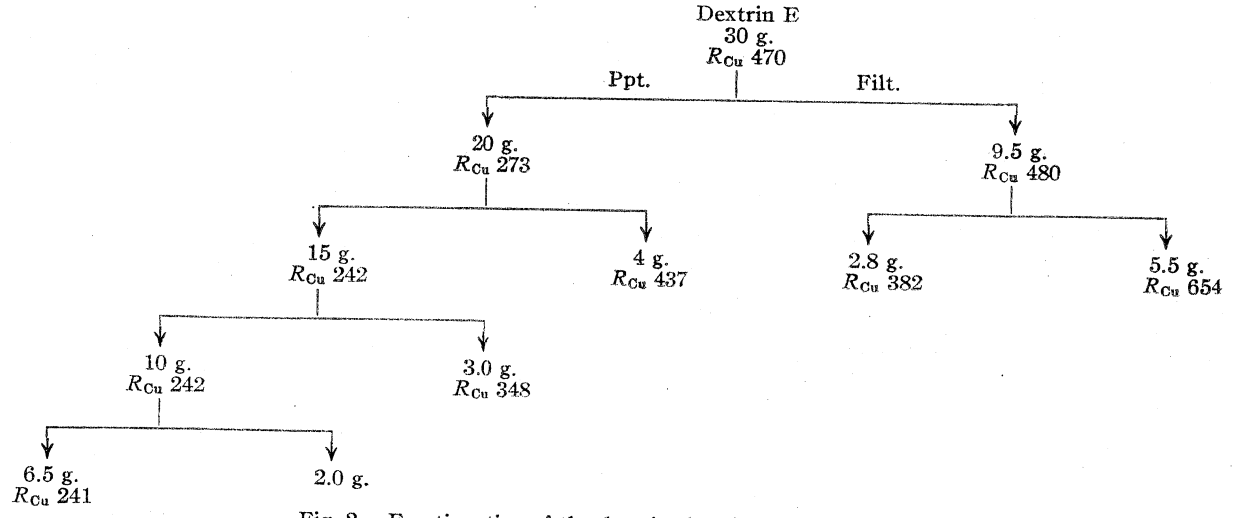


Fig. 2.—Fractionation of the dextrins by alcohol precipitation.

This material was repeatedly fractionated by dissolving in boiling absolute methanol and then cooling the solution in an ice-bath for about three hours until the dextrin acetate had settled. This came down as a white, very heavy

(7) Behrend and Roth, *Ann.*, **331**, 359 (1904).
(8) Haworth, Hirst and Plant, *J. Chem. Soc.*, 1214 (1935).
(9) Higginbottom and Richardson, *J. Soc. Chem. Ind.*, **57**, 234 (1938).

sirup which hardened on standing and was broken up and pulverized with a glass rod. The solution was filtered, the filtrate evaporated to dryness, and both the soluble and insoluble fractions dried and pulverized. Results of this type of fractionation are given in Fig. 3.

Oxidation of Dextrins and Isolation of the Dextrinic Acids.—It was found that these dextrins could be converted quantitatively to the potassium salts of the dextrinic acids by a large-scale modification of the Kline and Acree method for determining aldose sugars.[10] A small sample of the dextrin was first titrated with iodine and alkali according to their directions to determine the exact reducing value. Then a sample of from 10 to 20 g. was dissolved in a small volume of water, placed in a three-neck reaction flask equipped with a mechanical stirrer and two dropping funnels, and the calculated amount of iodine and potassium hydroxide (each approximately 0.1 *N*) added, the caustic being permitted to drop continuously and the iodine being added in about 5-ml. portions as the solution became colorless. The addition required two or three hours and an additional three hours with stirring was allowed for completion of the reaction. The solution was concentrated to a thick sirup under reduced pressure, and the oxidized dextrin isolated by repeatedly adding methyl alcohol to a concentration of 85%, centrifuging out the solid, which at this point was rather gummy, taking up in water and repeating the alcoholic precipitation until the aqueous solution gave no test for iodide. The solid was then shaken up several times with ether, and finally ground in a mortar and dried, giving a perfectly white powder. Yields were usually 90 to 95% of the theoretical.

The potassium salts were analyzed for potassium by ashing 20–30-mg. samples with a drop of concentrated sulfuric acid in a small electric muffle, and weighing the sulfate formed. The chain length calculated from per cent. of potassium was found to agree very well with that calculated from the amount of iodine and caustic used in the oxidation. For example, one fraction having a chain length of 14.2 glucose units by iodine titration was oxidized and the derivative found to contain 1.67% potassium, from which the chain length was calculated to be 14.4 glucose units.

Maltose was also oxidized to potassium maltobionate by the above method, but the derivative was found to be very hygroscopic and much harder to work with than in the case of the larger molecules.

Methylation of Dextrins.—Attempts to methylate these dextrins by the various methods which have been used for carbohydrates showed that by far the best results could be obtained by means of sodium and methyl iodide in liquid ammonia, which was first applied to starch by Freudenberg and Boppel.[11] By this method the theoretical per cent. of methoxyl could be attained in one treatment, and recovery was practically quantitative. However, due to the greater solubility of these materials in both water and ammonia, it was found impracticable to change solvent during the methylation, and recovery of the methylated product had to be effected by evaporating off the ammonia, and exhaustively extracting the thoroughly dried and pulverized residue in a Soxhlet extractor with chloroform, instead of adding the residue to boiling water as was done by these workers.

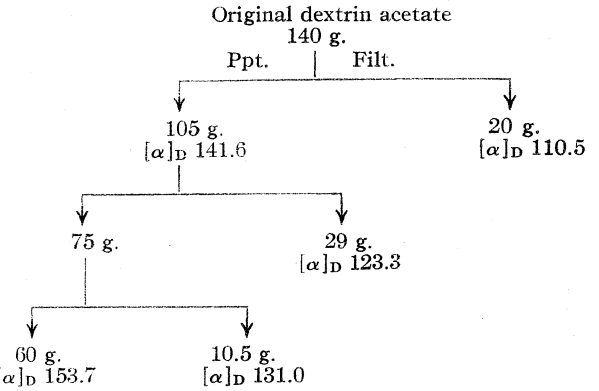


Fig. 3.—Fractionation of dextrin acetates.

Ten grams of a dextrin having an average chain length calculated from iodine titration of eleven glucose units was methylated by this procedure: yield, 12.5 g. of cream colored powder or 99% of theoretical (45.5% methoxyl, calculated for an 11 glucose dextrin, 46.3). Five grams of this material was hydrolyzed and the di-, tri- and tetramethyl glucose separated by the method of Bell,[12] which involves partition of tri- and tetramethyl glucose between chloroform and water. In this way, 0.515 g. of crystalline tetramethyl glucose was isolated (52.3% methoxyl, calculated 52.5). This corresponds to a chain length of 10.6 glucose units assuming no tetramethyl glucose to be lost. The amount of dimethyl glucose obtained was very small (about 30 mg.).

To check this result 3.8 g. of the methylated dextrin was hydrolyzed, converted to the glucosides, and analyzed for tetramethyl glucose by the method of fractional distillation.[13] By this method, 0.424 g. of tetramethyl methylglucoside was found in the distillate, and the chain length calculated to be 10.3 glucose units.

The molecular weight of the methylated dextrin was determined by two physical methods. By viscosity in chloroform, using Staudinger's equation and his value of K_m (namely, 1×10^{-4}),[14] the value obtained was 9700; cryoscopically, using bornyl bromide as solvent, 1530. This last value is in reasonable agreement with the value calculated from the chain length, or about 2000.

The salts of the dextrinic acids have also been methylated completely and in good yields following the same procedure as with the dextrins. To date no study of the methylated derivatives has been carried out.

Reaction of the Dextrins with Phenylhydrazine.—The procedure first tried was essentially that used by Bergmann and Machemer with the acetylated cellulose dextrins,[15] which involves preparation of the derivative in liquid phenylhydrazine, isolation by pouring into ether, and purification by solution in 50% acetic acid and precipitation with absolute methanol. Much better results were obtained in the case of the unacetylated materials by

(10) Kline and Acree, *Ind. Eng. Chem., Anal. Ed.*, **2**, 413 (1930).
(11) Freudenberg and Boppel, *Ber.*, **71**, 2505 (1938).
(12) Bell, *Biochem. J.*, **29**, 2031 (1935).
(13) Haworth and Machemer, *J. Chem. Soc.*, 2270 (1932).
(14) Staudinger and Eilers, *ibid.*, 2270 (1932).
(15) Bergmann and Machemer, *Ber.*, **63**, 322 (1930).

eliminating the use of acetic acid and using benzene instead of ether as the precipitant. The procedure finally established was as follows. One gram of the dextrin was dissolved in 5 cc. of phenylhydrazine by heating under reflux at 130° for two hours. The reaction mixture, after cooling, was poured with stirring into 50 cc. of benzene. The precipitate was recovered by filtration, washed several times with ether, thoroughly dried, pulverized, and extracted with ether in a Soxhlet extractor for twenty-four hours. By this procedure the recovery of the derivative was more complete and the results more consistent. The derivatives were analyzed for nitrogen by the micro Dumas method, and the molecular weight of the carbohydrate residue calculated.

These derivatives are amorphous powders, characteristically yellow in color in contrast to true phenylhydrazones, and are extremely susceptible to hydrolysis. When dissolved in water they give off a very noticeable odor of phenylhydrazine, and ether extraction of the aqueous solution or boiling with activated charcoal results in the removal of from 25 to as high as 85% of the nitrogen. For this reason it was at first thought that the materials were simply adsorption complexes; however, the fairly close agreement in the case of the smaller fractions between the molecular weight from nitrogen and iodine titration indicated that a definite reaction did take place.

To further investigate this question the derivatives of glucose and maltose were prepared following exactly the procedure used for the dextrins. The maltose derivative had the same characteristic yellow color as the dextrin derivatives and had the same amorphous appearance under the microscope. The glucose derivative was somewhat more orange in color and was essentially amorphous although there did seem to be some small crystals present which were birefringent. The rotations could not be determined accurately due to the dark color of the aqueous solutions, but the values were about −40° for the glucose derivative and +70° for the maltose derivative. Both derivatives melted over a wide range, indicating them to be non-homogeneous (maltose derivative, 115–118°; glucose derivative, 111–120°). Nevertheless the nitrogen analysis was in both cases very close to the theoretical (maltose derivative 6.46%, calculated 6.48; glucose derivative, 10.2, calculated 10.4). The maltose derivative showed the same instability in water as the dextrin derivatives, at least 25% of the phenylhydrazine being extractable. It is interesting to note that if the aqueous solution is exhaustively extracted with ether and then allowed to stand a few days, more phenylhydrazine can be removed, indicating that a reversible equilibrium is involved. The glucose derivative gave an odor of phenylhydrazine when dissolved, but the amount extractable was negligible.

The phenylhydrazine derivative of an acetylated dextrin was also prepared, following essentially the procedure of Bergmann and Machemer.[15] It was found that part of the acetyl groups were removed by the phenylhydrazine so that the derivative had to be reacetylated. The derivative was found to contain 1.70% nitrogen and 43.2% acetyl, from which the molecular weight of the carbohydrate residue was calculated to be 862, in good agreement with the value calculated from iodine titration, namely, 850.

Specific Rotations of the Dextrins.—Before running specific rotations the dextrins were carefully dried in a vacuum oven at 60° for twenty-four hours. Rotations were run at 25° on 1% solutions in water, using sodium D light. In Table I these results are compared with the values calculated assuming the additivity of molecular rotations as has been done by Freudenberg with the smaller molecules.[4] A value of 46,000 was assigned for the molecular rotation of maltose (or the sum of the reducing and non-reducing terminal glucoses in the dextrins) and 32,400 for the intermediate glucoses, the value for maltose being obtained from the observed rotation and iodine molecular weight and the value for the intermediate units by assuming a rotation of 200° for an infinitely long chain. The equation used is thus

$$\alpha_M = 46000 + \frac{M - 348}{162}(32400)$$

where α_M is the molecular rotation and M the molecular weight. The specific rotation is of course obtained by dividing the molecular rotation by the molecular weight.

TABLE I

COMPARISON OF SPECIFIC ROTATION CALCULATED FROM IODINE AND R_{Cu} REDUCING VALUES WITH THE OBSERVED VALUES

Fraction	Molecular wt. I_2	Weight from R_{Cu}	$[\alpha]_D$ calcd. from I_2	$[\alpha]_D$ observed	$[\alpha]_D$ calcd. from R_{Cu}
Maltose	348	342	...	132	...
A	310	354	118	114	148
B	469	461	150	149	149
C	888	734	172	172	168
M	924	778	175	175	170
F	1422	1036	184	184	178
V	1795	1383	187	187	183
R	1778	1340	187	185	183
E	1902	1450	188	185	183

Discussion

As can be seen from Fig. 2 the results of alcohol fractionation are not very satisfactory. The recovery is poor, the fractionation is slow and the materials very hard to work with. Nevertheless, from the crude dextrin, fractions were obtained having mean molecular weights ranging from less than the value of maltose up to about 26 glucose units, as calculated from iodine reducing value. The fractions are obviously heterogeneous since in no case was a fraction obtained which could not be further fractionated, although, in most cases, by the time the molecular weight had reached a value corresponding to about 25 glucose units the amount of the fraction was too small to permit further treatment. The result of the fractionation of the known mixture of maltose and dextrin V indicates that the higher fractions could not contain any appreciable amount of maltose or glucose, and it seems probable that the distribution of molecular sizes is fairly narrow.

Haworth and associates[16] have investigated the fractionation of the dextrins through their acetates with satisfactory results. The results obtained here indicate a fairly sharp fractionation as evidenced by the large difference in rotation between the fractions. The advantage of more rapid fractionation is, however, offset by the necessity of acetylating and regenerating the dextrins.

The excellent check between the per cent. potassium in the dextrinic acids and the iodine reducing value of the original dextrins indicates that the reaction is, as formulated by Kline and Acree,[10] a simple oxidation of aldehyde groups to the carboxylic acids, and that no iodine is used otherwise (for example, adsorbed). From this it would seem that iodine titration is the best criterion of chain length in these low molecular weight dextrins. In Fig. 4 the molecular weights calculated from R_{Cu} are compared with the corresponding values calculated from iodine reducing power. Results obtained in this Laboratory with higher molecular weight fractions indicate that the R_{Cu} molecular weights are too low by an almost constant value and hence it would appear that the curve bends upward and becomes parallel with the theoretical as is also indicated in the figure. It should be mentioned also that iodine methods are not very reliable in the case of very high molecular weight materials where tenacious adsorption occurs.

The reliability of the iodine values in this range is further indicated by the agreement between the specific rotations and the values calculated from the apparent molecular weights (Table I). Low observed values can be explained by moisture. In several cases the observed values are below those calculated from iodine molecular weight, but above those calculated from R_{Cu} molecular weight. Obviously specific rotation is not a very sensitive function for a high molecular weight fraction; nevertheless, even in the highest fractions studied here the calculated increase of specific rotation is approximately 1.5° per glucose unit.

The close agreement between the chain length calculated from reducing value and tetramethyl glucose analysis, even when we consider the limited accuracy of the available methods for separation of the methyl glucoses (the maximum relative accuracy is probably not more than about 5–10%) indicates the chains to be essentially linear. The almost complete lack of dimethyl glucose, which would arise at the points of branching, supports this conclusion (30 mg. of dimethyl glucose would permit a maximum of one branch to about 160 glucose units, or about 6% of branched molecules). This result is to be expected for fractions of this size from simple probability considerations, if we assume the 1–4 and 1–6 linkages to be broken at the same rate. It should perhaps be pointed out that the method of tetramethyl assay is not a very sensitive criterion for ascertaining whether or not a small portion of the molecules are branched. For example, a straight-chained fraction of ten glucose units would give 10% of tetramethyl glucose, whereas if even 25% of the molecules were branched only about 12.5% of tetramethyl glucose would be obtained. Hence the absence of dimethyl glucose is, perhaps, a safer criterion.

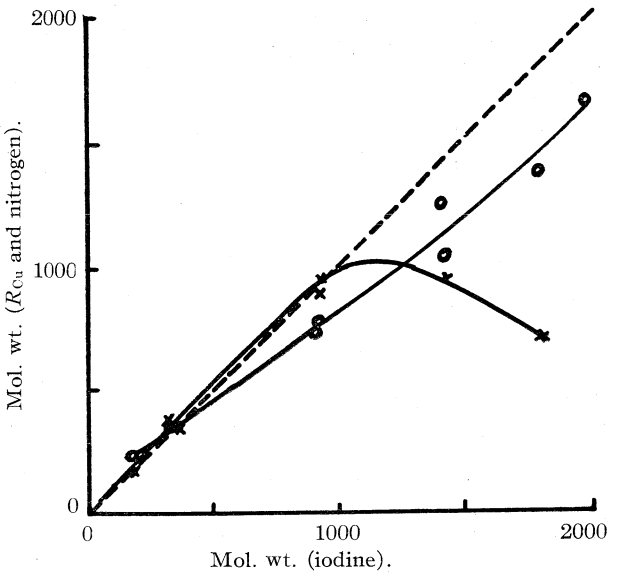
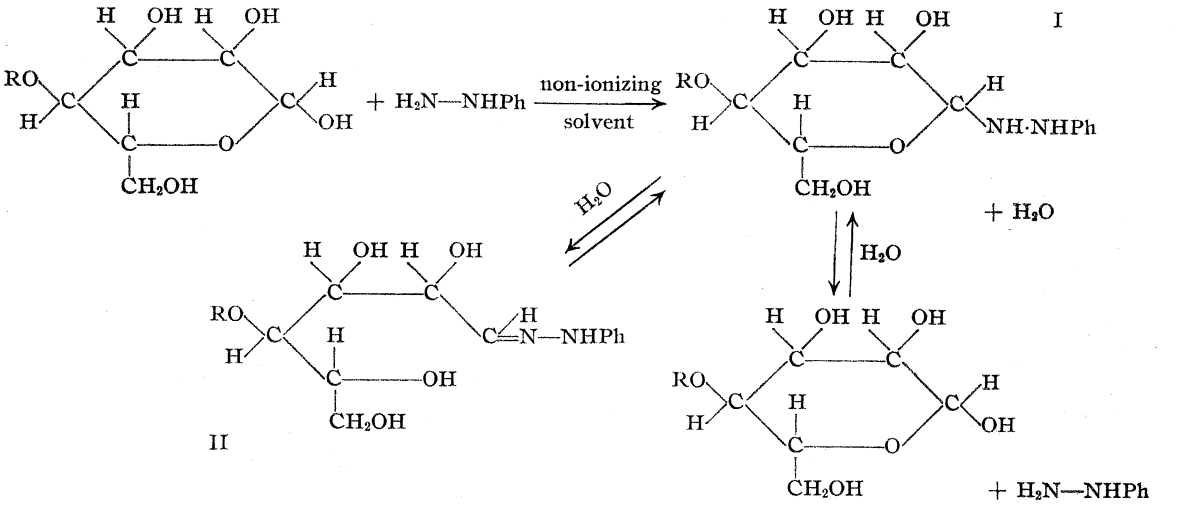


Fig. 4.—Comparison of molecular weights calculated from R_{Cu} and per cent. nitrogen in the phenylhydrazine derivatives, with the values obtained from iodine reducing values. Molecular weights were calculated from R_{Cu} by assuming the value for maltose (1900) to be correct and using the equation $M = 342 \times 1900/R_{Cu}$. The crosses are nitrogen values; the circles R_{Cu} values.

In considering the possible presence of non-reducing dextrins, two distinct types must be considered. In the first place, there is the possibility of dextrin structures in which the terminal aldehyde group is bound in a non-reducing fashion but the non-reducing end is free. This type of molecule would be detected by the tetramethyl end-group analysis since it would lead to a preponderance of tetramethyl groups over reducing groups. Conclusions based on this evidence are, of course, subject to the same experimental inac-

(16) Haworth, Hirst and Plant, *J. Chem. Soc.*, 1214 (1935).



curacies discussed above; however, it seems safe to conclude that at most not more than 10% of non-reducing material of this type could be present, and probably none. The other possibility which must be considered is the presence of ring dextrins of the Schardinger type which have neither reducing nor non-reducing ends and would hence not be detected by the tetramethyl glucose analysis. However, this possibility is completely eliminated by the agreement of the rotations with the calculated values. The Schardinger dextrins have rotations about 20–25° lower than that calculated for an open chain of equal molecular weight, and their presence would have to be offset by low-molecular weight dextrins to bring up the reducing power; the net effect would be a marked lowering of the rotation of the fraction. Thus the suggestion that these materials consist of glucose, maltose and non-reducing dextrins is completely out of the picture, and the possibility of the presence of even a small amount of non-reducing material seems dubious.

The reaction of phenylhydrazine with cellulose dextrins has been investigated by Staud and Gray[17] and by Bergmann and Machemer,[15] who concluded that nitrogen analysis of the reaction product is more trustworthy than copper numbers as a basis for estimating molecular size. The application of the method to the starch dextrins was investigated in the hope of using it as another criterion of chain length, and also in the hope that the derivatives might possess some advantages for fractionation in that any non-reducing material would not react. The results indicated that the reaction is quantitative but that the derivatives are unstable. These conclusions were substantiated by the preparation of the derivatives of glucose and maltose.

Both hydrazide and hydrazone forms of the phenylhydrazine derivatives of glucose have been reported.[18] The glucose derivative obtained here was apparently a mixture of the two forms but predominantly the hydrazide. Obviously rather complicated equilibria are involved, but the following simplified mechanism would seem to explain the phenomena so far observed.

The equilibrium between the phenylhydrazide form (I) and the phenylhydrazone form (II) has been recognized.[18] The fact that a large amount of the phenylhydrazine is immediately released from the maltose derivative upon solution in water, followed by a slow hydrolysis of the remainder, would seem to indicate that the hydrolysis of the phenylhydrazide is quite rapid whereas the shift between the two tautomeric forms is slow. The hydrolysis is evidently inhibited by acid, as is shown by the fact that derivatives prepared using 50% acetic acid for purification were found to contain about the same per cent. nitrogen as the derivatives prepared by the modified method.

Figure 4 shows reasonable agreement of the per cent. nitrogen with the calculated values up to a molecular weight of about 1000, corresponding to about six glucose units. From this point on the per cent. nitrogen is much too high, indicating adsorption of phenylhydrazine by the carbohydrate. There is considerable evidence that the chains in starch and its derivatives are coiled in the form of a helix with a periodicity of about six

(17) Staud and Gray, *Ind. Eng. Chem., Anal. Ed.*, **1**, 80 (1929).

(18) For a review of these compounds see Tollens and Elsner, "Kurzes Handbuch der Kohlenhydrate," Fourth Ed., J. A. Barth, Leipzig, 1935, pp. 231–232.

glucose units.[19,20] If the adsorption of phenylhydrazine is due to entrapment in the center of these helices, it might be expected that no noticeable amount of adsorption[21] would occur until the average chain length of the dextrin was approximately six to eight glucose units, as is observed. It is conceivable that by varying the solvents used and by controlling the conditions of precipitation it might be possible to eliminate adsorption and to obtain the derivatives in the more stable hydrazone form.

Summary

1. A method for isolating the dextrins from corn sirup in large quantities is given.

2. Repeated alcohol fractionation gives fractions ranging in mean molecular weight from less than two glucose units to 26 units, and the higher fractions are concluded to be relatively free of maltose and glucose.

3. Oxidation of the dextrins to the potassium salts of the dextrinic acids can be carried out in good yields and the potassium content of the products checks with the reducing value of the original dextrin, indicating the iodine reaction to be quantitative and a true measure of molecular size.

4. The specific rotations of the dextrins agree with the values calculated from iodine molecular weights, lending further evidence to the reliability of iodine values.

5. The Freudenberg and Boppel method of methylation is found to be very satisfactory for both the dextrins and dextrinic acids.

6. Tetramethyl glucose assay of the methylated dextrins indicates the chains to be essentially unbranched, and non-reducing fractions to be absent. The former conclusion is substantiated by the almost complete absence of dimethyl glucose, the latter, by the agreement of the rotations with the calculated values.

7. The reaction of phenylhydrazine with the smaller starch dextrins is found to be quantitative, but the derivatives are unstable and postulated to be largely of the phenylhydrazide type.

8. The dextrin fractions averaging greater than about six glucose units in length show a strong tendency to adsorb phenylhydrazine and a possible explanation is given.

(19) Hanes, *New Phytologist*, **36**, 101, 189 (1937).

(20) Bear, THIS JOURNAL, **64**, 1388 (1942).

(21) The word is here used with the realization that neither the term adsorption nor absorption as used in the usual sense fits this phenomenon.

AMES, IOWA RECEIVED MAY 8, 1942

[CONTRIBUTION FROM THE BIOCHEMICAL LABORATORY, STATE UNIVERSITY OF IOWA]

Antioxidants and Autoxidation of Fats. XIV. The Isolation of New Antioxidants from Vegetable Fats[1]

BY CALVIN GOLUMBIC

The tocopherols have been found in a wide variety of vegetable fats but are generally absent from animal fats.[2,3] The observations of Olcott and Emerson[4] and later those of Golumbic[5] have shown that they and related compounds function as fat antioxidants and they are responsible in part for the greater stability of vegetable fats toward oxidative deterioration.

When added to animal fats that are exposed to air or oxygen, tocopherols are rapidly oxidized during the period in which they exert their antioxygenic action and their complete disappearance practically coincides with the end of the induction period of the fat.[6] At this point there is a readily detectable increase in the rate of oxygen uptake and of peroxide formation[6] (Table I). In an autoxidizing hydrogenated vegetable fat, on the other hand, the pronounced acceleration of peroxide formation does not occur until a considerable time after the total disppearance of tocopherol (Table I). This observation suggested the presence of hitherto unrecognized antioxidants which were less susceptible to oxidation than the tocopherols. They were obviously not phenolic in nature because the oxidized fat gave no test with the ferric chloride–dipyridyl reagent of Emmerie and Engel.[7]

In some respects, the oxidized vegetable fat behaved as though it contained quinoid substances.

(1) Presented before the Division of Food and Agricultural Chemistry, American Chemical Society meeting, Memphis, Tenn., 1942.

(2) Olcott and Mattill, THIS JOURNAL, **58**, 1627 (1936).

(3) Karrer and Keller, *Helv. Chim. Acta*, **21**, 1161 (1938).

(4) Olcott and Emerson, THIS JOURNAL, **59**, 1008 (1937).

(5) Golumbic, *ibid.*, **63**, 1142 (1941).

(6) Golumbic and Mattill, *ibid.*, **63**, 1279 (1941).

(7) Emmerie and Engel, *Rec. trav. chim.*, **57**, 1357 (1938).

TABLE I

THE OXIDATION OF TOCOPHEROLS IN AN ANIMAL AND IN A VEGETABLE FAT AT 60°

Lard			Hydrogenated vegetable fat		
Time, days	Tocopherol,[a] per cent.	Peroxide value[b]	Time, days	Tocopherol,[a] per cent.	Peroxide value[b]
0	0.05[c]	1.3	0	0.105[d]	0.9
3	.01	3.2	14	.008	17.0
7	.004	10.3	35	.000	30.0
14	.003	19.0	49	.000	42.7
21	.001	27.7	58	.000	74.0
28	.000	61.5	63	.000	150.0

[a] Determined by the Emmerie–Engel method as modified by Parker and McFarlane, *Can. J. Res.*, **18**, 403 (1940). [b] Millimoles of peroxide oxygen per kg. of fat. [c] This amount of synthetic α-tocopherol was added to the fresh lard. [d] Naturally occurring tocopherol.

Thus, the light yellow color of the fresh fat gradually deepened to an orange-yellow during the course of the autoxidation. The oxidized fat was decolorized by treatment with reducing agents but its color soon reappeared after removal of the reducing agent and re-exposure to air. Upon continued exposure to air, no further change was noted until the period of accelerated peroxide formation was reached, whereupon the color of the fat faded out rapidly. Vegetable fats in general exhibit this decolorization at the point of extreme rancidity.[8] It seemed pertinent, therefore, to separate the substances responsible for the color production and to study their antioxidant and chemical properties.

For this purpose, hydrogenated vegetable fats were allowed to undergo sufficient atmospheric oxidation to destroy all the tocopherols and petroleum–ether solutions of these partially oxidized oils were twice chromatographed on permutit. This operation gave a red zone whose eluate yielded a red oil from which most of the sterols and fat were removed by cooling in alcoholic solution. Upon repeated adsorption of the residual oil on silicic acid, a homogeneous red zone was obtained which yielded a red oil possessing definite antioxygenic and quinoid properties (Table II).

The red concentrates prepared in this manner were subjected to the action of reducing, acetylating and cyclizing agents in order to gain further information as to the chemical nature of their antioxygenic constituents. In addition, their absorption spectrum was measured and their biological (vitamin E) activity was determined. In all these properties and reactions, these red anti-

(8) Joyner and McIntyre, *Oil and Soap*, **15**, 184 (1938).

TABLE II

ANTIOXYGENIC ACTION OF THE QUINONE CONCENTRATES

Substrate	% of inhibitor added	Anti-oxygenic index[a]
Lard	0.05 Quinone concentrate[b]	3
	.02 Red oxidation product of α-tocopherol	2–4
Purified ethyl esters of hydrogenated cottonseed oil	.80 Quinone concentrate	3

[a] Ratio of the induction period of stabilized fat to that of control. [b] Analytically equivalent to 0.025–0.035% red oxidation product of α-tocopherol.

oxygenic concentrates showed a marked similarity to the chroman-5,6-quinones resulting from the treatment of tocopherols with nitric acid.[9] Previous attempts[9] and our own efforts to purify these latter compounds have been unsuccessful, hence no direct qualitative comparison can be made between them and the antioxygenic quinoid concentrates just described. Until this is accomplished, the definitive chemical structure of the active constituents of the quinoid concentrates will remain open to question.

The red quinoid substances were found in oxidized cottonseed and soybean oils as well as in mixed hydrogenated vegetable fats. They do not occur as such in the fresh fats but are gradually formed in increasing amounts from colorless precursors as the fats undergo autoxidation. When the oxidized fats were dissolved in a butanol chloroform mixture[10] and compared colorimetrically with similar solutions of the chroman-5,6-quinone derived from α-tocopherol, the maximum amounts appearing in oxidized hydrogenated vegetable fats were of the order of 0.02 to 0.03%. Even at these low concentrations, chroman-5,6-quinones exhibit marked antioxygenic properties.[11]

The colorless precursors of these quinoid compounds are not the tocopherols. The quinoid compounds were never detected in autoxidizing animal fats or in purified fat substrates containing only added tocopherol. Furthermore, the addition of α-tocopherol or of α-tocoquinone to a fresh hydrogenated vegetable fat did not increase the amount appearing during the induction period.

Both the red quinoid substances and their precursors are destroyed by alkaline saponification; hence, methods analogous to those usually employed for concentrating vitamin E had to be

(9) Smith, Irwin and Ungnade, THIS JOURNAL, **61**, 2424 (1939).

(10) Quackenbush, Gottlieb and Steenbock, *Ind. Eng. Chem.*, **33**, 1276 (1941).

(11) Golumbic, THIS JOURNAL, **63**, 1163 (1941).

abandoned. The quinoid precursors could be separated with little apparent destruction by chromatographic adsorption on activated alumina according to the method introduced by Moss and Drummond for the isolation of tocopherols from wheat germ oil.[12] To secure selective adsorption of all the antioxygenic constituents of hydrogenated vegetable fats, it was first necessary to convert them to their crude ethyl esters by acid alcoholysis.[2] Petroleum ether solutions of these esters were adsorbed on activated alumina and afforded a yellow zone containing the quinoid precursors in association with the tocopherols. The antioxygenic activity of this adsorbed fraction was lost after acetylation but not after quantitative oxidation with gold chloride.

Tocoquinones, the expected oxidation products if tocopherols alone were present, are devoid of stabilizing action[5]; hence, the adsorbed zone contained phenolic inhibitors other than tocopherols. By repeated chromatographic adsorption on silicic acid, of the fraction oxidized by gold chloride, a homogeneous red zone was obtained which yielded a red antioxygenic oil exhibiting the chemical behavior of the chroman-5,6-quinones. The most likely source of these quinoid substances is thus their corresponding hydroquinones, possibly 5-hydroxy tocols.

Quackenbush, Gottlieb and Steenbock[10] found that the application of the Furter–Meyer method[13] to the determination of tocopherols in vegetable oils sometimes gave high results because of the presence of a chromogen other than tocopherol, which produced a color not unlike that obtained by vigorous oxidation of tocopherol. The fact that this unidentified chromogen was mainly lost upon saponification of the vegetable oils strongly suggests that it is the alkali-labile precursor of the red quinoid substances whose isolation is here reported.

These antioxygenic compounds are also responsible for certain characteristics of the autoxidative behavior of vegetable fats; a discussion of these relations will be presented elsewhere.

Experimental

Preparation of the Antioxygenic Quinoid Concentrates.—Hydrogenated vegetable fats were the most satisfactory starting materials; crude vegetable oils introduced complications because of the difficulty of removing the carotenoid pigments

(12) Moss and Drummond, *Biochem. J.*, **32**, 1953 (1938).

(13) Furter and Meyer, *Helv. Chim. Acta*, **22**, 240 (1939).

The hydrogenated vegetable fat (500 g.) was subjected to acid alcoholysis by refluxing with absolute alcohol containing 2–3% hydrogen chloride.[2] The crude ethyl esters obtained by this process were dissolved in sufficient petroleum ether (b. p. 60–70°) to make a 20% solution and chromatographed on 500 g. of activated alumina. The column exhibited one or two yellow zones depending on the kind of alumina used. When two bands were obtained, as with Brockmann's alumina, all the antioxygenic substances were confined to the second (lower) of the two bands whereas with other commercial aluminas, all the antioxygenic compounds were adsorbed in the single zone. The elutions were made with chloroform and evaporation of this solvent left a semi-solid residue. This was taken up in ethyl alcohol, cooled at −5° and the fat and sterols which crystallized were filtered off. Repetition of this process yielded a concentrate containing about 10% tocopherol (Emmerie–Engel analysis). It was quantitatively oxidized in alcoholic solution with gold chloride.[3] The precipitated gold was filtered off and the clear orange-red solution concentrated *in vacuo* to a small volume. This was taken up in ether, washed with water and dried. The ether residue was dissolved in petroleum ether (b. p. 60–70°) and chromatographed on 60 g. of silicic acid–hyflosupercel mixture (2 : 1). Two highly colored zones were obtained which were eluted with chloroform. The lower yellow band afforded an oil which gave a positive Furter–Meyer test but a negative Emmerie–Engel test and thus contained tocoquinones. The upper red zone yielded a red oil which on a colorimetric basis was equivalent to about 50 mg. of the chroman-5,6-quinone prepared from α-tocopherol. This fraction was cooled in alcoholic solution to remove further amounts of fats and sterols and the recovered oil was again adsorbed on the silicic acid–hyflosupercel mixture. Repetition of these last two steps yielded a concentrate which exhibited a chromatographically homogeneous zone upon adsorption and which contained 5–10% of the quinone, based on colorimetric comparison with the chroman-5,6-quinone from α-tocopherol.

To secure the red antioxygenic substance from incipiently rancid hydrogenated vegetable fats, these were allowed to undergo atmospheric oxidation, usually at 60°, until all the tocopherol had disappeared as determined by Emmerie–Engel analysis. Petroleum ether solutions of the partially oxidized oils were twice chromatographed on permutit, a process which afforded one red zone. Further purification of this adsorbed fraction was secured in essentially the same manner as with the gold chloride oxidized fractions, namely, by crystallization of fats and sterols from alcoholic solution and chromatographic adsorption on silicic acid. The antioxygenic red oil finally obtained was indistinguishable in properties from the concentrates secured from the fresh fat.

Another though less successful means of separating the antioxygenic quinoid substances from tocopherols was to extract petroleum ether solutions of their concentrates with Claisen alkali. It has previously been established that the reduced forms of the red oxidation products of the tocopherols are somewhat soluble in Claisen's alkali whereas according to Scudi and Buhs,[14] tocopherols themselves are not extracted by this reagent. Although this

(14) Scudi and Buhs, *J. Biol. Chen.*, **141**, 451 (1941).

method permits only partial recovery of the red antioxygenic substances, it was of some value in detecting their presence in highly pigmented vegetable oils.

Chemical and Biological Properties.—The absorption spectrum of the concentrates in the visible region, as measured in alcoholic solution by a Bausch and Lomb spectrophotometer, is identical with that of authentic chroman-5,6-quinones[9] and shows maximal absorption in the range 560–570 mμ.

The quinone concentrates are efficient stabilizers for lard and other fat substrates (Table II). They are instantly decolorized by reducing agents but quickly regain their initial color after separation from the reducing agent and re-exposure to air. Reductive acetylation, however, yields stable colorless oils which possess no antioxygenic properties. When the quinone concentrates react with *o*-phenylenediamine, they form products whose ether solutions exhibit the greenish fluorescence in daylight and in ultraviolet light, characteristic of the phenazines of authentic chroman-5,6-quinones.[9] The antioxygenic quinoid substances are destroyed when the concentrates are saponified. Their lability to alkali, first noted by John and Emte[15] with the authentic compounds, is markedly diminished when sodium hydrosulfite is present. However, when the quinone concentrates were saponified in the presence of this reducing agent, only a small proportion of the total quinone was isolated from the unsaponifiable matter. The greater proportion of it appeared to remain in the saponified fraction. Likewise, only partial recovery of the chroman-5,6-quinone oxidation product of α-tocopherol was secured when it was subjected to the same treatment.

(15) John and Emte, *Z. physiol. Chem.*, **261**, 24 (1939).

Conflicting statements have appeared regarding the vitamin E activity of the chroman-5,6-quinone derived from α-tocopherol. Evans, as reported in a paper of Smith and co-workers,[9] found that it was inactive in doses up to 6 mg. whereas Ridgway, Drummond and Wright[16] reported that it showed some activity in amounts of 5 mg. In our hands, the red oxidation product of α-tocopherol as well as its hydroquinone diacetate and the red quinoid substances obtained from vegetable oils were devoid of biological activity in doses of 10–15 mg. (eight animals).

The author is indebted to Lever Brothers Company, Cambridge, Massachusetts for a grant in support of this work.

Summary

Cottonseed and soybean oils and mixed hydrogenated vegetable fats contain alkali-labile antioxygenic substances other than the tocopherols. The chemical behavior of these fat antioxidants showed that they are similar to, if not identical with, the chroman-5,6-quinones and occur in fresh vegetable fats in a colorless, possibly quinol form. Their isolation and concentration were accomplished by chromatographic adsorption and the use of selective solvents. These antioxygenic quinoid substances, like the chroman-5,6-quinone product of α-tocopherol, were devoid of vitamin E activity.

(16) Ridgway, Drummond and Wright, *Biochem. J.*, **34**, 1569 (1940).

IOWA CITY, IOWA RECEIVED JUNE 15, 1942

[CONTRIBUTION FROM THE DERMATOLOGICAL RESEARCH LABORATORIES, DIVISION OF ABBOTT LABORATORIES]

N^1-Sulfanilylamino-alkyl-pyrimidines

BY GEORGE W. RAIZISS AND MORRIS FREIFELDER

The substitution of an amide hydrogen in sulfanilamide by some heterocyclic nuclei has resulted in compounds with increased therapeutic activity. In continuing our work[1] in this field, we have synthesized a series of sulfanilylamino alkylpyrimidines. Some of these were prepared concurrently by other investigators and have been described[2]; in addition, we have mentioned herewith several which were previously unpublished.

The 4-alkyl and 4,5-dialkyl substituted 2-aminopyrimidines reacted readily with *p*-acetsulfanilyl chloride, forming the acetsulfanilyl derivatives which were subsequently hydrolyzed to the sulfanilylaminoalkylpyrimidines. Our attempts to combine the acid chloride with amino hydroxypyrimidines, such as isocytosine (2-amino-4-hydroxypyrimidine) or divicine (2,5-diamino-4,6-dihydroxypyrimidine), and purines such as adenine or guanine, failed.

Most of the aminopyrimidines used were prepared according to Benary's method[3] by treating guanidine carbonate with sodium oxymethylene ketones; these were obtained by condensation of methyl alkyl ketone and ethyl formate in presence of sodium methylate. 2-Amino-4-ethyl-5-methylpyrimidine was prepared from sodium oxymethylene-α-methyl-methyl ethyl ketone (derived from diethyl ketone and ethyl formate); 2-amino-4-isobutylpyrimidine from sodium oxy-

(1) (a) Raiziss, Clemence and Freifelder, THIS JOURNAL, **63**, 2739 (1941); (b) Raiziss and Clemence, *ibid.*, **63**, 3124 (1941).

(2) (a) Roblin, Williams, Winnek and English, *ibid.*, **62**, 2003 (1940); (b) Caldwell, Kornfeld and Donnell, *ibid.*, **63**, 2189 (1941); (c) Sprague, Kissinger and Lincoln, *ibid.*, **63**, 3028 (1941).

(3) Benary, *Ber.*, **63**, 2601 (1930).

methylene methyl isobutyl ketone (derived from methyl isobutyl ketone), 2-amino-4-*n*-amylpyrimidine from sodium oxymethylenemethyl-*n*-amyl ketone (derived from methyl *n*-amyl ketone). 2,5-Diaminopyrimidine was prepared in excellent yield by catalytic reduction of 5-nitro-2-aminopyrimidine[4] using platinum oxide catalyst; 2-amino-4-hexylpyrimidine was prepared by combining guanidine carbonate with the sodium oxymethylene alkyl ketone derived from ethyl formate and methyl *n*-hexyl ketone. A product was obtained which melted at 92–93° (after several recrystallizations). This is in agreement with the melting point reported by Caldwell, Kornfeld and Donnell[2b] (named as 2-amino-4-methyl-5-*n*-amylpyrimidine) and the melting point reported by Sprague, Kissinger and Lincoln[2c] (named as 2-amino-4-hexylpyrimidine). Oxidation with nitric acid was performed by Caldwell,[2b] with the result that some material was obtained which he considered to be 2-amino-4-carboxy-5-*n*-amylpyrimidine. We carried out a number of oxidations with the hexylpyrimidine, which we obtained, and never had yields above 2–3% of the carboxy compound. It is our belief that the 2-amino-4-methyl-5-*n*-amylpyrimidine reported by Caldwell is essentially 2-amino-4-hexylpyrimidine (as reported by Sprague) containing a small amount of the isomeric 4-methyl-5-*n*-amyl derivative. Employing the same technique we were unable to obtain any oxidation of either 2-amino-4-isobutylpyrimidine or 2-amino-4-*n*-amylpyrimidine.

In Table II, it is interesting to note the solubilities of acetsulfanilylpyrimidines in urine, which may have some relationship to the deposition of crystals in the kidneys and the genito-urinary tract with the formation of urinary concretions. The acetyl-4,5-dimethylpyrimidine derivative is considerably more soluble in urine than any of the compounds. Next in solubility was the monomethyl product. Other acetyl products were very slightly soluble. The study of the therapeutic

TABLE I

AMINOPYRIMIDINES

-Pyrimidines	M. p., (uncor.) °C.	Formula	Nitrogen, % Calcd.	Found
2-Amino-4-isobutyl-[a]	119	$C_8H_{13}N_3$	27.8	27.2
2-Amino-4-amyl-[b]	90	$C_9H_{15}N_3$	25.55	25.39
2-Amino-4-ethyl-5-methyl-[a]	157	$C_7H_{11}N_3$	30.6	30.4
2,5-Diamino-[a,c]	200	$C_4H_6N_4$	50.9	50.3

[a] Recrystallized from hot water. [b] Recrystallized from petroleum ether. [c] Prepared as intermediate but not isolated by Roblin, Winnek and English, THIS JOURNAL, **64**, 567 (1942).

TABLE II

2-(N⁴-ACETYLSULFANILYLAMINO)-PYRIMIDINES

Compound[c]	Yield, %	Melting point, °C.	Solubility at 37°C., mg./100 cc. Water	Urine	Formula	Nitrogen, % Calcd.	Found
2-(N⁴-Acetylsulfanilylamino)-4-methylpyrimidine[a]	59	244	24.7	27.0	$C_{13}H_{14}N_4O_3S$	18.03	18.36
2-(N⁴-Acetylsulfanilylamino)-4-ethylpyrimidine	76	274	0.78	1.0	$C_{14}H_{16}N_4O_3S$	17.5	17.41
2-(N⁴-Acetylsulfanilylamino)-4-*n*-propylpyrimidine	82	258	.64	0.8	$C_{15}H_{18}N_4O_3S$	16.76	17.02
2-(N⁴-Acetylsulfanilylamino)-4-isobutylpyrimidine	68	233	.38	.825	$C_{16}H_{20}N_4O_3S$	16.09	15.67
2-(N⁴-Acetylsulfanilylamino)-4-*n*-amylpyrimidine	84	222–223	.44	.5	$C_{17}H_{22}N_4O_3S$	15 46	15.7
2-(N⁴-Acetylsulfanilylamino)-4-hexylpyrimidine[b]	55	216	.35	.7	$C_{18}H_{24}N_4O_3S$	14.89	14.56
2-(N⁴-Acetylsulfanilylamino)-4,5-dimethylpyrimidine[b]	78	272–273	11.25	43.5	$C_{14}H_{16}N_4O_3S$	17.5	17.3
2-(N⁴-Acetylsulfanilylamino)-4-ethyl-5-methylpyrimidine	84	286	0.36	0.65	$C_{15}H_{18}N_4O_3S$	16.76	16.6
2-(N⁴-Acetylsulfanilylamino)-4-phenylpyrimidine	95	287	.36	.51	$C_{18}H_{16}N_4O_3S$	15.21	14.95
2-(N⁴-Acetylsulfanilylamino)-5,6,7,8-tetrahydroquinazoline[b]	78	259	.76	.97	$C_{16}H_{18}N_4O_3S$	16.18	15.93
2,5-Di-(N⁴-acetylsulfanilylaminopyrimidine	56	295 dec.	.5	1.4	$C_{20}H_{20}N_6O_6S_2$	16.66	16.46

[a] Ref. 2a. [b] Ref. 2b. [c] The above 2-(N⁴-acetylsulfanilylamino) derivatives were crystallized at least twice from 50% alcohol.

(4) Hale and Brill, THIS JOURNAL, **34**, 91 (1912).

TABLE III

2-SULFANILYLAMINOPYRIMIDINES

	Yield, %[d]	Melting point, °C.	Solubility in H_2O, 37°C., mg./100 cc.	Formula	Nitrogen, % Calcd.	Found
2-Sulfanilylamino-4-methylpyrimidine[a,c]	45	235–236	40	$C_{11}H_{12}N_4O_2S$	20.82	20.72
2-Sulfanilylamino-4-ethylpyrimidine	51	242	17.2	$C_{12}H_{14}N_4O_2S$	20.14	20.16
2-Sulfanilylamino-4-propylpyrimidine[c]	50	212–214	25	$C_{13}H_{16}N_4O_2S$	19.1	18.89
2-Sulfanilylamino-4-isobutylpyrimidine	40	232	10	$C_{14}H_{18}N_4O_2S$	18.3	18.08
2-Sulfanilylamino-4-amylpyrimidine	46	226	20	$C_{15}H_{20}N_4O_2S$	17.5	17.21
2-Sulfanilylamino-4-hexylpyrimdine[b,c]	40	204	20	$C_{16}H_{20}N_4O_2S$	16.7	16.52
2-Sulfanilylamino-4,5-dimethylpyrimidine[b]	60	222	20	$C_{12}H_{14}N_4O_2S$	20.14	20.05
2-Sulfanilylamino-4-ethyl-5-methylpyrimidine	60	215	25	$C_{13}H_{16}N_4O_2S$	19.18	19.3
2-Sulfanilylamino-4-phenylpyrimidine[c]	45	264	0.9	$C_{16}H_{14}N_4O_2S$	17.17	16.85
2-Sulfanilylamino-5,6,7,8-tetrahydroquinazoline[b,c]	50	247	2.5	$C_{14}H_{16}N_4O_2S$	18.4	18.2
2,5-Disulfanilylaminopyrimidine[e]	42	241–242	5.4	$C_{16}H_{16}N_4O_2S$	20.00	20.04

[a] Ref. 2a. [b] Ref. 2b. [c] Ref. 2c. [d] Yields based on aminopyrimidines. [e] Roblin, *et al.*, THIS JOURNAL, **64,** 568 (1942), reported 231–232° for this compound.

effect in mice infected with pneumococcus type II (method described in publication)[5] disclosed good therapeutic results for sulfanilylamino 4,5-dimethyl- and 4-monomethylpyrimidines. The ethyl derivative showed slight therapeutic effect, while higher homologs and other derivatives were found to be inactive.

Experimental

The compounds in Table I were prepared according to Benary's method as has been previously mentioned.

2,5-Diamino-pyrimidine: 5.6 g. of 2-amino-5-nitropyrimidine (4) was suspended in 150 cc. alcohol and reduced in presence of 0.2 g. of platinum oxide by hydrogen at 3 atmospheres pressure. The reduction was complete in one hour and the almost clear solution was filtered and evaporated to dryness. The yield was quantitative. After two recrystallizations from water the yield was 3.5 g. (80%).

The acet-sulfanilylaminopyrimidines were all prepared and subsequently hydrolyzed according to the method described in the following example. All of the compounds were recrystallized from 50% alcohol.

2-Sulfanilylamino-4-*n*-amylpyrimidine: 3.3 g. (0.02 mole) of 2-amino-4-*n*-amylpyrimidine was dissolved in 4.8 cc. (0.06 mole) of pyridine and 4.7 g. (0.02 mole) of *p*-acetsulfanilyl chloride added gradually with mixing, keeping temperature below 60°. The mixture was then warmed at 60° for one hour and then stirred into 50 cc. of ice-water. The precipitate was filtered and washed with water and dried; yield 6.2 g. (84%). This material can be recrystallized from 50% alcohol, but for further hydrolysis to the amino compound, recrystallization was not necessary. The acetyl product was hydrolyzed by refluxing in ten volumes of 5% sodium hydroxide for two hours. The solution was cooled and neutralized by the addition of dilute hydrochloric acid. The precipitate was filtered, washed with water and dried. After two recrystallizations from 50% alcohol, the yield was 3 g. (48%).

(5) Raiziss, Severac and Moetsch, *Proc. Soc. Exp. Biol. Med.*, **40,** 434 (1939).

Summary

1. We have prepared and described the chemical and biological properties of various sulfanilylamino-mono- and dialkylpyrimidines and their corresponding acetyl products.

2. The sulfanilylamino-methyl and dimethylpyrimidine derivatives proved to have good therapeutic effect in the treatment of mice infected with Type II pneumococcus.

PHILADELPHIA, PA. RECEIVED JUNE 23, 1942

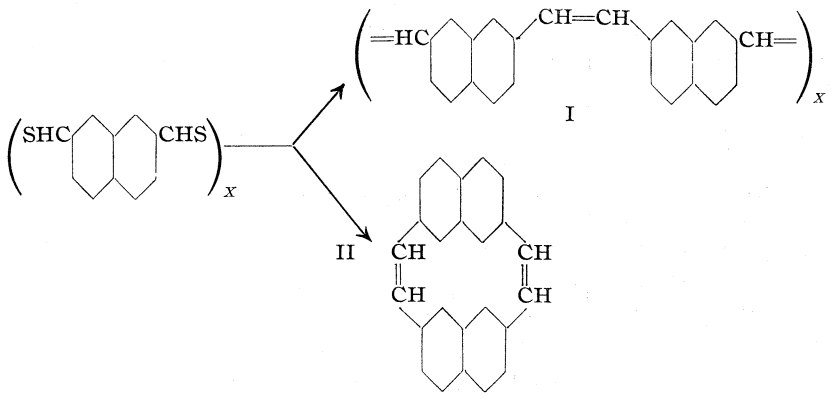
[PUBLICATION NO. 36 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Synthesis of 2,7-Naphthalenedialdehyde; an Attempted Synthesis of Coronene

BY J. H. WOOD AND J. A. STANFIELD

Although most of the 2,7-derivatives of naphthalene have been known for some time, the 2,7-dialdehyde has not been previously prepared. This aldehyde was synthesized by the Stephen[1] method wherein the corresponding 2,7-dinitrile was converted into the aldimine hydrochloride by the action of stannous chloride and hydrogen chloride in an ether solvent. The aldehyde was then obtained by hydrolysis. The structure of the aldehyde was established by the method of preparation, by oxidation by alkaline permanganate to the known 2,7-dicarboxylic acid, and by analysis of the aldehyde and its 2,4-dinitrophenylhydrazone.

The conversion of aryl thioaldehydes into stilbene analogs and homologs by heating with copper powder has been previously reported.[2] Such a conversion of 2,7-naphthalenedialdehyde might lead to two different types of ethylene derivatives as indicated



Ring closure of II by dehydrogenation at the alpha positions would give coronene.

Several attempts were made to prepare coronene as outlined above but all resulted in reaction products from which nothing definite was obtained. In this work, the thioaldehyde was readily prepared by the action of hydrogen sulfide upon naphthalenedialdehyde in the presence of hydrogen chloride. Upon heating the thioaldehyde with copper, non-sulfur containing materials were obtained. Attempts to convert this into coronene by heating alone and with selenium failed.

(1) Stephen, *J. Chem. Soc.*, **127**, 1874 (1925).

(2) Wood, Bacon, Meibohm, Throckmorton and Turner, THIS JOURNAL, **63**, 1334 (1941).

Experimental

Preparation of 2,7-Naphthalenedinitrile.—The method of Ebert and Merz[3] was followed, whereby the dinitrile was obtained by heating sodium 2,7-naphthalenedisulfonate with potassium cyanide. The yields in general were poor (10 to 15%).

Preparation of 2,7-Naphthalenedialdehyde.—Twelve grams of anhydrous stannous chloride and 150 ml. of dry ether were placed in a liter, three-necked flask equipped with a stirrer, reflux condenser, and an inlet for hydrogen chloride. Hydrogen chloride was bubbled in with stirring until solution of the stannous chloride was complete. This was indicated by the separation of a heavy, oily layer and the time required was about two and one-half hours. A suspension of 2 g. of 2,7-naphthalenedinitrile in 100 ml. of dry ether was then added with stirring over a period of forty minutes. Hydrogen chloride was passed in during this time. A viscous, yellow mass resulted. Stirring and the passage of hydrogen chloride were continued for a period of twenty-four hours by which time a yellow precipitate of the aldimine hydrochloride had formed. The mixture was cooled to zero before filtering to ensure as complete precipitation as possible. After filtration, the aldimine hydrochloride was hydrolyzed by refluxing in 250 ml. of water for twenty minutes. Upon cooling and filtering, the impure aldehyde mixed with inorganic material was obtained. Purification was partly accomplished through the bisulfite addition compound. Final purification was accomplished by two recrystallizations from water–alcohol solution which gave long, white needles, m. p. 142° (cor.). The yield was 0.5 g. (24.3%). 2,7-Naphthalenedialdehyde is soluble in methanol, ethanol, ether and benzene.

Anal. Calcd. for $C_{12}H_8O_2$: C, 78.26; H, 4.35. Found: C, 78.98; H, 4.19.

2,7-Naphthalenedialdehydedi-(2,4-dinitrophenylhydrazone).—The hydrazone was prepared from alcoholic solution catalyzed by a few drops of concd. hydrochloric acid. Recrystallization was not accomplished; color, orange; m. p., slight decomposition at 295°, complete decomposition at 312–313°.

Anal. Calcd. for $C_{24}H_{16}O_8N_8$: N, 20.59. Found: N, 20.13.

Summary

1. 2,7-Naphthalenedialdehyde was prepared by the action of stannous chloride on the corresponding dinitrile.

(3) Ebert and Merz, *Ber.*, **9**, 592 (1876).

2. The 2,4-dinitrophenylhydrazone of this aldehyde was prepared.

3. Attempts were made to obtain coronene by heating 2,7-polythionaphthalenedialdehyde with copper powder.

KNOXVILLE, TENNESSEE RECEIVED JULY 17, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Factors Influencing the Cresolase Activity of Tyrosinase. The Effect of Gelatin and *p*-Cresol Concentration

BY WILBUR H. MILLER[1] AND CHARLES R. DAWSON

Previous workers[2,3,4] have demonstrated that tyrosinase preparations from the cultivated mushroom *Psalliota campestris* show a marked variation in ratio of catecholase to cresolase activity,[5] depending on the procedure used to isolate the enzyme. Since during the process of purification, unless special precautions are taken, the major portion of the cresolase activity is apt to be lost, the ratio of the catecholase to the cresolase activity in the purified preparation is often high (greater than 2). In these so-called "high catecholase" preparations, the catecholase activity is proportional to the copper in the preparation whereas the cresolase activity is not.[3,7] Until recently it was this type of preparation that was used for several investigations in this Laboratory concerning the nature, properties and mode of action of the enzyme tyrosinase.[2,7,8] In 1940 Parkinson and Nelson[4] reported the development of tyrosinase preparations in which the ratio of catecholase to cresolase activity was low (2 or less), and in which both enzymic activities were proportional to the copper content of the preparation. Such preparations have been called "high cresolase" preparations.

The development of different type tyrosinase preparations, having different ratios of catecholase to cresolase activities, has resulted in conjecture as to whether or not the enzyme is in reality one copper protein possessing two types of enzymic action, or is a mixture of two copper proteins each with its own activity. Before any considerable progress can be made toward a solution of this interesting and fundamental problem, it is necessary to have reliable means of characterizing the different type preparations on the basis of their catecholase and cresolase activities. Because of the marked inactivation of the enzyme that is observed particularly during the oxidation of catechol, it has been the practice to measure the enzyme activities in the presence of a "protecting" agent, gelatin being commonly used for this purpose.[2,9] Thus previous studies designed to compare the two types of tyrosinase preparations on the basis of their catecholase and cresolase activities have been made with gelatin present in the reaction medium.[4,10]

Recently, however, it has been found that the presence of gelatin in the reaction medium during the enzymatic oxidation of catechol (catecholase activity) tends to obscure fundamental differences between the different type preparations,[11] and it has been found that gelatin need not be present in the reaction medium in order to obtain a reliable measurement of catecholase activity.[12] These observations made it seem advisable to reinvestigate, from the same point of view, the effect of gelatin on the other characteristic activity of the different type tyrosinase preparations, *i. e.*, the cresolase activity.

The results of such a study, described in detail below, reveal that the increase in rate of oxidation of *p*-cresol (increase in cresolase activity), that is observed when tyrosinase is used in the

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

(2) M. H. Adams and J. M. Nelson, THIS JOURNAL, **60**, 2474 (1938).

(3) D. Keilin and T. Mann, *Proc. Roy. Soc.* (London), **B125**, 187 (1938).

(4) G. G. Parkinson and J. M. Nelson, THIS JOURNAL, **62**, 1693 (1940).

(5) The ability of the enzyme preparation to catalyze the aerobic oxidation of the dihydric phenol catechol and the monohydric phenol *p*-cresol are referred to as catecholase and cresolase activities, respectively. One catecholase unit and one cresolase unit have been defined as the amount of enzyme required to cause the uptake of 10 cu. mm. of oxygen per minute when acting on 4 mg. of catechol and 4 mg. of *p*-cresol, respectively. For further details see Gregg and Nelson.[6]

(6) D. C. Gregg and J. M. Nelson, THIS JOURNAL, **62**, 2500 (1940).

(7) B. J. Ludwig and J. M. Nelson, *ibid.*, **61**, 2601 (1939).

(8) C. A. Bordner and J. M. Nelson, *ibid.*, **61**, 1507 (1939).

(9) M. H. Adams and J. M. Nelson, *ibid.*, **60**, 2472 (1938).

(10) D. C. Gregg and J. M. Nelson, *ibid.*, **62**, 2506 (1940).

(11) W. H. Miller and C. R. Dawson, *ibid.*, **63**, 3368 (1941).

(12) W. H. Miller and C. R. Dawson, *ibid.*, **63**, 3375 (1941).

presence of gelatin, is dependent on the type of tyrosinase preparation employed and also on certain environmental factors such as the substrate concentration. The variable effect of gelatin in these *p*-cresol–enzyme systems has been found to be complex in nature, and may be such as to obscure or unduly accentuate certain fundamental characteristics of the particular enzyme preparation.

The Enzymatic Oxidation of *p*-Cresol

When a typical high catecholase preparation is used, with and without gelatin in the reaction medium, the enzymatic oxidation of *p*-cresol, as followed by manometric measurements of oxygen consumption, proceeds as shown by the curves of Fig. 1. In these experiments a constant amount of the enzyme was employed and the substrate (*p*-cresol) concentration was varied tenfold, that is from 2.5 to 25 mg. in an 8.0-cc. reaction volume. In contrast to the enzymatic oxidation of catechol which starts at a maximum rate,[11] it can be seen from Fig. 1 that the enzymatic oxidation of *p*-cresol is characterized by an initial lag or induction period in the rate of oxygen absorption. The length of this induction period can be varied in a number of ways and this phase of the reaction has been studied[6,8] in attempts to distinguish more clearly the differences between cresolase and catecholase activity. From Fig. 1 it is apparent that a tenfold variation in *p*-cresol concentration has no pronounced effect on the length of the induction period, either in the presence or absence of gelatin. Only in the case where gelatin is present in the reaction medium (Curves I-G, II-G, etc.) might it be inferred that the induction period is significantly less with the lower substrate concentrations.

With the high catecholase preparation, the rate of oxygen absorption after the initial lag period in the *p*-cresol reaction reaches a maximum value, usually in twenty to thirty minutes. This rate then continues at nearly a constant value whether gelatin is used or not. Thus, in the case where 2.5 mg. of *p*-cresol was used (Curves I and I-G of Fig. 1) it can be seen that the maximum value was maintained until about 75% of the *p*-cresol was completely oxidized.[13]

When a typical high cresolase preparation is used, the general course of the reaction is some-

(13) The complete enzymic oxidation of *p*-cresol results in the absorption of three atoms of oxygen per mole of *p*-cresol,[8] which for 2.5 mg. of *p*-cresol corresponds to an oxygen uptake of 785 cu. mm.

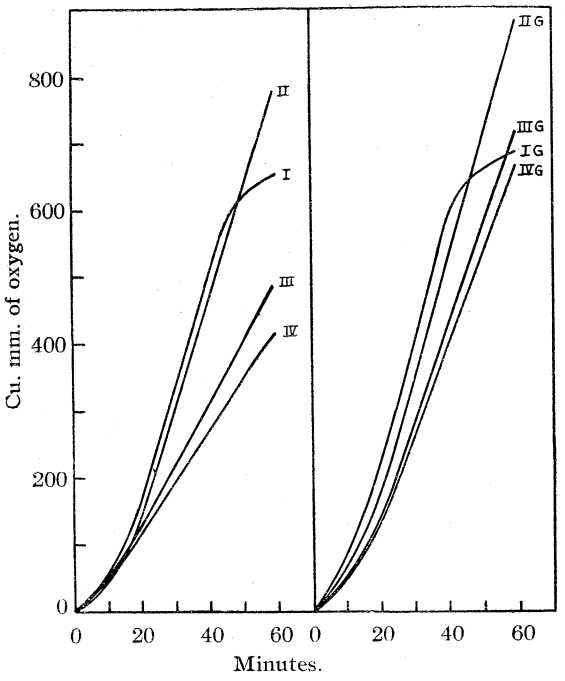


Fig. 1.—Showing the effect of gelatin and substrate concentration on the enzymatic oxidation of *p*-cresol by a high catecholase tyrosinase preparation. Oxygen absorption determined in Warburg Respirometer using flasks of 50-cc. capacity; 120 oscillations per minute; temperature 25°; *p*H 7.1. Total reaction volume was 8.0 cc., consisting of 1.0 cc. 0.2 *M* citrate–0.4 *M* phosphate buffer, 1.0 cc. (5 mg.) of gelatin solution where indicated, 1.0 cc. of *p*-cresol solution of indicated concentration (see data below), 1.2 cc. of a diluted (1:100) high catecholase tyrosinase preparation C144 added from the flask side arm to initiate the reaction, and water to bring to volume. Preparation C144 from the common mushroom, *Psalliota campestris*, had a catecholase to cresolase activity ratio of 13.8 and dry wt. (undiluted) of 2.6 mg. per cc.; contained 0.105% copper and 693 catecholase units per γ copper. Catecholase and cresolase activity were determined using methods previously described.[6,12] Each of the above curves is an average curve obtained from 3 to 5 experiments with readings taken at five-minute intervals. Such experiments are generally more reproducible when gelatin is a component of the system, *i. e.*, the points making up the average curve show less deviation. To compensate for this a greater number of experiments was employed in the systems containing no gelatin. The maximum rate values indicated below are obtained from the average curves over the time range where the oxygen uptake per five-minute interval was maximum and constant to within ±3 cu. mm.

No gelatin			Gelatin	
p-Cresol, mg.		Max. rate, cu. mm./ 5 min.		Max. rate, cu. mm./ 5 min.
2.5	I	88	I-G	93
5.0	II	81	II-G	90
15.0	III	46	III-G	74
25.0	IV	39	IV-G	69

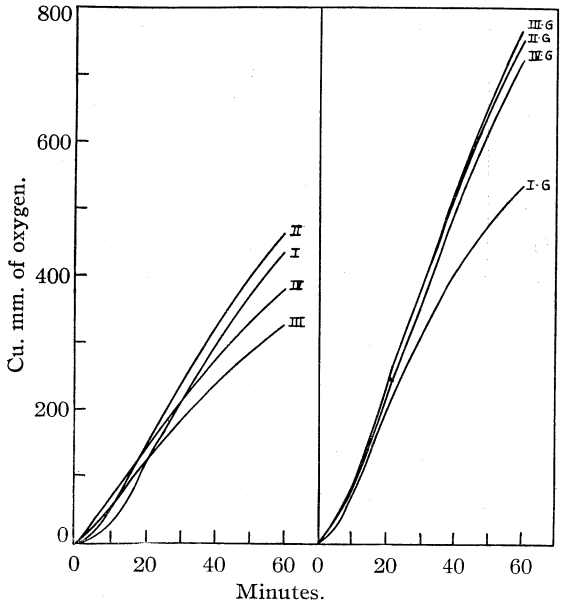


Fig. 2.—Showing the effect of gelatin and substrate concentration on the enzymatic oxidation of *p*-cresol by a high cresolase tyrosinase preparation. Reaction mixture and procedure the same as indicated in the legend of Fig. 1 except that 0.9 cc. of the diluted (1:500) high cresolase preparation C143F2 was used. This preparation has been previously described.[12] See legend of Fig. 1 for method of obtaining maximum rate values shown below.

	No gelatin		Gelatin	
p-Cresol, mg.		Max. rate, cu. mm./5 min.		Max. rate, cu. mm./5 min.
2.5	I	47	I-G	65
5.0	II	48	II-G	79
15.0	III	34	III-G	73
25.0	IV	40	IV-G	69

what different. This is apparent from Fig. 2 where the data plotted have been obtained from experiments exactly analogous to those described in Fig. 1, except that a constant amount of a high cresolase preparation was used. It is to be noted that in a reaction medium containing no gelatin (Curves I, II, etc., of Fig. 2), the length of the induction period is changed rather appreciably by change in substrate concentration. A longer induction period results from the use of lower *p*-cresol concentrations. Gelatin in the reaction medium practically eliminates this effect of substrate concentration on the length of the induction period (Curves I-G, II-G, etc., of Fig. 2). These results are in contrast to the effects of gelatin and substrate concentration on the induction period of a high catecholase preparation (Fig. 1).

With a high cresolase preparation the rate of oxygen absorption, after the initial lag period, approaches a maximum more rapidly, and maintains this rate constant for a much shorter period of time than is the case when a high catecholase preparation is employed (compare Figs. 1 and 2). This is true whether gelatin is present in the reaction medium or not, although gelatin does tend to increase somewhat the time a nearly constant rate of oxygen uptake is maintained with the high cresolase preparation.

For both types of preparations, the most pronounced effect of a tenfold variation in original substrate concentration is, on the maximum rate of oxygen absorption, obtained after the initial lag period (see maximum rate data Figs. 1 and 2). Thus, considering the data obtained using the high catecholase preparation (Fig. 1), it can be seen that when there is no gelatin in the reaction medium (Curves I, II, etc.), a marked lowering of the maximum rate of oxidation results when the original amount of *p*-cresol is increased from 2.5 to 25.0 mg. However, when gelatin is a component of the system (Curves I-G, II-G, etc.), the effect of increasing the original substrate concentration is much less pronounced. Gelatin appears to prevent, to an appreciable extent, inhibition of enzyme action caused by excessive amounts of *p*-cresol. The data obtained with the high cresolase preparation (Fig. 2) show qualitatively the same thing. It should be noted, however, that the inhibitory effect of excessive amounts of *p*-cresol in the absence of gelatin (Curves I, II, etc.) is considerably less pronounced for this type of preparation.

The manner in which the rate of enzymatic oxidation of *p*-cresol varies with the substrate concentration for both types of tyrosinase preparations, and the influence of gelatin on this variation, is shown more strikingly in Fig. 3. The data in Fig. 3 are those of Figs. 1 and 2 (see legend Fig. 3) plotted to show the rates as percentages of the optimum rate obtained in each series of experiments. It is apparent that in the absence of gelatin the rate of oxidation of *p*-cresol with a high catecholase preparation (Curve I) is considerably more sensitive to change in original substrate concentration than is the rate obtained with a high cresolase preparation (Curve II). Of particular interest is the quite different picture obtained when gelatin is present in the reaction medium. Although gelatin does not shift the position of the optimum substrate concentration for either type preparation, its effect on the substrate-rate curve is not the same for both type preparations.

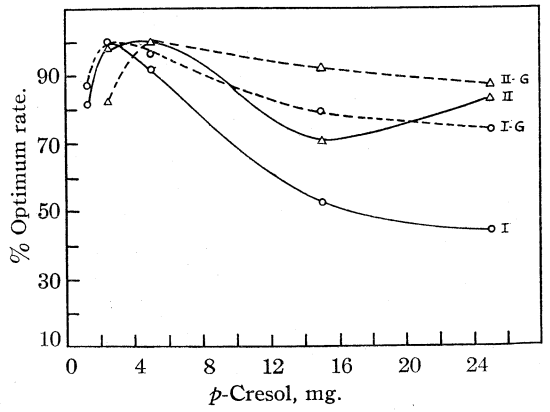


Fig. 3.—Showing the relationship between substrate concentration and cresolase activity when measured in the presence and absence of gelatin. The percentages of the optimum rates obtained with and without gelatin for each type preparation are calculated from the maximum rate data given in legends of Figs. 1 and 2 with one exception. Data obtained as indicated in the legend of Fig. 1 for 1.25 mg. of *p*-cresol have been added to show the optimum *p*-cresol concentration for the high catecholase preparation. Experimental points on the curves are: O, high catecholase; Δ, high cresolase; — — —, gelatin; ———, no gelatin.

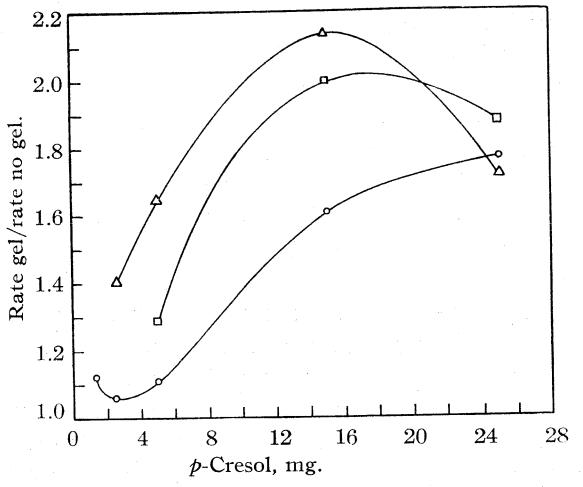


Fig. 4.—Showing that the effect of gelatin on cresolase activity varies markedly with the type of tyrosinase preparation and with the *p*-cresol concentration. For the high catecholase and the high cresolase preparations the ratios (rate gelatin/rate no gelatin) are calculated from the maximum rate data given in legends of Figs. 1 and 2 except for 1.25 mg. of *p*-cresol (see legend Fig. 3). The data shown for the intermediate preparation[14] were obtained as indicated in the legend of Fig. 1 using 0.8 cc. of the diluted (1:100) enzyme preparation C144PbAl. This preparation had a catecholase to cresolase activity ratio of 4.1 and a dry weight (undiluted) of 1.2 mg. per cc. contained 0.106% copper and had 690 catecholase units per γ of copper. Experimental points are: O, high catecholase; Δ, high cresolase; □, intermediate.

This difference in effect of gelatin is particularly noticeable on the low concentration side of the optimum.

Inspection of the rate data in Figs. 1 and 2 shows that when gelatin is present in the reaction medium, the maximum rate of the enzymatic oxidation of *p*-cresol is in all cases greater than that obtained when gelatin is not present. Gelatin causes an apparent increase in cresolase activity. The important point to note in this connection is the fact that the boosting effect of gelatin is not constant, but is variable, depending not only on the type of tyrosinase preparation, but also on the substrate concentration. This statement is emphasized by the data as shown in Fig. 4.

Discussion

Just how gelatin causes the effects described above is not clearly understood at the present time. The mechanism whereby one protein influences the state and action of another presents an interesting and fundamental problem, but it is a problem that cannot be solved until more data on the phenomena are available and more is known about protein structure. A study of the effect of inert protein material on the catalytic action of protein enzymes offers one of the most direct attacks on the problem, for the effects produced by the inert protein can be easily measured. It has been the purpose of this study to emphasize the fact that the effect of gelatin on tyrosinase cresolase activity and characterizing features of that activity is variable and markedly dependent on the type of tyrosinase preparation, *i. e.*, on the state of the tyrosinase protein material.

It has been suggested that the effect of gelatin results from the fact that it tends to prevent inactivation of the enzyme during the course of the oxidation,[9] primarily by preventing the enzyme from entering the air–liquid interface where surface denaturation of the protein–enzyme may occur.[15] Although it is probable that gelatin does "protect" the enzyme to some extent in this manner, certain of the data presented here, and elsewhere,[11] indicate that the function of gelatin is considerably more complex, and involves factors in addition to those which merely prevent inactivation of the enzyme. For the "protection" view of gelatin action to be completely logical and

(14) Tyrosinase preparations having a ratio of catecholase to cresolase activity in the range of 3.5–4.0 frequently are found to have properties intermediate to those characterizing the high catecholase and high cresolase preparations. Such enzyme preparations have been termed "intermediate" preparations.[11, 12]

(15) L. Tenenbaum, Dissertation, Columbia University, 1940.

satisfactory in explaining the very significant increase in cresolase activity that is observed when gelatin is employed in the measurements, one would expect to find considerable evidence of inactivation of the enzyme when gelatin is not employed. Furthermore, one would expect to find correspondingly less evidence of inactivation of the enzyme when gelatin is a component of the system. Yet when the cresolase activity of a high catecholase preparation is measured with no gelatin in the system (Curves I, II, etc., Fig. 1), constant rates of oxidation are observed for periods of over a half hour with the surface of the system changing at least 120 times per minute, *i. e.*, there is no evidence of serious inactivation of the enzyme in the absence of gelatin. With the other type of tyrosinase preparation (high cresolase preparation) there is evidence (short period of constant rate) indicating possible inactivation of the enzyme, when the activity measurements are made in the absence of gelatin (Curves I, II, etc., Fig. 2). However, the change toward a linear oxidation curve, effected by making gelatin a component of the system (compare Curves II and II-G, Fig. 2) appears to be hardly enough to explain a 65% increase in cresolase activity (compare maximum rate data for Curves II and II-G, Fig. 2).

Certain of the data obtained in this study suggest that gelatin increases the enzyme activity by perhaps modifying the enzyme molecule, or more likely by modifying the enzyme substrate relationships during the course of the reaction. Thus the influence of gelatin on the initial phase of the reaction, the induction period, was found to vary with the type of enzyme preparation and the substrate concentration. These same two factors were found also to influence the boosting effect of gelatin on the rate of oxidation obtained after the induction period (see Fig. 4).

It is possible that much may be learned in the future about the enzyme tyrosinase by studying its action in the presence of added protein material, such as gelatin. However, it would appear that when studies are made for the purpose of comparing the various type tyrosinase preparations, in reference to either their cresolase or catecholase activity, the use of gelatin is not to be recommended, at least not until more is known about its complex role in the system. With gelatin present, certain fundamental differences between the various type preparations are likely to be masked or possibly accentuated.

Summary

1. The effect of gelatin and *p*-cresol concentration on the cresolase activity of different type tyrosinase preparations from *Psalliota campestris* has been studied.

2. Over a tenfold range of substrate concentration, gelatin causes an increase in the rate of *p*-cresol oxidation as catalyzed by the enzyme tyrosinase.

3. The increase in rate of oxidation caused by gelatin varies markedly with the type of enzyme preparation and the substrate concentration.

4. The different type tyrosinase preparations show characteristic relationships of substrate concentration to cresolase activity and these relationships are affected differently by gelatin.

5. It appears that the role of gelatin in these systems is considerably more complex than just preventing inactivation of the enzyme during the course of the oxidation.

NEW YORK, N. Y. RECEIVED MAY 8, 1942

[CONTRIBUTION FROM THE LABORATORY OF PHYSICAL CHEMISTRY, UNIVERSITY OF WISCONSIN]

Some Physical Chemical Characteristics of Glycogen

BY WILBUR B. BRIDGMAN

The research described in this report was undertaken with a two-fold purpose. First, the particle size of glycogen has not been studied by sedimentation methods, and further information regarding its physical characteristics may be of value to the biological worker in understanding the relationship of glycogen to animal metabolism. Second, it was desired to gain experience and information in the application of ultracentrifuge experiments to inhomogeneous systems where the particle size varies continuously in contrast to the discrete size classes generally found in protein systems.

Much of the literature about glycogen is concerned with its determination in tissue and its relation to metabolism. While glycogen is widely distributed throughout the bodies of animals, about one-half of the total amount is concentrated in the liver. This organ is therefore the logical raw material for the preparation of glycogen. Two principal methods have been used for its extraction. The older method involves heating with concentrated alkali as the primary step. More recently the first extraction has been made with a dilute solution of trichloroacetic acid. Both methods have been shown to agree in the amount of glycogen obtained and no differences have been shown between the materials prepared by these two methods.[1] The properties of the glycogen samples that were compared were rotatory power, ash content, iodine color and reducing power. It seemed possible that the ultracentrifuge might be used to show differences in particle size that would not affect the properties previously studied.

In previous attempts to measure the particle size, osmotic pressure determinations[2] on glycogen or its derivatives have indicated high molecular weights (500,000 to 3,500,000). Early attempts to deduce the molecular size from substitution and end-group reactions were interpreted as indicating a much smaller molecule. In recent years these data have also been shown to be consistent with macro-molecules.[3] The only previous account of ultracentrifuge measurements with glycogen that the author has found in the literature is a statement by Mystkowski[4] that in preliminary experiments sedimentation of glycogen occurred at speeds of 17,000 to 25,000 r. p. m. and that it was very polydisperse.

Preparation

The glycogen used in this research was prepared from rabbit livers.[5] Two methods of preparation were used. Method A used 3% trichloroacetic acid to extract the glycogen from the liver and was essentially the same as that described by Sahyun and Alsberg.[6] In method B small pieces of liver were digested in concentrated solutions of potassium hydroxide on a steam-bath.[7] In both cases the glycogen was purified by dissolving in water and reprecipitating with ethyl alcohol three or four times.

The glycogen was kept in two forms. Some of the material was dried to constant weight in a vacuum desiccator over calcium chloride at room temperature. In other cases water solutions were dialyzed against distilled water to remove traces of salts or alcohol. The concentration of these stock solutions was determined by evaporation to dryness, assuming all non-volatile material to be glycogen. The following paragraphs describe the treatments applied to the individual samples of glycogen used in this investigation.

Glycogen II.—Five rabbit livers were treated by method A. About half of the material from the last precipitation was dried. This gave 2.4 g. of glycogen, designated as IIADd. The remainder was dissolved and dialyzed. This made a 7.14% stock solution, IIADl.

Glycogen IIIA.—Four rabbit livers were treated by method A. About half of this glycogen was dried from the last precipitation, giving 1.2 g. of IIIADd. The remainder, IIIADl, was used for the dialyzed stock solution of concentration 2.07%.

Glycogen IIIB.—Three livers obtained at the same time as those used in IIIA were worked up by method B, using 50% potassium hydroxide as solvent. The yield from this preparation was very small. All of the material obtained was dissolved to form a stock solution, IIIBDl, of 0.4% concentration.

Glycogen VA.—A single liver was frozen in dry-ice as soon as it was removed from the rabbit. The liver was crushed in the frozen state and divided into two approximately equal portions. One portion was treated by method A. All of the material was dialyzed in this case.

(1) D. J. Bell and F. G. Young, *Biochem. J.*, **28**, 882 (1934).

(2) H. B. Oakley and F. G. Young, *ibid.*, **30**, 868 (1936); S. R. Carter and B. R. Record, *J. Chem. Soc.*, 664 (1939).

(3) W. N. Haworth, *Chem. and Ind.*, **17**, 917 (1939). K. H. Meyer, "Recent Developments in Starch Chemistry," *Advances in Colloid Science*, Interscience Publishers, New York, N. Y., 1942, pp. 143–179.

(4) E. M. Mystkowski, *Biochem. J.*, **31**, 716 (1937).

(5) Grateful acknowledgment is made of the assistance of Drs. W. H. Jaeschke and E. A. Birge, Jr., of the College of Medicine, for assistance in obtaining these livers

(6) M. Sahyun and C. L. Alsberg, *J. Biol. Chem.*, **89**, 33 (1930).

(7) M. Sahyun, *ibid.*, **93**, 227 (1931); N. R. Blatherwick, P. J. Bradshaw, M. E. Ewing, H. W. Larson and S. D. Sawyer, *ibid.*, **111**, 537 (1935).

A 25-cc. sample of the dialyzed solution was evaporated to dryness. This gave 0.3966 g. of a residue which was designated VADd. The bulk of the solution was used as stock solution VADl.

Glycogen VB.—The other half of the liver used in preparation VA was treated by method B, using 30% potassium hydroxide as solvent. After the initial treatments with acid and alkali, respectively, the two samples VA and VB were purified simultaneously. Each sample received identical treatment in the process of purification. Drying 25 cc. of dialyzed solution gave 0.3884 g. of VBDd. The bulk of the solution was used for VBDl. Glycogen VBDd had an orange discoloration while VADd was clear white in appearance.

Experimental Results

Sedimentation Constants.—Sedimentation velocity experiments were performed in both the Svedberg oil turbine "velocity" ultracentrifuge and the Svedberg electrically driven "equilibrium" ultracentrifuge. At a speed of 18,000 r. p. m., which can be obtained with either centrifuge, sedimentation was rapid. In both centrifuges the solution was at a distance from 5 to 7 cm. from the center of rotation. Observation of the redistribution of the components of the solution was made by the Lamm scale displacement method. The sedimentation constant, s, was calculated by the procedure given by Svedberg and Pedersen.[8] Because of the heterogeneity of the material, the graphs of scale displacement, Z, against distance from the center of rotation had quite broad peaks, making it difficult to locate the maxima accurately. As a result, individual calculations of s for successive time intervals during a given experiment fluctuated widely. Average values of s from separate experiments on the same or comparable solutions show agreement with $\pm 5\%$ in most cases. Satisfactory agreement was found between sedimentation constants measured with the two centrifuges. However, the velocity centrifuge was considered to be more reliable. In some of the experiments in the equilibrium ultracentrifuge, very sharp boundaries were observed that were attributed to convection rifts because of their abnormal behavior and because of the failure to observe them in duplicate experiments in the velocity machine. The results obtained with the various samples are summarized below.

Glycogen II.—Ten measurements were carried out on solutions of this preparation. The concentration of glycogen was varied from 0.8 to 2.86%. Nine experiments were performed in the velocity ultracentrifuge, five at 42,000 r. p. m. and four at 18,000 r. p. m. One experiment was performed in the equilibrium ultracentrifuge at 17,500 r. p. m. The first two experiments made on the dialyzed material indicated the presence of two boundaries. Only the slower moving peak was sufficiently well-defined to permit the calculation of a sedimentation constant. All the remaining experiments showed one broad peak. The average values of s_{20} for these ten experiments varied from 60 to 70 S (one Svedberg unit, S, $= 1 \times 10^{-13}$ c. g. s. units). The average for the ten experiments was $s_{20} = 64.8\ S$. One of the measurements with glycogen IIDd was made more than a year after the preparation of the sample. This experiment gave $s_{20} = 60.2\ S$. An attempt to correlate s_{20} with the concentration of glycogen indicated a slight increase of s as the concentration was decreased. This trend was so small in comparison to the fluctuations of the individual values of s_{20}, that no significance was attached to it and no attempt was made to extrapolate s_{20} to infinite dilution. Likewise the solvent was varied from distilled water to 1% sodium chloride without producing any significant change. It was thus concluded that s_{20} was independent of the concentration of glycogen or of salt in the range studied within the accuracy of the observations. Subsequent experiments used 0.1% sodium chloride as solvent.

Glycogen IIIA.—Two experiments with glycogen IIIAdl and two with glycogen IIIADd were carried out at 17,000 r. p. m. in the equilibrium ultracentrifuge. These experiments showed two boundaries that gave s_{20} values in the range 65 to 88 S. A duplicate experiment in the velocity centrifuge at 18,000 r. p. m. indicated a single broad peak with $s = 61\ S$. It was concluded that convection must have occurred in the earlier observations and that this last value is the best that can be obtained under present conditions.

Glycogen IIIB.—Five experiments were performed in the equilibrium ultracentrifuge during the interval from eleven to forty-five days after the livers were obtained. The first two experiments indicated double peaks. The slower peak corresponded to values of $s_{20} = 138$ and 152 S, respectively, and the faster peak gave $s = 296$ and 441. The third experiment, carried out a week later than the first, gave a single broad peak with $s_{20} = 244\ S$. The next two experiments,

(8) T. Svedberg and K. O. Pedersen, "The Ultracentrifuge," Oxford University Press, New York, N. Y., 1940.

performed at approximately two week intervals, gave single broad peaks, with $s_{20} = 120$ and 92 S. A check experiment in the velocity ultracentrifuge with this last sample gave the same type of peak with $s = 105$ S. This behavior suggests a change had taken place in the material on standing, with the final state being a single maximum distribution with the maximum corresponding to $s_{20} = 100$ S.

Glycogen VA.—Two solutions of glycogen VADl gave values of $s_{20} = 85$ and 81 S. There was a suggestion of a second peak of lighter material (s_{20} of the order of magnitude of 10 S) (see Figs. VI and VII). Two experiments were also made with solutions of glycogen VADd. One of these gave $s_{20} = 79$ S. The other was inconclusive as the first two exposures showed a single maximum peak but in later pictures this had broken up into a series of four peaks that bore no resemblance to any of the other three experiments. The average of the three experiments is $s_{20} = 82$ S.

Glycogen VB.—Two solutions of glycogen VBDl and one of glycogen VBDd gave values of $s_{20} = 67$, 75, and 77 S, respectively. The average is $s_{20} = 73$ S. All experiments with glycogen VA and VB were made in the velocity ultracentrifuge.

Diffusion Constants.—Five diffusion experiments were performed in a glass Lamm diffusion cell. Observations of the blurring of the boundary were made by the scale line displacement method. The diffusion constant was calculated by means of the expression

$$D = \sigma^2/2t$$

where t is the time and σ is the standard deviation of the curve obtained by plotting the scale displacement, Z, against position in the cell. A method of second moments was used for evaluating σ. Values of D_{20} calculated from individual exposures during these five experiments are shown graphically in Fig. 1. The abscissas are times after the formation of the boundary. The observed values of D are seen to fall into two groups. The results for glycogen IIIB are distinctly lower than the other values which are fairly consistent among themselves. The three values for glycogen IIIB have an average $D_{20} = 0.69 \times 10^{-7}$. The average of all the remaining values is $D_{20} = 1.42 \times 10^{-7}$. Figure 1 shows that there is a definite trend toward lower values as time increases. It is often observed that diffusion constants decrease from an initial value to a limiting value that is considered to be the true value.

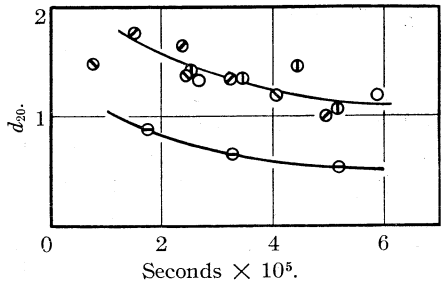


Fig. 1.—Variation of diffusion constant with time after formation of boundary: ○, glycogen IIDd; ⊘, glycogen IIIADl; ⊖, glycogen IIIBDl; ⊗, glycogen IIDd; ⊙, glycogen VADd.

While no limiting value is clearly indicated by the values in Fig. 1, they can be interpreted as approaching a value of $D_{20} = 1.1 \times 10^{-7}$ for the main group and $D_{20} = 0.5 \times 10^{-7}$ for glycogen IIIB. If the individual values are plotted against the reciprocal of the time and extrapolated by a straight line to infinite time, lower values of $D_{20} =$ 0.8 and 0.35×10^{-7}, respectively, are obtained. This extrapolation may overcorrect the value since the diffusion constants should eventually become constant, instead of continuing to decrease. It is thought that the values obtained from Fig. 1 represent the best interpretation of the data.

The experimental line displacement–distance curves were compared to a normal distribution curve by a transformation of coördinates. In Figs. 2 and 3 the points represent experimental data obtained with glycogens IIIB and VA, respectively, and the solid line is the ideal distribution curve plotted on the same scale. The other three experiments gave results similar to those which form Fig. 2, *i. e.*, good agreement with the ideal curve. For a curve of ideal shape the value of D calculated from the area and maximum height

$$D = A^2/tH^2_{\max.}$$

should be the same as that calculated by the first method. Good agreement was found between the values of D calculated by the two methods in all cases except for glycogen VA. In this case the height–area method gave consistently lower values.

Partial Specific Volume.—Densities of a series of water solutions of glycogen IIDd were determined pycnometrically at 25°. The most concentrated solution contained 1% glycogen. The apparent partial specific volume calculated from the density was 0.65.

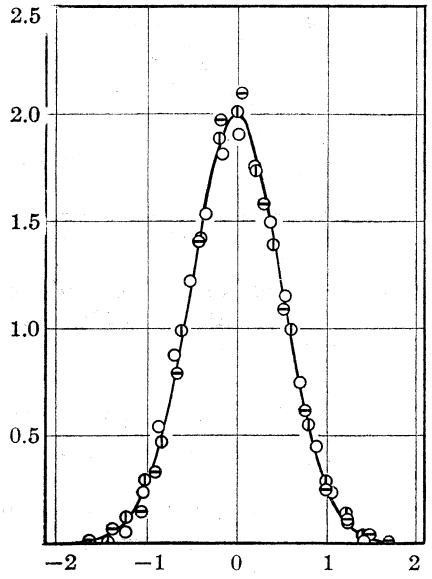


Fig. 2.—Comparison of normal distribution curve with scale line displacements obtained from diffusion experiment on glycogen IIIBD1. Solid line is theoretical curve. Points are calculated from experimental data at various times after the formation of the boundary: ⊖, 174,000 sec.; ⊙, 329,000 sec.; O, 521,000 sec.; arbitrary units.

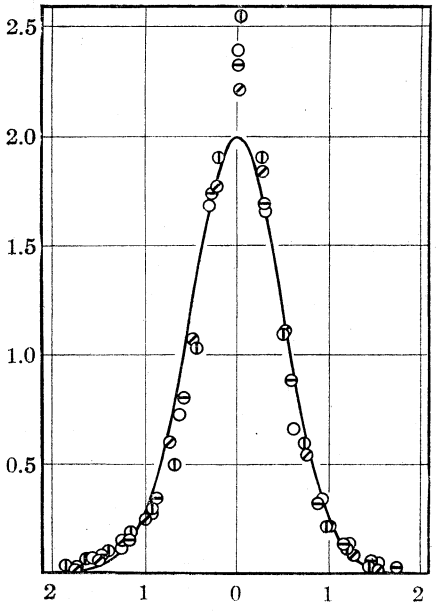


Fig. 3.—Comparison of normal distribution curve with the scale line displacements obtained from diffusion experiment on glycogen VADd. Solid line is theoretical curve. Points are calculated from experimental data at various times after the formation of the boundary: O, 254,000 sec.; ⊖, 347,000 sec.; ⊙, 432,000 sec.; ⊘, 518,000 sec.; arbitrary units.

Refractive Index.—Refractive indices of the solutions used in the density determinations were measured with a dipping refractometer. The value of the refractive index increment,[8] α, was found to be 1.38×10^{-3} for the sodium D line at 25°.

Discussion of Results

Sedimentation.—Sedimentation experiments with glycogen II performed at different centrifuge speeds appeared to give peaks of the same width when the boundary had moved a given distance from the meniscus. This suggested that the blurring of the boundary was due to inhomogeneity of the material and that diffusion was negligible during the time of the experiment. In such a case the shape of the sedimentation curve can be used to obtain the particle size distribution in the sample.

Mathematical functions relating the Z *vs.* x curves obtained at different times during the same experiment have been derived on the assumption of no diffusion taking place during the experiment.[8,9] If the experimental curves can be superimposed when transformed to the same basis by these relationships, that is proof that diffusion has been negligible.

These transformations were applied to the data from two of the experiments. The results are shown graphically in Figs. 4 and 6. In the

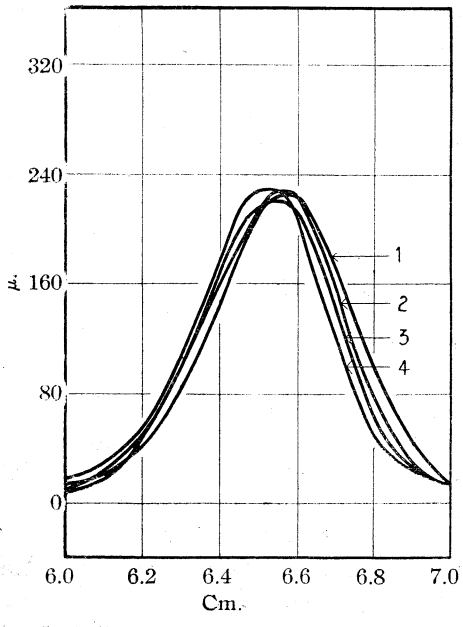


Fig. 4.—Scale line displacement *vs.* distance from center of rotation for a sedimentation experiment on glycogen IIDd. Curves corresponding to different times after the start of sedimentation have all been transformed to the same time (60 min.) assuming diffusion to be negligible: 1, 30 min.; 2, 40 min.; 3, 50 min.; 4, 60 min.

(9) R. Signer and H. Gross, *Helv. Chim. Acta*, **17**, 726–735 (1934).

case of Fig. 4 (a 1% solution of glycogen IIDd at 18,000 r. p. m.) the agreement is very satisfactory. The maximum heights of the four curves agree very well. The horizontal shifting of the curves may be due to error in the determination of the position of the meniscus or the starting time of the experiment. Both of these quantities are important in the calculations. The beginning of sedimentation was taken as the time when the ultracentrifuge had reached operating speed. Actually some sedimentation has probably occurred during the period when the machine is coming up to speed (about seven minutes in this case). The agreement of these curves is taken as proof of the absence of diffusion during this experiment. In Fig. 5 is given a distribution curve indicating the relative concentrations of components as a function of the sedimentation constant. This distribution curve has been constructed from the last curve of Fig. 4 by using the expressions

$$s = \ln \frac{x}{x_0} \Big/ t\omega^2$$

and

$$\frac{dc}{ds} = \left(\frac{x}{x_0}\right)^2 xt\omega^2 \frac{dc}{dx}$$

The scale displacement, Z, is used to evaluate dc/dx.[8]

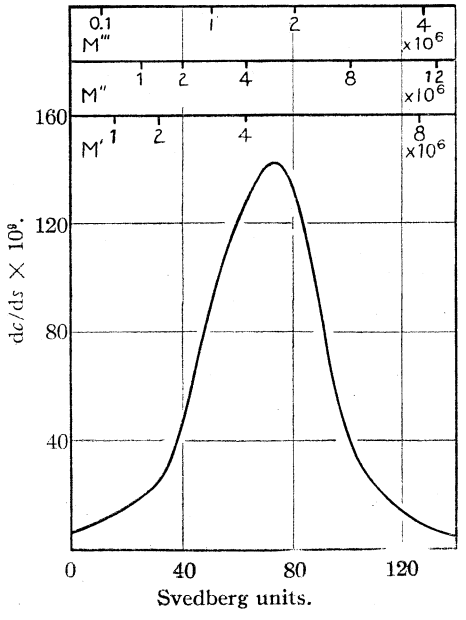


Fig. 5.—Distribution curve calculated from curve 4 of Fig. 4 showing variation of concentration as a function of the sedimentation constant.

Figure 6 shows the results of attempting to superimpose the data from an experiment with

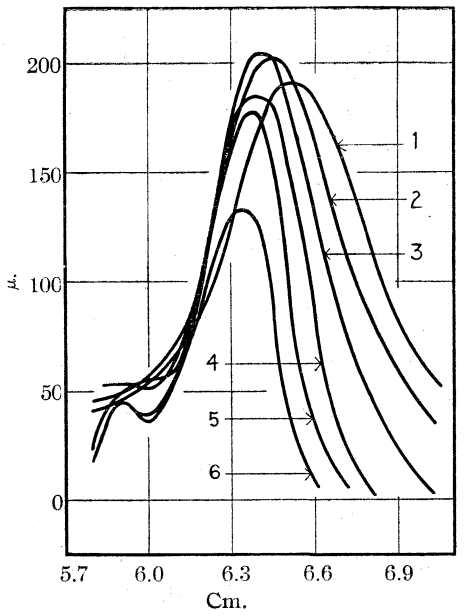


Fig. 6.—Scale line displacement *vs.* distance from center of rotation for a sedimentation experiment on glycogen VADd. Curves corresponding to different times after the start of sedimentation have all been transformed to the same time (53 min.) assuming diffusion to be negligible: 1, 13 min.; 2, 23 min.; 3, 38 min.; 4, 53 min.; 5, 68 min.; 6, 83 min.

glycogen VBDl. With the exception of the first and last curves, the agreement is quite satisfactory on the left side of the peak. Toward the bottom of the cell there is a marked decrease with increasing time. This may be accounted for in several ways. These curves were obtained during the period from thirteen to eighty-three minutes after the centrifuge had reached operating speed. The curves of Fig. 4 cover the interval from thirty to sixty minutes. Thus any error in the position of the meniscus or the initial time will be much more apparent in Fig. 6 than in Fig. 4. Furthermore, the calculations show that positions corresponding to size classes in the leading edge of the peak in the early pictures will fall beyond the bottom of the cell in the last exposures (*i. e.*, the time is sufficient for some of the material to have sedimented to the bottom of the cell). This fact makes questionable the usual practice of using the z values at the bottom of the cell to determine the base line. In the later exposures of this experiment no portion of the cell could be expected to have the original unchanged concentration present. The curves given in Fig. 6 were obtained by drawing in a base line in the conventional manner. Another cal-

culation in which the displacements measured in the comparator were used directly without any base line correction gave somewhat more erratic results but did not show any essential differences from Fig. 6.

In spite of the failure of the curves to superimpose exactly there is considerable indication that diffusion is not the cause of the discrepancy. The maximum heights of the curves (omitting the last two) agree within 10%. The heights of the original experimental curves, *i. e.*, before the transformation was made, varied tenfold. The original curves of Z against x without any base line correction are shown in Fig. 7. The first two curves have been corrected for differences in the optical arrangement so as to be comparable with the rest. The broken lines in Fig. 7 are the theoretical functions for the variation of the height of the peak with position in the cell. The upper one is for the case of a homogeneous material, the blurring being entirely due to diffusion. The lower one represents the case of no diffusion. The observed heights of the curves agree very well with the prediction for no diffusion. If blurring is due to diffusion, the application of the transformation

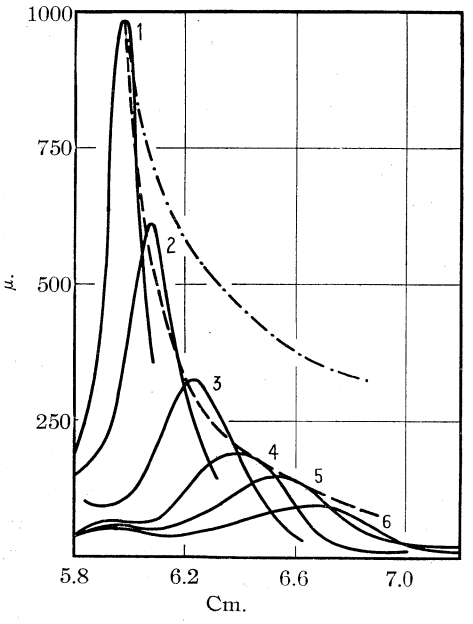


Fig. 7.—Scale line displacement *vs.* distance from center of rotation for a sedimentation experiment on glycogen VADd. Solid lines are observations of the boundary at various times: 1, 13 min.; 2, 23 min.; 3, 38 min.; 4, 53 min.; 5, 68 min.; 6, 83 min. Broken lines are the theoretical functions for the decrease in maximum height of the curves based on different assumptions: · — · — · — homogeneous material with diffusion; — — — inhomogeneous material with negligible diffusion.

equations will result in the later curves being higher than the curves obtained from exposures at an earlier time.[9] Actually the trend of Fig. 6 is in the opposite direction. In spite of the evidence pointing to the absence of diffusion in this experiment, the failure of the individual curves to superimpose completely makes it undesirable to calculate a size distribution curve from any one of them.

The later curves in both Figs. 6 and 7 show a small but definite peak of lighter material that was not resolved in the earlier exposures.

Analysis of the transformation equations shows that the scale line displacements corresponding to the more rapidly moving components decrease more rapidly than those for the components which move more slowly. This means that as sedimentation proceeds the maximum of the Z curve shifts toward the lighter components. Thus a sedimentation constant calculated from the maxima of successive Z curves might be expected to decrease as the length of the experiment increases and it would not represent the specific sedimentation constant for a particular component. The extent of this effect would depend upon the shape of the distribution curve, being greatest for a curve with a very broad maximum. A calculation applied to the data for the thirty-minute and sixty-minute curves in Fig. 4 showed that in this case the apparent sedimentation constant calculated from the maximum points would differ by less than 2% from the actual sedimentation constant of the component in the maximum at one time. In view of the experimental error in determining the position of the maximum this effect is not considered for correction. This effect does not explain the shifting of the maxima in Figs. 4 and 6 since the transformations should correct the apparent shift of the maximum caused by the more rapid separation out of the heavier components.

By combining values of the sedimentation constant, diffusion constant and partial specific volume, molecular weight and shape factor data for glycogens can be obtained.[8] In Table I are summarized average values of s_{20} and D_{20} for each of the samples of glycogen which were studied, together with the values of molecular weight and shape factor calculated from them. Aside from glycogen IIIB the variations between the samples are not considered significant. In preparation IIIB a glycogen of definitely greater particle size was ob-

tained. This may be connected with the small yield of glycogen obtained in this preparation. It seems likely that an unintentional fractionation may have occurred in the extraction or purification of this sample. It is of interest in showing that glycogen exists or can be prepared in samples of varying size.

TABLE I

MOLECULAR KINETIC DATA FOR GLYCOGENS

Glycogen	S_{20} (S units)	$D_{20} \times 10^{7}$	f/f_0	$M \times 10^{-6}$
II	65	1.1	1.90	4.1
IIIA	61	1.1	1.94	3.9
IIIB	100	0.5	2.78	13.9
VA	82	1.1	1.76	5.2
VB	73	1.1	1.83	4.6

Some experiments, particularly those with glycogen IIIB, suggested that when first prepared larger sized particles were present. On standing in water solution, the distribution changed to a function with a single maximum at a lower molecular weight. The evidence for this is, however, not conclusive. This possibility is of interest in the light of K. Meyer's conclusion that starch undergoes a continual aggregation in water solution.[10]

Samples of glycogen VA and VB, which should provide the most critical test for any differences in the products obtained by the acid method or basic method, do not show significant differences.

A shape factor of 1.9 corresponds to an ellipsoid of revolution having an axis ratio of 1 to 18 for a prolate ellipsoid or a ratio of 1 to 25 for an oblate ellipsoid. This dissymmetry is much greater than other investigations of glycogen have indicated. A larger value of the diffusion constant would lower the shape factor.

In order to translate the sedimentation constants used as abscissa in Fig. 5 into molecular weight, it is necessary to make assumptions regarding the particle shape. At the top of Fig. 5 are three molecular weight scales based on different assumptions. M' is calculated on the assumption that the diffusion constant, 1.1×10^{-7}, is the same for all components. M'' is based on the assumption that the shape factor 1.9 is constant for all species. M''' is the value for spherical particles. Probably no one of these scales represents the actual relationship exactly, but together they give an indication of the range of sizes possible.

(10) K. H. Meyer (see ref. 3), p. 146–165.

An interpretation of diffusion measurements on polydisperse material has been made by Gralén.[11] His investigation shows that for a polydisperse system the value of the diffusion constant calculated will be greater, the higher the moments used in its calculation. This difference in diffusion constant, calculated by the different moments, can be used as a measure of polydispersity but requires very accurate data. The results with glycogen lead to the conclusion that comparison of the observed scale line displacement curve with the Gaussian error curve is not a sensitive test of homogeneity. The one diffusion experiment which did not show good agreement with the normal distribution curve was with sample VA where the ultracentrifuge also had indicated some lighter material grouped about a second maximum (see Figs. 6 and 7).

Apparently, polydispersity of the degree observed here is not sufficient to cause marked deviation from the ideal case as long as the particle size distribution can be described by a simple curve with a single maximum.

There is no proof that the principal component in sedimentation would be the principal factor in determining the diffusion constant. The molecular weight calculated from sedimentation and diffusion may be questioned on this basis that the two average values do not necessarily apply to the same component. A process of fractionation followed by sedimentation and diffusion studies with the more homogeneous fractions should be very helpful in interpreting data of this type.

Acknowledgment.—The author wishes to express his appreciation to Professor J. W. Williams for his coöperation and advice in the preparation of this report.

Summary

Glycogen solutions prepared by either the acidic or basic method give an inhomogeneous product. The bulk of the material prepared by the methods used lies in the range of sedimentation constant from 20 to 120 S with the maximum component having a value of $s_{20} = 70$ S. This maximum corresponds to a molecular weight of 2,000,000 if the particle is spherical or a molecular weight of 4,000,000 if the measured diffusion constant can be used to evaluate the frictional resistance to sedimentation. It has not been proven that the glycogen in the tissue is of this same par-

(11) N. Gralén, *Kolloid. Z.*, **95**, 188 (1941).

ticle size or that this particle represents the chemical molecule rather than an aggregate. This investigation indicates the possibility of further work on the natural state of glycogen, methods of its preparation and the interpretation of experimental results on inhomogeneous systems in general.

MADISON, WISCONSIN RECEIVED JUNE 29, 1942

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

The Structure of Copolymers of Vinyl Chloride and Vinyl Acetate[1]

BY C. S. MARVEL, GIFFIN D. JONES, T. W. MASTIN AND G. L. SCHERTZ

It is widely recognized that the simultaneous polymerization of two monomers in a mixture leads to products that are quite different from the mixtures obtained by polymerizing the two monomers separately and then combining the polymers. The copolymerization of the monomers thus must lead to mixed units of two monomers in a single polymer chain.

Considerable experimental evidence supporting this generally accepted fact can be cited. Hill, Lewis and Simonsen[2] have made copolymers of butadiene and methyl methacrylate and then ozonized them. The ozonolysis products were such as to show that in general the methyl methacrylate units were sandwiched between butadiene units and that the latter were usually attached by the 1 and 4 carbon atoms in the chain. There was also evidence of direct union between butadiene units and between methyl methacrylate units in the polymer chain. Thus in this particular case almost every possible type of union between the monomers seems to have occurred when the mixture of monomers was polymerized.

Staudinger,[3] Norrish,[4] and others[5] have shown by their studies of copolymers of styrene and *p*-divinylbenzene that cross-linking of chains occurs due to the participation of the divinylbenzene in the reaction. Hence real copolymers must form.

Staudinger and Schneiders[6] have shown that a copolymer of vinyl chloride and vinyl acetate can be separated into products containing varying amounts of chlorine by means of fractional precipitation. This suggests considerable non-homogeneity of product.

Previous work in this Laboratory has shown that vinyl chloride when polymerized alone gives a 1,3 product[7] and likewise when vinyl acetate alone polymerizes,[8] a 1,3 product results. The present work on the copolymers of these two compounds was undertaken to see whether the two monomers entered the copolymer chains in the same arrangement. The first samples examined were some high-chlorine experimental "Vinylites" prepared in the research laboratories of Carbide and Carbon Chemicals Corporation and furnished to us with that Company's permission by Dr. G. H. Young at Mellon Institute. An attempt was made to study the distribution of chlorine in the polymer chain by statistical methods using the dehalogenation of the polymer by zinc.[7] The results of these experiments seemed to be what was expected for a chance distribution in the polymer chains of vinyl chloride and vinyl acetate units.[9]

Next an attempt was made to apply the same procedure to some low-chlorine vinyl chloride–vinyl acetate copolymers made in our own Laboratory. In early results we found the chlorine was removed in far greater quantities than should have been the case if the vinyl chloride units were distributed in the polymer chains according to chance alone. The dehalogenation experiments did not prove to be too satisfactory and were, in fact, not readily reproducible but they did prove that the chlorine atoms were closer together than chance alone would explain.

At this stage of our work, Wall[10] pointed out that two monomers may have quite different tendencies to enter the growing chain of the copolymer. If the two monomers do enter the chain at different rates the polymer found will not have a uniform composition. Wall's equation[10] can be used to express this relation. When α is 1, the

(1) This paper was first presented at the Gibson Island Conference on Polymers in July, 1941, and it is the fourteenth communication on the structure of vinyl polymers. For the thirteenth see THIS JOURNAL, **64**, 1675 (1942).

(2) Hill, Lewis and Simonsen, *Trans. Faraday Soc.*, **35**, 1073 (1939).

(3) Staudinger, *ibid.*, **32**, 323 (1936).

(4) Norrish and Brookman, *Proc. Roy. Soc.* (London), **163A**, 205 (1937).

(5) Blaikie and Crozier, *Ind. Eng. Chem.*, **28**, 1155 (1936).

(6) Staudinger and Schneiders, *Ann.*, **541**, 151 (1939).

(7) Marvel, Sample and Roy, THIS JOURNAL, **61**, 3241 (1939).

(8) Marvel and Denoon, *ibid.*, **60**, 1045 (1938).

(9) Wall, *ibid.*, **62**, 803 (1940); *ibid.*, **63**, 821 (1941).

(10) Wall, *ibid.*, **63**, 1862 (1941).

$$\frac{dn_x}{dn_y} = \alpha \frac{n_x}{n_y}$$

two monomers enter the chain at the same rate and the polymer formed at any instant will be of the same composition as the mixture of monomers from which it is produced.

Since our low chlorine copolymer of vinyl chloride and vinyl acetate lost more chlorine than was expected when treated with zinc, it was thought that the α value for this pair of monomers was probably not unity for the experimental conditions used in preparing the samples studied. To test this we ran some interrupted polymerizations to see how the chlorine content of the growing copolymers change. A wide variety of mixtures of vinyl chloride and vinyl acetate were prepared. These mixtures were polymerized under different conditions and for different lengths of time. The complete details are recorded in the experimental part but one example here shows the general trend. A mixture of vinyl chloride and vinyl acetate containing 12.48% of chlorine was divided into four sealed tubes. A little benzoyl peroxide was added and the tubes were allowed to stand for various times. The tubes were opened and the polymers isolated. The molecular weights of the polymers formed at different stages were not markedly different as indicated by viscosity measurements. The tube opened first gave a 49% yield of a copolymer containing 17.65% of chlorine; the second tube gave a yield of 65% containing 15.08% of chlorine; the third tube gave a yield of 78% containing 13.90% of chlorine and the last tube gave a 95% yield of polymer containing 12.48% of chlorine. It is thus obvious that vinyl chloride enters the polymer chain much more rapidly than does vinyl acetate when these two monomers are copolymerized from a mixture. It is also obvious that each polymer chain laid down from this mixture is probably different from every other one, for as the composition of the monomer changes, the ratio of units which enter the polymer will change.

From the examination of a wide variety of copolymerization mixtures of vinyl chloride and vinyl acetate the value of α in Wall's equation at 40° seems to be between 1.5 and 2 and the ratio seems to approach 1 as the temperature of the polymerization is increased.

Once these facts were established, it was clear that the suggestion contained in certain patents[11] that copolymers of improved uniformity could be obtained by the addition of portions of one constituent during the polymerization was based on information of the same sort which we have rediscovered.

Likewise, it has been shown in other cases that the composition of a copolymer is not necessarily related to the composition of the monomer mixture from which it is produced. Thus, in a thorough study of copolymers of vinylidene chloride, it has been found that in general, vinylidene chloride enters the growing polymer chain faster than do vinyl esters,[12] various esters of allyl alcohol derivatives[13] and vinyl ethers.[14] In the case of the copolymers of vinylidene chloride and the acrylate esters, temperature appears to be an important factor since at 45° vinylidene chloride enters the chain faster than ethyl acrylate, whereas at 30° methyl methacrylate and methyl acrylate enter the growing chains more rapidly than does vinylidene chloride.[15] In the case of copolymers of styrene and vinylidene chloride, a copolymer containing 60% by weight of styrene has been obtained from a monomer mixture containing about 30% by weight of styrene.[15]

Further experiments on the removal of chlorine from copolymers of vinyl chloride and vinyl acetate have yielded results which are not as readily reproducible as would be desired. Yet they are of interest when compared with the statistical calculations made by Wall.[9,10]

In Fig. 1 we have reproduced certain curves which Wall has published[9,10] and have superimposed on them certain points which were arrived at by averaging the results of many dehalogenation experiments on different copolymers. While the degree of accuracy of the dehalogenation is not all that one may desire yet the apparent trend is for these points to follow the curves based on a "head to tail" arrangement of the monomer unit in the chain.

The dehalogenated product did not decolorize a dilute solution of potassium permanganate in acetone but did decolorize a solution of bromine in carbon tetrachloride. These reactions indicate that dehalogenation may have produced cyclopropane units in the chain and do not indicate an

(11) Johnson, British Patent 467,084 (*C. A.*, **31**, 8077 (1937)).

(12) Wiley, U. S. Patent 2,160,931 (*C. A.*, **33**, 7443 (1939)).

(13) Britton, Davis and Taylor, U. S. Patents 2,160,940, 2,160,941, 2,160,942 (*C. A.*, **33**, 7441 (1939)); Britton and Taylor, U. S. Patent 2,160,946 (*C. A.*, **33**, 7442 (1939)).

(14) Britton and Davis, U. S. Patent 2,160,943 (*C. A.*, **33**, 7442 (1939)).

(15) Wiley, U. S. Patent 2,160,932 (*C. A.*, **33**, 7443 (1939)).

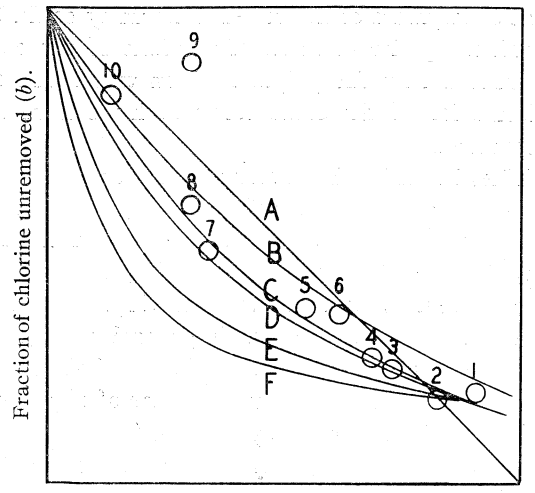


Fig. 1.—A, $f = l - x$ "head to head" arrangement of monomer units; B, $f = e^{-x}(1-(x/2))$ random arrangement of monomer units; C, $f = e^{-2x}$ "head to tail" arrangement of monomer units, $\alpha = 1$; D, $f = \left(\frac{R+2}{2}\right)^2 e^{-4/(2\ R)} - \left(\frac{R}{2}\right)^2$, where R is the ratio of vinyl acetate to vinyl chloride in the completed polymer and $\alpha = 2$; E, f as function of x for $\alpha = 5$; F, f as a function of x for $\alpha = 10$.

olefin structure. Further evidence of the absence of 1,2-chlorine atoms was the fact that no iodine was produced when a sample of "Vinylite" was refluxed in acetone with potassium iodide.

Careful hydrolysis of a copolymer of vinyl acetate and vinyl chloride by treating the ester with water, ethyl alcohol and hydrochloric acid in dioxane solution has given the chlorohydrin.[16] This product is not oxidized by periodic acid. The best available evidence thus indicates that the vinyl chloride and the vinyl acetate enter the copolymer chain to give "head and tail" units just as they do when polymerizing alone. The fact that the chlorohydrin is actually obtained is further proof that a real copolymer is in hand and that the reaction does not merely produce mixtures of individual polymers.

The relative homogeneity of some of these copolymers has been further tested by solubility methods. 1-Heptyne will dissolve polyvinyl acetate[17] but does not dissolve "Vinylite." Phenylacetylene will dissolve low-chlorine "Vinylites" but will not dissolve high-chlorine "Vinylites" or polyvinyl chloride. Mixtures of polyvinyl acetate, polyvinyl chloride and the copolymer were separated into different fractions but due to the non-homogeneity of the copolymer the separation was not 100%. These solubility experiments showed that none of the copolymers tested in this work was strictly homogeneous.

It should be pointed out that most of the molecular weights reported in this manuscript were determined by viscosity methods and are, therefore, only of relative value. Since the results of Staudinger and Schneiders[6] do not permit an unequivocal choice of a K_m for "Vinylite" in dioxane solution and since viscosity molecular weights are of comparative significance only, an approximate K_m value was used in this work. This value was obtained by determining the viscosity of a single polymer in dioxane and in methyl *n*-propyl ketone. Douglas and Stoops[18] have determined that K_m has the value 3.2×10^{-4} for "Vinylites" in ketone solvents. Our comparisons indicated a value 4.1×10^{-4} would be an approximate K_m in dioxane.

Experimental

Molecular Weight Determination.—All molecular weights were obtained by making viscosity measurements on solutions containing 0.1 g. of polymer in 50 cc. of pure dioxane at 20° in an Ostwald viscometer, and then calculating the molecular weight by the Staudinger equation using the K_m value 4.1×10^{-4}. This value was ascertained by determining the relative viscosities of a given polymer in dioxane and in methyl propyl ketone. Only this one experiment is recorded in detail.

An experimental "Vinylite" containing 37.7% chlorine was used. The following results were obtained at 20° using a 5-cc. Ostwald viscometer.

Liquid	Time in seconds
Pure dioxane	122.2 122.6 122.5
0.10 g. of polymer in 10 cc. of dioxane	132.2 133.2 132.5 132.2
0.10 g. of polymer in 10 cc. of dioxane	131.2 132.3 132.8 132.8
Pure methyl *n*-propyl ketone	65.5 65.5 65.1 65.1 65.3
0.10 g. of polymer in 10 cc. of methyl *n*-propyl ketone	69.5 69.5
0.10 g. of polymer in 10 cc. of methyl *n*-propyl ketone	69.5 69.6

$\eta_{rel.}$ in dioxane 1.0817; $\eta_{rel.}$ in methyl *n*-propyl ketone 1.064

$$\frac{\eta_{rel.} - 1}{K_m C} = M = \frac{\eta_{rel.} - 1}{K_m C}$$

(dioxane) (methyl *n*-propyl ketone)

$$\frac{0.0817}{K_m(\text{dioxane})} = \frac{0.064}{3.2 \times 10}$$

$$K_m \text{ (dioxane)} = 4.08 \times 10^{-4}.$$

This figure was rounded off to 4.1×10^{-4} for further use.

(16) The hydrolysis of such a copolymer by means of sulfuric acid, alcohol or benzene has been reported in French Patent 724,910 (1931).

(17) Marvel, Harkema and Copley, THIS JOURNAL, **63**, 1609 (1941).

(18) Douglas and Stoops, *Ind. Eng. Chem.*, **28**, 1152 (1936).

TABLE I

PREPARATION AND PROPERTIES OF LOW-CHLORINE COPOLYMERS OF VINYL CHLORIDE AND VINYL ACETATE

Reagents used, g.			Time of experiment in hr.	Yield of product, g.	Chlorine,[20] %	Mol. wt. (viscosity)
Vinyl chloride	Vinyl acetate	Benzoyl peroxide				
0.86	3.06	0.03	63	3.72	12.48	14,000
2.53	2.24	none	100	3.82	30.2	8,100
3.45	4.79	0.03	100	7.29	23.9	14,000
1.27	3.85	none	70	4.17	13.7	21,000
1.10	2.97	0.03	40	3.20	15.4	12,000

Higher Chlorine Copolymers.—Four experimental "Vinylites"[19] containing 87, 77, 65 and 60% vinyl chloride, respectively, were used in the early part of this work. These polymers were white powders which softened at about 110° and were reported to have molecular weights in the range of 28,000. Chlorine analyses in our Laboratory confirmed the compositions reported. In the interrupted polymerizations reported later in this manuscript a few other high-chlorine "Vinylites" were obtained.

Low-Chlorine Copolymers.—Copolymers containing less than 50 mole per cent. of vinyl chloride (42% vinyl chloride or 23.9% chlorine) were prepared by adding freshly distilled vinyl acetate to liquefied vinyl chloride and adding a small amount of benzoyl peroxide ("Lucidol"). The mixture was cooled in dry-ice and sealed in a glass tube. The mixture was allowed to come to room temperature and in most cases irradiated with ultraviolet light at about 40°. The tubes were usually exposed at this temperature for about thirty hours or until they contained a milky opaque solid. Longer exposure to ultraviolet light gave deeply colored products.

After polymerization had apparently stopped, the tubes were opened and the contents dissolved in dioxane to give a solution containing from 0.5 to 2% of polymer. The lower concentrations were used for the lower chlorine polymers. This solution was then aspirated in a fine spray on the surface of vigorously stirred running water. The outfit used is shown in the diagram (Fig. 2). The right-hand tube carried water and the left-hand tube compressed air. Only in this way could low-chlorine copolymers be isolated as solids which could be handled. The precipitation of one lot of polymer usually required about eight hours per liter of dioxane solution. The polymer which was collected in the filter cloth was dried by squeezing out most of the water and then heating at 55° (boiling acetone) in a drying pistol over phosphorus pentoxide at about 20 mm. until the weight was constant.

Copolymers having more than 10% chlorine can be isolated easily as fluffy powders by this method. Copolymers with less than 10% chlorine are very hard to get in a powdery form. They adhere together in a tough mass but these tough masses seem to give constant analyses if carefully dried.

Table I shows the results of some of these experiments. All the experiments were carried out at 40°.

Interrupted Polymerizations.—Various mixtures of vinyl chloride and vinyl acetate containing benzoyl peroxide were prepared and divided into tubes. The mixtures were allowed to polymerize for various lengths of time and then the polymer isolated as above and examined. In other cases a solution of vinyl chloride and vinyl acetate of known chlorine content was allowed to polymerize for a certain period and then the polymer isolated to determine the yield and chlorine content. Other experiments were made with solutions and emulsions. In every case where polymerization was stopped before the yield of polymer was essentially quantitative the polymer contained a higher percentage of chlorine than had been present in the original polymerization mixture. The results of these experiments are summarized in Table II.

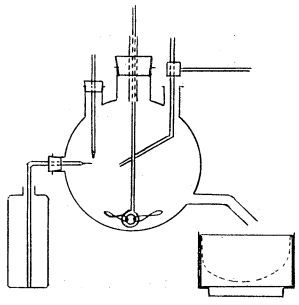


Fig. 2.—Apparatus.

Dehalogenation Experiments on "Vinylites."—In general, the zinc dehalogenation experiments were carried out as described previously[7] except that the solutions were only one-half as concentrated in this work. Usually, 0.2 g. of polymer was dissolved in 50 cc. of dioxane. In some runs large amounts of solute and solvent were used but this ratio was always maintained. That boiling alone did not affect the polymer was shown by refluxing a sample of "Vinylite" having 26.5% chlorine and a molecular weight of 17,000 for five days in dioxane. After isolation of the polymer the molecular weight was found to be 17,000 and the chlorine content 25.9%.

Boiling a "Vinylite" sample (1 g.) having 15.4% chlorine in dioxane (750 cc.) containing 0.148 g. of zinc chloride for five days gave a red-brown solution. On isolation the polymer contained only 9.18% chlorine after this treatment. In a similar experiment the following analyses before and after treatment, respectively, were obtained: C, 48.3; H, 6.23; Cl, 23.9; and C, 52.8; H, 5.8; Cl, 15.0.

These experiments indicate that dehalogenation by zinc may be accompanied by other reactions which account for the erratic results in some experiments recorded in Table III.

No evidence that acetate groups were removed by the zinc treatment was obtained by applying the lanthanum nitrate test[21] or by comparing the analyses of the polymer before and after the treatment.

There is some indication that the dehalogenation does not cause as much degradation and side reaction as does the zinc chloride treatment. For example, in the zinc

(19) These were obtained from Carbide and Carbon Chemical Corp. through the courtesy of Dr. G. H. Young of Mellon Institute. We are grateful to Dr. Young and to the Carbide and Carbon Chemicals Corp. for their aid.

(20) Analyses by Parr bomb fusion, followed by Volhard titration.

(21) Reedy, "Elementary Qualitative Analysis," 3rd ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1941.

TABLE II

RESULTS OF SOME INTERRUPTED POLYMERIZATION EXPERIMENTS

Expt.	Chlorine content mixture, %	Conditions of polymerization	Time, hr.	Yield of polymer, %	Chlorine content of polymer, %	Mol. wt. (viscosity method)	α Wall's equation
7.1	12.48[a]	Peroxide,	24	49	17.65	9,900	2.24
7.2		light, 40°	28	65	15.08	17,000	1.81
7.3			33	78	13.90	12,000	1.83
7.4			63	95	12.48	14,000	
8.1	30.2[a]	Light, 40°	23	3.4	37.4		1.73
8.2			30	26	37.3	7,600	1.83
8.3			14	16	35.3	8,600	1.49
8.4			100	80	30.2	8,100	
11	34.1	Light, 40°	15	5.6	42.4	7,600	2.01
13	47.7	Peroxide, 60°	120	53	49.3	8,600	1.41
14.1	15.4[a]	Light, 40° emulsion	24	16	33.9	7,600	4.80
14.2			23	17	33.4	10,000	4.65
14.3			31	56	13.4	11,000	0.74
14.4			62	79	15.4	12,000	
15.1	26.0[a]	Light, peroxide, 40° soln.	33	51	30.0	3,500	1.56
15.2			34	66	26.9	1,900	1.14
15.3			82	82	26.0	3,800	
17.1	26.1[a]	Light, 18°	71	11	38.5	18,000	2.47
17.2		peroxide 80°	25	..	33.2	4,100	1.62
17.3		40°		90	26.1	14,000	
20.2	10.13[a]	Peroxide 122°	12	26	14.6	5,000	1.77
20.4		135°	6	26	14.4	4,500	1.73
20.5		149°	6	25	12.0	4,400	1.12
20.1		Light 40°	48	90	10.13	46,000	
19	17.9	Peroxide 123°	10.5	25	21.6	3,800	1.37
		5% tetrapropyl tin added					

[a] Inferred from composition of polymer in completely polymerized case.

TABLE III

DEHALOGENATION EXPERIMENTS WITH VARIOUS EXPERIMENTAL "VINYLITE" SAMPLES

Description of polymer used					Calcd. fraction	
% Cl	% vinyl Cl	Mole fraction vinyl Cl	% yield (where not complete polym.)	Fraction chlorine remaining	For 1,3-arrangement, $\alpha = 2$	Random arrangement
49.4	87	0.905		0.198	0.163	0.221
43.7	77	.823		.193	.190	.260
36.9	65	.718		.242	.230	.311
34.1	60	.674		.278	.250	.338
21.0	36.9	.447		.290	.377	.497
13.2	23.25	.302		.409	.502	.628
11.7	20.65	.260		.320	.548	.671
5.85	10.3	.137		.820	.720	.812
15.08	26.5	.332	65	.863	.473	.599
37.4	65.8	.726	3.4	.216	.229	.308
37.3	65.7	.725	26	.205	.229	.308
35.3	62.2	.693	16	.216	.241	.327
30.2	53.2	.611	80	.305	.280	.377
43.2	76.0	.813	53	.160	.194	.263
23.9	42.1	.499	89	.307	.344	.456
42.4	74.7	.802	5.6	.106	.198	.268
13.7	24.1	.304	82	.891	.500	.626
49.3	86.9	.901	53	.138	.163	.223
33.9	59.7	.670	16	.503	.250	.341
33.4	58.8	.663	17	.144	.255	.345
13.4	23.6	.297	56	.589	.508	.632
15.4	27.1	.339	79	.494	.476	.592
30.0	52.8	.607	51	.237	.282	.380
26.9	47.4	.553	66	.362	.312	.416
26.0	45.8	.537	82	.372	.321	.428

TABLE IV

SOLVENT FRACTIONATION OF COPOLYMERS OF VINYL CHLORIDE AND VINYL ACETATE

Copolymer, g.	% Chloride in copolymers	Mol. wt. (viscosity)	Extracted by 1-heptyne, g.	% Chlorine	Extracted by phenyl-acetylene, g.	% Chlorine	Insoluble fraction, g.	% Chlorine
1.984	47.5	4,500	0.195	..	0.627	35.8	1.611	47.9
2.003	36.9	13,000	.286	..	1.947	23.6	0.851	47.4
2.282	49.3	8,600	.088	..	0.394	..	2.059	48.6
2.226	25.0	3,800	.800	14.4	1.576	29.8	trace	
1.741	30.0	3,500	.220	26.4	1.487	30.7	trace	

chloride treatment, the solution becomes red, but the dehalogenation solution does not; also the color of the former solution is destroyed by refluxing an hour with zinc. Furthermore, analyses indicate that loss of chlorine is the major result of the dehalogenation treatment. For example, a polymer which had been 35% dehalogenated (the dehalogenation was incomplete, since the theory would have predicted 65% removal) had the composition before treatment: C, 47.45; H, 5.83; Cl, 27 (ratio, C:H:Cl:O = 1.00:1.46:0.193:0.312) and after treatment: C, 52.9; H, 6.5; Cl, 17.5; (ratio: C:H:Cl:O = 1.00:1.46:0.112:0.328).

In a theoretically complete dehalogenation of a polymer having initially 26.1% chlorine, there was obtained a product that had poorer agreement with the calculated composition. Calcd.: C, 58.7; H, 7.4. Found: C, 58.3; H, 6.31; Cl, 9.5.

The results of a large number of dehalogenation experiments are summarized in Table III. It should be pointed out that it is not entirely correct to obtain from Wall's formulas[9, 10] values for the calculated mole fraction of chlorine remaining in the case of polymers isolated after incomplete polymerization.

There were dozens of other similar experiments performed but these can be taken as illustrative. In some of these experiments polymer precipitated; in others it did not. In a few experiments the reactions were carried on for as long as thirteen days. In general, this made little difference in the results. The reaction does not seem to be sufficiently quantitative to be useful.

The polymer remaining after the zinc treatment of a "Vinylite" having a chlorine content of 43.7% was soluble in dioxane, did not decolorize a cold dilute potassium permanganate solution in acetone, but did decolorize a solution of bromine in carbon tetrachloride.

Solubility Experiments.—A mixture made up of 2.010 g. of polyvinyl acetate, 2.018 g. of polyvinyl chloride and 1.986 g. of a "Vinylite" containing 36.9% chlorine was extracted with 40 cc. of 1-heptyne. After filtering and evaporating the solution 1.589 g. of residue was obtained. This residue was purified by dissolving in dioxane and precipitating the polymer in water. The chlorine content was 1.49%. The residue from the first extraction was then treated with 25 cc. of phenylacetylene. This solution on evaporation gave 1.480 g. of polymer containing 18.7% chlorine. The material insoluble in the two acetylenes weighed 3.154 g. and contained 50.9% chlorine. The weight of the total recovered material is somewhat higher than that used, because the surplus amount of solvent is held by the polymer under the conditions of the experiment. This is lost in the purification of the product, but also a considerable amount of polymer is lost, and that introduces a still greater error into the figures.

This experiment was typical of several which showed that only a small amount of very low chlorine "Vinylite" would be found in the heptyne extract whereas "Vinylite" containing up to 65% vinyl chloride was soluble in phenylacetylene. By using these two solvents on samples of copolymers separation into fractions was obtained. Some of these separations are listed in Table IV.

The last two samples of copolymer reported in Table IV were prepared by the interrupted technique. The last one which was obtained by stopping polymerization at a 51% yield seems to be more homogeneous than the preceding sample which was made by stopping the polymerization after an 83% yield.

Hydrolysis of "Vinylite" to a Polychlorohydrin.—To a solution of 10 g. of "Vinylite" in 1 l. of dioxane was added 25 cc. of concentrated hydrochloric acid and 25 cc. of 95% ethyl alcohol. The mixture was heated to 50° for twelve hours and a deep red color developed. An additional 25 cc. of alcohol was added and the solution was boiled under a reflux condenser for eleven hours. The polymer was then precipitated by spraying the solution into water. A brownish polymer was obtained which was richer in chlorine than was the original. Two different copolymers were hydrolyzed by this procedure. The analytical figures before and after hydrolysis indicate conversion of the acetate groups to hydroxyl groups.

	Sample 1			Sample 2
	% C	% H	% Cl	% Cl
Anal. before hydrolysis	47.45	5.83	26.5	46.6
Anal. after hydrolysis	45.65	6.48	34.0	49.4
Calcd. for polychlorohydrin	44.4	6.42	35.8	51.1

The polychlorohydrin obtained in this manner did not show reduction of periodic acid solution. The chlorine atoms could not be hydrolyzed to hydroxyl by moist silver oxide or by treatment with mercuric acetate. The polychlorohydrin did not liberate iodine from an acetone solution of potassium iodide.

Contrary to the statements in the literature[22] we could not hydrolyze by means of aqueous alkali a copolymer of vinyl chloride and vinyl acetate prepared by exposing a methanol solution of the monomers and uranyl nitrate to sunlight.

Summary

1. Vinyl chloride and vinyl acetate copolymerize to produce polymer chains containing both units. However, the polymer molecules produced in a given case differ widely in composition and the first chains produced are richer in vinyl chlo-

(22) German Patents 362,666, 516,996.

ride than is the monomer mixture from which they are formed. The copolymers made by complete polymerization of a given starting mixture of monomer vary in composition from chain to chain.

2. The monomer units appear to be oriented in a 1,3-fashion in the polymer chain.

3. Some reactions of these copolymers have been described.

URBANA, ILLINOIS RECEIVED MAY 27, 1942

[CONTRIBUTION NO. 34 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Acid Catalyzed Hydrolysis of Phenyl Substituted Aliphatic Esters[1]

BY HILTON A. SMITH AND R. R. MYERS

In a recent publication[2] a study of the effect of the character of an alkyl chain on the reaction velocity of acid hydrolysis was reported for a number of esters of aliphatic acids. It was demonstrated that the effects were similar to those produced in the processes of esterification[3] and of saponification of the same (ethyl) esters.[4]

The purpose of the present paper is to report the results of a study of the velocity of hydrolysis of a number of phenyl substituted aliphatic esters, and to compare these results with those previously reported for saponification of the same esters[5] and for the acid-catalyzed esterification of phenylacetic, hydrocinnamic and γ-phenylbutyric acids in absolute methanol.[6]

Experimental

All of the esters were prepared by esterification of the corresponding organic acid with absolute ethanol using sulfuric acid as a catalyst. The esters were purified by fractionation in efficient distillation columns. Each sample used for rate measurements distilled at a constant head temperature and was also shown by analysis using the method already described[4] to be, within the precision of the method, 100% pure.

Phenylacetic, hydrocinnamic, phenylethylacetic and **diphenylacetic** acids were obtained from Eastman Kodak Co.; γ-phenylbutyric, δ-phenylvaleric, cyclohexylacetic and hydratropic acids were all prepared by methods which have been previously described.[5,6,7]

The hydrolyses were all carried out in 70% acetone solution, the concentration of both ester and catalyst (hydrochloric acid) being 0.1 *M*. The acetone used in making up the medium was carefully purified by fractionation from alkaline permanganate in a five-foot, one-inch diameter column packed with glass helices. The fraction retained distilled at constant head temperature. The method employed in making up the reaction mixtures was the same as that already described by Smith and Steele,[2] and the general experimental procedure was also the same. Corrections were made for the contraction in volume which occurs when acetone is mixed with water and also for thermal expansion of the solvent. The reactions were run in electrically heated water thermostats which gave temperatures constant to ±0.01°.

Experimental Calculations and Results

The rate constants were calculated using the expression for a first order reaction

$$k = \frac{2.303 \log a/(a - x)}{(\text{catalyst})t}$$

where a is the initial ester concentration, x is the concentration of organic acid formed after time t, and the (catalyst) is the concentration of added

TABLE I

ACID CATALYZED HYDROLYSIS OF ETHYL δ-PHENYLVALERATE IN 70% ACETONE AT 30°

a = (ester) = (HCl) = 0.100 *M*

t, minutes	$(a - x)$	10^6k, liters moles^{-1} sec.$^{-1}$
5	0.0999	....
2080	.1246	22.6
2690	.1304	22.6
2980	.1331	22.5
3500	.1379	22.7
4240	.1429	22.0
4360	.1449	22.8
5025	.1497	22.9
5440	.1539	23.8
	Average, 20–50%	22.6

(1) Presented at the Memphis meeting of the American Chemical Society, April 22, 1942.

(2) Smith and Steele, THIS JOURNAL, **63**, 3466 (1941).

(3) Smith, *ibid.*, **62**, 1136 (1940).

(4) Levenson and Smith, *ibid.*, **62**, 1556 (1940).

(5) Levenson and Smith, *ibid.*, **62**, 2324 (1940).

(6) Smith, *ibid.*, **61**, 1176 (1939).

(7) The authors are indebted to Mr. H. S. Levenson and Mr. J. H. Steele for the preparation and analysis of some of the esters used in this research.

hydrochloric acid. Table I gives the results of a typical run.

For each run, the individual rate constants were averaged over the range of about 20–50% reaction. These limits were set in order to avoid any possible effects due to errors in making up the reaction mixture, due to loss of solvent as samples were withdrawn from the reaction flask, or caused by the reverse esterification reaction. The number of values averaged was usually six or seven, and the ±errors were of the order of one per cent. The average rate constant for each run is listed in Table II.

TABLE II

REACTION RATE CONSTANTS FOR ACID HYDROLYSIS OF ETHYL ESTERS OF PHENYL-SUBSTITUTED ACIDS IN 70% ACETONE

a = (ester) = (HCl) = 0.100 M

Ethyl ester	10^6k (liters moles^{-1} sec.$^{-1}$) t = 20°	t = 30°	t = 40°	t = 50°
Phenylacetate	9.35	23.8	55.0	120
	9.32	23.6	54.9	120
			54.9	
Av.	9.34	23.7	54.9	120
Hydrocinnamate	8.03	20.7	47.5	110
	8.07	20.3	47.7	109
Av.	8.05	20.5	47.6	110
γ-Phenylbutyrate	8.08	20.8	48.6	114
	7.99	19.7	48.6	111
	7.95	19.6		
		21.1		
		21.0		
Av.	8.00	20.4	48.6	112
δ-Phenylvalerate	8.56	22.0	53.2	123
	8.65	22.6	53.7	119
		22.6		
Av.	8.61	22.4	53.5	121
Hydratropate	0.169	0.443	1.11	2.46
	.172	.451	1.11	2.55
				2.52
Av.	.171	.447	1.11	2.51
Phenylethylacetate	.0669	.177	0.435	0.99
	.0669	.179	.430	1.07
				1.04
Av.	.0669	.178	.433	1.03
Diphenylacetate	.0296	.0839	.210	0.506
	.0296	.0833	.207	
Av.	.0296	.0836	.209	.506
Cyclohexylacetate	3.01	7.80	19.0	44.7
	2.99		19.0	43.9
				43.9
Av.	3.00	7.80	19.0	44.1

Figure 1 gives a plot of log k against $1/T$ for the hydrolysis of these esters. The activation energies were calculated from the slopes of these lines, and were checked by the method of least squares. These activation energies together with reaction rate constants at 25° are found in Table III. Included in this table are also k_{25} and activation energies for the processes of esterification and saponification. Figures for several unsubstituted esters are given for comparison purposes.

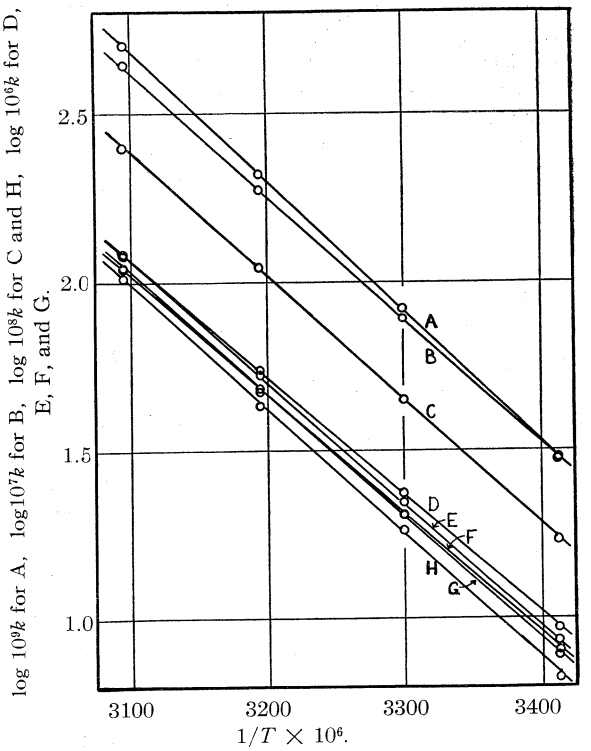


Fig. 1.—Temperature coefficients for acid hydrolysis of phenyl substituted aliphatic esters: A, ethyl diphenylacetate; B, ethyl cyclohexylacetate; C, ethyl hydratropate; D, ethyl phenylacetate; E, ethyl δ-phenylvalerate; F, ethyl hydrocinnamate; G, ethyl γ-phenylbutyrate; H, ethyl phenylethylacetate.

The relative entropies of activation of these acids and esters have been calculated for the processes of esterification, acid hydrolysis and saponification, and are given in Table III. These values were calculated from the equation

$$\Delta S^* - \Delta S_0^* = R \ln A/A_0$$

where $\Delta S^* - \Delta S_0^*$ is the relative entropy of activation and A is the "temperature independent" factor in the Arrhenius equation

$$k = Ae^{-E/RT}$$

The subscript zero refers to ethyl acetate for acid hydrolysis and saponification and to acetic acid for the process of esterification.

TABLE III

REACTION RATE CONSTANTS, ACTIVATION ENERGIES AND RELATIVE ENTROPIES OF ACTIVATION (REFERENCE SUBSTANCE ACETIC ACID OR ETHYL ACETATE) FOR THE PROCESSES OF ACID HYDROLYSIS, ESTERIFICATION AND SAPONIFICATION

Acid or ethyl ester	Acid hydrolysis			Esterification[9]			Saponification[10]		
	10^5k_{25}[8]	E	$\Delta S^* - \Delta S_0^*$	10^2k_{25}	E	$\Delta S^* - \Delta S_0^*$	10^3k_{25}	E	$\Delta S^* - \Delta S_0^*$
Phenylacetate	1.47	16,100	−2.58	2.62	9,900	−1.96	10.1	14,100	−1.26
Phenylacetate[11]	1.54	16,200							
Hydrocinnamate	1.28	16,300	−2.19	2.67	9,600	−2.93	5.04	14,500	−1.30
γ-Phenylbutyrate	1.27	16,500	−1.53	2.67	10,100	−1.25	2.69	14,900	−1.21
δ-Phenylvalerate	1.39	16,600	−1.02				2.28	14,700	−2.21
Hydratropate	0.277	16,900	−3.22				0.802	15,400	−1.93
Phenylethylacetate	.110	17,100	−4.38				.264	15,900	−2.47
Di-phenylacetate	.0503	17,700	−3.92				.560	16,000	−0.63
Cyclohexylacetate	.481	16,900	−2.12				.509	15,600	−2.17
Acetate	4.55	16,200	0	5.93	10,000	0	6.92	14,700	0
Propionate	3.77	16,300	−0.03	5.73	10,000	−0.07	3.55	14,700	−1.33
Butyrate	1.86	16,400	−1.11	2.90	10,000	−1.42	1.83	15,100	−1.30
Valerate	1.82	16,500	−0.81	3.08	10,000	−1.30	1.92	14,700	−2.55

Discussion

As seen from an inspection of Table III, the substitution of a phenyl group on the terminal carbon atom of an alkyl chain causes an increase in the reaction rate for the process of saponification, and this is accompanied by the expected decrease in the activation energy. These changes are apparently caused by the fact that the phenyl group, when not a part of a conjugated system, acts as an electron sink, thus drawing electrons away from the carboxyl group, and so facilitating the approach of the hydroxyl group. The magnitude of this effect decreases as the phenyl group is moved farther from the carboxyl group, as would be expected. When, however, substitution of the phenyl group takes place in the alpha position of an ester such as ethyl propionate or butyrate, the reaction rate is decreased, and the activation energy increased. This is evident from inspection of Table III.

This apparent discrepancy in the influence of the introduction of a phenyl group on the velocity of saponification has been explained as being due to the fact that this group not only acts as an electron sink, but also exhibits a rather large steric effect.[5] The former causes an increase in the rate of reaction and a lowering of E. The latter causes a decrease in the reaction rate, and apparently an increase in the activation energy.

The data for acid hydrolysis as given in Table III offer no direct evidence that the phenyl group acts as an electron sink, since its introduction always decreases the reaction velocity. Other data, however, may lead one to expect the opposite result.[12] In fact, the postulated mechanisms for acid and alkaline hydrolysis involve the same intermediate,[13] although the influence of substituents is smaller for the acid catalyzed reaction.[14]

Some idea of the relative magnitude of the inductive effect may be gained from a comparison of the rates of ethyl cyclohexylacetate with those for ethyl phenylacetate. In saponification the activation energy is 15,600 calories per mole for cyclohexylacetate and 14,100 for the phenylacetate. For acid-catalyzed hydrolysis the corresponding values are 16,900 and 16,100. Assuming the steric influence of the phenyl and cyclohexyl groups to be the same, the inductive effect is represented by some 700 calories less influence in the activation energy for acid hydrolysis than for base catalyzed hydrolysis. Since the drop in activation energy caused by introduction of a phenyl group into ethyl acetate is only 600 calories for saponification, one would expect little change in the activation energy for the process of acid hydrolysis. This agrees with the experimental findings as shown in Table III.

This type of reasoning also explains the fact that ethyl diphenylacetate is hydrolyzed about twice as fast as ethyl phenylethylacetate in the

(8) Interpolated from the data in Table II and from those of Smith and Steele, ref. 2.

(9) Calculated from the data of Smith, ref. 6, and of Smith and Reichardt, THIS JOURNAL, **63**, 605 (1941).

(10) From the data of Levenson and Smith, ref. 5.

(11) From the data of Davies and Evans, *J. Chem. Soc.*, 339 (1940). These values were determined using 0.05 *M* solutions of ester and catalyst. Under these conditions the reaction rate is greater by about 5% than when 0.10 *M* concentrations are employed (see Smith and Steele, ref. 2).

(12) *Cf.* Ingold and Nathan, *J. Chem. Soc.*, 222 (1936); Timm and Hinshelwood, *ibid.*, 862 (1938).

(13) Waters and Lowry, "Physical Aspects of Organic Chemistry," D. Van Nostrand Co., New York, N. Y., 1937, page 268.

(14) Glasstone, Laidler and Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 451.

TABLE IV

EFFECT OF α-PHENYL SUBSTITUTION ON SAPONIFICATION AND ACID HYDROLYSIS

	Saponification		Acid hydrolysis	
	Δ log k	ΔE	Δ log k	ΔE
Acetate → phenylacetate	+ .1642	− 600	− .4907	− 100
Propionate → hydratropate	− .6460	+ 700	−1.1338	+ 600
Butyrate → phenylethylacetate	− .8409	+1000	−1.2281	+ 700
Phenylacetate → diphenylacetate	−1.2561	+1900	−1.4657	+1600

base-catalyzed reaction, but only half as fast when the acid catalyst is employed. It is also substantiated by noting that in both processes the introduction of a phenyl group into the alpha position causes a much greater effect when another substituent is already present on the same carbon atom. This is shown in Table IV.

Unfortunately, the data for esterification are not sufficiently complete to allow many deductions, but apparently this process is similar to that of acid hydrolysis in that the steric effect due to phenyl substitution always outweighs the inductive influence, even when such substitution takes place on the terminal carbon atom. The fact that phenylacetic, hydrocinnamic and γ-phenylbutyric acids esterify with almost identical rates is perhaps better explained as a fortuitous balance between inductive and steric effects than as caused by ring formation.[6]

Summary

The kinetics of acid catalyzed hydrolysis in 70% acetone has been studied for ethyl phenylacetate, ethyl hydrocinnamate, ethyl γ-phenylbutyrate, ethyl δ-phenylvalerate, ethyl hydratropate, ethyl phenylethylacetate, ethyl diphenylacetate and ethyl cyclohexylacetate.

The introduction of a phenyl group into an aliphatic ester results in a decrease in the reaction rate for all esters studied, even though the phenyl group acts as an electron sink, and should cause an increase in the rate of hydrolysis. The results may be explained on the assumption that the steric effect of the phenyl group always outweighs its inductive effect for this process.

A comparison is made of the effect of phenyl substitution on the processes of acid hydrolysis, saponification and esterification.

KNOXVILLE, TENN. RECEIVED JUNE 8, 1942

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

The Reduction of Unsaturated Hydrocarbons at the Dropping Mercury Electrode. II. Aromatic Polynuclear Hydrocarbons[1]

BY S. WAWZONEK AND H. A. LAITINEN

Aromatic compounds possessing a high degree of resonance, such as benzene, do not undergo reduction at the dropping mercury electrode. On the other hand, aromatic polynuclear hydrocarbons showing a diminished degree of resonance are reducible. The polarographic reduction of such hydrocarbons is described in the present paper.

Results

The behavior of various aromatic polynuclear hydrocarbons was studied in a 0.175 M tetrabutylammonium iodide, 75% dioxane solution.[1] A summary of the observed half-wave potentials and individual diffusion current constants is given in Table I.

In general, all of the hydrocarbons gave well-defined reduction waves similar to that shown in Fig. 1 for 3-methylcholanthrene. Exceptions to this behavior were treated in the following manner. For compounds (phenanthrene and pyrene) showing two waves of equal height close together such as those shown in Fig. 2 for phenanthrene, the half-wave potentials were calculated by using one-fourth and three-fourths of the total diffusion current. In the table for such cases only the total diffusion current is reported even though two waves were obtained. For compounds (chrysene and 3,4-benzpyrene) which gave indefinite waves such as that shown in Fig. 3 for 3,4-benzpyrene, only the total diffusion current is given. For indene which gave a wave at a potential too negative to be measured, the starting point of the wave is given.

(1) Paper I, Laitinen and Wawzonek, THIS JOURNAL, 64, 1765 (1942). This paper was presented before the Division of Organic Chemistry of the American Chemical Society at the Buffalo meeting, September, 1942.

TABLE I

HALF-WAVE POTENTIALS AND DIFFUSION CURRENT CONSTANTS OF VARIOUS COMPOUNDS IN 0.175 *M* TETRABUTYLAMMONIUM IODIDE–75% DIOXANE

Compound	$\pi_{1/2}$ volts *vs.* S. C. E.			i_d microamperes		*C*, millimoles/liter	i_d/C, microamperes/millimole/liter	
Naphthalene		2.49		5.19		1.01	5.14	
		2.51		10.40		2.02	5.15	
1,2-Dihydronaphthalene		2.57		9.55		2.154	4.44	
Acenaphthene		2.57		5.46		1.11	4.92	
		2.58		10.85		2.22	4.89	
Indene		starting point 2.54						
3-Phenylindene		2.33		4.28		9.12	4.69	
		2.32		8.40		1.823	4.61	
Fluorene		2.65		7.50		1.33	5.65	
Biphenyl		2.70		5.19		0.745	6.96	
Phenanthrene		2.46	2.71	19.9		2.252	8.84	
		2.44	2.67	14.1		1.376	10.25	
9,10-Dihydrophenanthrene		2.62		6.70		0.932	7.18	
Chrysene		....		14.3		1.11	12.88	
Pyrene	2.10	2.46	2.67	2.38	3.89	0.740	3.22	5.25
	2.10	2.47	2.69	4.77	8.26	1.580	3.22	5.59
Anthracene		1.94		4.17	(3.48)	0.933	4.47	
1,2-Benzanthracene		2.03	2.54	6.80	(5.73)	1.66	4.10	4.54
				7.53				
1,2,5,6-Dibenzanthracene		2.07	2.53	3.18	(2.18)	0.773	4.12	7.55
				5.83				
9,10-Dimethyl-1,2-benzanthracene		2.05	2.53	3.62	(2.85)	.875	4.14	4.32
				3.78				
3-Methylcholanthrene		2.11	2.51	4.86	5.44	1.313	3.70	4.15
3,4-Benzpyrene		1.88	....	2.71	4.52	0.966	2.72	4.54

The reduction of anthracene gave a wave of constant diffusion current of 3.48 microamperes which, at more negative potentials, increased to 4.17 microamperes. The larger value is probably the true diffusion current since it is closer to that observed for phenanthrene (5.15 microamperes). A similar phenomenon occurred with the substituted anthracenes. A small wave always preceded the second reduction wave as shown in Fig. 4 for 9,10-dimethyl-1,2-benzanthracene. The figures in parentheses in the table are the lower diffusion current values used in calculating the half-wave potential of the first wave. The figures without parentheses include the small wave.

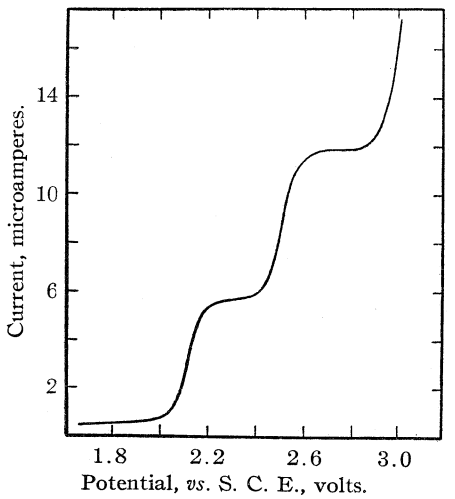


Fig. 1.—Curve for 0.001313 *M* 3-methylcholanthrene in 0.175 *M* $(C_4H_9)_4NI$, 75% dioxane.

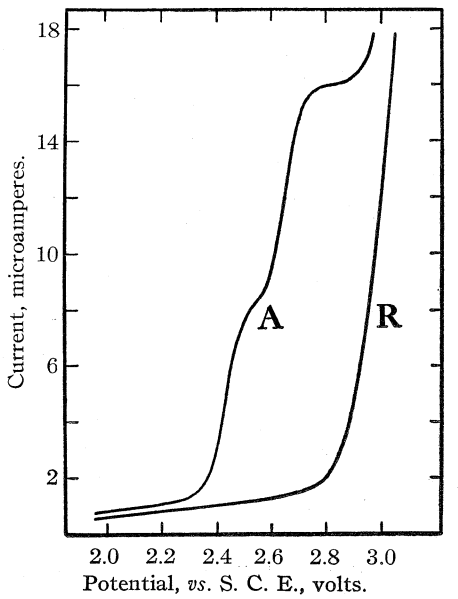


Fig. 2.—Curves in 0.175 *M* $(C_4H_9)_4NI$, 75% dioxane; R, residual current; A, 0.001376 *M* phenanthrene.

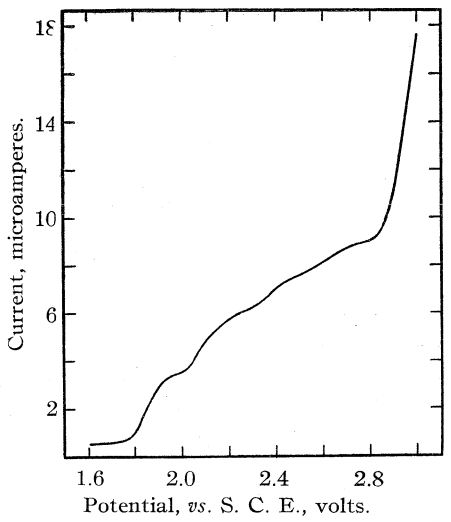


Fig. 3.—Curve for 0.000966 *M* 3,4-benzpyrene in 0.175 *M* $(C_4H_9)_4NI$, 75% dioxane.

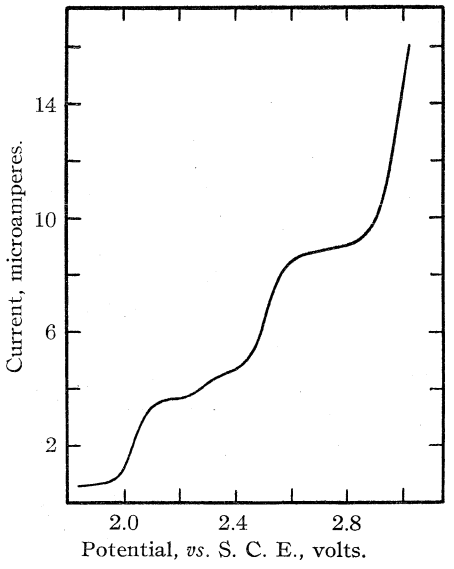


Fig. 4.—Curve for 0.000875 *M* 9,10-dimethyl-1,2-benzanthracene in 0.175 *M* $(C_4H_9)_4NI$, 75% dioxane.

The half-wave potential was found to be independent of the concentration of the hydrocarbons. From this behavior it is assumed that the half-wave potential is independent of the *p*H of the solution, as was the case with the phenyl substituted olefins and acetylenes.[1]

The diffusion current was proportional to the concentration in every case studied. An apparent exception is phenanthrene but in this case two different samples of phenanthrene were used. One sample (diffusion current constant of 10.25) was obtained from Gesellschaft für Teervertung while the other (diffusion current constant of 8.84) was prepared by purifying crude phenanthrene by the method of Bachman.[2] It is evident that the polarographic method offers a possible quantitative procedure for the determination of these hydrocarbons in the absence of more readily reducible substances.

Comparison of the diffusion current constants and of the half-wave potentials for the various hydrocarbons indicates that the reduction resembles the phenomenon of the addition of alkali metals to aromatic polynuclear hydrocarbons or their reduction by alkali metals and alcohol. Polarographic data likewise offer a means of determining the arrangement of the double bonds in the various nuclei.

The reduction of naphthalene involved only two electrons and must take place by a 1,4-mechanism since 1,2-dihydronaphthalene was reducible at a more negative potential. The low diffusion current obtained in the latter case was probably due to the presence of some 1,4-dihydronaphthalene which is not reducible at the dropping mercury electrode. The electroreduction of a double bond conjugated with a phenyl group is apparently not affected by its presence in a ring since the value of 2.57 volts obtained for 1,2-dihydronaphthalene is very close to the value obtained for β-methylstyrene (2.54 volts).[1] Tetralin, the reduction product from 1,2-dihydronaphthalene, was not reducible at the electrode. Acenaphthene was reduced similarly to naphthalene since it gave a wave involving two electrons.

Indene gave a wave at a potential too negative to be evaluated. This behavior is probably due to resonance of the double bond in the five-membered ring. The resonance apparently disappears or is diminished with the introduction of a phenyl group into the ring as it is shown by the more positive value of 2.32 volts obtained for 3-phenylindene. This value would point to the conjugation of the double bond with the phenyl group since the value is approximately equal to the value of 2.27 volts obtained for 1,1-diphenylethylene. Reduction of a double bond in the other position would certainly give a value closer to that of 1,2-dihydronaphthalene or β-methylstyrene. Hydrindene did not reduce at the dropping mercury electrode.

The reduction of biphenyl and fluorene seems to be similar in nature. The course of the reduction is probably through a 1,4-addition like that proposed for the reaction of lithium with biphenyl.[3]

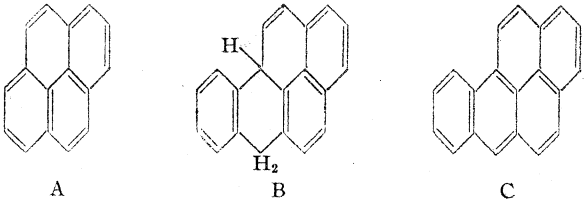
(2) W. E. Bachman, THIS JOURNAL, **57**, 557 (1935).

(3) Schlenk and Bergmann, *Ann.*, **463**, 1–97 (1928).

Phenanthrene gave two waves involving two electrons each, with the first wave at 2.44 volts corresponding to the reduction of the 9,10-double bond since 9,10-dihydrophenanthrene reduces at 2.62 volts, a value approximately equal to the 2.67 volts observed for the second wave of phenanthrene. This second reduction wave corresponds to that observed for biphenyl and fluorene, and probably involves a 1,4-reduction in one of the rings similar to the 1,4-addition of lithium to biphenyl observed by Schlenk and Bergmann.[3]

Chrysene gave rather ill-defined waves starting at 2.18 volts with a diffusion current constant of 12.88 microamperes per millimoles per liter. This indicates the introduction of six electrons, two for either the 5,6- or the 11,12-double bond, two for the resulting substituted naphthalene nucleus and two for the resulting substituted dihydrophenanthrene.

Pyrene gave three waves involving two electrons each. The first wave, at 2.10 volts, corresponds to that observed for stilbene[1] at 2.14 volts and must be due to the reduction of the 1,2-double bond. The remaining two waves at 2.46 and 2.69 volts are identical with the two waves observed for phenanthrene at 2.46 and 2.71 volts, respectively. A structure for pyrene which would fit these facts is shown by formula A and is in agreement with ozonolysis studies carried out with this compound.[4]



A B C

Anthracene gave a wave at 1.94 volts involving two electrons and a 1,4-reduction at the 9,10-positions. Substituted anthracenes, such as 1,2-benzanthracene, 1,2,5,6-dibenzanthracene, 9,10-dimethyl-1,2-benzanthracene and 3-methylcholanthrene, which possess carcinogenic properties, were also studied. All showed one half-wave potential value approximately equal to that for anthracene and another of 2.53 volts, which corresponds to the reduction of the resulting naphthalene residue. This latter value is apparently a very characteristic reduction potential for the naphthalene nucleus. For 3,4-benzpyrene the first wave at 1.88 volts, involving two electrons, indicates a reduction similar to that occurring in anthracene. This type of reduction is likewise indicated by a second wave of two electrons, which would necessarily be the reduction of the naphthalene residue in structure B. The total reduction is in agreement with structure C proposed for 3,4-benzpyrene by Cook and Hewett[5] on the basis of absorption spectra.

(4) Vollmann, Becker, Corell and Streeck, *Ann.*, **531**, 1–160 (1937).

Experimental

The conditions and electrode used were exactly the same as described in the first paper of this series.[1]

Materials.—Naphthalene, tetralin, acenaphthene, indene, 3-phenylindene, fluorene, biphenyl, phenanthrene, chrysene and pyrene were obtained from stock and purified before using. Anthracene and all carcinogenic hydrocarbons were obtained from Eastman Kodak Company and used without further purification. 1,2-Dihydronaphthalene,[6] 9,10-dihydrophenanthrene[7] and hydrindene[8] were prepared by appropriate methods given in the literature.

Summary

A polarographic study has been made of the reduction of certain aromatic polynuclear hydrocarbons.

The compounds gave half-wave potentials which were independent of their concentration and characteristic of certain structures. The diffusion current was found to be proportional to the hydrocarbon concentration. The polarographic method has been shown to be useful in the quantitative determination of the hydrocarbons and in determining the arrangement of double bonds in their various rings.

URBANA, ILLINOIS RECEIVED JULY 9, 1942

(5) Cook and Hewett, *J. Chem. Soc.*, 400 (1933).
(6) Tiffeneau and Orechow, *Bull. soc. chim.*, [4] **27**, 787 (1920).
(7) Durland and Adkins, THIS JOURNAL, **59**, 135 (1937).
(8) V. Braun, Arkuszewski and Kohler, *Ber.*, **51**, 291 (1918).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

The Apparent Energy of the N–N Bond as Calculated from Heats of Combustion[1]

BY CARL M. ANDERSON AND E. C. GILBERT

Heats of combustion of suitable simple compounds in the gaseous state have offered the most direct approach to the calculation of bond energies,[2] and results recently obtained in this Laboratory on hydrazine[3] have been used thus to calculate the energy of the covalent N–N bond.[2] This calculation has also been made from data on the heat of combustion of phenylhydrazine and methylphenylhydrazine[2,4] giving somewhat different values. The combustion data on phenylhydrazine[5] are very discordant and it was thought that new and accurate data on combustion might give better agreement in the bond energy calculation. Redetermination of the heat of combustion was undertaken and in the meantime measurements on the velocity of dissociation of tetraphenylhydrazine by Cain and Wiselogle[6] indicated to them the possibility that the value for the N–N bond was subject to revision or re-interpretation of the data. Lewis and Lipkin[7] in turn have examined the conclusions of Cain and Wiselogle.

In an effort to provide additional data for the elucidation of this problem the heat of combustion of tetraphenylhydrazine has now been determined. Calculation of bond energies in the ordinary manner is precluded with such a compound since the heats of fusion and vaporization are unknown and presumably unobtainable. Were these available, there remains the question of resonance energy, which for complex molecules is still only a matter of estimate. This is true for instance with phenylhydrazine, which contains an undetermined amount of resonance energy.

An interesting approach is possible however in which the effect of several of these variables can be reduced to a minimum. This may be done by comparing the heat of combustion of structurally similar molecules in pairs. For this purpose the following pairs were chosen and the various heats of combustion determined: (1) tetraphenylhydrazine and diphenylamine (2 moles); (2) phenylhydrazine and aniline; (3) benzamide (2 moles) and dibenzoyl hydrazide; (4) hydrazobenzene and aniline (2 moles). In the last instance the recent combustion data of Swietoslawski and Bobinska on hydrazobenzene were utilized.[8]

Experimental

The Calorimeter.—The calorimeter used was of the adiabatic type and has been described previously.[3,9] It was recalibrated with the use of benzoic acid, Standard Sample No. 39e, Natl. Bur. Standards, and found to have the same heat capacity as reported in the earlier work, *i. e.*, 2607.3 cal. per degree. The precision attainable under optimum conditions with this calorimeter is 0.01–0.02%.

Materials.—The materials used in the combustions were prepared in the following ways. The physical constants given have only a general significance since the calorimetric measurements are much more sensitive to very small amounts of impurities than common criteria of purity.

Aniline.—A single sample, enough for twelve combustions, was prepared from Eastman Kodak Co. white label grade by vacuum distillation from zinc dust in a nitrogen atmosphere, collected over stick sodium hydroxide and redistilled.

Benzamide.—Benzamide was recrystallized from alcohol three times and dried at 60° in a vacuum oven twenty-four hours and over phosphorus pentoxide two days. The sample had a melting point of 130°.

***sym*-Dibenzoylhydrazide.**—A large sample of dibenzoylhydrazide had been previously prepared by Albert Hughes of this Laboratory in 1938. A portion of this was recrystallized from ethanol and ethanol–water, dried in vacuum at 60° twenty-four hours and over phosphorus pentoxide three days. A melting point of 237–238° was found.

Diphenylamine.—Samples of diphenylamine were purified by each of the following methods: (1) recrystallized four to six times by precipitation from ethanol solution by adding water. (2) recrystallized three to four times from high boiling petroleum-ether. (3) the residues from the above procedure were steam distilled and recrystallized once from ethanol–water. The samples were dried over phosphorus pentoxide for two to four days before using them. Each of the samples had a melting point of 53°.

Phenylhydrazine.—Eastman Kodak Co. white label grade of phenylhydrazine was crystallized in a nitrogen atmosphere by cooling with cold water. About one-half of the material was crystallized out and the mother liquor was removed with a filter stick by suction. A given sample was crystallized four to six times before filling the bulbs

(1) Taken from the thesis submitted by C. M. Anderson in partial fulfillment of the requirements for the Ph.D. June 1942. Published with the approval of the Monographs Publication Committee, Oregon State College, as Research Paper No. 62, School of Science, Department of Chemistry.

(2) L. Pauling, "The Nature of the Chemical Bond," 2nd ed., Cornell University Press, Ithaca, New York, 1940; O. K. Rice, "Electronic Structure and Chemical Binding," 1st ed., McGraw-Hill Book Company, Inc., New York, N. Y., 1940.

(3) Hughes, Corruccini and Gilbert, THIS JOURNAL, **61**, 2639 (1939).

(4) Sidgwick, Sutton and Thomas, *J. Chem. Soc.*, 406 (1933).

(5) Kharasch, *J. Research Natl. Bur. Standards*, **2**, 359 (1929).

(6) Cain and Wiselogle, THIS JOURNAL, **62**, 1163 (1940).

(7) Lewis and Lipkin, *ibid.*, **63**, 3232 (1941).

(8) Swietoslawski and Bobinska, *C. A.*, **24**, 1790 (1930).

(9) Davies and Gilbert, THIS JOURNAL, **63**, 2730 (1941).

The freezing point of each sample was 19.6° for at least the last two crystallizations. Phenylhydrazine purified in this manner retained a faint yellow color and slight odor.

Colorless and odorless samples were obtained by vacuum distillation in a nitrogen atmosphere of 400–500 cc. of the material collecting the middle 100-cc. fraction over stick sodium hydroxide and redistilling. These samples had a freezing point of 19.6° and rapidly turned yellow in contact with air.

Additional amounts of phenylhydrazine were prepared in this Laboratory according to the procedure given by Coleman.[10]

Tetraphenylhydrazine.—Tetraphenylhydrazine was prepared by the oxidation of diphenylamine with potassium permanganate in acetone solution according to the procedure given by Gattermann and Wieland.[11] Samples were recrystallized from benzene by precipitation with ethanol and were well washed with cold ether. These were then dried in the vacuum desiccator over phosphorus pentoxide for twenty-four hours. After standing three to four days the samples were rewashed with cold ether or recrystallized again. Melting points anywhere in the range of 145–175° could be obtained depending upon the rate of heating the melting point bath and the temperature at which the melting point tube was placed in the bath.

Calculations.—All weighings were *in vacuo*. The data are referred to a standard temperature of 25°. The energy unit used is the arbitrary calorie obtained by multiplying the international joule by the factor 4.1833. The technique and precautions were the same as described in the earlier work.[3,9] $-\Delta U_B$, the heat experimentally evolved in the bomb process per gram formula weight was first calculated. From this was obtained $-\Delta U_R$ the decrease in energy for the combustion reaction at the standard state at constant volume, as defined by Washburn.[12] In making this calculation it was assumed that the nitrogen produced in the reaction may be treated as if it were oxygen and the correction equations modified appropriately. $-\Delta H_R$, the heat evolved in the isothermal process in the standard state at constant pressure was also calculated. The 1941 table of atomic weights was used.

Results

The combustion data are shown in Tables I–VI, and collected values for the isothermal heats of combustion in comparison to earlier results in Table VII. Of the substances investigated the latent heat of vaporization at 25° is obtainable for only two, aniline[13] (*ca.* 12,000 cal./mole) and phenylhydrazine[14] (14,690 cal./mole). Utilizing these data and the accurately established heats of formation of water and carbon dioxide,[15] $\Delta H_{298.1}$ for formation of aniline in the gaseous state is

(10) O. M. Coleman, "Organic Syntheses," Collective Volume I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 442.

(11) L. Gattermann and H. Wieland, "Laboratory Methods of Organic Chemistry," The Macmillan Co., New York, N. Y., 1937, p. 355.

(12) Washburn, *J. Research, Natl. Bur. Standards*, **10**, 544 (1933).

(13) Garrick, *Trans. Faraday Soc.*, **23**, 560 (1927).

(14) Williams, G. E., M.S. Thesis, 1942, Oregon State College.

(15) Rossini, *J. Research Natl. Bur. Standards*, **22**, 407 (1939).

TABLE I

HEAT OF COMBUSTION OF ANILINE[a]

True mass of sample in grams	ΔT,[b] °C.	Total[b] heat, cal.	Heat from HNO_3, cal.	$-\Delta U_B/m$, cal./g.	Dev. from mean
0.84186	2.8107	7339.2	18.20	8696.2	−3.9
.74038	2.4729	6457.0	17.84	8697.7	−2.4
.73698	2.4623	6429.9	16.25	8702.7	+2.6
.81119	2.7103	7077.5	17.85	8702.9	+2.8
.86075	2.8748	7507.3	17.97	8700.9	+0.8

Mean $\Delta U_B/m$ = −8700.1 cal./g.

[a] Professor H. M. Huffman of the California Institute of Technology very kindly communicated his own values for the heat of combustion of aniline obtained some years ago. The few results here shown agree, perhaps fortuitously, almost exactly with his more precise determinations (see Table VII). [b] Corrected for the heat of stirring and for the combustion of the iron wire.

TABLE II

HEAT OF COMBUSTION OF BENZAMIDE

True mass of sample in grams	ΔT,[a] °C.	Total[a] heat, cal.	Heat from HNO_3, cal.	$-\Delta U_B/m$, cal./g.	Dev. from mean
0.98378	2.4052	6280.9	16.51	7008.8	+1.4
.75424	2.0291	5298.4	13.93	7006.3	−1.1
.74775	2.0112	5251.9	12.40	7006.9	−0.5
.91260	2.4553	6411.5	16.39	7007.6	+0.2
.76797	2.0671	5395.0	14.13	7006.7	−0.7
.83282	2.2389	5846.4	14.18	7002.9[b]	
.87296	2.3488	6133.4	15.89	7007.8	+0.4

Mean $\Delta U_B/m$ = −7007.4 cal./g.

[a] Corrected for the heat of stirring and for the combustion of the iron wire. [b] Not used in calculating the mean value.

TABLE III

HEAT OF COMBUSTION OF DIBENZOYLHYDRAZINE

True mass of sample in grams	ΔT,[a] °C.	Total heat, cal.	Heat from HNO_3, cal.	$-\Delta U_B/m$, cal./g.	Dev. from mean
0.41701	1.11687	2916.2	8.28	6973.2	−0.1
.57335	1.53517	4008.5	10.29	6973.4	+0.1
.87038	2.4195	6084.1	14.13	6973.9[b]	+0.6
.85797	2.3845	5996.1	13.74	6972.7[b]	−0.6

Mean $\Delta U_B/m$ = −6973.3 cal./g.

[a] Corrected for heat of stirring and for the combustion of the iron wire. [b] These values were obtained previously by Hughes.

TABLE IV

HEAT OF COMBUSTION OF DIPHENYLAMINE

True mass of sample in grams	ΔT,[a] °C.	Total heat, cal.	Heat from HNO_3, cal.	$-\Delta U_B/m$, cal./g.	Dev. from mean
0.75908	2.6347	6880.0	11.45	9048.6	+1.2
.75902	2.6352	6881.2	10.87	9051.6	+1.8
.97940	3.4008	8880.9	16.99	9050.3	+0.5
.74002	2.5677	6705.1	8.89	9048.7	−1.1
.71390	2.4792	6473.9	13.89	9048.8	−1.0
.94402	3.2765	8556.4	11.59	9051.5	+1.7
.85398	2.9635	7738.9	10.85	9049.4	−0.4

Mean $\Delta U_B/m$ = −9049.8 cal./g.

[a] Corrected for the heat of stirring and for the combustion of the iron wire.

TABLE V

HEAT OF COMBUSTION OF PHENYLHYDRAZINE

True mass of sample in grams	ΔT,[a] °C.	Total[a] heat, cal.	Heat from HNO_3, cal.	$-\Delta U_B/m$, cal./g.	Dev. from mean
1.03210	3.1937	8340.4	25.81	8056.0	+0.6
0.68679	2.1259	5551.5	19.52	8054.8	− .6
.60413	1.8705	4884.3	17.99	8055.1	− .3
.81049	2.5084	6550.4	19.75	8057.7[b]	...
.86707	2.6812	7001.8	19.13	8053.2[b]	...
.99564	3.0804	8044.5	24.30	8055.3	− .1
1.00967	3.1253	8161.7	27.54	8056.2	+ .8
0.79900	2.4736	6459.4	23.65	8054.7	− .7

Mean $\Delta U_B/m$ = −8055.4 cal./g.

[a] Corrected for the heat of stirring and for the combustion of the iron wire. [b] Not used in calculating the average value.

TABLE VI

HEAT OF COMBUSTION OF TETRAPHENYLHYDRAZINE

True mass of sample in grams	ΔT,[a] °C.	Total[a] heat, cal.	Heat from HNO_3, cal.	$-\Delta U_B/m$, cal./g.	Dev. from mean
0.36953	1.2843	3353.4	5.14	9060.8[b]	+0.8
.36252	1.2612	3293.1	7.93	9062.0	+2.0
.33084	1.1509	3005.1	7.68	9060.0	+0.0
.57309	1.9936	5205.5	13.76	9059.1	−0.9
.36897	1.2829	3349.7	7.50	9058.1	−1.9

Mean $\Delta U_B/m$ = −9060.0 cal./g.

[a] Corrected for the heat of stirring and for the combustion of the iron wire. [b] A heavy nickel crucible was used in the bomb and the combustion was carried out under 20 atmospheres pressure of oxygen. Appropriate corrections were made in the calculations.

TABLE VII

SUMMARY OF THE HEATS OF COMBUSTION MEASURED AND THE VALUES RECORDED IN THE LITERATURE

Substance	Heat of combustion, ΔH_R kcal./mole Found	reported[b]	Observer
Aniline	− 810.55	− 812.7	Stohmann
		− 811.7	Lemoult
		− 816.7	Swartz
		− 810.48	Huffman[c]
Benzamide	− 848.76	− 847.6	Stohmann and Schmidt
Dibenzoylhydrazide	−1675.5		
Diphenylamine	−1531.9	−1536.2	Stohmann
		−1530.2	Lemoult
Phenylhydrazine	− 871.68	− 875.4	Lemoult
		− 805.4	Petit
Tetraphenylhydrazine	−3048.7		

[b] These values are those reported by Kharasch.[5] [c] Private communication (1942).

found to be +48.91, and for phenylhydrazine +19.25, kcal./mole. From the structures of the two compounds it is seen that the difference ΔH = 29.66 kcal./mole, involves any difference in resonance energies, the formation of an atom of hydrogen and an atom of nitrogen, respectively, from their molecules (ΔH = 136.7 kcal.),[2] the formation of one N–H bond and the formation of one N–N bond. If the approximation used by Pauling is now made for the formation of the N–H bond, *i. e.*, ΔH = 83.7 kcal. (one-third of the energy required to dissociate the ammonia molecule completely in the gaseous state) the apparent energy of formation of the N–N bond becomes ΔH = 23.3 kcal. That the assumption of equality of resonance energy in the two molecules and the equivalence of the 3 N–H bonds in ammonia to each other and to N–H bonds in substituted ammonias is only an approximation is shown by the appreciable lack of agreement between the figure thus obtained for the N–N bond and that derived from combustion data on hydrazine itself (ΔH = −20.0 kcal.).[2]

If the heat of formation of gaseous phenylhydrazine alone is used, assuming a resonance energy of 6 kcal. per mole (the same as aniline[2]) and using Pauling's values for the remaining bonds, the energy of the N–N bond is 23.7 kcal.

The remaining compounds investigated are solids (except for aniline whose heat of fusion is known) and examination of the pairs chosen shows that in each case the difference in the heat of formation lies in the energy of two N–H bonds and one N–N bond. For solids however objection may be made to the simple assumption used previously that the energy of the N–H bond is one-third of the total required to dissociate the gaseous ammonia molecule, although such an assumption serves as a basis to show definite trends in the apparent value of the N–N bond in different compounds. A reasonable compromise can be made however by combining the heat of vaporization and fusion with the gaseous data on ammonia to arrive at an energy for the reaction

(N–H) in solid ammonia ⟶ N(g) + H(g)

ΔH = −85.9 kcal.

By the use of this value qualitative allowance is made for lattice energies, etc. To test the comparative effect of such assumption the fusion and vaporization data for hydrazine[16] were also incorporated with the gaseous data on that compound and calculation made for the N–N bond in solid hydrazine. A value N–N = 22.3 kcal. was thus obtained, compared to 20.0 kcal. from the gaseous data.

Similarly for use with some of the pairs for

(16) Hieber and Woerner, *Z. Elektrochem.*, **40**, 252 (1934).

which liquid data or heats of fusion are available a value of

(N–H) in liquid ammonia ⟶ N(g) + H(g), $\Delta H = -85.4$ kcal.

may be obtained.

A summary of the apparent values of the N–N bond calculated from the various pairs, and using the three assumptions for the N–H bond is shown in Table VIII.

TABLE VIII

CALCULATED ENERGY OF N–N BOND

Compounds compared		Assumption N–H = 85.9 kcal.	Assumption N–H = 83.7 kcal.	Assumption N–H = 85.4 kcal.
Tetraphenylhydrazine / Diphenylamine	solids	14.8	(10.5)	..
Dibenzoylhydrazide / Benzamide	solids	22.1	(17.7)	..
Hydrazobenzene / Aniline	solids	29.4	(25.0)	..
Hydrazobenzene / Aniline	liquid	..	..	28.4
Phenylhydrazine / Aniline	gas	..	23.3	..
Phenylhydrazine / Aniline	liquid	..	..	24.5
Phenylhydrazine / Aniline	solids	25.9	..	..
Hydrazine—solid		22.3	..	..
Hydrazine—liquid		..	..	23.3
Hydrazine—gas		..	20.0	..

These values, calculated on any basis, support the contention of Lewis and Lipkin[7] that the apparent strength of the N–N bond is dependent upon the substituents in the molecule. Further work is under way in this Laboratory which it is hoped will throw additional light on this issue. By all calculations the value of the N–N bond in tetraphenylhydrazine thus obtained is considerably less than in any of the other compounds. The values for hydrazobenzene are somewhat out of line. Previous experience with the data of Swietoslawski and Bobinska indicate that their results may be on the low side.[17] Upward revision of their combustion data would reduce the value assigned to the N–N bond.

Grateful acknowledgment is due to the Cyrus M. Warren Fund of the American Academy of Arts and Sciences and the General Research Council of the College for financial assistance which made this work possible.

Summary

1. New data for isothermal heats of combustion of tetraphenylhydrazine and *sym*-dibenzoylhydrazide are reported.

2. Revisions of earlier data for the heat of combustion of aniline, benzamide, diphenylamine and phenylhydrazine are given.

3. Using certain arbitrary assumptions, values are computed for the energy of the N–N bond in tetraphenylhydrazine, *sym*-dibenzoylhydrazide, hydrazobenzene, and phenylhydrazine. The apparent value thus obtained depends on the substituents attached to the nitrogen.

(17) Corruccini and Gilbert, THIS JOURNAL, **61**, 2925 (1939).

CORVALLIS, OREGON RECEIVED JULY 6, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

The Heat Capacity of Organic Vapors. III. A Comparison of Flow Calorimeters

BY JAMES B. MONTGOMERY[1] AND THOMAS DE VRIES

The constant-flow calorimeter for measuring the heat capacity of vapors was devised by Callendar and adapted by Swann[2] to measure the specific heat of air. An improved calorimeter was described by Scheel and Heuse.[3] An outstanding example of good design is the calorimeter used by Osborne, *et al.*[4] Typical of the calorimeters used recently for measuring the heat capacity of organic vapors have been those described by Bennewitz and Rossner, De Vries and Collins, and Pitzer.[5]

In this investigation modifications of the flow calorimeter were studied as part of a general program to measure the heat capacity of organic vapors.

Experimental

Flow calorimeters may be arbitrarily classified on the basis of the method used for correcting for heat losses. In

(1) Present address: Hercules Experiment Station, Wilmington, Del. This paper is an abstract from the thesis submitted by J. B. Montgomery in partial fulfillment of the requirements for the degree of Doctor of Philosophy. The second paper of this series appeared in THIS JOURNAL, **64**, 1224 (1942).

(2) Callendar and Barnes, *Trans. Roy. Soc.* (London), **199A**, 55–263 (1902); Swann, *Proc. Roy. Soc.* (London), **82A**, 147 (1909).

(3) Scheel and Heuse, *Ann. Physik*, (4) **37**, 79 (1912).

(4) Osborne, Stimson, Sligh and Cragoe, *U. S. Bur. of Standards, Sci. Papers*, **20**, 65–110, 119–151 (1925).

(5) Bennewitz and Rossner, *Z. physik. Chem.*, **B39**, 126 (1938), De Vries and Collins, THIS JOURNAL, **63**, 1343 (1941); Pitzer, *ibid.*, **63**, 2413 (1941).

the calorimeters of the first class there is a direct flow of vapor over the first thermometer, the heater, the second thermometer and out of the calorimeter. The heat loss varies inversely with the rate of flow and may be corrected for by extrapolating the data to infinite rate of flow. The calorimeters described by Swann and by Pitzer belong to this class. In the second class, represented by the Scheel and Heuse design, a reversed flow of the vapor returns part of the lost heat to the calorimeter, and the heat loss varies inversely as the square of the rate of flow.

Apparatus.—The calorimeters were placed in a thermostat filled with hydrogenated vegetable oil and regulated to within 0.005°. Electrical measurements were made with a Rubicon, Type B, potentiometer. The vaporizer used in our earlier work[5] was found to have insufficient capacity to permit attainment of equilibrium at high rates of flow. A recycling vaporizer was designed which proved to be satisfactory. It consisted of a "Pyrex" glass boiler of 600-ml. capacity with an exposed twelve-ohm internal chromel wire electrical heater at the bottom and a spray trap at the top (Fig. 1). The vaporizer was supported in a copper hypsometer in which was placed either the same type of liquid as was used in the vaporizer or a liquid having the same boiling point.

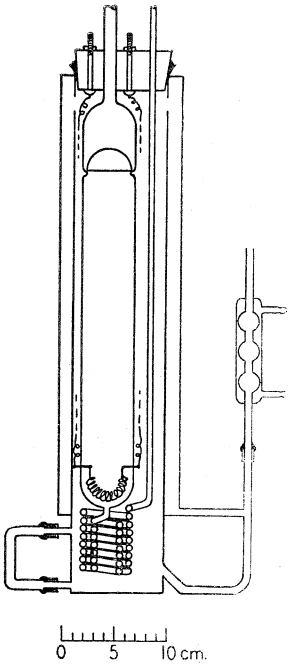


Fig. 1.—Recycling vaporizer.

Electrical heaters in the calorimeters were constructed from chromel wire and supported on glass supports. The current through the heater was computed from the potential drop across a standard resistance of 0.9339 ± 0.0003 ohm in series with the heater, and from the potential across the heater.

In the first two calorimeters platinum resistance thermometers were used. They had a resistance of approximately 60 ohms, and were constructed from no. 40 B. and S. gage platinum wire which was bifilarly wound on mica supports and fused to gold lead out wires (two at each end). The thermometers were annealed to remove strains and were found to give reproducible calibrations at the ice, steam and boiling sulfur points. In the third calorimeter a five-junction copper–constantan thermel of no. 30 gage wire was used. Measurements made with and without a heat block[5] on the outlet end of the thermel proved the value of using the heat block.

The calorimeters were constructed from "Pyrex" glass tubing. Their jackets were silvered, evacuated with a mercury vapor pump while being slowly heated to 500°, cooled to 400°, and sealed off. The cross-sections of the three calorimeters are shown in Fig. 2.

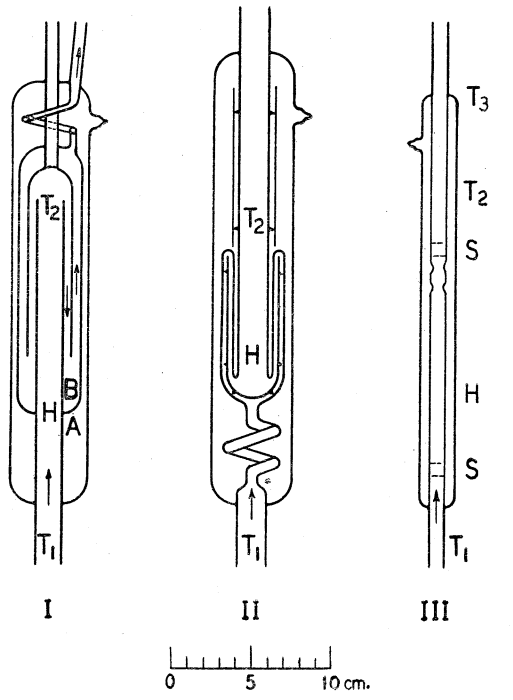


Fig. 2.—Sketch of calorimeters, details not shown.

Results.—The first calorimeter (I) was designed to provide a double layer of heated vapors around the outlet thermometer. Measurements were made upon methyl alcohol vapor at 109°. Steady state conditions were attained slowly because of the large amount of glass which had to be heated. The precision of the experimental points was excellent. The results (see Fig. 3) with the heater exposed to region A were too high because of a direct loss of heat to the surroundings which is only partially corrected for by increasing the rate of flow (F) and extrapolating the data to infinite rate of flow according to the equation, $C_p = H(1 - k/F)/F\Delta T$, which obtains for this type of calorimeter. With the heater further into the calorimeter at position B, the results were about 8% lower than those reported by De Vries and Collins.[5] These low results were explained by assuming that heat from the hot vapors in region B was conducted along the wall of the tube to the entering vapor, thus being used twice.

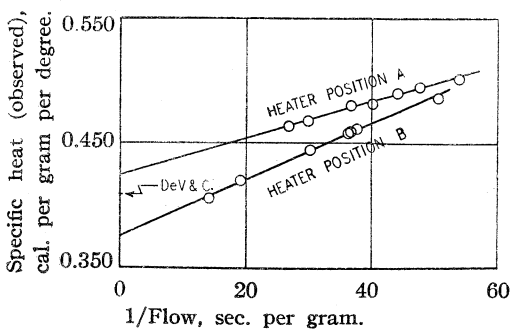


Fig. 3.—Test runs, calorimeter I: methyl alcohol at 109°.

From the results obtained with the first calorimeter it became evident that the Scheel and Heuse modification is

preferable for the arrangement which returns part of the lost heat to the incoming vapor with the result that the heat loss varies inversely as the square of the rate of flow.[5] The second calorimeter (II) was built with a short reverse section to minimize the time required to obtain steady state conditions. Measurements were made with carbon tetrachloride at 107°. The observed specific heats gave a curved line when plotted against $1/F^2$ indicating that the heat loss, which was proportional to $1/F$ in the region around the outlet thermometer (T_2), was becoming appreciable at low rates of flow. A straight line could be obtained even at low rates of flow by plotting the results against $1/F^{1.8}$. Extrapolation to infinite rate of flow gave 0.1417 cal. per gram degree (see Fig. 4). About two hours were required to obtain steady temperatures before weighed samples of the compound were collected for five to twenty minutes.

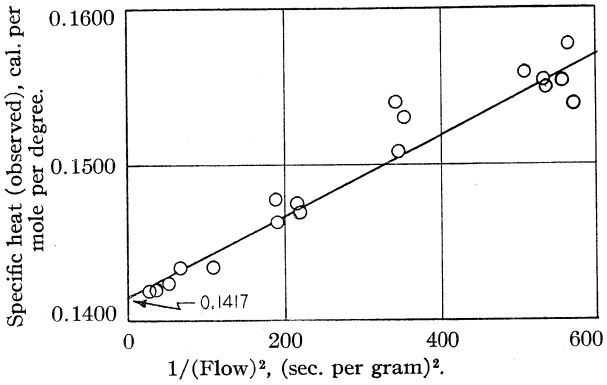


Fig. 4.—Test runs, calorimeter II: carbon tetrachloride at 107°.

A third (III) calorimeter was built in which steady temperatures were obtained in about fifteen minutes. For the first heater arrangement (not shown) the results were about 3% low. It was believed that radiation from the heater direct to the thermel junction at T_2 made ΔT too large. This belief was substantiated by the fact that higher results were obtained when the heat input was held constant and ΔT was decreased at the higher rates of flow.

Another heater arrangement (III in Fig. 2) gave satisfactory results. The method of measurement with either ΔT constant or ΔH constant had no effect on the result. It appeared that the radiation error had been eliminated. In this arrangement the heater, 4 cm. long, was supported on a glass tube, 10.5 cm. long, with two radiation shields (S) of nickel gauze at the upper end. The current carrying leads of no. 26 copper wire were in the vapor region for 5 cm., passed inside the glass tube for one cm. to avoid the radiation shields, then reappeared in the vapor space and passed the thermel junctions at T_2. Just beyond this point the potential leads were attached to the current carrying leads. With this arrangement no heat is lost from the heater without first passing into the vapor. A failure to obtain this condition gives a positive error in the data.

The performance of the third calorimeter was checked by measuring the heat capacity of oxygen at 100°. Compressed oxygen from a tank was used and purified to remove ammonia and water vapor. At atmospheric pressure the value 7.158 cal. per mole degree was found, based upon the use of 4.1833 joules per cal. (see Fig. 5). This value is 0.2% higher than 7.143, calculated from spectroscopic data by Johnston and Walker,[6] and experimentally determined by Henry.[7] The above value includes the correction from the Berthelot equation for the difference between the ideal state of zero pressure and one atmosphere.

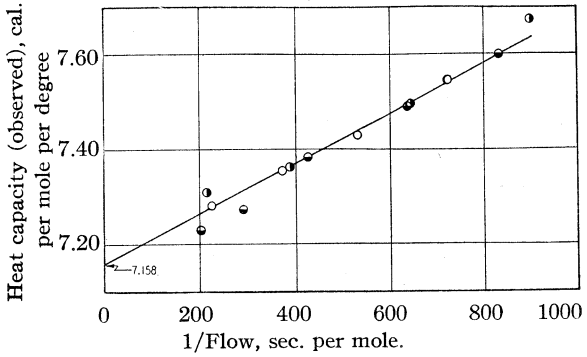


Fig. 5.—Test runs, calorimeter III, oxygen at 100°, ΔT: ○, 2°; ◑, 4°; ◒, 8°.

The heat capacity of carbon tetrachloride was measured at various rates of flow at 107° (Fig. 6). The result 21.82 cal. per mole degree agrees well with 21.80, measured with the second calorimeter of this investigation, and with the value 21.68, measured by Mr. Chas. F. Coleman[8] of this Laboratory using the apparatus of De Vries and Collins.[5] The above value is about 1% lower than 22.05 reported by Pitzer[5] and calculated by Vold[9] from spectroscopic data. But Pitzer's value at 107° was based upon measurements at only two rates of flow and Vold claimed an accuracy of only 3% (5% for C_p calculated to atmospheric pressure). A definite positive error may result from the use of vibrational frequencies determined in liquids, an error which may only be partially compensated by the fact that Vold used the rigid rotator–harmonic oscillator formulas.

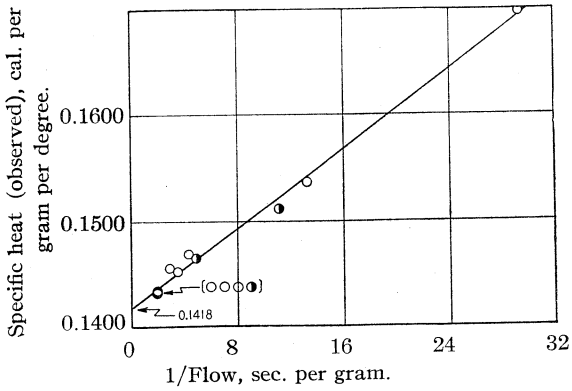


Fig. 6.—Test runs, calorimeter III, carbon tetrachloride at 107°: ○, ΔT constant; ◑, ΔH constant.

This study has indicated that it is possible to construct flow calorimeters in which the results may be precise to

(6) Johnston and Walker, THIS JOURNAL, **55**, 172 (1933).
(7) Henry, *Proc. Roy. Soc.* (London), **A133**, 492 (1931).
(8) Purdue Research Foundation Fellow, unpublished data.
(9) Vold, THIS JOURNAL, **57**, 1192 (1935).

within ±0.3%, and to make measurements in which accidental errors are reduced to values within this limit of precision. However, the elimination of constant errors from design and the construction of flow calorimeters which will give accurate measurements of specific heat to better than a few per cent. is much more difficult. Also these results would suggest that some of the high degree of accuracy which has been claimed for published data on heat capacity might be actually a high degree of precision.

Some essentials of a properly designed flow calorimeter include: (a) a minimum rate of heat loss, obtained by reducing the radiating surface to a minimum, by evacuating the jacket space around the calorimeter, and by using properly spaced radiation shields to prevent radiated heat from being used twice; (b) a proper arrangement of the vapor heater and thermometers to eliminate constant errors due to the effect of direct radiation and conduction from the heater; and (c) a construction which uses a minimum volume of material of low heat capacity to reduce the time-lag to temperature changes.

One of the authors (J. B. M.) is grateful to E. I. du Pont de Nemours and Co., Inc., for a fellowship which made this work possible.

Summary

A study was made of flow calorimeters for the determination of the heat capacity of organic vapors. The simpler calorimeter, following the design of Callendar, was preferred.

A recycling vaporizer for producing a constant rate of vapor flow was designed.

WEST LAFAYETTE, INDIANA RECEIVED JUNE 24, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

The Heat Capacity of Organic Vapors. IV. Benzene, Fluorobenzene, Toluene, Cyclohexane, Methylcyclohexane and Cyclohexane

BY JAMES B. MONTGOMERY[1] AND THOMAS DE VRIES

This paper is a continuation of a program for measuring the heat capacity of organic vapors. The heat capacities of benzene, fluorobenzene, toluene, cyclohexane, methylcyclohexane and cyclohexene vapors have been measured at atmospheric pressure at temperatures from their boiling points to 410°K. With the exception of benzene, little information is available on the heat capacity of these compounds. There are no published data for fluorobenzene and cyclohexene.

Experimental

The heat capacity of the vapor was determined by a flow-calorimeter method, using the modified Callendar direct-flow calorimeter described in the preceding paper of this series.[2] To correct for heat losses in the calorimeter, the observed heat capacities were plotted against the reciprocal of the rate of flow and extrapolated to infinite rate of flow. At each temperature approximately ten determinations were made at different rates of flow. The method of least squares was used to make the extrapolations. The precision of the results is within ± 0.3%.

Purification of Chemicals.—The observed boiling points and refractive indexes of the compounds are compared with reported values in Table I. The compounds were rectified in a twelve plate column, and only the middle fractions with boiling point ranges within 0.1° were used. Several compounds were distilled from a flask before rectification in a column.

TABLE I

PHYSICAL CONSTANTS OF COMPOUNDS

Compound	Boiling point, °C. Obs.	Boiling point, °C. Lit.	Refractive index, $n^{20}D$ Obs.	Refractive index, $n^{20}D$ Lit.
Benzene	80.0	80.09[a]	1.5004	1.5017[b]
Fluorobenzene	84.6	84.85[c]	1.4657	1.4677[b]
Toluene	110.8	110.70[d]	1.4962	1.49675[d]
Cyclohexane	80.6	80.80[e]	1.4262	1.4262[f]
Methylcyclohexane	100.7	100.8[g]	1.4224	1.4230[f]
Cyclohexene	82.8	83.25[h]	1.4465	1.44646[i]

[a] Smith and Matheson, *Bur. Stand. J. Research*, **20**, 641 (1938). [b] Lange, "Handbook of Chemistry," Handbook Publishers, Inc., Sandusky, Ohio, 1939, pp. 794, 781. [c] Timmermans and Hennaut-Roland, *J. chim. phys.*, **32**, 501, 589 (1935). [d] Mathews, see ref. 4. [e] Timmermans and Martin, *J. chim. phys.*, **23**, 733 (1926). [f] Wibaut and Langedijk, *Rec. trav. chim.*, **59**, 1220 (1940). [g] Hicks-Bruun and Bruun, *Bur. Stand. J. Research*, **8**, 525 (1932). [h] Timmermans, *Bull. soc. chim. Belg.*, **30**, 62 (1921). [i] Vogel, *J. Chem. Soc.*, 1323 (1938).

Benzene.—Thiophene-free benzene from the Barrett Company was dried over phosphorus pentoxide, rectified and stored over sodium.

Fluorobenzene.—The fluorobenzene was prepared by the method of Flood.[3] It was dried over calcium chloride, distilled through a Glinsky type column and rectified.

Toluene.—A Merck and Company purified grade of toluene was treated successively with concentrated sulfuric acid, 5% sodium hydroxide solution and water. It was dried with calcium chloride, allowed to stand over mercury

(1) This paper is an abstract from the thesis submitted by J. B. Montgomery in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Montgomery and De Vries, THIS JOURNAL, **64**, 2372 (1942).

(3) Flood, "Org. Syntheses," **13**, 46 (1933).

for ten days, dried over phosphorus pentoxide, rectified and stored over sodium.[4]

Cyclohexane.—An Eastman Kodak Co. practical grade of cyclohexane was treated with nitrating acid to remove benzene, washed, dried over calcium chloride, distilled, rectified and stored over sodium.

Methylcyclohexane.—The methylcyclohexane, obtained from the Paragon Testing Laboratories, was treated with nitrating acid, distilled, dried over sodium, rectified and stored over sodium.

Cyclohexene.—The cyclohexene was prepared by the method of Coleman and Johnstone,[5] dried over calcium chloride and rectified.

Results.—The results are summarized in Table II and in Fig. 1. Data from this investigation are indicated by open circles which are connected by lines to facilitate comparison. All data are reported in terms of the defined calorie equal to 4.1833 Int. joules. The experimental results were corrected for gas imperfections by means of the Berthelot equation. The critical point data for benzene, fluorobenzene, toluene and methylcyclohexane were taken from the literature.[6] The critical temperature for cyclohexene was estimated to be 534°K. The critical pressures of methylcyclohexane and cyclohexene were estimated to be 34.6 and 31.6 atmospheres, respectively. The uncertainty involved in these estimations and calculations is negligible, since the gas imperfection correction is of the order of one per cent.

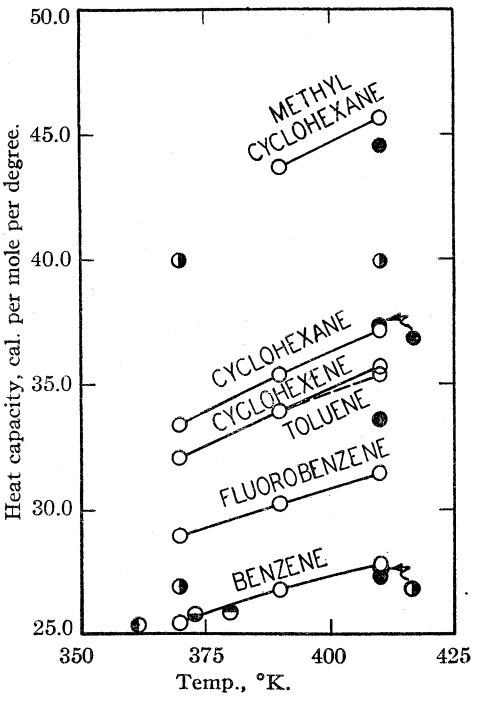


Fig. 1.—Experimental heat capacities: ●, Bennewitz and Rossner (benzene, toluene, cyclohexane, methylcyclohexane); ◑, Jatkar (benzene, cyclohexane); ◐, Dixon and Greenwood; ◒, Déjardin; ◓, Wiedemann.

TABLE II

EXPERIMENTAL HEAT CAPACITIES

(Units are cal. per mole per degree C.)

T, °K.	C_p (1 atm.)	C_p^0	C_p^0 (calcd.)	% Diff.
		Benzene		
370	25.43	25.1	24.6	−2.0
390	26.81	26.5	25.9	−2.3
410	27.81	27.6	27.1	−1.8
		Fluorobenzene		
370	28.98	28.6	26.8	−6.3
390	30.24	29.9	28.1	−6.0
410	31.45	31.2	29.4	−5.8
		Toluene		
390	33.93	33.5	31.6	−5.7
410	35.35	35.0	33.2	−5.1
		Cyclohexane		
370	33.41	33.0	34.8	+5.5
390	35.38	35.0	36.5	+4.6
410	37.13	36.8	38.4	+4.4
		Methylcyclohexane		
390	43.69	43.2	42.4	−1.9
410	45.63	45.2	44.5	−1.5
		Cyclohexene		
370	32.08	31.9	30.5	−4.4
390	33.91	33.8	32.1	−5.0
410	35.62	35.5	33.7	−5.1

The results for benzene agree reasonably well with previous work. The result taken from Dixon and Greenwood's[7] measurement of C_p/C_v at 363°K. by a velocity of sound method was 2.5% above the extrapolated curve. Déjardin's result[8] from C_p/C_v at 373°K. was 0.8% above the curve. Wiedemann's[9] average value of 25.9 cal. per mole degree over the temperature range from 308 to 453°K. was 0.6% below the curve. Regnault's[10] average value of 29.3 for the temperature range from 389 to 491°K. falls on a straight-line extrapolation of the experimental curve. Bennewitz and Rossner's[11] value at 410°K., obtained with a flow calorimeter, was 1.6% lower than the measurement in this investigation.

Bennewitz and Rossner also reported the follow-

(4) Mathews, THIS JOURNAL, **48**, 562 (1926).

(5) Coleman and Johnstone, "Org. Syntheses," **5**, 33 (1925).

(6) "International Critical Tables," Vol. III, p. 248; Nogornov and Rotinyantz, *Ann. inst. anal. phys. chim.*, **3**, 162 (1926).

(7) Dixon and Greenwood, *Proc. Roy. Soc.* (London), **105A**, 199 (1924).

(8) Déjardin, *Ann. phys.*, (9) **11**, 253 (1919).

(9) Wiedemann, *Wied. Ann.*, **2**, 195 (1877).

(10) Regnault, *Mem. de l'Acad.*, **26**, 1 (1862).

(11) Bennewitz and Rossner, *Z. physik. Chem.*, **B39**, 126 (1938).

ing values at 410°: toluene, 33.6 cal. per mole degree; cyclohexane, 37.3; and methylcyclohexane, 44.5. With the exception of cyclohexane, these values are lower than the results found in this investigation. Other investigators have obtained higher results than Bennewitz and Rossner for acetone,[12] heptane and pentane.[13]

Discussion

For the more complex organic molecules, which have not yet yielded to the methods of calculating heat capacity from spectroscopic data, semi-empirical equations for the calculation of heat capacity have great practical importance. An excellent general equation is the one which was proposed by Bennewitz and Rossner[11] and modified by Fugassi and Rudy[14] and by Dobratz.[15] In this equation, the vibrational contribution to heat capacity is calculated by means of the Einstein functions, using valence-bonding frequencies evaluated from Raman spectra and deformation frequencies empirically calculated from experimental data.

(12) De Vries and Collins, unpublished data.
(13) Pitzer, THIS JOURNAL, **62**, 1224 (1940); *ibid.*, **63**, 2413 (1941).
(14) Fugassi and Rudy, *Ind. Eng. Chem.*, **30**, 1029 (1938).
(15) Dobratz, *ibid.*, **33**, 759 (1941).

Heat capacities calculated with the modified equation of Dobratz are represented in Table II. The agreement with toluene, fluorobenzene, cyclohexane and cyclohexene is not very satisfactory. In both the aromatic and alicyclic series the calculated results are relatively lower for the compounds in which the ring symmetry has been destroyed by substituted groups. The discrepancy between the experimental and calculated results suggests that the empirically assigned deformation frequencies should be corrected to bring the calculated values into closer agreement with recent experimental data. Further work is in progress on this problem.

One of the authors (J. B. M.) is grateful to E. I. du Pont de Nemours and Co., Inc., for a fellowship which made this work possible.

Summary

Measurements have been reported for the heat capacities of benzene, fluorobenzene, toluene, cyclohexane, methylcyclohexane and cyclohexene vapors at atmospheric pressure from their boiling points to 410°K.

The experimental results have been compared with semi-empirically calculated heat capacities.

WEST LAFAYETTE, INDIANA RECEIVED JUNE 24, 1942

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

The Preparation and Physical Properties of Trimeric Phosphonitrilic Chloride

BY R. STEINMAN, F. B. SCHIRMER, JR., AND L. F. AUDRIETH

The phosphonitrilic chlorides, which may be represented by the empirical formula $PNCl_2$, may be looked upon as the ammono analogs of phosphoryl chloride. Like their aquo analog they are capable of undergoing a wide variety of solvolytic reactions. However, they differ from phosphoryl chloride in their ability to undergo polymerization with formation of compounds of high molecular weight, some of which resemble rubber in appearance and properties. In addition to these highly polymerized forms a series of stable polyhomologs is known ranging from $(PNCl_2)_3$ to $(PNCl_2)_7$.

The preparation of the phosphonitrilic chlorides involves the partial ammonolysis of phosphorus pentachloride. Ammonia,[1] ammonium chloride and ammonobasic mercuric chloride[2] have been employed as ammonolytic agents. However, only ammonium chloride has been used successfully, first by Stokes,[3] who heated mixtures of the reactants in closed tubes under pressure, and later by Schenck and Römer,[4] who employed *s*-tetrachloroethane as a medium for the reaction. Mixtures of the various polyhomologs are always obtained.

It has also been reported by Besson and Rosset[5] that phosphonitrilic chlorides may be obtained by heating together equimolecular quantities of phosphorus pentachloride and ammonium chloride; in other words, neither solvent nor reaction under pressure are necessary. Unfortunately, neither yields nor conditions are specified by

(1) Liebig and Wöhler, *Ann.*, **11**, 139 (1834).
(2) Gladstone and Holmes, *J. Chem. Soc.*, **17**, 225 (1864).
(3) Stokes, THIS JOURNAL, **17**, 275 (1895); **19**, 782 (1897).
(4) Schenck and Römer, *Ber.*, **57B**, 1343 (1924).
(5) Besson and Rosset, *Compt. rend.*, **143**, 37 (1906).

these investigators. A careful study of all three procedures led to choice of the Besson and Rosset method, after the influence of ratio of reactants and of temperature conditions had been determined. The present paper describes the preparation of the phosphonitrilic chlorides, the separation and the purification of the trimer and a study of the vapor pressure of the latter over the temperature range 75.2 to 189.3°.

Experimental

Preparation of the Phosphonitrilic Chlorides.—The equation $PCl_5 + NH_4Cl \longrightarrow PNCl_2 + 4HCl$ indicates that the extent and speed of the reaction can be determined readily by observing the rate of evolution of hydrogen chloride and by weighing the reaction product. All experiments were carried out in 50-cm. test-tubes made from 35 or 50-mm. Pyrex tubing. Intimate mixtures of phosphorus pentachloride, 52.1 g. (0.25 mole), and varying quantities of ammonium chloride (25 to 100 g.) were placed in the bottom of the tube and then covered with a capping of ammonium chloride one to three inches in thickness. The tube was immersed in an oil-bath to such a depth that the ammonium chloride cap was kept largely above the liquid level. The outlet to the reaction tube was connected to a trap containing sulfuric acid.

Heating was continued at bath temperatures varying from 120 to 160° until the evolution of hydrogen chloride had practically ceased. During the course of the reaction considerable amounts of the trimer were observed to sublime and collect in the cooler portions of the reaction vessel. On the basis of a large number of experiments optimum yields of trimer–tetramer fractions are obtained if the bath temperature is kept between 145 and 160°. A heating time of four to six hours is necessary to achieve 90–95% conversion to the phosphonitrilic chlorides.

After completion of the reaction, the residue was extracted with low-boiling petroleum ether (50–70°) which removes quantitatively the trimeric and tetrameric homologs. Evaporation of the solvent yielded mixtures of these corresponding to 38 to 43% of theory based upon the amount of phosphorus pentachloride used. Using the amounts specified above, 11 to 12.5 g. of the trimer–tetramer mixture was obtained consistently.[6]

For preparation of the pure trimer it was necessary to distill fractionally the mixture under reduced pressure to give a trimer-rich fraction (12–14 mm. with a bath temperature of 140°). This product was then recrystallized by solution in a minimum amount of hot 100% acetic acid and subsequent cooling. It was then further purified by repeated fractional sublimation at 100 ± 5° at a pressure of one mm. or less. Products prepared in this manner were used for the determination of the vapor pressure.

Vapor Pressure of Trimeric Phosphonitrilic Chloride.—The apparatus and method employed in the measurement of the vapor pressures of trimeric phosphonitrilic chloride were those previously described by Laubengayer and Schirmer.[7] Two series of measurements using different samples were carried out representing a total of 37 readings whose maximum deviation from calculated values, with one exception, amounted to ±0.5 mm. with an average deviation of 0.2 mm. A plot of these results as a function of log p and $1/T$ gives two straight lines which represent the solid–vapor and the liquid–vapor equilibria, the equations for these lines being

$$\log p = -3978(1/T) + 11.187 \text{ (where } t = 75.2 - 114.9)$$

and

$$\log p = -2880(1/T) + 8.357 \text{ (where } t = 114.9 - 189.3)$$

respectively. The intersection of these curves, the triple point, representing the melting point of the trimer, corresponds to a temperature of 114.9°. This agrees well with the value 114° reported by other investigators.[3,4] The normal boiling point obtained by extrapolation of the liquid–vapor curve to 760 mm. pressure is 252.7° which is somewhat lower than the previously accepted value 256° reported by Stokes[3] in 1897.

The molal heat of vaporization calculated from the slope of the liquid–vapor curve is 13.2 kilocalories; the molal heat of sublimation calculated from the slope of the solid–vapor curve is 18.2 kilocalories; and the molal heat of fusion obtained by difference is 5.0 kilocalories.

Summary

1. A simplified procedure for the preparation of the phosphonitrilic chlorides is described.

2. The trimer has been carefully purified and its vapor pressure determined over the temperature range 75.2 to 189.3°.

URBANA, ILLINOIS RECEIVED JUNE 26, 1942

(6) After the trimer and tetramer have been removed, the higher polyhomologs can then be obtained from the residue by extraction with benzene, carbon tetrachloride or chloroform. Evaporation of these solutions invariably resulted in the formation of thick, viscous oils or rubbery solids. This extraction also removes the unreacted phosphorus pentachloride, and it is the opinion of the authors that the presence of this material causes extensive polymerization to take place.

(7) Laubengayer and Schirmer, THIS JOURNAL, **62**, 1578 (1940).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE COLLEGE OF WASHINGTON]

Partial Molal Volumes of Nickel Sulfate Solutions

BY R. W. GELBACH AND H. M. LOUDERBACK

Densities of nickel sulfate solutions have been determined at 25 ± 0.02°.

Materials, Apparatus, Method.—Mallinckrodt Analytical Reagent nickel sulfate was thrice recrystallized from distilled water. A stock solution was prepared by dissolving the purified salt in redistilled water. The nickel sulfate content was determined by precipitation of the nickel dimethylglyoxime salt from weighed samples of the stock solution. The precipitates were filtered into weighed Gooch crucibles and brought to constant weight at 105°.[1] The accepted value was the average of three analyses in which the maximum deviation was less than 0.08% of error. Molal solutions in low concentrations were prepared by diluting weighed samples of stock solution to volume in calibrated flasks at 25°, then weighing the diluted solutions. In this way both molar and molal concentrations were obtained. The concentrated solutions were made up to volume, then weighed portions were analyzed. A saturated solution was prepared by allowing a warm concentrated nickel sulfate solution to cool to 25°, thus permitting it to come to equilibrium with the solid phase which separated. Weighed samples of the supernatant liquid were analyzed as previously. The solubility was found to be 28.42 g. of (±0.02) nickel sulfate per 100 g. of solution.

For density determinations, Weld precision specific gravity bottles of approximately 25-ml. capacity were used. All weighings were corrected to vacuum. The density given for each concentration is the average of two series of determinations. The maximum deviation between each series is 0.005%.

Apparent molal volumes have been calculated from the equation

$$\phi = \frac{F}{d} - \frac{1000}{md}\frac{d - d_0}{d_0} \qquad (1)$$

where ϕ is the apparent molal volume, F the formula weight of nickel sulfate, d_0 the density of water, 0.99707, d the density of the solution and m the molal concentration. Densities and the corresponding values of ϕ are shown in Table I.

(1) Kolthoff and Sandell, "Textbook of Quantitative Inorganic Analysis," The Macmillan Co., New York, N. Y., 1936, p. 684.

TABLE I

Concentration Molar	Concentration Molal	d_4^{25}	ϕ	$\delta\phi$
0.06343	0.06357	1.00758	−10.98	−0.01
.34504	.34537	1.05250	− 5.92	+ .10
.74331	.74465	1.11332	− 1.64	− .24
1.1612	1.1659	1.17592	+ 0.77	+ .07
1.6448	1.6575	1.24685	2.90	+ .06
2.0538	2.0774	1.30646	4.12	+ .09
2.3467	2.3806	1.34889	4.84	+ .01
2.5246	2.5658	1.37460	5.22	− .09

From the data, an equation expressing ϕ as a function of m was found by the method of averages,[2] employing finally the principle of least squares to obtain best values of the coefficients

$$\phi = -14.88 + 15.10m^{1/2} + 1.80m - 2.14m^{3/2} \qquad (2)$$

In column 5 are shown the deviations, $\delta\phi$, of the observed values from those calculated by equation (2).

Redlich[3] has on the basis of the Debye–Hückel theory given as a limiting relationship

$$\phi = \phi_0 + kw^{3/2}c^{1/2} \qquad (3)$$

where $w = {}^1/_2\,\Sigma\nu_i z_i^2$; ν_i is the number of ions of species i and z is the valence. Assuming $k = 1.86$, expressing ϕ as a function of m and applying the equation to nickel sulfate, a bi-bivalent electrolyte, the equation becomes

$$\phi = \phi_0 + 14.88m^{1/2} \qquad (4)$$

The slope, $d\phi/dm^{1/2}$, as m approaches 0, is 15.1 for equation (2) as compared to 14.88 in equation (4). The deviation in slope from that corresponding to $k = 1.86$ is within limits of experimental error, thus further confirming the validity of the limiting equation, (3). The partial molal volume at zero concentration was determined as −14.88 ml. per gram formula weight.

Summary

1. Densities at 25° of nickel sulfate solutions ranging from 0.0634 molar to 2.525 molar (saturated) have been determined.

2. The solubility of nickel sulfate at 25° was determined: 28.42 g. per 100 g. of solution.

3. Nickel sulfate was found to conform to the limiting equation as developed from Debye–Hückel theory.

PULLMAN, WASHINGTON RECEIVED JULY 20, 1942

(2) Lipka, "Graphical and Mechanical Computation," John Wiley and Sons, Inc., New York, N. Y., 1918, p. 163.

(3) Redlich, *J. Phys. Chem.*, **44**, 619 (1940).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

The Solubility Relations of Mercuric Oxide in Aqueous Solutions of Hydrogen Chloride[1]

BY A. B. GARRETT AND JAMES LEMLEY

This paper presents data on the solubility of mercuric oxide (yellow) and basic mercuric chloride ($2HgO \cdot HgCl_2$) in dilute solutions of hydrochloric acid. The data on the mercuric oxide–hydrochloric acid equilibria are similar to those obtained in a study of the mercuric oxide–nitric acid equilibria[2] which involve the hydrogen ion effect, but these have the additional interest in that they include the reaction with the chloride ion. Hence, the following equilibria are involved in interpreting the mercuric oxide–hydrochloric acid data in the very dilute range.

$$HgO(s) + H_2O \rightleftarrows Hg(OH)_2(aq.) \quad (1)$$

$$HgO(s) + H^+ \rightleftarrows Hg(OH)^+ \quad (2)$$

$$HgO(s) + 2H^+ \rightleftarrows Hg^{++} + H_2O \quad (3)$$

$$HgO(s) + H^+ + Cl^- \rightleftarrows Hg(OH)Cl(aq.) \quad (4)$$

$$HgO(s) + 2H^+ + 2Cl^- \rightleftarrows HgCl_2(aq.) + H_2O \quad (5)$$

$$HgO(s) + 2H^+ + 3Cl^- \rightleftarrows HgCl_3^- + H_2O \quad (6)$$

$$HgO(s) + 2H^+ + Cl^- \rightleftarrows HgCl^+ + H_2O \quad (7)[3]$$

Since the compound $2HgO \cdot HgCl_2$ was identified as the solid phase in the higher concentrations of acid, the following additional reactions are to be considered

$$3HgO(s) + 2H^+ + 2Cl^- \rightleftarrows 2HgO \cdot HgCl_2(s) + H_2O \quad (8)$$

$$2HgO \cdot HgCl_2(s) + H_2O + H^+ + Cl^- \rightleftarrows 3Hg(OH)Cl \quad (9)$$

$$2HgO \cdot HgCl_2(s) + 4H^+ + 4Cl^- \rightleftarrows 3HgCl_2(aq.) + 2H_2O \quad (10)$$

$$2HgO \cdot HgCl_2(s) + 4H^+ + Cl^- \rightleftarrows 3HgCl^+ + 2H_2O \quad (11)$$

$$2HgO \cdot HgCl_2(s) + 4H^+ + 7Cl^- \rightleftarrows 3HgCl_3^- + 2H_2O \quad (12)$$

The preparation of this trimercuric oxychloride is described in this paper. The existence of it is reported in early work.[4]

The constants for the equilibria represented by equations (1), (2), and (3) have been evaluated.[2]

Procedure.—The general procedure is identical to that described in earlier work.[2] The hydrochloric acid used was Grasselli C. P. acid. The samples from which the data were obtained for Table II were made by adding the same amount of Baker and Adamson Reagent mercuric oxide (6.000 g.) to each flask to which was then added 200 ml. of the standard hydrochloric acid solution. This procedure was followed in order that we might attempt to observe the progressive change in the solid phase as well as the change in solubility. The samples from which the data were ob-

TABLE I

SOLUBILITY OF YELLOW MERCURIC OXIDE IN HYDROCHLORIC ACID

Varying amounts of HgO and HCl. Samples of mercuric oxide were washed repeatedly in conductivity water previous to preparation in order to remove fine particles.

Moles HCl/1000 g. H_2O	10^{-4} × moles HgO (yellow)/1000 g. H_2O	Moles HCl/1000 g. H_2O	10^{-4} × moles HgO (yellow)/1000 g. H_2O
5.0×10^{-5}	2.47[s]	8.0×10^{-3}	18.7
1.0×10^{-4}	2.52	8.0×10^{-3}	36
3.0×10^{-4}	3.7	8.2×10^{-3}	18.1
3.0×10^{-4}	4.1	8.4×10^{-3}	18.6[u]
5.0×10^{-4}	4.9	8.6×10^{-3}	41.3
7.0×10^{-4}	6.5	9.0×10^{-3}	19.0
9.0×10^{-4}	8.4	1.0×10^{-2}	18.5
9.0×10^{-4}	7.1	1.0×10^{-2}	56
1.0×10^{-3}	6.7	1.0×10^{-2}	50.3
1.1×10^{-3}	7.2	1.2×10^{-2}	31
1.3×10^{-3}	9.8	3.0×10^{-2}	18.9
1.7×10^{-3}	11.7	5.0×10^{-2}	16.3
1.9×10^{-3}	13.0	8.0×10^{-2}	17.7
2.0×10^{-3}	13.1	1.0×10^{-1}	19.8[u]
4.0×10^{-3}	25.4	1.2×10^{-1}	22.8[u]
5.0×10^{-3}	26.2	1.2×10^{-1}	34[s]
5.0×10^{-3}	25.8[u]	1.4×10^{-1}	47[s]
6.0×10^{-3}	29.6	1.8×10^{-1}	232[u]
7.0×10^{-3}	36.6	2.0×10^{-1}	414[s]
7.0×10^{-3}	28.7	2.8×10^{-1}	534[s]
7.5×10^{-3}	20.1[u]	4.0×10^{-1}	1490[s]
		5.0×10^{-1}	1480[s]

[s] and [u] indicate approach to equilibrium from the side of saturation and unsaturation, respectively; these symbols are also used in Tables II and III.

(1) Original manuscript received April 5, 1940.

(2) Garrett and Howell, THIS JOURNAL, **61**, 1730 (1939).

(3) Other equilibria may be indicated by writing such equations as

$$HgO + Cl^- \rightleftarrows HgOCl^- \quad (a)$$

$$2HgO + 2Cl^- + H_2O \rightleftarrows 2Hg(OH)Cl \quad (b)$$

However, equations (a) and (b) seem very improbable due to the pronounced hydrogen ion effect in this reaction.[2]

(4) See Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans and Company, London, 1923, Vol. IV, pages 839–844, for a discussion of the oxychlorides of mercury. Reference is given here to several of the early workers who crystallized $2HgO \cdot HgCl_2$ from a hot solution containing mercuric oxide and mercuric chloride. See Roucher, *Ann. chim. phys.*, [3] **27**, 353 (1849); *Compt. rend.*, **19**, 773 (1844); Thummel, *Arch. Pharm.*, **223**, 919 (1885); **227**, 589 (1889); Schroek, THIS JOURNAL, **29**, 332 (1903); and Droit, *Compt. rend.*, **152**, 960 (1911).

tained for Table I were made from Baker and Adamson Reagent mercuric oxide (yellow) which was washed ten times with conductivity water before use.

The Basic Mercuric Chloride, $2HgO \cdot HgCl_2$ (Trimercuric Oxychloride).—The black solid phase in the samples (Table II) containing 0.1 *N* to 0.28 *N* hydrochloric acid was identified by mercury and chloride analysis as conforming to the formula $2HgO \cdot HgCl_2$. Basic mercuric chloride was prepared by adding mercuric oxide to 0.15 *N* solutions of hydrochloric acid, in a slight excess of the amount sufficient to convert the mercuric oxide to the basic salt in accordance with the equation

$$3HgO(s) + 2HCl \rightleftarrows 2HgO \cdot HgCl_2(s) + H_2O \quad (8)$$

The mixture was stirred vigorously, during which time its color turned from a yellow to black; this color change usually occurred within the first two hours. The solution was then decanted and the black solid washed repeatedly with conductivity water containing a small amount of hydrochloric acid. The samples used to obtain the water solubility (Table III) were washed carefully with water before they were made. The mercury analysis of four of these samples analyzed was 85.5%, the chloride analysis was 9.9% (theoretical, Hg 85.4% and Cl 10.06%).

The data are given in Tables I, II and III and are shown grapnically in Figs. 1 and 2. All values are expressed in moles per 1000 g. of water.

TABLE II

SOLUBILITY OF YELLOW MERCURIC OXIDE IN HYDROCHLORIC ACID

200 ml. of standard HCl solution added to each sample containing 6.000 g. of dried reagent HgO.

Moles of HCl/ 1000 g. H_2O	$10^{-4} \times$ moles of HgO/ 1000 g. of H_2O	*p*H (glass electrode)	Character of solid phase Color	%Hg
0.00100	9.0	5.0	Yellow	
.00300	20.8[a]	4.9	Yellow	
.00500	3.18	4.9	Yellow	
.00700	40.7	4.7	Yellow and black	
.0090	28.9	4.9	Yellow and black	
.0120	30.9	5.1	Yellow and black	
.0160	29.1	5.0	Yellow and black	
.0200	22.1	4.8	Yellow and black	
.0300	15.0	5.0	Yellow and black	
.0400	10.0	5.2	Yellow and black	
.0500	21.6	5.1	Brown	
.1007	82[a]	4.0	Black	
.1210	237	4.1	Black	
.1412	387	4.2	Black	85.4
.1614	545	4.0	Black	
.2018	880	3.8	Black	85.5
.2425	1150	3.9	Black	85.6
.2832	1410		Black	85.4

Theoretical normality of 200 ml. of HCl to change 6.000 g. HgO to $2HgO \cdot HgCl_2$ is 0.0922 *N*. Theoretical % of Hg in $2HgO \cdot HgCl_2$ is 85.4%.

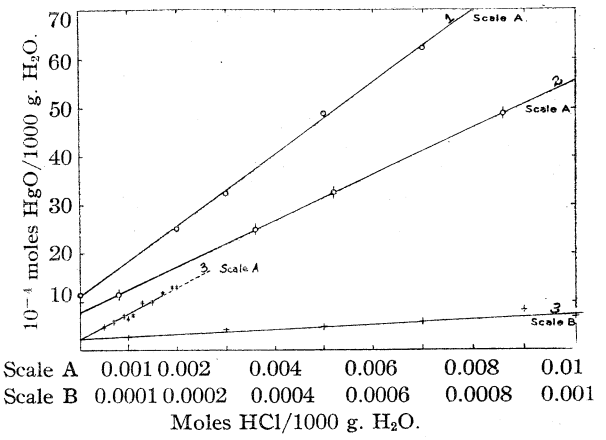


Fig. 1.—Curves 1 and 3, HCl as samples were made up; Curve 2, HCl corrected for HCl added by reaction due to the equation $2HgO \cdot HgCl_2(s) + H_2O = 3HgO + 2HCl$.

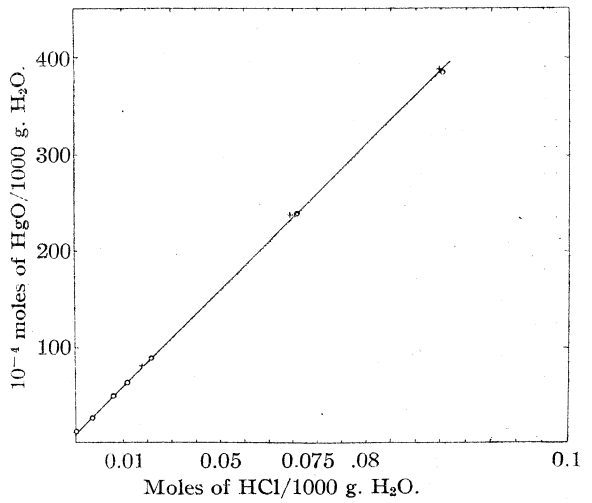


Fig. 2.—+, Table II data corrected for HCl necessary to convert HgO to $2HgO \cdot HgCl_2$; O, Table III data; data corrected for the amount of HCl added due to the reaction $2HgO \cdot HgCl_2(s) + H_2O = 3HgO + 2HCl$.

The data in Table II show a definite change in the solubility which is accompanied by a change in the solid phase from yellow HgO to black $2HgO \cdot HgCl_2$. This indicates that reactions represented by equations (4), (5), (6) and (7) are applicable to the data only below the region of the change; above this region and up to $m_{HCl} = 0.1$ a new solid phase is being formed, equation 8; above $m_{HCl} = 0.1$ a new equilibrium is estab-

lished which may be represented by equations (9), (10), (11), and (12).

The value of the water solubility of this basic chloride ($2HgO \cdot HgCl_2$) is 11.4×10^{-4} (Table III).

TABLE III

SOLUBILITY OF BASIC MERCURIC CHLORIDE $2HgO \cdot HgCl_2$ IN WATER AND IN DILUTE SOLUTIONS OF HYDROCHLORIC ACID

(Calculated as moles of HgO to compare with data in Table II.)

Moles of HCl/ 1000 g. H_2O	$10^{-4} \times$ moles of HgO/ 1000 g. H_2O	Molality of HCl at equilibrium (molality of HCl at start $+ \frac{2}{3}n$ HgO. (See Eq. 8)	pH (glass electrode)	Solid phase analysis Hg, %	Cl, %
0.00	11.9				
.00	12.5				
.00	12.3				
.00	12.3				
.00	10.5				
.00	11.4				
.00	11.6				
.00	11.3				
.00	11.6				
.00	12.1				
.00	9.9				
.00	11.4				
.00	9.8				
.00	13.0				
.00	10.0				
.00	10.5				
.00	11.2				
.00	11.9				
.00	11.4				
Average	11.4	0.00076			
0.00200	25.8	0.00372	4.8	85.2	9.9
.00200	24.7	.00364	4.9		
.00300	32.5	.00517	4.8		
.00500	48.2	.00821	5.1	85.2	
.00500	49.6[a]	.00831	4.7		
.00701	62.2	.0112	5.0		
.00801	68.4	.0126	4.6		
.01002	87.8	.0159	4.6	84.8	9.8
.03003	238	.0459	4.6		
.0501	385	.0757	4.2		
.0801	626	.122	4.2		
.1008	760	.151		85.0	

Solid phase removed from flasks of samples, reported in Table II, containing HCl varying from 0.12 to 0.28 N; this material was washed with conductivity water previous to making these samples: theoretical % Hg in $2HgO \cdot HgCl_2$, 85.4%; theoretical % Cl in $2HgO \cdot HgCl_2$, 10.1%.

Above $m_{HCl} = 0.1$ Table II only one phase (black) is observed. This phase gave the mercury and chlorine analysis in agreement with the formula $2HgO \cdot HgCl_2$. Further evidence of the identity of this phase is the fact that 200 ml. of $m_{HCl} = 0.0922$ should convert the 6.00 g. of mercuric oxide to $2HgO \cdot HgCl_2$. It is to be observed from the data in Table II that the solid phase becomes homogeneous at approximately 0.1 M hydrochloric acid and the inflection of the solubility curve appears here. Additional evidence is obtained from the data in Table III also shown in Fig. 1. In this experiment samples of $2HgO \cdot HgCl_2$ were prepared by the method described above, and their water and acid solubility determined. These data were then plotted on the same graph (Fig. 1) as is used for the data in Table II. In order to compare these two sets of data the ordinate is moved to the right to $m_{HCl} = 0.0922 + m_{HCl}$ (due to solution of $2HgO \cdot HgCl_2$) which is the point at which all the HgO should be converted to $2HgO \cdot HgCl_2$ and at which the data from Tables II and III should be comparable. The agreement is excellent.

The equilibrium constants, K_4, K_{10}, K_{11} and K_{12}, are difficult to evaluate due primarily to the uncertainty of the value of a_{Cl^-}. Some information can be obtained about the relative distribution of the dissolved mercury among the forms $Hg(OH)Cl$, $HgCl_2$, $HgCl^+$ and $HgCl_3^-$ above the transition point if one makes the safe assumption that the two mercury bearing ions $HgCl^+$ and $HgCl_3^-$ only appear in appreciable concentrations at higher concentrations of mercury. The relative distribution of the dissolved mercury between $Hg(OH)Cl$ and $HgCl_2$ above the transition point is given in Table IV.

TABLE IV

APPROXIMATE DISTRIBUTION OF DISSOLVED MERCURY IN THE REACTION OF $2HgO \cdot HgCl_2$ WITH HCl

Calculated from the equation below; smooth data from graph.

C Moles of added HCl/1000 g. H_2O	S $2HgO \cdot HgCl_2$ expressed as 10^- moles HgO/ 1000 g. H_2O	X % HCl transformed to $HgO \cdot HCl$ assuming only $HgO \cdot HCl$ and $HgCl_2$ are formed
0.001	18.4	49
.0015	22.0	32
.002	25.6	24
.004	40.3	12
.006	55.3	8
.008	70.0	6
.01	85.3	4
.02	161	3
.04	308	1

$$X = \frac{(S/C) - 0.75}{2.25}$$

The Transition.—No definite statement can be made of the exact value of m_{HCl} at the

transition point. The problem yet to be solved is to determine the equilibrium concentrations of HCl, HgO and 2HgO·HgCl at the triple point.

Summary

The solubilities of mercuric oxide and of basic mercuric chloride, $2HgO \cdot HgCl_2$, have been measured in hydrochloric acid solutions. A break occurs in the solubility relationships due to the formation of a new solid phase ($2HgO \cdot HgCl_2$). This basic mercuric chloride, $2HgO \cdot HgCl_2$, has been prepared and identified; the water solubility is 11.4×10^{-4}. The relative distribution of mercury among several different ion species is indicated.

COLUMBUS, OHIO RECEIVED JULY 25, 1942

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CHICAGO]

Adsorption and the Energy Changes[1] at Crystalline Solid Surfaces

BY G. E. BOYD AND H. K. LIVINGSTON[1a]

Theory

Adsorption is accompanied by a change both in the total and in the free surface energy of a surface. The classical relation of J. W. Gibbs[2] for interfaces between fluids has been used extensively and certainly must be regarded as valid when properly applied. The question of the applicability of the theorem to the interface between solids and fluids must be considered, and we are fortunate that Gibbs has discussed the problem in detail in the case in which the solid is anisotropic.

Thus, if the total surface energy, E_{so}; surface entropy, S_{so}; surface densities of chemical species, Γ_i; chemical potentials, μ_i; and temperature, T, are used, it is possible to define a quantity, ζ, for the arbitrarily restricted case of a system of two components by the equation[3]

$$\zeta = E_{so} - TS_{so} - \mu_1\Gamma_1 - \mu_2\Gamma_2 \qquad (1)$$

In Gibbs' words, "The quantity ζ evidently represents the tendency to contraction in that portion of the surface of the fluid which is in contact with the solid. It may be called *the superficial tension of a fluid in contact with a solid.* Its value may be either positive or negative.

"It will be observed for the same solid surface and for the same temperature but for different liquids the values of γ_{sf} (in all cases to which the definition of this quantity is applicable) will differ from those of ζ by a constant, *viz.*, the value of γ_{so} for the solid surface in a vacuum."

Obviously, ζ is defined by

$$\zeta = \gamma_{sf} - \gamma_{so} = -\pi \qquad (2)$$

or, the spreading pressure, π, is equal to the difference between the free surface energy of the clean solid surface (in a vacuum) and the free surface energy when in equilibrium with a chemically dissimilar fluid component (*i. e.*, gas or liquid).

Utilizing Gibbs' general thermodynamic methods, from equation (1), it is possible to obtain for a system consisting of a crystalline adsorbent and one adsorbate

$$d\pi = S_{so}dT + \Gamma_1 d\mu_1 + \Gamma_2 d\mu_2 \qquad (3)$$

If isothermal conditions are maintained, and if the Gibbs plane from which adsorption is reckoned is chosen so that the surface density of adsorbent, Γ_1, is zero, one may write

$$d\pi = \Gamma_2^{(1)} d\mu_2$$

or

$$\Gamma_2^{(1)} = \left(\frac{\partial \pi}{\partial \mu_2}\right)_{T,\,P,\,\mu_1} \qquad (4)$$

For the case in which the fluid contiguous to the solid surface is a gas or a vapor

$$d\mu_2 = RT\ d \ln f_2 \qquad (5)$$

where f_2 is the fugacity, and for vapors at low pressures

$$RT\ d \ln f_2 = RT\ d \ln p_2 \qquad (6)$$

is true with sufficient accuracy, so that equation (4) may be written as

$$d\pi = RT\Gamma_2^{(1)} d \ln p_2 \qquad (7)$$

where p_2 is to be taken as the equilibrium pressure of a gas or vapor above the crystal surface upon which adsorption has occurred.[4]

(1) Original manuscript received February 4, 1942.

(1a) Present address: Jackson Laboratory, E. I. du Pont de Nemours and Co., Deepwater, N. J.

(2) J. W. Gibbs, "Collected Works," Longmans, Green & Co., New York, N. Y., 1928, p. 314.

(3) It will be noticed that we have taken the liberty of modifying part of Gibbs' original nomenclature in order to bring it into approximate correspondence with present-day usage in chemical thermodynamic literature.

(4) Extensive calculations to establish the correctness of Eqn. (6) for a number of vapors are given in Appendix C of H. K. Livingston, Ph.D. Thesis, University of Chicago, December, 1941.

Evidently, values of p_2 may range from zero to the saturation vapor pressure, p_2^0, of the pure liquid from which the vapor is formed. An integration of equation (7) gives

$$\int_0^{\pi} d\pi = \gamma_{so} - \gamma_{sv} = RT \int_0^{p_2} \Gamma_2^{(1)} \, d \ln p_2 \qquad (8)$$

where γ_{sv} represents the free surface energy of the solid in equilibrium with the vapor of the foreign component 2 at pressure p_2. The quantity $\gamma_{so} - \gamma_{sv}$ may be looked upon as either the two-dimensional spreading pressure of the adsorbed film on the solid surface,[5] or, as the free energy of immersion at constant temperature of a unit surface of clean solid in an infinite amount of vapor at pressure p_2. If the solid be immersed in a saturated vapor, of pressure p_2^0, equation (8) becomes

$$\gamma_{so} - \gamma_{sv^0} = RT \int_0^{p^0} \Gamma_2^{(1)} \, d \ln p_2 \qquad (9)$$

A determination of the important free energy of immersion of a solid in a saturated vapor is possible if the right-hand member of (9) can be integrated. This might be effected if an equation for the adsorption isotherm up to the pressure of the saturated vapor were known (*i. e.*, $\Gamma_2^{(1)}$ as a function of p_2). Recent attempts[6] in this direction have been partially successful, but, for the problem at hand, it was found that a graphical integration of (9) was the least time-consuming.

Two special points need be made concerning this procedure. From (9) it is evident that at $p_2 = 0$ the integrand approaches negative infinity, whereas, as $p_2 = p_2^0$, experimentally the adsorption, $\Gamma_2^{(1)}$, appears to increase without bound.

The first difficulty may be overcome by observing that

$$RT \int_0^{p_2^0} \Gamma_2^{(1)} \, d \ln p_2 = RT \int_0^{p_2^0} \frac{\Gamma_2^{(1)}}{p_2} \, dp_2 \qquad (10)$$

Since the ratio $\Gamma_2^{(1)}/p_2$ approaches a constant value (Henry's law for surfaces) for the adsorption of gases or vapors at low pressures, the integral may be evaluated at the lower limit. At the upper limit, the value of the integral is obtained by a short extrapolation when suitable methods are used.[7,8]

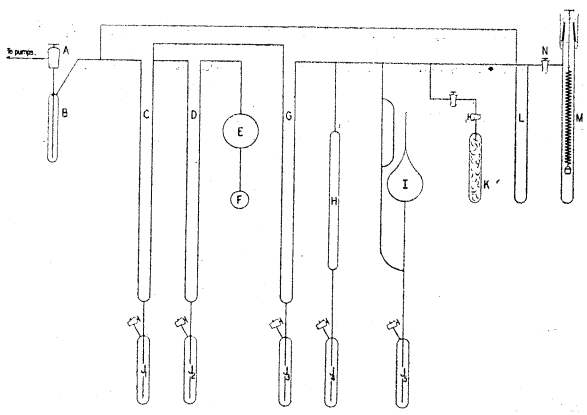


Fig. 1.—Vapor adsorption apparatus showing silica spring and platinum powder bucket, M; manometer, L; charcoal trap, K; McLeod gage, I; vapor compressing chamber, H; cutoffs, G, D and C; vapor pipets, E and F, and trap, B.

Experimental

In order to carry out the calculations described in the previous section it is necessary to have accurate adsorption data up to the saturation pressure of the vapor studied. An examination of the volumetric adsorption method as used in these laboratories[9] indicates that it is not a feasible technique to employ at pressures higher than half-saturation. Consequently, in these more recent studies the technique of McBain and Bakr[10] was used in which the amount of material adsorbed, q, is determined directly by the increase in weight of a given mass of crystalline non-porous adsorbent shown by the increased extension of a fine silica spring which supports the adsorbent, as in Fig. 1, M. The method has numerous advantages for this type of work, among which are: it is (1) rapid and accurate; (2) buoyancy corrections are small; and (3) organic vapors may be utilized without difficulty. Isotherms by this method are shown in Figs. 2–5.

It is important to make clear the connection between the adsorption experimentally meas-

(5) The concept that the molecules of a substance adsorbed on a crystal surface exert a two-dimensional spreading pressure was used first by Volmer, (*Z. physik. Chem.*, **115**, 253 (1925)) and arose quite naturally out of the researches on mobile films on solids. In this paper no assumptions are made concerning the physical state of the adsorbed films, but rather a thermodynamic viewpoint is maintained.

(6) Brunauer, Deming, Deming and Teller, THIS JOURNAL, **62**, 1723 (1940).

(7) See Appendix D of H. K. Livingston, Ph.D. Thesis, University of Chicago, 1941.

(8) Although the ideas presented in this section stem directly from the classic paper of J. W. Gibbs on the "Equilibria of Heterogeneous Substances," the authors wish to acknowledge the stimulation they have received from the very recent publications of Bangham and his co-workers (Bangham and Razouk, *Trans. Faraday Soc.*, **33**, 1459, 1463 (1937); *Proc. Roy. Soc.* (London), **A166**, 572 (1938)). The experimental work from the laboratory at Cairo has dealt so far only with a porous charcoal in which it is likely that the effects of capillary condensation were present.

(9) Gans, Brooks and Boyd, *Ind. Eng. Chem., Anal. Ed.*, **14**, 396 (1942).

(10) McBain and Bakr, THIS JOURNAL, **48**, 690 (1926).

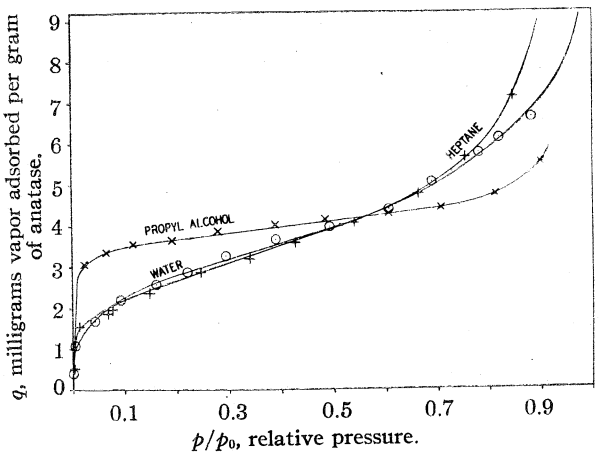


Fig. 2.—Adsorption of water, propyl alcohol and heptane vapors on crystalline, non-porous TiO_2 (anatase).

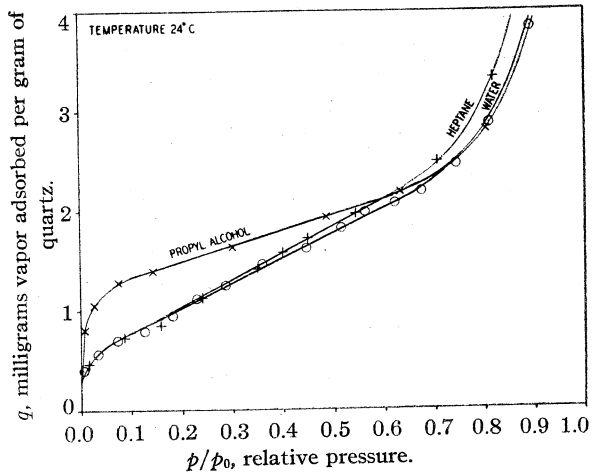


Fig. 3.—Adsorption of water, propyl alcohol and heptane vapors on crystalline SiO_2 (quartz).

ured, expressed in milligrams (or micromoles) adsorbate per gram adsorbent, and the quantity, $\Gamma_2^{(1)}$, of equation (9). This latter adsorption has units of moles of adsorbate per sq. cm. adsorbent, and is defined by Gibbs[2] as, " . . . the surface density of fluid (in our case, vapor) component determined by the excess of matter in the vicinity of the surface over that which would belong to the solid if it were bounded by a vacuum in place of the fluid, and to the fluid, if it extended with a uniform volume–density of matter just up to the surface of the solid . . . . "

Thus, equation (11) serves to define $\Gamma_2^{(1)}$ experimentally

$$\Gamma_2^{(1)} = \frac{q}{M\Sigma} - \frac{\tau}{v_2} \qquad (11)$$

where q is the measured adsorption given in milligrams per gram of adsorbent, M the molecular weight of the vapor, Σ the area in sq. cm. per gram

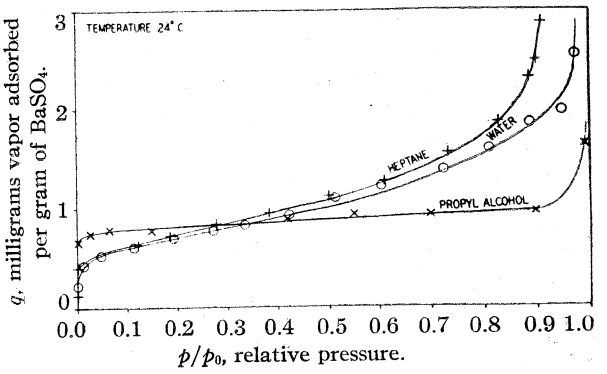


Fig. 4.—Adsorption of water, propyl alcohol and heptane vapors on crystalline $BaSO_4$ (X-ray grade).

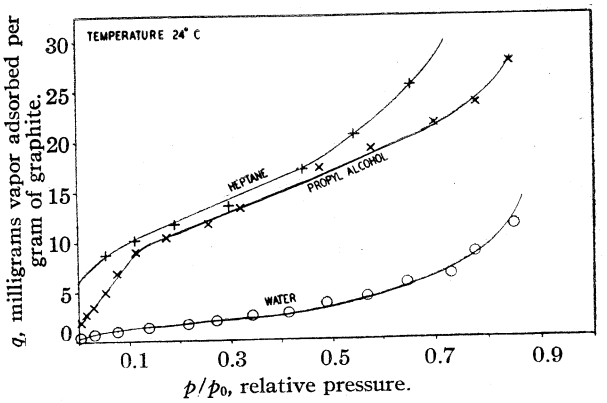


Fig. 5.—Adsorption of water, propyl alcohol and heptane vapors on graphite (Dixon 0708).

of solid, τ the thickness of the surface region, and v_2 is the molal volume of the vapor. Since the vapor behaves as a perfect gas

$$v_2 = RT/p_2 \qquad (12)$$

so that

$$\Gamma_2^{(1)} = \frac{q}{M\Sigma} - \frac{\tau p_2}{RT} \qquad (13)$$

Substituting equation (13) into (9)

$$\gamma_{so} - \gamma_{sv0} = \frac{RT}{M\Sigma}\left[\int_0^{p^0} \frac{q}{p_2}\,dp_2\right] - \left[\int_0^{p_2^0} \tau\,dp_2\right] \qquad (14)$$

A simple numerical computation shows that the term $\int_0^{p^0} \tau dp_2$ makes no significant contribution; therefore

$$\gamma_{so} - \gamma_{sv0} = \frac{RT}{M\Sigma}\int_0^{p_2^0} \frac{q}{p_2}\,dp_2 \qquad (15)$$

If the adsorption isotherm for a vapor on a crystalline non-porous powder is obtained, and if the total area per gram of powder, Σ, is determined, it is possible to calculate the change in the free energy of a clean solid surface upon immersion in a saturated vapor. The surface areas em-

ployed in this calculation were determined by the method of Brunauer, Emmett and Teller.[11]

Table I summarizes the results of the graphical integrations carried out on the data obtained in this work, as well as on selected data from the literature.

TABLE I

FREE SURFACE ENERGY CHANGES UPON IMMERSION IN SATURATED VAPOR ($\gamma_{so} - \gamma_{sv0}$) AT 25.0° (ergs c.m.$^{-2}$)

Values calculated from the data of (a) Gans, Brooks and Boyd, *op. cit.;* (b) Palmer and Clark, *Proc. Roy. Soc.* (London), **A149,** 360 (1935); and Palmer, *ibid.*, **A160,** 254 (1937).

Vapor	TiO_2-I	TiO_2-VI	SiO_2	$BaSO_4$	Graphite	SnO_2
Water	214[a]	228	244	246	59	220[a]
n-Propyl alcohol	85[a]	90	110	77	73	80[a]
Acetone	...	...	85[b]	...	..	..
Benzene	53[a]	...	52[b]	...	..	..
n-Heptane	...	38	39	38	56	..

The Change of the Free Energy of a Solid Surface upon Immersion in Bulk Liquid.[12]—In order to determine the magnitude of the free energy of immersion of a clean solid surface, $\gamma_{so} - \gamma_{sl}$, in a large amount of bulk liquid, it is necessary to find some relation of this quantity to the magnitude in Table I.

If a drop of liquid is placed upon a freshly cleaved crystal surface, in the absence of any other components, a number of possibilities arise: (1) the droplet will extend over the solid surface until it appears to cover the surface with an extremely thin film of uniform thickness; (2) the droplet flattens under gravity to an equilibrium shape in which an angle of contact is formed between the liquid and the crystal surface now covered with a film which may be monomolecular or of somewhat greater thickness as is shown in Fig. 6.[13]

According to Gibbs[2] the condition for the formation of an equilibrium contact angle is

$$\zeta_{sB} - \zeta_{sA} = \gamma_{AB} \cos \theta_E \qquad (16)$$

where ζ_{AB} and ζ_{sA} are quantities related to the film pressures π_{sB} and π_{sA} and θ_E is the equilibrium contact angle[14]

Since

$$\pi_{sB} = \gamma_{so} - \gamma_{sB} = -\zeta_{sB}$$

and

$$\pi_{sA} = \gamma_{so} - \gamma_{sA} = -\zeta_{sA}$$

equation (16) may be written

$$\pi_{sA} - \pi_{sB} = \gamma_{AB} \cos \theta_E$$

or

$$\gamma_{sB} - \gamma_{sA} = \gamma_{AB} \cos \theta_E$$

If fluid phase B is the saturated vapor and phase A the pure liquid with which the vapor is in equilibrium, then

$$\gamma_{sv0} - \gamma_{sl} = \gamma_{lv0} \cos \theta_E \qquad (17)$$

where γ_{sv0} is the free surface energy for the interface between solid and saturated vapor, γ_{sl} for the solid-bulk liquid interface, and γ_{lv0} for the bulk liquid and its own saturated vapor.

Equation (17) may be written as

$$(\gamma_{so} - \gamma_{sl}) - (\gamma_{so} - \gamma_{sv0}) = \gamma_{lv0} \cos \theta_E \qquad (18)$$

from which the free energy of immersion in bulk liquid may be computed if the quantities ($\gamma_{so} - \gamma_{sv0}$), γ_{lv0}, and θ_E are known.

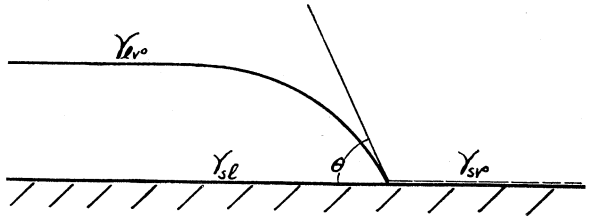


Fig. 6.—Equilibrium contact angle diagram: γ_{lv^0}, surface tension of pure liquid in equilibrium with its saturated vapor; γ_{sl}, interfacial tension between solid and liquid; γ_{sv^0}, surface free energy (or tension) of film covered solid in equilibrium with the saturated vapor of the pure bulk liquid.

In the special case in which $\theta_E = 0$, equation (18) assumes the form

$$(\gamma_{so} - \gamma_{sl}) - (\gamma_{so} - \gamma_{sv0}) = \gamma_{lv0} \qquad (19)$$

An examination of the relatively limited amount of reliable contact angle data[15-20] indicates that (a) clean polar solid surfaces are completely wet

(11) Brunauer, Emmett and Teller, THIS JOURNAL, **60,** 309 (1938).

(12) The material in the following section was given on September 24, 1941, in a paper read by G. E. B. at the Symposium on Surface Chemistry in celebration of the Fiftieth Anniversary of the University of Chicago under the title: Some Aspects of the Properties of Solid Surfaces. Subsequently, Professor W. D. Harkins has incorporated a portion of the data presented (Table II) and some of the conclusions in a recent publication, W. D. Harkins and H. K. Livingston, *J. Chem. Phys.*, **10,** 341 (1942).

(13) In his pioneering researches on this subject W. B. Hardy [*Phil. Mag.*, **38,** 49 (1919); Institut International de Chimie Solvay, Brussels (1925)] has described the diverse phenomena involved in the spreading and lens formation by liquids on clean solid surfaces. It is of interest that he remarks that mechanism (1) never occurs for a pure liquid and that the process whereby a film is built in (2) involves a transfer of molecules of liquid through the vapor phase from the lens to the solid (*i. e.*, "vapor spreading").

(14) This is the equilibrium value theoretically assumed by the angle between the solid and liquid surfaces when movement of the liquid over the solid surface is such as to alter this angle; *cf.* C. G. Sumner, "Wetting and Detergency," Chemical Publishing Co., New York, N. Y., 1937, p. 15.

(15) "International Critical Tables," **4,** 434 (1928).

(16) Richards and Carver, THIS JOURNAL, **43,** 827 (1921).

(17) Hunten and Maass, *ibid.*, **51,** 156 (1929).

(18) Carver and Hovorka, *ibid.*, **47,** 1325 (1925).

(19) Bartell, Culbertson and Miller, *J. Phys. Chem.*, **40,** 881 (1936).

(20) Bartell and Zuidema, THIS JOURNAL, **58,** 1449 (1936).

(*i. e.*, $\theta_E = 0$) by water and by polar and non-polar organic liquids,[21] (b) that non-polar liquids wet non-polar solids; but that generally, (c) polar liquids show finite angles with non-polar solids.[22]

The values of the free energy change upon immersion in bulk liquid, $\gamma_{so} - \gamma_{sl}$, calculated using (19) for the polar solids given in Table I are given in Table II. A comparison with the values for a non-polar solid, graphite, is included. In this case the free energy change was calculated from (18) using the measured contact angle of 85.7° with water taken from the work of Fowkes.[23]

The Work of Adhesion of a Liquid to a Solid. The Spreading of a Liquid over a Crystal Surface.—The work of adhesion[24] of a pure liquid to a clean solid surface is given by equation (20)

$$W_a = \gamma_{so} + \gamma_{lv^0} - \gamma_{sl} \qquad (20)$$

and this quantity may be calculated from the previous value of the free energy of immersion in bulk liquid. These values are shown in Table II.

An important consequence of a knowledge of the free energy of immersion in bulk liquid, $\gamma_{so} - \gamma_{sl}$, is that a measure of the tendency of a bulk liquid to spread over an initially clean crystalline surface can be obtained. Although the spreading of liquids on clean crystalline surfaces bears an analogy to the spreading of immiscible liquids on water or mercury, a special consideration of the coefficients of spreading must be given in the light of the fundamental differences in mechanism in the two cases.[25]

For the spreading of a liquid as a *duplex* film over a solid surface, the initial spreading coefficient, $S_{lv^0/so}$, may be defined by equation (21)

$$S_{lv^0/so} = \gamma_{so} - \gamma_{sl} - \gamma_{lv^0} \qquad (21)$$

and the final spreading coefficient, S_{lv^0/sv^0}, by equation (22)

$$S_{lv^0/sv^0} = \gamma_{sv^0} - \gamma_{sl} - \gamma_{lv^0} \qquad (22)$$

Combination of equations (22) and (17) yields

$$S_{lv^0/sv^0} = \gamma_{lv^0}(\cos\theta_E - 1) \qquad (23)$$

which is a useful form for the purpose of calculation of the latter coefficient.

(21) However, mercury, a non-polar liquid, shows a large contact angle on glass, a polar solid. Published values of θ_E range from 128 to 148°, since effects of roughness and contamination of the solid or liquid surface all combine to cause angles greater than 90° to be too large; the value of 128° mgy be the more reliable.

(22) This generalization is again not without exception as has been shown by the work of Bartell and Zuidema (ref. 20) where zero angles for butyl acetate and amyl alcohol on talc are reported.

(23) F. M. Fowkes, Ph.D. Dissertation, University of Chicago, 1938.

(24) Dupré, "Théorie Mécanique de la Chaleur," 1869, p. 369.

(25) N. K. Adam, "The Physics and Chemistry of Surfaces," Oxford Press, New York, N. Y., 1941, p. 215.

TABLE II

ENERGY RELATIONS WITH SOLIDS SHOWING ZERO CONTACT ANGLES AT 25°

(Values expressed in ergs cm.$^{-2}$)

Solid–Liquid[a]	$\gamma_{so} - \gamma_{sl}$	W_a	$S_{lv^0/so}$	S_{lv^0/sv^0}
TiO_2–H_2O	300	370	228	0
TiO_2–C_3H_7OH	114	138	90	0
TiO_2–C_6H_6	85	114	56	0
TiO_2–C_7H_{16}	58	78	38	0
SiO_2–H_2O	316	388	244	0
SiO_2–C_3H_7OH	134	158	110	0
SiO_2–$(CH_3)_2CO$	109	133	85	0
SiO_2–C_6H_6	81	110	52	0
SiO_2–C_7H_{16}	59	79	38	0
$BaSO_4$–H_2O	318	390	246	0
$BaSO_4$–C_3H_7OH	101	125	77	0
$BaSO_4$–C_7H_{16}	58	78	38	0
SnO_2–H_2O	292	364	220	0
SnO_2–C_3H_7OH	104	128	80	0
Graphite–H_2O	64	136	− 8	−67
Graphite–C_3H_7OH	95	118	73	0
Graphite–C_7H_{16}	76	96	56	0
Hg–H_2O	101	174	32	0[b]
Hg–C_3H_7OH	108	132	85	0[b]
Hg–$(CH_3)_2CO$	86	110	62	0[b]
Hg–C_6H_6	119	148	90	0[b]
Hg–C_8H_{18}	101	123	79	0[b]

[a] Surface tensions of pure liquids and mercury were taken from "International Critical Tables," **4**, 436 (1928). [b] *Cf.* Bartell, Case and Brown, THIS JOURNAL, **55**, 2769 (1933).

However, equations (21) and (22) refer to the tendency of the film of liquid to spread over the solid surface without change of the angle between solid and liquid at the line of contact, whereas θ_E of equation (23) refers to equilibrium conditions. Now this restriction may be satisfied if in spreading the movement of the liquid over the crystal surface is made to take place infinitely slowly, for then the contact angle would theoretically achieve its equilibrium value. Under these circumstances evaporation from the liquid and condensation on the crystal (*i. e.*, Hardy's secondary spreading) may be the actual physical process whereby the solid is covered. The final result at equilibrium in either case will be that the crystal face is covered with an exceedingly thin film, which is duplex if $\theta_E = 0$ and non-duplex for $\theta_E > 0$.

Equation (23) shows us that if $\theta_E = 0$, the final spreading coefficient vanishes or, that the free surface energy of the solid in equilibrium with a saturated vapor, γ_{sv^0}, is equal to the sum for the surface tension of the bulk liquid against its own vapor, γ_{lv^0} and the interfacial tension between

solid and liquid, γ_{sl}. This equality can be taken as the definition of a duplex film on a solid surface. Values for the initial and final spreading coefficients are included in Table II. Also it is instructive to note that combination of equations (19) and (21) gives

$$S_{lv^0/so} = \gamma_{so} - \gamma_{sv^0} \quad (24)$$

or, if a liquid forms a zero contact angle with a solid, the initial spreading coefficient of that liquid on the solid surface has the same value as the free energy change upon immersion in the saturated vapor of that liquid.

Energy Changes for Solids Showing Finite Contact Angles.—Inspection of equation (23) shows that S_{lv^0/sv^0} cannot be positive for finite values of θ_E. In such cases the final spreading coefficient is more appropriately a "recession coefficient," and measures the tendency of a *duplex* film, produced by some means over the surface, to contract. However, this does not mean that the withdrawal of the duplex film will denude the solid of molecules of the liquid substance. In fact, some evidence can be obtained that a non-polar crystalline surface is actually partially covered with a monolayer when a drop of liquid showing a finite contact angle rests upon another part of the surface.

The work of adhesion defined by equation (20) gives the amount of energy necessary to destroy one sq. cm. of liquid–solid interface and to form a unit area of liquid and of clean solid surface. However, since it is physically impossible to separate a solid and a liquid without leaving the solid covered with at least a monolayer in equilibrium with the vapor of the bulk liquid, it is convenient to define the work for such a process, W'_a, shown in equation (25)

$$W'_a = \gamma_{sv^0} + \gamma_{lv^0} - \gamma_{sl} \quad (25)$$

Substitution of (25) into (17) gives the work of separation, W'_a, as

$$W_a = \gamma_{lv^0}(1 + \cos\theta_E) \quad (26)$$

It is evident also that

$$W_a - W'_a = \gamma_{so} - \gamma_{sv^0} = S_{lv^0/so} \quad (27)$$

Table III gives a summary of values for a number of liquids on a few hydrophobic solids compared with a value of mercury on glass.

TABLE III

ENERGY RELATIONS WITH SOLIDS SHOWING FINITE CONTACT ANGLES

Liquid–Solid	θ_E	S_{lv^0/sv^0}	W'_a	W_a	$W_c = 2\gamma_{lv^0}$
Mercury–glass[a]	90	−476	476	...	952
Water–paraffin	109.0	− 97	47	48	144
Water–stibnite[c]	84.0	− 65	79	...	144
Water–graphite[c]	86.0	− 67	77	136	144
Water–talc[b]	88.0	− 69	75	...	144
CH_2I_2–talc[b]	53.0	− 20	80	...	100
CH_2Br_4–talc[b]	47.0	− 16	83	...	98
α Br. naphthalene–talc.[b]	34.0	− 7.5	80	...	88
Benzyl alcohol–talc[b]	32.0	− 6.0	73	...	79
$C_2H_4Br_2$–talc[b]	26.0	− 3.8	72	...	76
C_6H_5Br–talc[b]	12.0	− 0.8	71	...	72
Water–TiO_2	0.0	0.0	144	370	144

[a] Bate, *Phil. Mag.*, 28, 252 (1939). [b] Bartell and Zuidema, ref. 20. [c] Fowkes, ref. 23.

A deduction consistent with the data of Table III is that in separating bulk water from a non-polar solid, since the amount of work, W'_a, is considerably less than the work of cohesion, W_c, of water, the film left on the solid does not possess the properties of a liquid. It is possible that this film is even somewhat less than a complete monolayer.

Summary

1. The determination of the fundamentally important free energy change upon immersion in a saturated vapor for the non-porous crystalline solids, TiO_2 (anatase), SiO_2 (quartz), $BaSO_4$, SnO_2 and graphite has been made. This was accomplished through the graphical integration of vapor adsorption data utilizing the Gibbs adsorption relation.

2. The free surface energy change upon immersion in bulk liquid was obtained for these solid surfaces from the data of (1) combined with the correct equilibrium contact angle equation.

3. The data of (2) were employed to obtain the work of adhesion of a liquid to a solid surface, and to determine values of the changes in free energy associated with the spreading of a liquid as a duplex film over a crystal face.

4. An examination of the free energy changes for solids and liquids where the equilibrium contact angle is greater than zero indicates that, although a duplex film cannot exist, a monolayer may cover the solid surface.

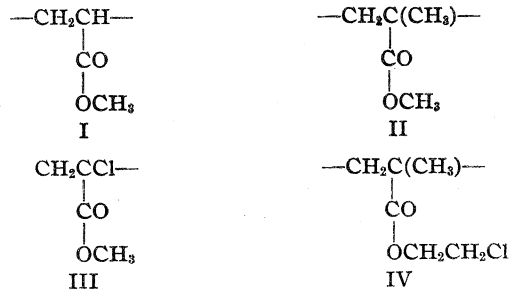
CHICAGO, ILLINOIS RECEIVED JULY 29, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE GENERAL ELECTRIC CO.]

Electrical Properties of Solids. XIII. Polymethyl Acrylate, Polymethyl Methacrylate, Polymethyl-α-chloracrylate and Polychloroethyl Methacrylate[1]

BY DARWIN J. MEAD AND RAYMOND M. FUOSS

1. **Introduction.**—In a recent paper,[2] we presented some measurements on several high polymers in which the polar groups were attached to chain carbons by flexible bonds. In this paper, we present data covering the following four systems: I, polymethyl acrylate; II, polymethyl methacrylate; III, polymethyl-α-chloracrylate and IV, polychloroethyl methacrylate.



In these, the polar carbonyl group is attached to a chain carbon, and then a second polar group is attached to the carbonyl. In addition, two of them contain C–Cl dipoles. These compounds are the first of a series of polymers of the general type $(—CH_2 \cdot CXY—)_n$ which we planned to investigate.

Polymethyl acrylate is an isomer of polyvinyl acetate. The reversal of position of the —CO·O— group with respect to the chain produces several distinct changes in the electrical properties. The static dielectric constant of polymethyl acrylate is lower than that of polyvinyl acetate at a given temperature, and the peak loss factor is much lower. The distribution of relaxation times[3] is wider for the acrylate, because the highly polar carbonyl group is attached to the chain carbon, and only the weaker methoxy group is relatively free from the restrictions of motion imposed by the chain configurations.

Substituting a methyl group for a chain hydrogen of I gives II ("Lucite"), polymethyl methacrylate, which is markedly different in its electrical behavior from the simple acrylate. Apparently the methyl group on the same carbon which carries the polar group stiffens the chain so that free rotation[4] is very much reduced. Consequently we find here a low static dielectric constant and a very broad distribution of relaxation times. Furthermore, the low temperature maximum in loss factor which has appeared for the other polar polymers which we have investigated fails to appear. Replacing the ester methyl group by a chloroethyl group again raises the dielectric constant, as expected. The chloracrylate is quite similar to the methacrylate, when allowance is made for the dielectric contribution of the halogen. Like Lucite, it also does not have a secondary low temperature maximum in loss factor, which confirms the idea that steric hindrance due to two groups on a chain carbon prevents crystallization.

2. **Experimental Details.**—Cells, electrical apparatus and general procedure were much the same as those used in previous papers of this series.

Polymethyl acrylate was otained from a commercial sample. It was freed from monomer and some material of low molecular weight by dissolving in acetone (17 g. to 800 cc.) and precipitating by adding an excess of cold methyl alcohol slowly to the chilled acetone solution. The original polymer was rather soft and the precipitate coagulated, instead of remaining flocculent. It was vacuum dried and stored over phosphorus pentoxide in an evacuated desiccator for a week before use. Discs were made by pressing for five minutes in a closed mold at 145°. Aquadag electrodes were painted on the discs, after which they were dried in a desiccator over phosphorus pentoxide. The index of refraction, measured on a Benford refractometer,[5] was 1.48.

The viscosities at 25° in cyclohexanone were measured for solutions containing 0.0288, 0.0528 and 0.0784 monomoles per liter of polymethyl acrylate. The measurements at each concentration were made at a series of pressures, and extrapolated to zero pressure.[6] The pressure dependence was about four times as large as for polyvinyl chloride. The three data give a straight line when $\lambda = (\ln \eta_r)/c$, the equivalent viscosity, is plotted against concentration. The corresponding equation is

$$\lambda = 12.38\,(1 - 1.92\,c) \qquad (1)$$

No estimate of molecular weight can be made because no absolute determination for polymethyl acrylate is available.

(1) Paper XII, THIS JOURNAL, **64**, 283 (1942).
(2) Mead and Fuoss, *ibid.*, **63**, 2832 (1941).
(3) Kirkwood and Fuoss, *J. Chem. Phys.*, **9**, 329 (1941).
(4) Bunn, *Proc. Roy. Soc.* (London), **180**, 67, 82 (1942).
(5) Benford, *J. Optical Soc. Am.*, **29**, 352 (1939).
(6) Mead and Fuoss, THIS JOURNAL, **64**, 277 (1942).

Polymethyl methacrylate was obtained in powder form by pouring a dilute (25 g./1300 cc.) dioxane solution of a commercial polymer into water. After digesting to degelatinize the precipitate, it was thoroughly washed with water and vacuum dried. Discs for measurements were hot pressed, five minutes at 170°. Aquadag would not wet the polymer satisfactorily, so thin tin-foil electrodes[7] rubbed on with a little vaseline were used to eliminate the air film. The index of refraction was 1.47.

Several plasticized samples were made, by dissolving diphenylmethane in petroleum ether and mixing the solution with the powdered polymer.[8] After evaporation of the ether, discs were hot pressed: five minutes at 155° for the 20% sample, and five minutes at 150° for the 30% sample. The indices of refraction were 1.53 and 1.68.

Viscosities of solutions of the polymethyl methacrylate in cyclohexanone at 25° were determined. Concentrations were 0.0232, 0.0502 and 0.0760 monomole per liter; the data, after extrapolation to zero pressure, gave a straight line when λ was plotted against c

$$\lambda = 5.29(1 - 0.44\,c) \qquad (2)$$

Although the methyl methacrylate probably has a higher molecular weight than the acrylate, the constant λ_0 is smaller for the former; this may mean that the methyl groups on the chain carbon inhibit curling of the chain in the methacrylate.

Polymethyl-α-chloracrylate was used without any fractionation. A piece of resin was crushed cold, and then hot pressed for five minutes at 155°, to form a test disc. The d. c. conductance was rather high, either due to pyrolysis or to impurities in the sample. The conductance, however, was not high enough to interfere with the low temperature measurements, which were the main point of interest for this polymer.

Chloroethyl methacrylate was prepared by ester interchange between methyl acrylate and ethylene chlorohydrin: 200 g. (2 moles) of monomethyl methacrylate, 241 g. (3 moles) of ethylene chlorohydrin, 6 g. of concd. sulfuric acid in 40 cc. of water and 4 g. of pyrogallol were refluxed for two hours, and then distillation of methyl alcohol was started. After the expected amount of alcohol was removed, the contents of the flask were washed several times with water containing 2.5% pyrogallol (to inhibit polymerization), in order to remove sulfuric acid and excess chlorohydrin, and then the chloroethyl methacrylate was distilled; it came over at 78° at about 18 mm. The normal boiling point was found to be 170°, by the usual micro-method. (By using the micro-method, a boiling point determination could be made before appreciable polymerization took place.) The ester was then polymerized by heating for five days at 40–45°. A hard, transparent solid was obtained. Chlorine analyses gave 20.87, 20.80% Cl, as compared with 23.8% theoretical. Apparently, some hydrogen chloride split out during the heating, giving a small amount of vinyl methacrylate. This was confirmed by the behavior of the polymer toward solvents: it swelled in ketones and ethylene chloride, but would not dissolve. Vinyl methacrylate is a bifunctional polymerant, and hence could give cross bonds in the final product, which would account for the insolublity. For electrical measurements, discs were pressed (ten minutes at 150°) from a coarse powder made by crushing a piece of the polymer. The samples were not quite smooth, so they were polished flat before painting on the aquadag electrodes. The index of refraction was 1.51.

(7) Fuoss, THIS JOURNAL, **59**, 1703 (1937).

(8) Fuoss, *ibid.*, **63**, 369 (1941).

3. Experimental Results and Discussion.—

A summary of the 60-cycle data for the four polymers is given in Table I; data at other frequencies are summarized in tabular form[9] as American Documentation Institute Document No. 1642.

TABLE I

ELECTRICAL PROPERTIES AT 60 CYCLES OF POLYMETHYL ACRYLATE (I), POLYMETHYL METHACRYLATE (II), POLYMETHYL-α-CHLORACRYLATE (III) AND POLYCHLOROETHYL METHACRYLATE (IV)

	I		II		III		IV	
t, °C.	ϵ'	ϵ''	ϵ'	ϵ''	ϵ'	ϵ''	ϵ'	ϵ''
−70	3.942	0.045	2.850	0.035	3.264	0.055	4.01	0.032
−60	3.990	.040	2.882	.040	3.330	.062	4.08	.034
−50	4.04	.036	2.916	.045	3.394	.067	4.14	.035
−40	4.09	.034	2.952	.053	3.473	.075	4.21	.037
−30	4.13	.032	2.998	.066	3.559	.087	4.28	.041
−20	4.19	.035	3.057	.085	3.650	.102	4.36	.049
−10	4.26	.041	3.130	.111	3.764	.123	4.44	.059
0	4.36	.053	3.206	.137	3.885	.151	4.50	.069
5	4.44	.068	...	...	...	...	..	...
10	4.64	.119	3.322	.177	4.01	.176	4.59	.083
15	4.96	.236	...	...	...	...	..	...
20	5.42	.424	3.453	.217	4.14	.209	4.69	.099
24	6.12	.620	...	...	...	...	..	...
30	6.98	.541	3.590	.251	4.37	.278	4.78	.116
35	7.33	.299	...	...	...	...	..	...
40	7.21	.083	3.79	.283	4.56	.343	4.95	.138
45	7.13	.032	...	...	...	...	..	...
50	7.05	.014	4.00	.298	4.83	.443	5.19	.179
55	6.89	...	...	...	...	...	..	...
60	6.84	...	4.20	.283	5.12	.554	5.46	.244
70	6.61	...	4.40	.250	5.42	.591	5.78	.347
80	6.53	...	4.61	.218	5.77	.622	6.23	.444
90	6.28	...	4.82	...	...	...	6.62	.421
100	6.13	...	...	...	...	...	6.79	.402

The results for several frequencies in the dispersion range for the polymers are shown in Figs. 1, 2, and 3. A definite similarity between the behavior of polymethyl acrylate (I) and that of its isomer, polyvinyl acetate (PViAc),[10] will be noticed, as well as some marked differences. Both show a dispersion and absorption which is describable in terms of a distribution of relaxation times, as indicated by the fact that the maximum loss

(9) For a copy of these tables, order Document 1642 from the American Documentation Institute, Offices of Science Service, 2101 Constitution Ave., Washington, D. C., remitting 25 cents for microfilm or 60 cents for photocopies readable without optical aid. The tables give dielectric constants and loss factors for the following: Table S-I, polymethyl acrylate at 60, 600, 6000 cps. 0 to −70°; S-II, polymethyl acrylate at 60, 120, 240, 480, 1000, 2000, 4000 and 8000 cps., 5 to 100°; S-III, polymethyl methacrylate at 1000 cps., −20 to −70° and at 60, 600 and 6000 cps., 40 to 90°; S-IV, polymethyl methacrylate–diphenylmethane, 80:20 at 60–8000 cps., 20 to 90°; S-V, polymethyl methacrylate–diphenylmethane, 70:30 at 60–8000 cps., 20 to 70°; S-VI, polychloroethyl methacrylate at 60, 600 and 6000 cps., −70 to +100°; and S-VII, polychloroethyl methacrylate at 60–8000 cps. and −73°.

(10) Ref. 2, Fig. 2.

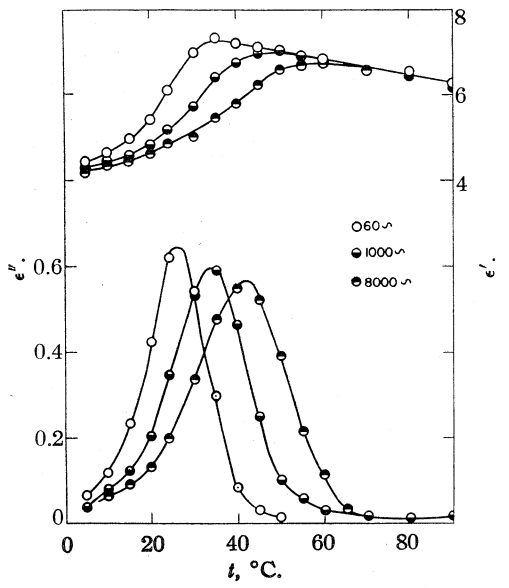


Fig. 1.—Electrical properties of polymethylacrylate.

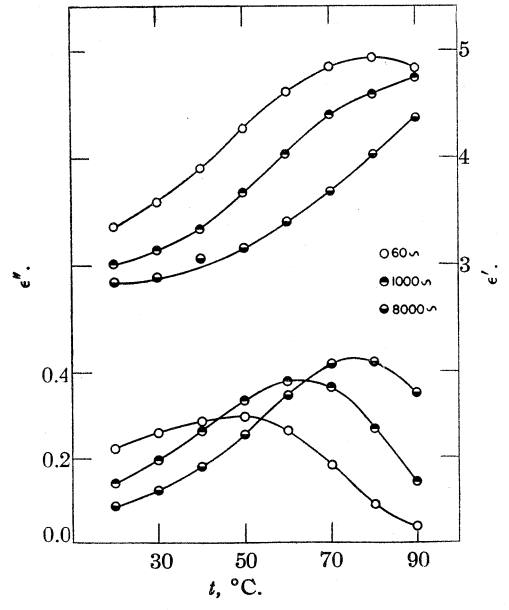


Fig. 2.—Electrical properties of polymethylmethacrylate–diphenylmethane, 80 :20.

factor is considerably less than half the difference between the square of the index of refraction and the static dielectric constant.[11] For I, the ratio $2\epsilon''_m/(\epsilon_0 - \epsilon_\infty) = 0.245$ while for PViAc, it is 0.536, nearly twice as large. (These figures are calculated from the 60 cycle data; $\epsilon'' = 0.645$ at 27° for I and 1.78 at 57° for PViAc. The static dielectric constants were determined by extrapolating the asymptotic envelopes of the corresponding $\epsilon' - T$ curves to the temperatures of the

(11) Fuoss and Kirkwood, THIS JOURNAL, 63, 385 (1941).

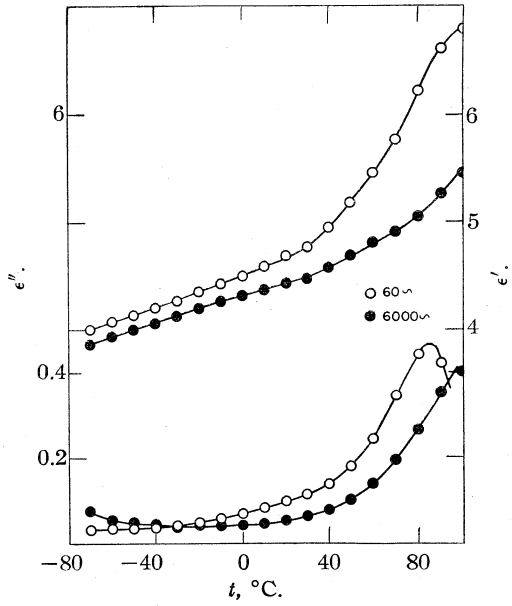


Fig. 3.—Electrical properties of polychloroethylmethacrylate.

loss factor maxima.[2]) For a system describable by a single relaxation time, this ratio is unity, of course. It is interesting to note that the spatial reversal of the —CO·O— ester group from PViAc to I broadens the distribution considerably; in the former, the strongly polar carbonyl is attached to the chain by a flexible oxygen hinge and hence is relatively free to move, while in the latter it is directly attached to the chain carbon (like the halogen in PViCl) and its orientation is controlled by the configurations of the polymeric chain. The moment per monomer unit[11] of polymethyl acrylate is 2.0×10^{-18}, as compared with 2.3×10^{-18} for polyvinyl acetate.

The mechanical properties of polymethyl acrylate are also quite different from those of polyvinyl acetate. The former was soft and flexible at room temperatures, while both Gelva 15 and 60 were hard. The corresponding limiting viscosities in cyclohexanone were: I, 12.38; Gelva 15, 4.25 and Gelva 60, 9.25. If we assume that the loss factor maximum at a given frequency comes at lower temperatures for compounds of lower molecular weight,[12] then the acrylate had the lower molecular weight, because its 60-cycle maximum is at 27°, while those for the Gelvas are at nearly 60°. If it is argued, however, that the acrylate is soft, because it has a low molecular weight, then it must have a very much larger Staudinger constant than the acetate; ultracentrifuge or os-

(12) Fuoss, *ibid.*, 63, 2401 (1941).

mometer data on these compounds would be very valuable aids in clearing up this point.

The only structural difference between the acrylate and methacrylate (aside from differences in molecular weight and distribution) is that, in the latter, the hydrogen atom on the carbon carrying the polar group has been replaced by a methyl group. This substitution has a far-reaching effect on the properties of the polymer. The 60-cycle loss factor maximum is shifted up to 50° from 27°, which indicates a very considerable increase in internal viscosity. At the same time, the static dielectric constant is reduced from 7+ to 5+, showing that internal rotations are very much hindered, even at low frequencies.

The most striking difference between polymethyl methacrylate and the other polymers so far studied, however, appears in the low temperature properties. Instead of showing a secondary loss factor maximum at low temperatures, polymethyl methacrylate has a single absorption peak in the high temperature range, from which it drops uniformly with decreasing temperature.

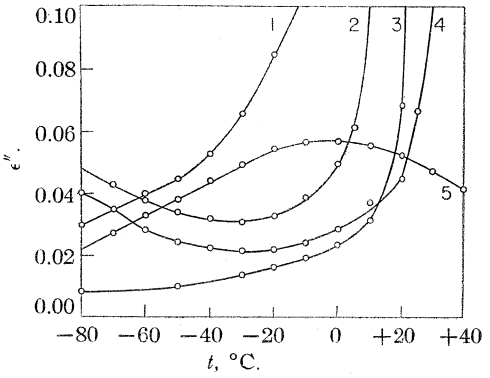


Fig. 4.—Comparison of polymers at low temperatures: 1, *p*-methyl-methacrylate; 2, *p*-methyl acrylate; 3, 20% plasticized *p*-vinyl chloride; 4, *p*-vinyl chloroacetate; 5, *p*-vinyl chloride.

As is shown in Fig. 4, the shape of the curve resembles most closely that of a plasticized polymer, which contains enough plasticizer to eliminate the low temperature maximum. It is not likely that polymethyl methacrylate exhibits a secondary maximum at temperatures below −70°, the lower limit of our experimental range, because the Cole plots[13] are symmetrical and, as was shown in the case of polyvinyl chloride and acetate, they are necessarily unsymmetrical when a low temperature maximum appears. Data for polymethyl methacrylate in the dispersion range are given in Table II. A circular arc through these points extrapolates at $\epsilon'' = 0$ ($f = \infty$) very closely to 2.16, the square of the index of refraction, n. In all cases where a low temperature maximum appeared, a circular arc through the $\epsilon' - \epsilon''$ points in the dispersion range terminated at a point on the ϵ'-axis much larger than n^2.

TABLE II

ELECTRICAL PROPERTIES OF POLYMETHYL METHACRYLATE: DISPERSION CURVES

	t = 60°		t = 70°		t = 80°	
f	ϵ'	ϵ''	ϵ'	ϵ''	ϵ'	ϵ''
60	4.16	0.282	4.36	0.252	4.56	0.216
120	4.03	.305	4.24	.289	4.46	.259
240	3.88	.311	4.09	.316	4.33	.294
480	3.72	.309	3.93	.330	4.18	.333
1 kc.	3.55	.297	3.75	.335	4.00	.348
2	3.42	.258	3.58	.318	3.80	.358
4	3.28	.227	3.42	.291	3.62	.343
8	3.17	.207	3.26	.255	3.43	.311

It has been argued[2] that the secondary maximum was characteristic of a polymer which was largely crystalline, while the high temperature maximum was due to dipole orientation in the liquid-like disordered or amorphous state. If this hypothesis is correct, then we assume that the methyl groups on the chain carbon interfere with close packing of the polymeric chains, and thus prevent crystallization, much as does the addition of a plasticizer of low molecular weight to a polymer of the $(—CH_2 \cdot CHX—)_n$ type. The addition of plasticizer[9] to polymethyl methacrylate affects the electrical properties in the expected way: it shifts the loss factor peak for a given frequency to lower temperatures.

Polymethyl-α-chloracrylate resembles polymethyl methacrylate in its mechanical and electrical properties. Data through the dispersion range were not obtained, on account of difficulties due to warping, and to the high d. c. conductance ($\kappa_0 = 0.078 \times 10^{-10}$ at 90°). Enough of the curve was obtained, however, to show that the 60-cycle maximum in absorption comes at about 90°, and an estimate of 9.2 as the lower limit for the static dielectric constant at 90° can be made. The chlorine atom on the chain raises the dielectric constant by about the expected amount, and, like the methyl group in Lucite, gives a uniformly decreasing loss factor with decreasing temperature (Table I).

Polychloroethyl methacrylate (IV) has a higher static dielectric constant than II, on account of the halogen, and the relatively free rotation of the

(13) Cole and Cole, *J. Chem. Phys.*, **9**, 341 (1941).

latter at the end of the —$CH_2 \cdot CH_2Cl$ group. It is, however, much lower than the static dielectric constant of polyvinyl chloroacetate,[2] although it contains the same kind and number of polar groups. Two reasons for this difference may be advanced: (1) the methyl group in IV inhibits the rotation of the polar ester group, as shown by the comparison of I and II, and (2) the carbonyl group is attached directly to the chain, instead of through an oxygen. There is also a possibility that the side-chain carrying the chlorine is long enough to permit some intramolecular association of dipoles, which reduces the polarization much as intermolecular dipole interaction decreases the polarization of ordinary polar liquids.

A detailed discussion of IV is not possible, because the chlorine analysis and the insolubility suggest that it is somewhat cross-linked, instead of being a simple linear polymer. Other preparations, made under milder conditions, gave higher chlorine analyses, but the polymers were also insoluble in solvents which might be expected to dissolve polymers of the structure IV. However, only a few hundredths of a per cent. of bifunctional polymerant is enough to produce an insoluble polymer. It will be noted that IV, in contradistinction to II, shows the presence of a secondary maximum at low temperatures. Probably the replacement of a methyl hydrogen of II by the —CH_2Cl group changes the spatial relationships so that crystallization becomes possible again; this is indicated by some simple experiments with models. But considerable work remains to be done on the $(—CH_2 \cdot CXY)_n$ polymers before a detailed correlation between structure and mechanical and electrical properties can be made.

Summary

1. The dielectric constants and loss factors of polymethyl acrylate, polymethyl methacrylate (alone and plasticized with 20 and 30% diphenylmethane), polymethyl-α-chloracrylate and polychloroethyl methacrylate at temperatures in the range −70° to +100° and at frequencies from 60 to 8000 cycles have been determined.

2. The preparation of chloroethyl methacrylate (b. p. 170°) is described.

3. Some preliminary results on a correlation between structure and electrical properties for polymers of the type $(—CH_2 \cdot CXY—)_n$ are given.

SCHENECTADY, N. Y. RECEIVED JULY 7, 1942

[CONTRIBUTION FROM EASTERN REGIONAL RESEARCH LABORATORY, BUREAU OF AGRICULTURAL CHEMISTRY AND ENGINEERING, UNITED STATES DEPARTMENT OF AGRICULTURE]

The Hydration of β-Lactoglobulin Crystals*

BY THOMAS L. MCMEEKIN AND ROBERT C. WARNER

Knowledge of the composition of protein crystals is of importance in the interpretation of solubility, precipitation and X-ray data on proteins.

Several methods have been utilized in calculating hydration of protein crystals. Sørensen and Høyrup[1] developed the "Method of Proportionality" for evaluating the water content of protein crystals. Adair and Adair[2] applied density determinations to the measurement of hydration. A further method was devised by Crowfoot and Riley,[3] which is based on X-ray measurements of wet and dry crystals. The present report deals with the direct measurement of hydration by the loss in weight of a single protein crystal as well as hydration deduced from density determinations.

β-Lactoglobulin crystals as described by Palmer[4] are particularly valuable for direct study of hydration, since the crystals are quite large and may be prepared in the absence of salt or in the presence of high concentrations of salt.

Materials and Methods

β-Lactoglobulin was prepared from skim milk by the method of Palmer.[4] After several recrystallizations by dialysis, a further crystallization was made by adding concentrated ammonium sulfate solution to the protein solution through a rotating cellophane membrane. When the concentration of ammonium sulfate reached 2.66 molar, needle-shaped crystals appeared. The crystals were separated from the supernatant liquid and dissolved in a small volume of water. Salt was then removed by dia-

* Not copyrighted.

(1) S. P. L. Sørensen and Høyrup, *Compt. rend. trav. lab. Carlsberg*, **12**, 169 (1917).

(2) Adair and Adair, *Proc. Roy. Soc.* (London), **B120**, 422 (1936).

(3) Crowfoot and Riley, *Nature*, **141**, 521 (1938).

(4) Palmer, *J. Biol. Chem.*, **104**, 359 (1934).

lyzing for two days against distilled water in the presence of toluene. The solution contained 3% protein and had a *p*H of 5.2. This solution, with a small amount of toluene, was stored at 4° in a closed Erlenmeyer flask. After several weeks large crystals of β-lactoglobulin appeared. Both tabular and plate crystals were present; however, only the stable tabular crystals were used in obtaining the reported measurements. Many of the crystals were from 2 to 3 mm. in length and about 1 mm. in each of the other dimensions. The nitrogen content of a single oven-dried crystal was found to be 15.7% in good agreement with Palmer's[5] most recent value of 15.6%.

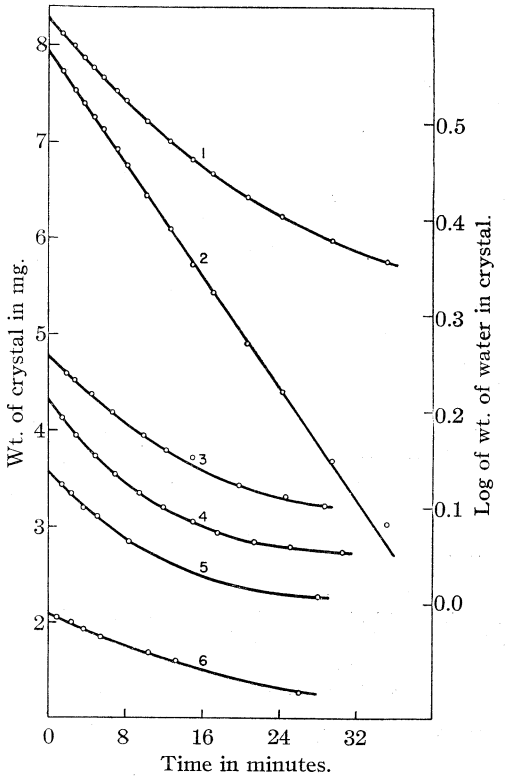


Fig. 1.—Rate of loss of water by β-lactoglobulin crystals at room temperature: Curves 1, 4 and 5, crystals from salt free solution; Curve 3, crystal from ammonium sulfate solution; Curve 6, crystal of $Na_2SO_4 \cdot 10H_2O$; Curve 2, plot of logarithm of weight of water in the crystal shown in Curve 1.

Hydration of the protein crystal was determined by weighing the wiped crystal on a rapid-weighing spring balance sensitive to 0.01 mg. The loss in weight by the crystal from the moment of its removal from the mother liquor until it reached the equilibrium weight obtained after drying in a vacuum oven at 80°, or over phosphorus pentoxide at room temperature was considered to be the water of hydration. The loss in weight with time was plotted (Fig. 1) and the weight of the crystal at zero time was determined by extrapolation. The adhering mother liquor was removed by placing the crystal between the smooth sides of two small pieces of absorbent cotton flannel. This operation required about thirty seconds. The drying crystal was kept on a removable weighing pan during the entire drying and weighing operation. The effectiveness of the method of removing the adhering mother liquor was demonstrated on crystals of ammonium sulfate, sodium sulfate decahydrate and copper sulfate pentahydrate. The crystals of ammonium sulfate or copper sulfate did not lose weight in air after being wiped with the cloth as described. The copper sulfate crystal lost 29.1% of its weight in a vacuum oven at 80°. The theoretical loss in weight is 28.8% when four molecules of water are removed. The amount of water in the hydrated sodium sulfate crystals was found by this method to be: (a) 55.8%, and (b) 57.2%. The theoretical value for 10 molecules of water is 55.9%. While it seems probable that a small amount of mother liquor would adhere to the crystal, these results on crystals with and without water of crystallization indicate that the amount of mother liquor adhering to the crystal is small and within the experimental error of other measurements involved.

The amount of protein in the β-lactoglobulin crystal was determined from the dry weight in vacuum at 80°, or in vacuum over phosphorus pentoxide at room temperature. In the case of the experiments with added ammonium sulfate, the weight of ammonium sulfate was deducted from the total dry weight to give the weight of the protein. Ammonium sulfate was determined by direct nesslerization in a volume of 50 ml. The presence of the protein during the development of the color with ammonia and Nessler reagent caused a small increase in the color, amounting to 3.5%. Correction for this effect has been applied to the measurements.

Densities were determined in mixtures of bromobenzene and xylene and, in some cases, in solutions of saturated ammonium sulfate containing added sodium sulfate or in solutions of sucrose. The crystals were removed from the mother liquor on the end of a thin strip of paper, pressed against a piece of cotton flannel and then placed in a test-tube containing the flotation medium in a water-bath at 25°. The composition of the solutions was adjusted so that the crystals just sank in one solution and just floated in another. The densities of the two solutions, referred to water at 4°, were then determined pycnometrically at 25°. The density of the crystal was taken as the mean of the two values.

Hydration of β-Lactoglobulin at *p*H 5.2 in the Absence of Salt.—The loss of water by single protein crystals at room temperature and at 80° *in vacuo* was determined. The amount of water present in the crystal was independent of the temperature at which the crystal had been stored. Thus, the amount of water in a crystal kept at 4° was the same as that of a similar crystal stored at 25°. The results of the measurements on the rate of evaporation at room temperature and total amount of water present in β-lactoglobulin crystals are shown in Fig. 1 and Table I. The average values of 0.66 g. of water per g. of air-dried protein and 0.84 g. of water per g. of vacuum-dried protein are of the same order as the value of 0.54 g. of water per g. of air-dried protein calculated from the data of Crowfoot.[6] The rate of evaporation follows a first-order equation, the rate of loss of water being proportional

(5) M. Sørensen and Palmer, *Compt. rend. trav. lab. Carlsberg*, **21**, 283 (1938).

(6) Crowfoot, *Chem. Rev.*, **28**, 215 (1941).

TABLE I

HYDRATION OF β-LACTOGLOBULIN CRYSTALS AT *p*H 5.2 IN THE ABSENCE OF SALT

Wet crystals (extr. to zero time), mg.	Air dry crystals, mg.	Water per g. of air dried protein, g.	Oven dry crystals, mg.	Water per g. of oven dry protein, g.
1.80	1.07	0.68	0.96	0.87
3.10	1.82	.70	1.64	.89
3.12	1.92	.62	1.71	.82
2.64	1.58	.67	1.48	.78
2.95	1.79	.65	1.55	.90
3.59			2.03[a]	77
1.07			0.57[a]	.88
1.41			0.77	.83
8.27			4.56	.81
4.32	2.60	.66	2.35	.84
	Average	0.66 ≈ 40% water		0.84 ≈ 46% water

[a] Dried over phosphorus pentoxide at room temperature.

to the amount of water remaining. This is shown by Curve 2 in Fig. 1, in which the logarithm of the weight of water in the crystal is plotted as a function of time. A straight line is obtained up to the point at which about 70% of the water has been lost. Beyond this the rate falls below that calculated from a first-order equation. It might be inferred from this calculation that the vapor pressure of water in the crystal does not change while most of the water is being lost. The first-order constant obtained for the rate of loss of water increases as the size of the crystal is decreased, presumably because of the increase in surface per volume ratio. Ferry and Oncley[7] analyzed dielectric dispersion curves of β-lactoglobulin solutions and compared the results with those obtained from ultracentrifuge, diffusion and viscosity measurements. The data are interpreted in terms of an elongated ellipsoidal molecule and hydration of 0.3 g. of water per g. of protein. Since their measurements were made on solutions, it is not necessarily to be expected that such hydration would be the same as that of the crystal.

Hydration of β-Lactoglobulin in the Presence of Concentrated Ammonium Sulfate Solutions.—β-Lactoglobulin crystals freed from adhering solution were placed into 28.9, 30.2 and 31.6% by weight solutions of ammonium sulfate. All of the crystals floated at first and later sank to the bottom, the time of sinking increasing with increase in concentration of salt. The crystals and salt solutions were allowed to equilibrate for two days at 25° and then the crystals were removed and their surfaces freed from adhering liquid. The amounts of water and ammonium sulfate in the crystal were determined as previously described. The results are recorded in Table II.

The amount of water associated with 1 g. of protein remained unchanged when the salt-free crystals were placed in concentrated salt solutions. However, ammonium sulfate diffused into the crystal and, on the assumption that ammonium sulfate goes into the water of the protein crystal rather than becoming attached to the protein, the concentration of salt in the water of the protein crystal

(7) Ferry and Oncley, THIS JOURNAL, **63**, 272 (1941).

TABLE II

COMPOSITION OF β-LACTOGLOBULIN CRYSTALS IN THE PRESENCE OF AMMONIUM SULFATE SOLUTIONS AT *p*H 5.2 AND 25°

Am. sulfate in filtrate, wt. %	Hydrated crystal (extr. to zero time), mg.	Dry crystal, mg.	Am. sulfate in crystal, mg.	Am. sulfate in crystal water, wt. %	Concn. am. sulfate in crystal expressed as % of concn. in filtrate	Water per g. dry protein, g.
28.9	(a) 3.30	1.97	0.415	23.8	82.3	0.86
	(b) 5.85	3.55	.719	23.8	82.3	.82
30.2	(a) 7.80	4.82	.915	(23.5)[a]	(77.8)[a]	(.76)[a]
	(b) 2.64	1.62	.328	24.3	80.4	.79
31.6	(a) 4.78	2.88	.683	26.4	83.4	.86
	(b) 6.55	4.00	.910	26.3	83.2	.82
				Average	82.3	.83

[a] Not included in the average.

amounts to about 82% of the salt concentration in the surrounding liquid. This finding is confirmed by density determinations as recorded in the next section.

Direct measurements were made of the length and width of a crystal by means of a micrometer at low magnification before and after placing it in the concentrated salt solution. No change in crystal dimensions was noted. However, the method was sensitive to only about 2% and the calculated increase in the linear dimensions of the crystal due to the presence of ammonium sulfate would be about 2%, assuming that the partial specific volumes of the constituents remain unchanged in the presence of salt. The protein crystals break more easily in the presence of salt than in its absence. This may be an indication of an increase in volume of the protein crystal due to the added salt.

When a β-lactoglobulin crystal, in equilibrium with a 30.2% by weight solution of ammonium sulfate of *p*H 5.2, was heated in boiling water for thirty minutes, the crystal became opalescent and insoluble in water without obvious loss of form. The heat-coagulated crystal contained less water than the uncoagulated crystal, the water content being 0.53 g. per g. of protein. However, the salt concentration calculated on the basis of the water present in the coagulated crystal was found to be the same as in the uncoagulated crystal. When the method of proportionality is applied to the data obtained on the heat-coagulated β-lactoglobulin crystal, a value of 0.15 g. of water per g. of protein is obtained. Adair and Adair[2] obtained values of 0.17 to 0.19 for coagulated egg albumin by means of the method of proportionality.

Density of β-Lactoglobulin Crystals.—The data obtained on density determinations are recorded in Table III. The "density difference" given in the table is the difference between the densities of the solutions of higher and of lower density than the crystal.

The wet crystals were found to increase gradually in density after immersion in the bromobenzene–xylene mixture. There was essentially no change for about five minutes and the densities recorded are based on the initial behavior of the crystals on being placed in the solutions. Since this behavior was independent of the size of the crystal over a range of more than tenfold in weight, it is improbable that the results are appreciably influenced by occlusion of air or other possible surface effects. When the wet crystals had stood for as long as twenty-four hours in

TABLE III

DENSITY DETERMINATIONS ON β-LACTOGLOBULIN CRYSTALS

Preparation	Flotation medium	Density	Density difference
Wet crystals	BBX[a]	1.146	0.004
Dry crystals	BBX	1.260	.003
Wet crystals after standing 24 hrs. in BBX[a]	BBX	1.260	.001
Crystals equilibrated with 30.2% $(NH_4)_2SO_4$	BBX	1.214	.005
Wet crystals	Satd. $(NH_4)_2SO_4$ + Na_2SO_4	1.240	.007
Wet crystals	Sucrose	1.256	.008

[a] BBX refers to mixtures of bromobenzene and xylene.

the flotation medium, their density had increased so that it was precisely equal to that of the dry ones. The water in the crystal had thus evidently been removed, leaving only the anhydrous protein. Crystals which were dried over phosphorus pentoxide did not change in density following immersion and were not influenced by placing the system in a vacuum.

The density of 1.260 for the anhydrous crystal is in good agreement with determinations on other dry proteins. The specific volume of 0.794 for the crystal is thus much higher than the partial specific volume of 0.751 determined in dilute solution.[8] Cohn[9] has pointed out that this difference cannot be accounted for by electrostriction of the solvent as is the case with amino acids.

The density of 1.146 found for the wet crystals is lower than any density previously reported for protein crystals. It is, however, consistent with the high fraction of water found in the crystal. Using the partial specific volume of lactoglobulin $v_p = 0.751$ determined by Pedersen,[8] and assuming that of water to be $v_{H_2O} = 1$, the specific volume of the crystal, $\bar{v}$, can be calculated from the formula $\bar{v} = v_p X_p + v_{H_2O} X_{H_2O}$, where X_p = fraction of protein = 0.54, and X_{H_2O} = fraction of water = 0.46. The density $(1/\bar{v})$ is found to be 1.155. The partial specific volumes of proteins have been found in general to be independent of concentration over a range up to 10 or 15% protein. It is probable that this constancy does not extend to a system which has the composition of the crystals and that v_p is higher than the value assumed above (and v_{H_2O} consequently lower). Any change of this sort would tend to give a better agreement with the observed value.

The higher values reported in the literature for the density of wet protein crystals have all been obtained in aqueous media. In view of the results reported above on the salt content of crystals in ammonium sulfate solution which demonstrate the ease with which salt exchange takes place with the environment, it can be concluded that the density of a protein crystal in equilibrium with its mother liquor cannot be determined by immersion in an aqueous medium of different composition. This is well shown by the density determinations in aqueous media given in Table III. The crystals which had a density of 1 146 in bromobenzene–xylene increased to 1.240 in $(NH_4)_2SO_4$ + Na_2SO_4 and to 1.256 in sucrose because of the diffusion of salt or sugar into the water in the crystal. The difference between the densities in the two aqueous media is similar to that found by Adair and Adair[2] and is evidently due to a difference in the distribution of salt and sugar between the inside and the outside of the crystal. The fact that the observed density in the sugar solution approaches the value for the density of the anhydrous protein indicates that the distribution must be nearly equal in this case.

The density of crystals equilibrated with 30.2% ammonium sulfate was determined in bromobenzene–xylene to be 1.214. The analytical results on such crystals (Table II) show the concentration of ammonium sulfate in the water of the crystal to be 24.4% and the composition of the crystal to be 48.7% protein and 51.3% salt solution. The ammonium sulfate solution in the crystal would have a specific volume of 0.877. From these data and the assumption that the partial specific volume of the β-lactoglobulin is 0.751, the density of the crystal can be calculated to be 1.225 by the method used above for the salt-free solution. The error in the calculation is probably referable to the value assumed for the partial specific volume of the protein.

The use of organic solvents for density determinations on wet crystals has been criticized because of the possibility of irreversible changes caused by the solvents. We have found that crystals which have stood for several days in the bromobenzene–xylene are completely soluble in dilute salt solutions, indicating the absence of denaturation. Any error incurred by the use of such solvents is certainly less than that inherent in the use of salt solutions which yield densities bearing little relation to the density of the crystal in its mother liquor.

Discussion

The hydration of proteins as determined by the "method of proportionality" of Sørensen and Høyrup[1] involves the determination of the nitrogen factor (x) as calculated from the equation $x = 100/P_b[1 - a_b/a_f]$ where a_f is weight per cent. of ammonia nitrogen in the filtrate, a_b is weight per cent. of ammonia nitrogen in the crystal and adhering mother liquor, and P_b is weight per cent. of protein nitrogen in the crystal. The hydration value is obtained by comparing the nitrogen factor of the wet crystals with the nitrogen factor of the anhydrous salt-free protein. Adair and Adair[2] have derived a formula to give the same information from density determinations as is obtained by the "method of proportionality" from analytical data.

Sørensen and Høyrup[1] found the nitrogen factor (x) to be independent of the concentration of salt in the presence of varying concentrations of ammonium sulfate. They considered this to be evidence that salt did not go into the crystal. Table IV shows the results obtained when our data are calculated by means of the proportionality formula.

The nitrogen factor here is found to be independent of the concentration of salt. Direct analysis of these identical crystals shows a con-

(8) Pedersen, *Biochem. J.*, **30**, 961 (1936).

(9) Cohn, *Ann. Rev. Biochem.*, **4**, 93 (1935).

TABLE IV

COMPOSITION OF β-LACTOGLOBULIN CRYSTALS IN THE PRESENCE OF AMMONIUM SULFATE SOLUTIONS AT *p*H 5.2 AND 25° CALCULATED ACCORDING TO SØRENSEN AND HØYRUP

NH_3-N in filtrate (a_f), wt. %	NH_3-N in crystal (a_b), wt. %	Protein N in crystal (P_b), wt. %	Wt. of protein containing 1 g. N (x)
6.13	(a) 2.66	7.35	7.70
	(b) 2.60	7.55	7.63
6.40	(a) 2.49	7.80	7.83
	(b) 2.63	7.64	7.71
6.70	(a) 3.02	7.17	7.68
	(b) 2.94	7.36	7.64
		Average	7.70

centration of salt in the crystal which is apparently a constant ratio of the concentration of salt in the surrounding liquid. If the total water in the crystal and the ratio of the concentration of salt inside the crystal to that outside are independent of the salt concentration, it follows that the nitrogen factor (x) will show a variation of about 0.5% for the salt concentration range used in our experiments. Thus the constancy of the nitrogen factor is not a measure of the freedom of the crystal from salt, and the value of this factor is not related to the total amount of water associated with the protein crystal. This view, that the salt penetrates the protein crystal and that the concentration of the salt in the crystal is about 82% of the salt concentration in the surrounding liquid, independently of the concentration, is strengthened by the results of Chick and Martin[10] on egg albumin in ammonium sulfate solutions. Chick and Martin found that the water in pressed crystalline egg albumin contained less salt than the filtrate. In three experiments the salt present in the pressed crystals amounted to 17.6, 22.1 and 22.4% by weight of ammonium sulfate, while the corresponding filtrates contained 26.9, 27.2 and 28.1% by weight of ammonium sulfate. The percentage ratio of salt inside of the crystals to that of the filtrate is 65.4, 81.2 and 80.0 which compares with our value of 82.3% for β-lactoglobulin.

The finding that ammonium sulfate diffuses into the protein to the extent of 82% of the outside concentration on the basis of water of crystallization may be considered to indicate that the water of crystallization is bound in two different ways, as is the case of water in copper sulfate crystals.[11] The present measurements do not furnish evidence of the distribution of salt in the crystal, although in the calculation of a numerical value for the ratio of the concentration of salt in the crystal to the outside salt concentration, the assumption is tacitly made that the salt is equally distributed in the water of the crystal. Following the formula of Sørensen and Høyrup,[1] the water of hydration for β-lactoglobulin may be calculated as (7.70 − 6.41)/6.41 = 0.20 g. of water per g. of protein, in contrast to the direct experimental finding of 0.83 g. of water per g. of protein.

Adair and Adair's[2] formula may be applied to the experiment in 30.2% ammonium sulfate for which density determinations on the crystals were made. Their formula requires the density of the crystal to be equal to that of the salt solution in which it is suspended and hence it is not directly applicable to the case considered above. However, by the use of the additional analytical data available, a value for the water of hydration of 0.294 g. water per g. of protein can be calculated by their method as compared with the above value of 0.20 g. The application of the method of proportionality to β-lactoglobulin in very dilute salt solutions led M. Sørensen and Palmer[5] to conclude that β-lactoglobulin does not contain "surplus water but, on the contrary, surplus ammonia or ammonium chloride."

Density determinations on protein crystals have been made in connection with X-ray measurements. Crowfoot and Riley[3] thus report values for β-lactoglobulin of 1.257 for the wet crystal in sugar solutions and 1.27 for the dry crystal in organic solvents. These values are in agreement with those found here under similar experimental conditions. Crowfoot realized that the value for the wet crystal was an upper limit, but nevertheless discarded the value for the dry crystal because it was so close to that for the wet crystal. She assumed 1.31 (dry density of insulin) in making her calculations when it was the wet density that was in error. A recalculation from the data of Crowfoot[6] using the density 1.146 for the wet β-lactoglobulin crystal gives a value for the wet molecular weight of 61,100 and on a dry basis (46% water) a value of 33,000.

The molecular weight for an air-dried crystal calculated from the data of Crowfoot,[6] using a density of 1.26, is 39,700. The data in Table I show that our air-dried crystals contained 9.78% water. Applying this correction, an anhydrous molecular weight of 35,800 is obtained.

(10) Chick and Martin, *Biochem. J.*, **7**, 392 (1913), and correction on page 548 of the same volume.

(11) Beevers and Lipson, *Proc. Roy. Soc.* (London), **A146**, 570 (1934).

Crowfoot[6] also has given the dimensions of the unit cell in wet and in air-dried β-lactoglobulin crystals, and the following shrinkages on drying can be calculated for the various dimensions: $a = 11.1\%$, $b = 6.7\%$, and $c = 28.6\%$. In order to correlate the unit cell shrinkage with the macroscopic behavior of the crystal, we have observed the change in dimensions of the crystal on drying in the air in a low power microscope with a micrometer eyepiece. The shrinkages observed in two experiments were: length, 8.5% and 9.9%; height, 6.8% and 7.8%; width, 29.5% and 26.4%. These changes are of the same order as those in the unit cell. The shrinkage of the crystal was also measured in a mixture of bromobenzene–xylene over a period of twenty-four hours. The change in dimensions observed was 9.8% and 31.5% in the length and width, respectively. This confirms the conclusions from density determinations that a dehydrated crystal is obtained after contact with bromobenzene–xylene for twenty-four hours. It also indicates that the water in the crystal is not replaced by the organic liquid. In order to check this point a crystal which had been dehydrated in xylene was wiped and weighed by the technique used previously. There was no change in weight after putting the crystal on the balance or after placing the crystal in an oven at 105°. These measurements, together with the consideration that the densities of vacuum-dried crystals and crystals which stood in bromobenzene–xylene are the same, indicate that in the dry crystal there is no space occupied by air.

The dehydrated crystals obtained with bromobenzene–xylene had good form and a high degree of birefringence as compared with the air-dried crystal. This technique might be used with advantage to obtain completely dehydrated crystals for X-ray examination. In any such application xylene alone should be used as the dehydrating agent because of the tendency of the crystal to become discolored after long standing in the presence of bromobenzene.

It seems likely that previous estimates of the water of hydration of protein crystals are entirely too small, because of the effect of diffusion of salt into the crystals. It may be calculated that the cell shrinkage reported by Crowfoot[6] for crystalline hemoglobin amounting to 46.6% would lead to a hydration value nearer to 0.9 g. of water per g. of protein than the value of 0.18 to 0.30 g. calculated by Adair and Adair.[2,12]

Summary

1. β-Lactoglobulin crystals were found to contain 0.83 g. of water for each g. of anhydrous protein over a wide range of temperature in the absence of salt or in the presence of high concentrations of ammonium sulfate.

2. Ammonium sulfate diffuses rapidly into the β-lactoglobulin crystal; however, the concentration of ammonium sulfate on the inside of the crystal reaches only 82.3% of the salt concentration in the surrounding liquid.

3. The density of wet β-lactoglobulin crystals was measured in organic liquids and was found to be 1.146. This value is consistent with the high water content of the crystal. Values for the density of β-lactoglobulin crystals under various conditions are reported. It is shown that the method of measuring the density of wet crystals in aqueous media is subject to large errors.

PHILADELPHIA, PA. RECEIVED JULY 3, 1942

(12) Since the preparation of this paper, Bailey (*Trans. Faraday Soc.*, **38**, 186 (1942)), has reported that crystalline edestin contains about 0.67 g. of water per g. of protein.

[CONTRIBUTION FROM BELL TELEPHONE LABORATORIES]

Macromolecular Disorder in Linear Polyamides. Relation of Structure to Physical Properties of Copolyamides

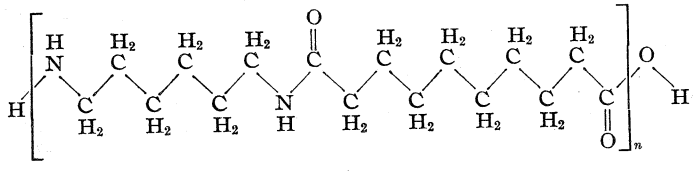
BY W. O. BAKER AND C. S. FULLER

Macromolecular solids are supposed to gain especial strength and continuity because the primary valence bonds of a single chain extend for hundreds of Ångström units and it thus reacts with the force fields of numerous other polymer molecules. Also, the ends of adjacent chain molecules in a given cell are presumed not to be coplanar. Rather, the chains overlap,[1] and thus planes along which ordinary molecular solids are easily sheared and ruptured are actually absent in the polymers. It is desirable to investigate what general chain arrangements (such as dipole association) are characteristic of these especial physical properties of polymer solids.

The present report includes the results of X-ray diffraction and elastic modulus measurements on several linear polyamides.[2] Simple relations between the mechanical properties of the molecular solids, and the atomic constitution and relative positions of the long chains have been found.

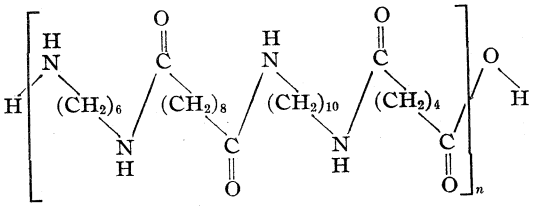
Experimental

Materials.—The linear polyamides studied are obtained from the controlled reaction of dibasic acids and diamines.[3] For the aliphatic series, a single dibasic acid and a single diamine yield a simple linear polyamide which is described by two numbers: the first, the number of C atoms in the diamine chain; the second, the number in the acid chain. Thus, polyhexamethylene adipamide, from hexamethylenediamine (1,6-diamino-hexane) and adipic acid, is a 6–6 polyamide, polyhexamethylene sebacamide is a 6–10 of the typical formula



Various diamines and various dibasic acids may react together to form copolyamides, as shown by Carothers' work.[4] These contain the base units presumably randomly distributed (see a later discussion) along the chain, but always in the sequence dibasic acid–diamine–dibasic acid–, etc. The randomness varies with the relative amounts of different diamines and/or different acids.

A representative copolyamide chain containing 50–50 proportions of the 6–6 and 10–10 base units is



For convenience in describing the copolyamide series studied here, each composition has been considered to arise from the random mixture of the components of simple polyamides which have also been studied. No polymers containing more than two different diamines and two different dibasic acids are discussed below, so that the compositions of the series are recorded as the molar percentage of one pair (giving one simple polyamide), say 6–6, in another, say 6–10. Such grouping of constituents does not, of course, imply that order in the reaction products.

The polymers were obtained either commercially or according to the published procedures. The intermediates were carefully purified and each polymer represents a well-characterized compound containing a statistical distribution of chain lengths. All polymers were of weight average molecular weight, M_w, greater than 10,000, as estimated from viscosities.

X-Ray diffraction patterns were obtained for both unoriented and cold drawn[2] polyamides. The latter were highly oriented fibers; both types of samples were first studied quenched from the melt, and then annealed to states of maximum crystallinity.[5,6] The determinations of Young's modulus and moisture sorption were made on sheets molded in a nitrogen atmosphere between plane plates and uniformly annealed. Each was 3 × 2 cm. and 0.051 cm. thick. These specimens were conditioned or dried over phosphorus pentoxide before measurement.

X-Ray Methods.—Copper characteristic radiation, nickel filtered and carefully collimated, was directed through rigidly mounted samples onto a cassette containing the film. Each oriented sample employed for estimation of the repeating distance, I, along the fiber axis was dusted with finely ground and screened sodium chloride, whose Debye–Scherrer rings superposed on the fiber pattern served as a primary standard for the distance determinations on each photograph. The fibers were flat, and of approximately 18-mil thickness; the salt was always dusted on both sides. Repeated exposures of each composition facilitated selection of an exposure time giving the optimum intensity of the features measured. This was essential for the copolyamides possessing the middle concen-

(1) This was suggested by H. Staudinger, see Staudinger and Signer, *Z. Krist.*, **70**, 193, 202 (1929).

(2) "The Collected Papers of W. H. Carothers," Interscience Publishing Company, New York, N. Y., 1940.

(3) Carothers, U. S. Patent 2,071,250.

(4) U. S. Patents 2,130,948 and 2,191,367.

(5) Fuller, Baker and Pape, THIS JOURNAL, **62**, 3275 (1940).

(6) Baker, Fuller and Pape, *ibid.*, **64**, 776 (1942).

trations of components, since their "identity period" spots were relatively diffuse. The X-ray negatives were measured on an improved light box of the type described by Klug.[7]

All of the I, Å. values reported were obtained on separately repeated photographs with a precision of ±0.3 Å.

Elastic Modulus.—Young's modulus was computed from the elastic indentation of a spherical quartz segment in a plane panel of the polymer. For such a penetration

$$E = c\frac{L}{d^{3/2}D^{1/2}} \qquad (1)$$

where E is Young's modulus in dynes per sq. cm., c is a constant, L is the load on the sphere, in grams, D is its diameter, in cm., and d is the depth (cm.) to which the sphere sinks below the surface under the weight.[8,9] This depth was read five seconds after application of the load. The latter was chosen so that only elastic and no permanent deformation occurred, except for a few of the softest compositions. For the latter, E is modified by a plasticity factor (yield point), but it still characterizes the polymer.

The measuring apparatus is essentially a Pfund hardness tester. A heavy steel lever with the fulcrum at one end contains the quartz spherical segment in the center and a platform for the load weights on the other end. The quartz segment is ground on the end of a quartz cylinder. Coaxially with this cylinder and above the lever is mounted a microscope fitted with a Leitz ocular micrometer. Since the refractive index of the quartz–polymer interface differs from that of the quartz–air interface, the intersection of the plane of the surface of the test material with the periphery of the quartz segment produces a dark disc in the microscope field. The diameter of this highly magnified disc is measured with the micrometer. The radius of the sphere corresponding to the quartz section, $D/2$, is 3.24 mm. When r is the radius of the dark disc, the depth of impression, d, is given by

$$d = 0.324 - \sqrt{(0.324)^2 - r^2} \qquad (2)$$

Numerous readings were obtained and averaged for each dried sample, at 25 ± 2°.

Moisture Sorption.—Samples of equal dimensions were dried to equilibrium over phosphorus pentoxide, in glass-stoppered weighing bottles, weighed and reweighed after equilibration at 100% R. H. in water at 25.0 ± 0.5°.

Results and Discussion

Crystalline Nature of Linear Polymers.—The molecules of *n*-paraffins and their derivatives have been shown to lie in the crystal as extended chains whose terminal groups formed planes in some cases perpendicular and in others oblique to the long chain axes.[10,11,12] Linear polymers such as polyoxymethylenes, polyesters and polyamides likewise possess chains, and a series of studies has indicated analogous structures except that the repeating polar groups of the polymers replace the terminal groups of the monomers in generating the characteristic planes recurring along the chain axes.[1,13,14,15] However, other investigations[5,6] have emphasized sharp differences, and especially imperfections, in the crystalline state of macromolecules compared to ordinary molecular crystals. The molecules are of non-uniform size; the chains comprise a distribution of lengths clustering about an average value.[16] Also, they presumably do not lie like extended rods for their whole length in the polycrystalline solid but are highly kinked.[17,18] The crystalline content profoundly affects the physical properties of the solid polymers and can be readily varied by thermal treatment: quenching produces minimum and annealing maximum crystallinity.

Amid the complexity, striking generalities about these polymer solids appear. The polar groups which repeat along the chains always associate strongly to form dipole layers. The interaction in these layers and their concentration per unit volume govern the internal energy, melting point and strength of the solids. Such interaction is especially significant in the polyamides, where, as in the proteins, both ordinary dipole attraction and also hydrogen bonding obtain. Laterally, the chains pack somewhat similarly in all of the compounds, although even the lateral packing is a function of the structure of the polar layers. (Also, the chains do not necessarily assume planar zigzag configurations.) We shall thus regard the dipole layers, distributed through the polycrystalline mass as though imbedded in a paraffin chain matrix, as the critical factors in the solid structure. In the studies below, (1) the separation of these planes has been varied by varying the number of methylene group "spacers" in the base units of the simple polyamides. The (2) population of polar groups in the average planes has been varied by copolymerization, for, in adjacent chain sections containing mixed base units, if the polar groups coincide at one point, they will often fail to do so further along the same chains, because of unequal methylene group spacing. This factor is represented to scale in Fig. 1, for the 50% composition of the 6–6:6–10 copolyamide. The circles indicate the polar groups

(7) Klug, *Ind. Eng. Chem., Anal. Ed.*, **12**, 753 (1940).
(8) Larrick, *Bull. Am. Phys. Soc.*, **14**, 17 (67) (1937).
(9) Davies, Miller and Busse, THIS JOURNAL, **63**, 361 (1941).
(10) Müller, *J. Chem. Soc.*, **123**, 2043 (1923).
(11) Müller, *Proc. Roy. Soc.* (London), **A120**, 437 (1928).
(12) Malkin, *J. Chem. Soc.*, 2796 (1931).
(13) Hengstenberg, *Ann. Physik*, **84**, 245 (1927).
(14) Fuller, *Chem. Rev.*, **26**, 143 (1940).
(15) Fuller, Frosch and Pape, THIS JOURNAL, **64**, 154 (1942).
(16) Schulz, *Z. physik. Chem.*, **B32**, 27 (1936).
(17) Kuhn, *ibid.*, **A161**, 1, 247 (1932).
(18) Meyer, *Z. Elektrochem.*, **45**, 225 (1939).

along the chains. Thus, fewer of them can inhabit the average planes, and, also, the displaced polar units are, in general, surrounded by hydrocarbon groups. They are effectively sheathed from contributiing to the dipole interaction. The copolymerization also alters the apparent average plane separation (in addition to the plane population) in striking and still unexplained fashion. Finally, (3) the order in the dipole planes has been modified by both changes in population (whereby hydrocarbon chains occupy defect sites in the layers) and by quenching (whereby the groups are turned out of the most stable positions in the layers[5]).

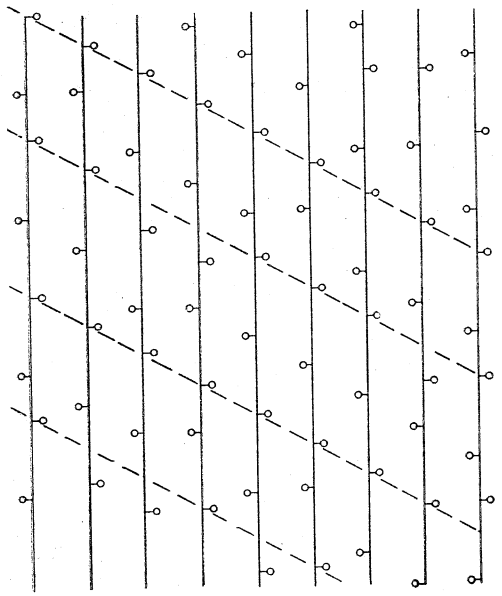


Fig. 1.—Formation of polar layers in 50% 6-6 and 50% 6-10 copolyamide (schematic).

Spacing of Dipole Layers.—Either layer-line or meridian reflections[19,20] on the fiber diagrams yielded several orders of the identity period, I. This we associate with the separation of successive planes of polar groups tilted or normal, as the case may be, to the chain axes. Less directly, I represents the identity period within the molecules. A possible formation of these layers in the 6–6 polyamide is represented schematically in Fig. 2. Actually, disorder may occur in this idealized arrangement. For instance, a polar linkage in a given chain is formed by an A–D (acid–diamine) union. The associated linkage in an adjacent chain may result (in the same direction along the

(19) Polanyi, *Z. Physik*, **7**, 149 (1921).

(20) Katz, "Die Röntgenspektrographie als Untersuchungsmethode," Urban and Schwarzenberg, Berlin, 1934.

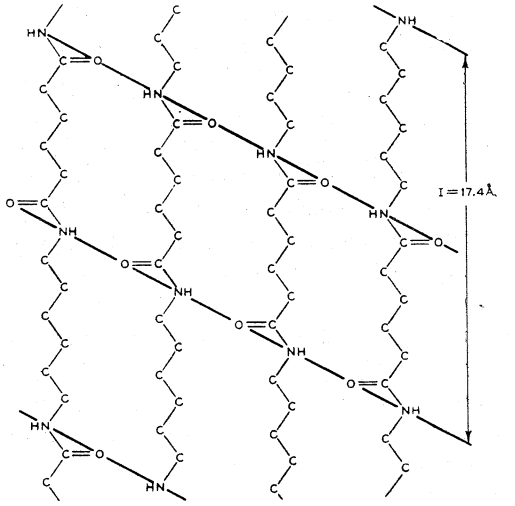


Fig. 2.—Layer structure resulting from association of polar groups in polyhexamethylene adipamide (schematic).

chain axis as above) from a D–A union. This phenomenon leads to a displacement of certain succeeding polar groups along the chains, and thus causes disorder in the system. This condition can be seen by turning one of the chains in Fig. 2 end-for-end about a C=O axis. Such "chain inversion" in adjacent segments in the solid must be considered in the structures of all polymers of the types considered here.

Figure 3 relates the structural property, I, to a thermodynamic quality, the melting point, of simple polyamides. The triangles are the spacings calculated for a plane, zigzag chain containing no kinks or bends between the diffracting planes. The best interatomic distances were used.[21]

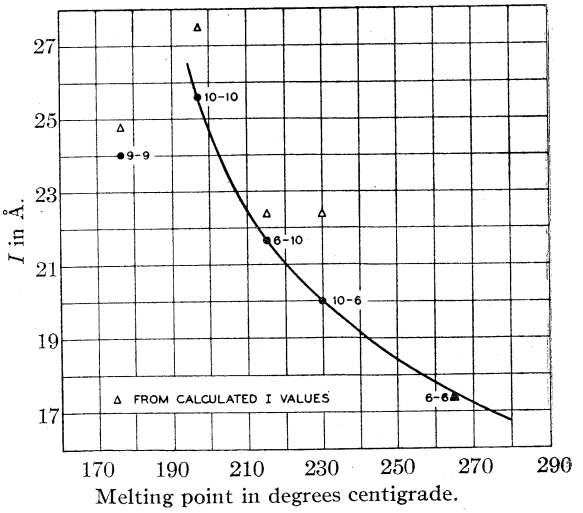


Fig. 3.—Relation of interplanar spacing, I, to melting points of linear polyamides.

(21) Astbury, *Chem. and Ind.*, **60**, 491 (1941).

Only for polyhexamethylene adipamide (6–6) do the calculated agree with the observed values. The observed spacings in the other polyamides are, although carefully checked, always short. It appears that chain tilting or twisting *between* the planes defining the period I may occur. Figure 3 gives independent evidence of diminished plane separation and attendant closer packing. The observed points, except those of polynonamethylene azelamide (9–9), lie on a smooth curve; the calculated points cannot be thus connected. The greater the I, the lower the melting point, because the fewer the polar groups per unit volume to contribute to the mol cohesion. But, the comparison of polyhexamethylene sebacamide (6–10) with polydecamethylene adipamide (10–6) and of 9–9 with the rest of the series emphasizes further significance of the separation. When the dipole planes are oblique to the chain axes, the chains are "tilted" and pack more closely than when the chains are vertical and the planes perpendicular; the lattice energy is higher. This was strikingly demonstrated for the paraffin derivatives.[12,22,23,24] From the X-ray results for 9–9, its chain sections are essentially in the perpendicular form; a low melting point is implied. If its chains were in the form of the other polyamides, it should melt at 202°; a 27° lower value is found, 175°. Further, 6–10 and 10–6 have the same calculated I, their chains are in the tilted form, and if they had the same sort of interplanar modification to explain the shortened observed I, they should melt at the same temperature. However, 10–6 exhibits a markedly reduced I, closer packing is expected, and the observed melting point is 15° higher than for 6–10. The association

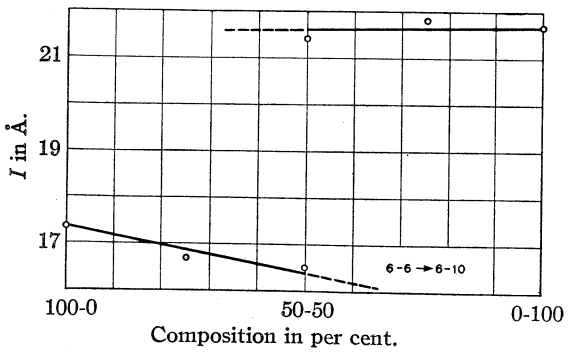


Fig. 4.—Variation of the spacing I with composition of a mechanical mixture of the polyamides 6-6 and 6-10.

(22) Müller and Saville, *J. Chem. Soc.*, **127**, 599 (1925).
(23) Garner, van Bibber and King, *ibid.*, 1533 (1931).
(24) King and Garner, *ibid.*, 1449 (1934).

of the lattice energy with the spacing between dipole layers and their concentration per unit volume is thus established. The vertical form of the odd-membered (9–9) polyamide chains has been proposed to result from the alternating directions of the interchain dipole association, as generally found for polymers formed from odd-membered base units,[25] in addition to the favorable hydrogen bonding of the vertical form.

Mechanical Mixture Patterns.—We proceed next to consider the effect on I and on the solid state properties of mechanical mixtures of two simple polyamides. Can the effective spacings in the lattice be thus altered? The molar proportions indicated in Fig. 4 of 6–6 and 6–10 were fused and thoroughly mixed under hydrogen at 280°. Fibers were drawn, and the patterns of both polymers appeared on each photograph obtained. These are illustrated in Fig. 5C. However, the component present in 25% amount gave features too weak to measure well, and these points have been omitted from the graph. While there appears to be some systematic decrease of I with increase in added polymer, the respective contributions to the structure are relatively independent. Similarly, the crystallization appears to be separate, although the melting points of the mixtures lie surprisingly near the figures for the higher melting component, 6–6. The mechanical and structural effects of mechanical mixture are slight. Interestingly, although the two polymers differ by only four carbon atoms in the acid chains, mixed crystal formation was undetected. The same result arose for mixtures of polyesters[26] and also of ten- and twelve-membered polyoxymethylenes[13]; the individual patterns (from the end-group planes) persisted. When, however, the polyoxymethylene chains were very long and of a distribution of lengths, a single pattern was found, involving repeating distances within the chains. We show below that when a mixture of base units in the solid is effected by co-reaction rather than mechanical mixture of chains, a single pattern with an "identity period" depending on composition is obtained.

Copolyamide Patterns.—The curve for the copolyamide 6–6 :6–10 in Fig. 6 (the data for all of the series are in Table I) resembles Fig. 4 but the diagrams of the former showed always but one set of I spacings, in contrast to the mechanical mix-

(25) Yager and Baker, THIS JOURNAL, **64**, 2164 (1942).
(26) Fuller, *Ind. Eng. Chem.*, **30**, 472 (1938).

tures. The copolyamide structure exhibits a rapid change in the neighborhood of 50%, and here, also, the diffuse scattering is greatest and the population of the scattering planes least. The melting point is near the minimum and the polymer is softest, with greatest molecular disorder. The concentration variation of I in the similar system containing the components of 6–6:10–6 also has a rapid change in the 50% region, but here the altered structure of the 10–6, remarked above, is evident as a down slope of the I curve on the 10–6 side. In both the 6–6:6–10 and 6–6:10–6 series, and the 6–10:10–10 and 10–6:10–10 subsequently discussed, the introduction of a single new acid or single new diamine so that it just exceeds in molar concentration the other acid or other diamine, respectively, causes the sharp change in spacing. That is, keeping the diamine constant and changing the relative concentration of the dibasic acids, or keeping the acid constant and changing the diamines, causes this characteristic sharp shift of I around 50%.

TABLE I

Composition, mole per cent. 6–6	9–9	I, Å. calcd.	I, Å. obs.	$E \times 10^{-9}$ (dynes, sq. cm.)	Per cent. water sorption 100% R. H.
100	0	17.4	17.4		
80	20		16.6		
66	33		16.2		
60	40		16.8		
50	50		20.2		
33	66		20.9		
0	100	24.9	24.0		
6–6	6–10				
100	0	17.4	17.4	3.6	10.1
66	33		16.8	2.2	5.6
59	41		17.0		
30	50		20.9	1.1	4.3
33	66		21.1	1.6	5.0
0	100	22.4	21.7	2.2	3.0
6–6	10–6				
100	0	17.4	17.4		
60	40		20.9		
40	60		20.9		
20	60		20.7		
0	100	22.4	20.0		
6–6	10–10				
100	0	17.4	17.4	3.6	10.1
80	20		16.5	1.9	5.7
66	33		16.1	1.2	4.5
50	50		22.3	0.8	4.7
33	66		24.1	1.1	3.7
20	80		26.3	1.3	3.5
0	100	27.5	25.6	1.3	2.0
6–10	10–6				
100	0	22.4	21.7		
66	33		21.7		
50	50		22.6		
33	66		21.2		
0	100	22.4	20.0		
6–10	10–10				
100	0	22.4	21.7		
60	40		20.5		
45	55		21.5		
30	70		24.4		
0	100	27.5	25.6		
10–6	10–10				
100	0	22.4	20.0		
60	40		23.7		
45	55		25.9		
30	70		26.6		
0	100	27.5	25.6		

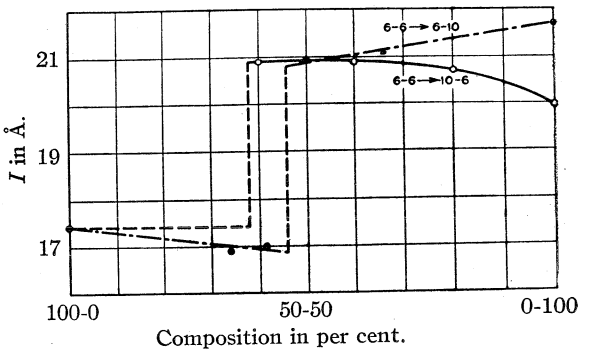


Fig. 6.—Variation of the spacing I with composition of copolyamides: hollow circles, 6-6:10-6; filled circles, 6-6:6-10.

When the constituent units are made longer, but when still only an acid or a diamine, not both, is varied, the phenomena of Fig. 7 result. For the system 6–10:10–10, the "transition" range is broadened. The concentration of the dipole layers per unit volume is decreased, compared to the earlier series, and there is enhanced opportunity for defects in their population, *i. e.*, there is more hydrocarbon matter in which a polar linkage may become isolated. Some illustrative patterns from this series are shown in Fig. 8. The 55–45 (8C) copolymer exhibits the characteristically diffuse reflections corresponding to the layer line spots of the ordered structures. Throughout the series, normal equatorial features can be obtained, in support of the concept that the lateral packing is essentially constant despite changes in the dipole layer spacing. The data for 10–6:10–10 really only define the 10–10 side of the curve in Fig. 7, but have a pronounced maximum in I when about 70% 10–10 is introduced. This may occur partly because the peculiar 10–6 structure perturbs and lessens the factors causing the generally shortened I.

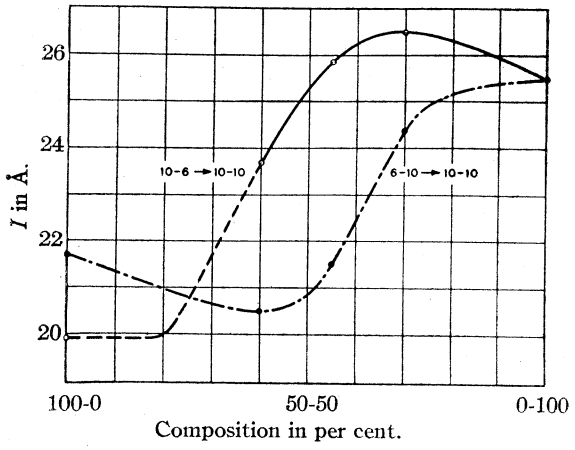


Fig. 7.—Variation of the spacing I with composition of copolyamides: hollow circles, 10-6:10-10, filled circles, 6-10:10-10.

Figure 9 represents the behavior of series in which two dibasic acids and two diamines occur as variables. All of the base units are of different lengths; there is increased scrambling, and the change in I occurs over a very broad concentration range. For 6–6:10–10, addition of the longer components first depresses the I values, then a steep and broad increase leads to a maximum from which still further addition of longer units again decreases I to the figure for pure 10–10. The crystallinity, melting point and elastic modulus are persistently low through the 20 to 80% range. The large and rapid change in the average interplanar spacing is accompanied by much defection in the layers.

The 6–6:9–9 data reflect a new variable of structure. As noted before, the dipole planes of polynonamethylene azelamide (9–9) are essentially vertical to the chain axes, whereas those of 6–6 are tilted. Thus, different features as well as different distances appear on the photographs. At high concentrations of either (arbitrary) pair of components, the patterns of the other are invisible, but at intermediate proportions, features suggestive of both patterns appear and yield the same d values. Thus, each structure is modified quantitatively by components leading to the presence of the other. Figures 10A and 10D illustrate the different structures of 6–6 and 9–9 whereas 10B represents qualitatively the 6–6 structure. However, the 50% composition is dominated by the 9–9 form. The contrast in sharpness of the 50% and 100% 9–9 meridian spots again emphasizes the disorder in the copolyamides.

Figure 11 provides independent evidence for previous interpretations. The components plotted there, 6–10 and 10–6, have the same calculated I. Thus, various molar percentages of the pairs should result in constant identity periods. Of course, this is affected by the shortening found in pure 10–6, but, further, a maximum in I occurs near the usual 50% transition region. It is again as though in the region of maximum scrambling of polar groups, where there are most defects in plane population, the additive scattering produces a concentration on the film corresponding to an increased average plane separation. That is, planes capable of producing the I features occur with diminished frequency throughout the crystals because beginning with one plane, additional progression (than normal) is needed to find enough polar groups organized together to form another.

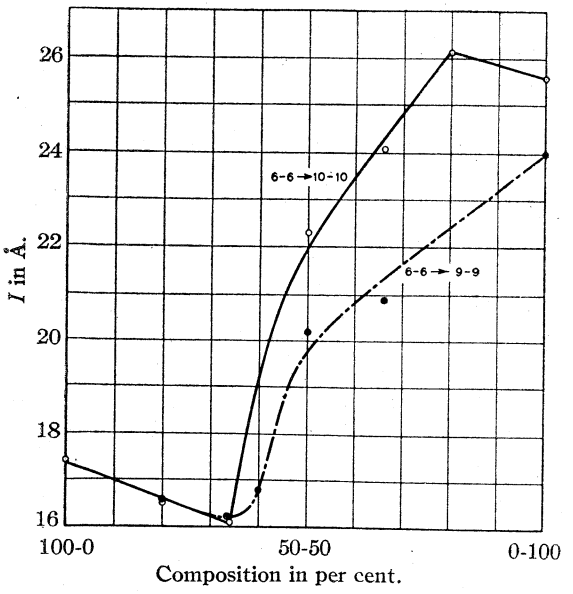


Fig. 9.—Variation of the spacing I with composition of copolyamides: hollow circles, 6-6:10-10; filled circles, 6-6:9-9.

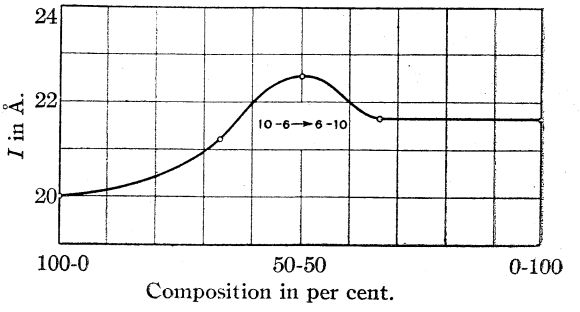


Fig. 11.—Variation of the spacing I with composition of the copolyamide 10-6:6-10.

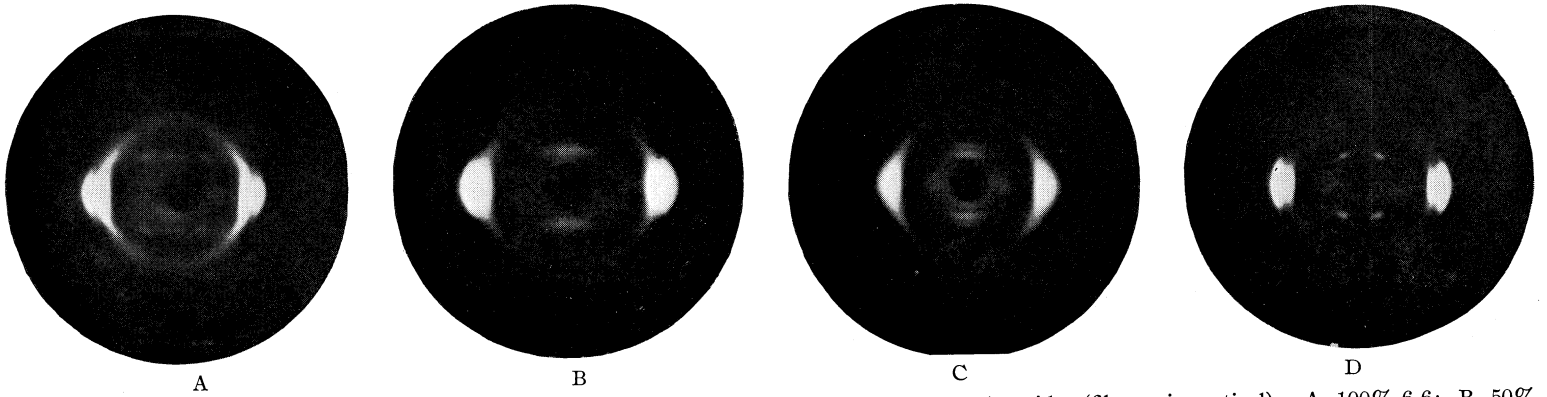


Fig. 5.—Effects of copolymerization and mechanical admixture on X-ray patterns of oriented polyamides (fiber axis vertical): A, 100% 6-6; B, 50% 6-6 :6-10 copolymer; C, 50% 6-6 :6-10 mechanical mixture (quenched); D, 100% 6-10.

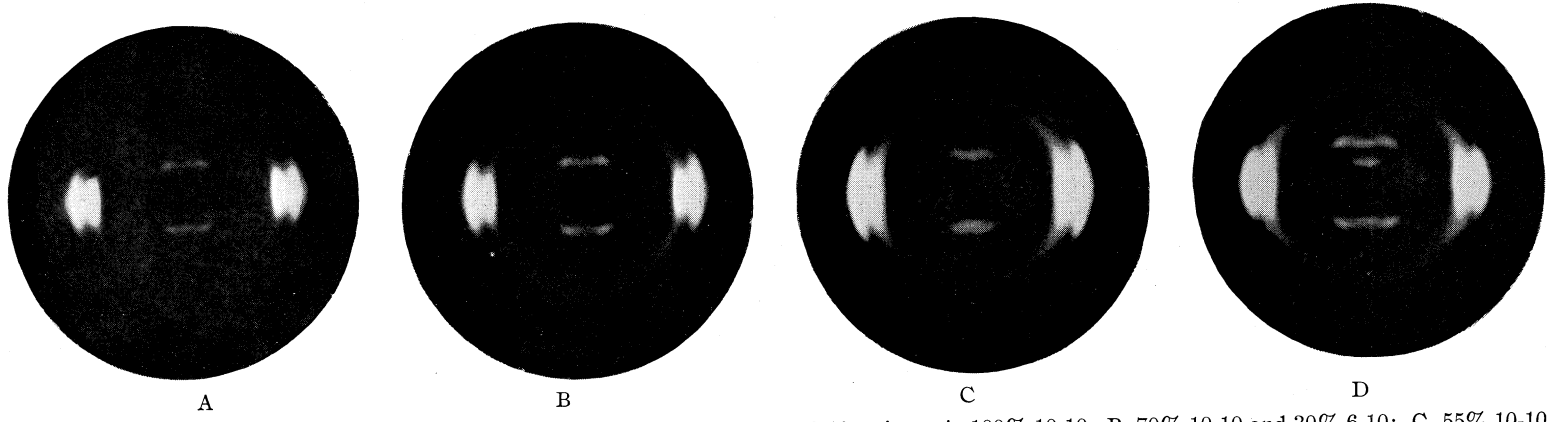
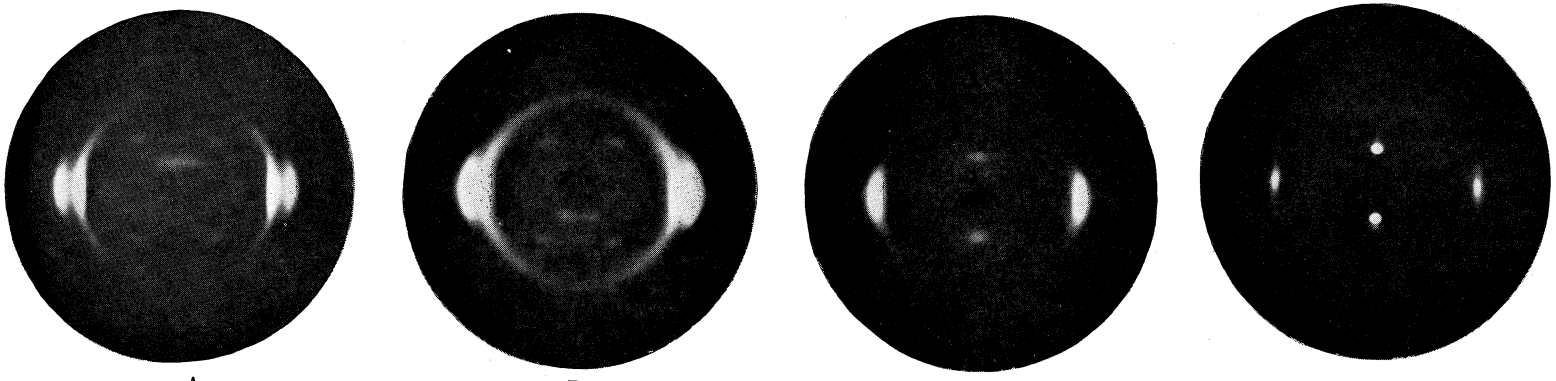
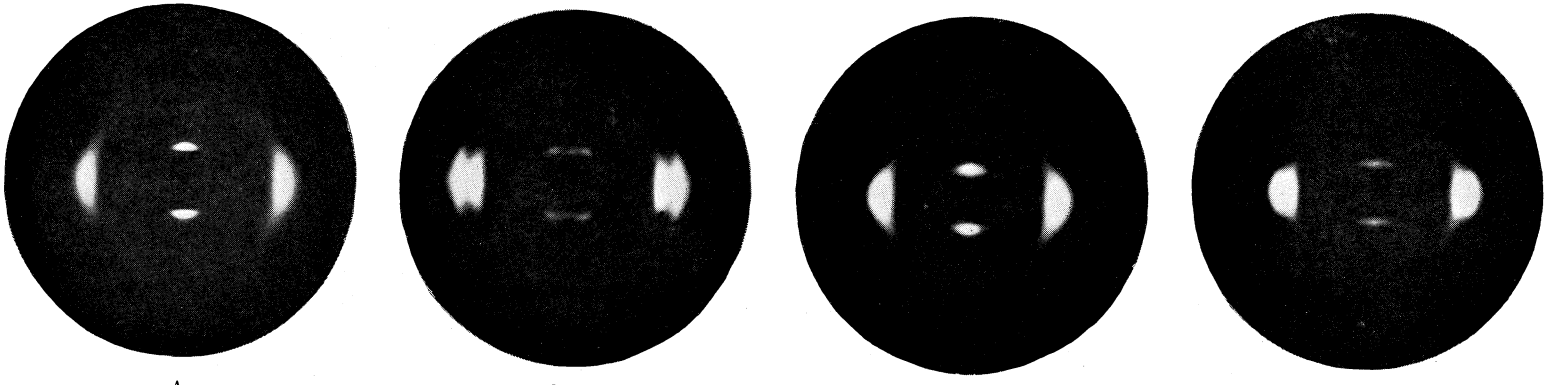


Fig. 8.—X-Ray patterns of oriented polyamides and copolyamides of the 10-10 :6-10 series: A, 100% 10-10; B, 70% 10-10 and 30% 6-10; C, 55% 10-10 and 45% 6-10; D, 100% 6-10.



A B C D

Fig. 10.—X-Ray patterns of oriented polyamides and copolyamides of the 6-6 :9-9 series: A, 100% 6-6; B, 80% 6-6 and 20% 9-9; C, 50% 6-6 and 50% 9-9; D, 100% 9-9.



A B C D

Fig. 12.—Effect of heat treatment on X-ray fiber patterns of typical polyamide and copolyamide: A, 100% 10-10, quenched; B, 100% 10-10 annealed; C, 80% 10-10 and 20% 6-6 quenched; D, 80% 10-10 and 20% 6-6, annealed.

Equivalently, a large I may result from irregularities in a given long molecule, such as periodic twisting. This is adjunctive to the decreased plane population and enhanced amorphous content already noted for the middle concentrations. A statistical analysis would be required for proof of the preceding hypothesis.

Salt pairs reacted in the formation of the present polyamides,[3] *i. e.*, the salt of the organic base (diamine) and acid was used for a given polymer. If the components react randomly, independent of this salt grouping (which is reflected in the symbols 6–10:10–6, etc.), the 50% concentration in the 6–6:10–10 and 6–10:10–6 series should be the same. Accordingly, equal melting points are found and the I values agree, as seen from Table I.

None of the copolyamide series follows the linear change of I with composition calculated by simple weighted averaging of the constituent units. Thus, they do not follow Vegard's rule for ordinary mixed crystal formation. This rule was approximately observed for the single spacings from mixtures of *n*-fatty acids, by Ott and Slagle.[27] The intrachain nature of the polyamide mixture causes the new behavior.

Quenching of all the copolyamides caused extensive lateral disorder of the chains, including the groups in the dipole layers. This was inferred from the large background scattering and blurring of features, and especially from the characteristic[5] replacement of the two side spacings (4.40 and 3.70 Å.) occurring in the highly crystalline state by a single spacing (4.18 Å.). This indicates that the chains are turned in all directions about their long axes. Annealing (at 20 to 50° below the melting points, in general) was found in all cases to cause rotation of segments in the solid state into the ordered, crystalline array, and a marked hardening of all samples. The temperature (thermal energy) necessary for annealing was in all cases, however, less the greater the dipole layer separation, and the larger the number of defects introduced into the layers by copolymerization. Annealing of the fiber samples always effected a sharpening of the I features as well as resolution of the equatorial spots. Typical examples of these changes appear in Fig. 12, where quenched fiber patterns are compared with those produced by annealing in the solid state. This annealing was evidently effected without loss of orientation since the drawn fibers were annealed and not redrawn.

(27) Ott and Slagle, *J. Phys. Chem.*, **37**, 257 (1933).

Incidentally, when certain of the oriented copolyamides were annealed, especially near the 50% compositions, spontaneous elongation, as observed on cooling stretched rubber, occurred on cooling. This indicates again a partial content of amorphous, kinked chains[5] which straighten as they crystallize.

Elastic Properties.—The graph of Young's modulus in Fig. 13 shows the composition dependence and the abrupt change at 50% of the 6–6:6–10 copolyamide. The diffraction results predict such behavior in support of the concept that the separation, order and population of the dipole layers dominate the internal energy. If the E values reflect the force necessary to displace the chain sections from their equilibrium positions, such motion is markedly easiest when disorder is greatest. We regard the 50% composition as representing the minimum of both crystalline content and order in the crystallites. The elastic modulus can thus be interpreted by structural knowledge of the dipole layers.

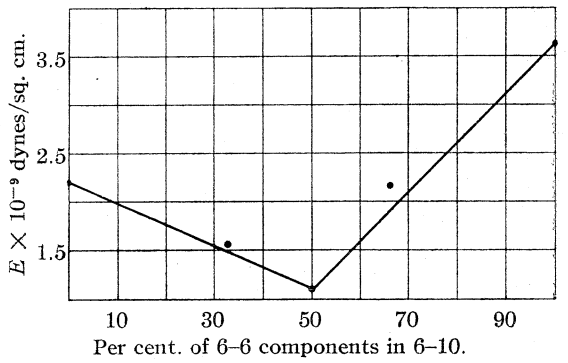


Fig. 13.—Dependence of Young's modulus, E, on composition of the copolyamide 6-6 :6-10.

The dependence of E on composition in the 6–6:10–10 series of Fig. 14 differs from Fig. 13, again in agreement with the X-ray results. The minimum for E is shallow and broad, corresponding to the relatively continuous I variation through the system. Traced from the 6–6 side, E in Fig. 14 falls off on addition of 10–10 components considerably more steeply than in Fig. 13, from addition of 6–10 components, in which only one new unit, the 10 acid, is introduced. The I values follow, respectively, a similar course. The triangle in Fig. 14 was obtained for a sample of relatively short chain-length in which crystallization was more complete than in the high polymers. The higher E shows the importance of crystallite formation as well as copolymeriza-

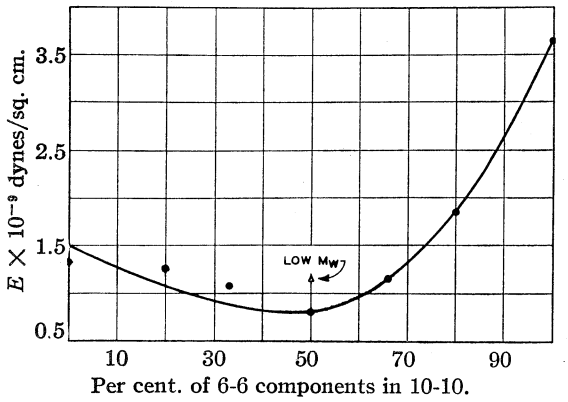


Fig. 14.—Dependence of Young's modulus, E, on composition of the copolyamide 6-6:10-10.

tion in the solids' properties. On the other hand, the significance of the latter factor is repeatedly evident; a new example appears from comparison of the pure 6–10 and the 33% 6–10 polymers of the 6–6:6–10 series in the plot of Fig. 15. These have the same E and virtually the same melting points. Although the disorder is greater in the 33% compound than in the 100%, the former's crystallites contain so many more polar groups because of the 6–6 content that the lattice energies of the two are nearly equal. The maximum disorder in the 50% composition causes it to fall off the line in Fig. 15. Its crystallite content is so sharply reduced compared to the rest of the series that E is reduced beyond the value proportional to the melting point of the remaining crystalline regions.

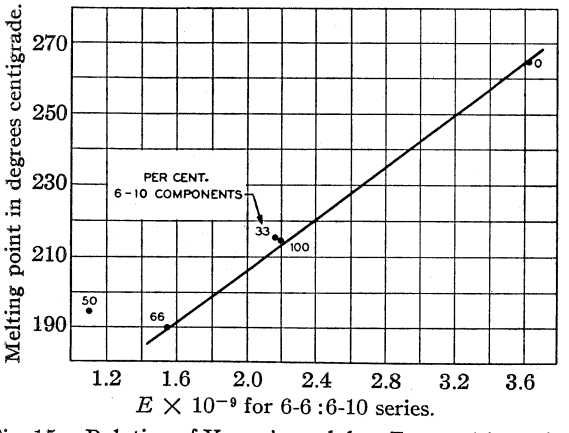


Fig. 15.—Relation of Young's modulus, E, to melting point in 6-6 :6-10 series.

Moisture Sorption.—The polar groups in polymers provide loci of water sorption; only minute amounts of moisture are taken up by non-polar solids like polystyrene or polyethylene. Hence, the preceding ideas of dipole layer population may be further tested by sorption measurements. The greater the concentration of polar groups in the simple polyamides, the higher their sorption; this is the chief factor also in the copolyamides and appears for both types in Figs. 16 and 17. Both series show inflection of the sorption

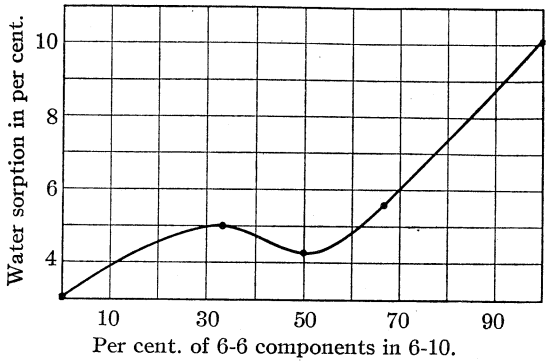


Fig. 16.—Relation of water sorption at 100% R. H. and 25° to composition of the copolyamide 6-6 :6-10.

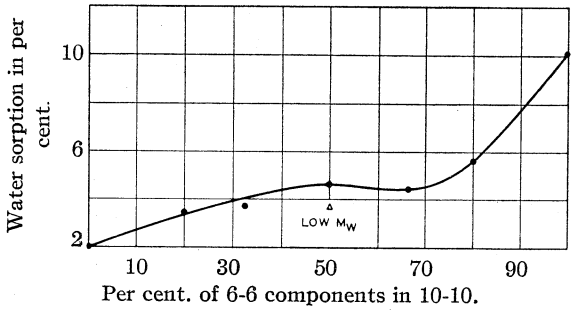


Fig. 17.—Relation of water sorption at 100% R. H. and 25° to composition of the copolyamide 6-6:10-10.

curves in the middle regions of concentration, in accord with the X-ray and elastic modulus determinations. When defects are introduced in the layers by copolymerization, the displaced polar groups are uncompensated by association with other dipoles and can bond with water. This presumably causes the maxima in Figs. 16 and 17. However, the exact significance of the maxima's positions is obscured because the "freed" polar linkages occur immersed in paraffin surroundings (from the methylene portions of the chains). This is a hydrophobic environment, so the water content is not affected as sensitively by disorder as the other properties studied. However, such qualities of technical importance as moisture sorption have not previously shown this direct connection with molecular structure in polymer materials.

A large portion of the water sorption is sup-

posed to be in non-crystalline regions of the polymers. Furthermore, the total polar group concentration changes gradually and continuously in a given series. Hence, the percentage taken up should not be so sensitive a function of composition as I, the spacing in the crystallites. This is confirmed by the data of Table I or by comparison of Figs. 16 and 17.

Acknowledgment.—We are grateful to Dr. B. S. Biggs and Mr. R. H. Erickson, who prepared many of the polymers, especially to Mr. N. R. Pape, who gave valuable assistance in the X-ray studies, and to Mr. J. H. Heiss, Jr., for the determinations of Young's modulus and moisture sorption.

Summary

Thirty-one linear polyamides and copolyamides of varying crystal structures and concentrations of polar linkages along the chains have been studied as fibers and as polycrystalline sections by X-ray diffraction. Also, the elastic modulus and moisture sorption were determined on typical samples of the polymers.

The series represents a range of solid polymers from soft to porcelain-like in properties, with several-fold variation in Young's modulus. The polar linkages which join the paraffin sections of the base units together in the long chains associate in adjacent macromolecules to form hydrogen-bonded dipole layers. This interaction is supposed to govern the physical properties of the solids. By this concept it was possible to interpret systematically the melting points, hardness, elastic modulus and moisture sorption of the solids in terms of the concentration, separation, population and perfection of the dipole layers. Disorder introduced by copolymerization in which dipoles were shifted randomly along the chains altered the average dipole layer separations and also replaced polar groups in the layers by hydrocarbon chain sections. Such disorder caused marked softening of the solids. It likewise caused the X-ray identity periods along the chains to vary with composition of the copolyamides in a novel fashion. Periods were found in the copolymers both larger and smaller than those which arise from any simple polyamides made from the same base units.

Macromolecular solids containing some crystalline regularity may apparently be treated as defect systems in which, nevertheless, relatively simple factors such as the position and organization of interacting polar groups govern physical properties.

NEW YORK, N. Y. RECEIVED MAY 20, 1942

[COMMUNICATION NO. 38 FROM THE LABORATORIES OF DISTILLATION PRODUCTS, INC.]

Crystalline Aliphatic Esters of Vitamin A[1]

BY JAMES G. BAXTER AND CHARLES D. ROBESON

This Laboratory is engaged in the preparation of the pure growth promoting factors in fish liver oils. As part of this program three crystalline aliphatic esters of vitamin A have been prepared: vitamin A acetate, vitamin A palmitate, and divitamin A succinate. Since in fish liver oils vitamin A is esterified with aliphatic acids, such as palmitic,[2] these crystalline esters are suitable for the study of vitamin A as it occurs naturally. Vitamin A β-naphthoate, a previously prepared crystalline ester,[3] was also made to compare it with the aliphatic esters. It had the undesirable property that the aromatic nucleus contributed extraneous absorption at 328 mμ.

This paper is concerned with these properties of the esters: (a) their resistance to atmospheric oxidation, (b) their extinction coefficients at 328 mμ and of their antimony trichloride blue colors at 620 mμ, (c) their biological potency compared with that of crystalline vitamin A. Part (c) is a preliminary report of bioassays made by Dr. P. L. Harris of this Laboratory.

The esters were made by esterifying crystalline vitamin A[4] with the appropriate acid halide. The yields of ester were sharply reduced when potent vitamin A concentrates ($E^{1\%}_{1\,cm.}$ 328 mμ = 1200 or greater) were esterified instead of crystalline vitamin A.

(1) Presented in part before the Division of Biological Chemistry of the American Chemical Society, Atlantic City meeting, Sept., 1941.

(2) Tischer, *J. Biol. Chem.*, **125**, 475 (1938).

(3) Hamano, *Sci. Pap. Inst. phys. chem. Res.*, Tokyo, **28**, 69 (1935); Mead, *Biochem. J.*, **33**, 589 (1939).

(4) Baxter and Robeson, THIS JOURNAL, **69**, 2411 (1942).

Resistance to Atmospheric Oxidation.—In crystalline form, vitamin A acetate was the most stable of the esters prepared. The stability test consisted of exposing thin layers of the crystals to air at 5° in darkness. The percentage decomposition at various times was determined by the percentage drop in the extinction coefficient at 328 mμ (Table I).

TABLE I

RELATIVE RESISTANCE OF CRYSTALLINE VITAMIN A ESTERS TO ATMOSPHERIC OXIDATION AT 5°

	% of initial $E^{1\%}_{1\,cm.}$ (328 mμ) value after weeks			
Vitamin A	1	2	7	16
Acetate			97	88
β-Naphthoate			95	40
Palmitate	89	73		
Succinate	84	68		

The superior stability of vitamin A acetate may be partly due to the crystal size (Fig. 1).[5] The large prisms expose a smaller area to the action of air, per unit amount of vitamin A, than do the smaller prismatic crystals of di-vitamin A succinate or the plate-like crystals of vitamin A palmitate and vitamin A β-naphthoate (Fig. 2, 3, 4). The excellent stability of vitamin A β-naphthoate cannot be attributed to the size of its crystals. Possibly they have less tendency to adsorb air than vitamin A palmitate and succinate.

All the esters could be stored in evacuated, sealed glass tubes at −35° for long periods of time without change in the extinction coefficient. Thus, the extinction coefficient of vitamin A palmitate at 328 mμ was unchanged after nine months of storage under these conditions. The tubes were evacuated with a high vacuum condensation pump for four hours before they were sealed off. This removed most of the air adsorbed on the surface of the crystals.

Extinction Coefficients at 328 and 620 mμ.—The extinction coefficients of the esters at 328 mμ, in ethyl alcohol, are given in Table 2A.[6] The extinction coefficient of the vitamin A obtained by saponifying the esters is also compared with the equivalent extinction coefficient of vitamin A calculated from the coefficients of the esters. It appears that the equivalent absorption of vitamin A at 328 mμ is slightly depressed in the fatty acid esters. A marked depression in the equivalent absorption of vitamin A was observed in di-vitamin A succinate and a smaller one was observed in vitamin A β-naphthoate.

The extinction coefficient and melting point obtained for vitamin A β-naphthoate ($E^{1\%}_{1\,cm.}$ 328 mμ = 1090, m. p. 74–75°) were lower than the values reported by Mead ($E^{1\%}_{1\,cm.}$ 328 mμ = 1180, m. p. 78°).[3] Our value for the melting point agreed more closely with the value of 76° determined by Hamano. However, through the kindness of Dr. Mead we were able to examine a sample of his vitamin A β-naphthoate. We found an $E^{1\%}_{1\,cm.}$ (328 mμ) value of 1000 and a melting point of 74–75°. Hence, the β-naphthoate crystals made in the two laboratories appear to be equally pure. Probably the values of the constants were not the same because the experimental technique was different.

The extinction coefficients at 620 mμ of the antimony trichloride blue colors of the esters are given in Table 2B.[7] The equivalent extinc-

TABLE II

EXTINCTION COEFFICIENTS OF (A) THE VITAMIN A ESTERS AT 328 mμ, IN ETHYL ALCOHOL, (B) THE ANTIMONY TRICHLORIDE BLUE COLORS OF THE VITAMIN A ESTERS AT 620 mμ

Vitamin A	$E^{1\%}_{1\,cm.}$ (328 mμ)	Equiv. $E^{1\%}_{1\,cm.}$ (328 mμ) calcd. for vit. A	$E^{1\%}_{1\,cm.}$ (328 mμ) for vit. A by saponification of esters[a]
	(A)		
Ester:			
Acetate	1510	1730	1710
Palmitate	940	1720	1700
Succinate	1240	1420	1700
β-Naphthoate	1090	1640[b]	1700
Alcohol:	1780[4]		
Vitamin A	$E^{1\%}_{1\,cm.}$ (620 mμ)	Equiv. $E^{1\%}_{1\,cm.}$ (620 mμ) calcd. for vit. A	
	(B)		
Ester:			
Acetate	4580	5250	
Palmitate	2535	4640	
β-Naphthoate	2940	4520	
Succinate	4450	5090	
Alcohol:	4800[4]		

[a] Amber glassware was used during saponification and ether extraction to prevent decomposition of vitamin A by light. The estimations were kindly done by H. Rawlings of this Laboratory. [b] In calculating this from $E^{1\%}_{1\,cm.}$ (328 mμ) for vitamin A β-naphthoate, a correction was needed for the absorption of the naphthoate radical at 328 mμ. The correction used was the molecular extinction coefficient of ethyl β-naphthoate at 328 mμ. This we found to be 1058.

(5) Photomicrographs, Figs. 1, 2, 3, 4, courtesy of Mr. R. P. Loveland, Eastman Kodak Company, Research Laboratories.

(6) Spectrographic measurements were made with a Hilger quartz spectrograph, model E-498, with a Spekker ultraviolet photometer. The light source was a tungsten-steel spark.

(7) We are indebted to Mr. E. Richardson, Eastman Kodak Company, Research Laboratories for measuring the absorption spectra. A Hardy recording visual spectrophotometer was used.

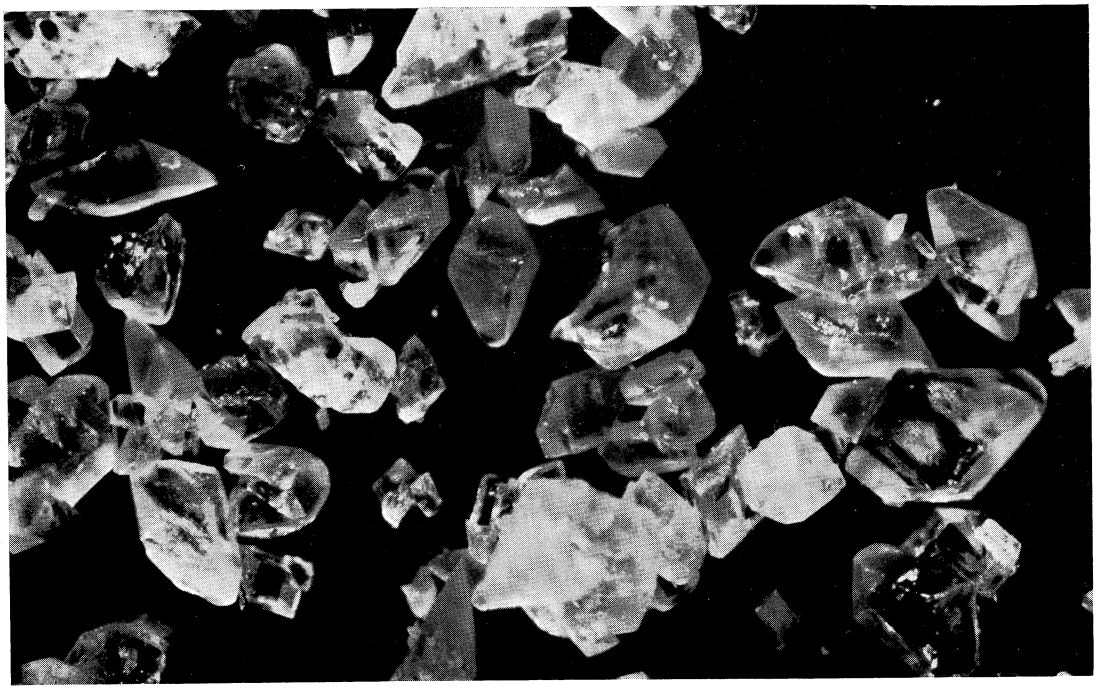


Fig. 1.—Vitamin A acetate, 30×.



Fig. 2.—Di-vitamin A succinate, 30×.

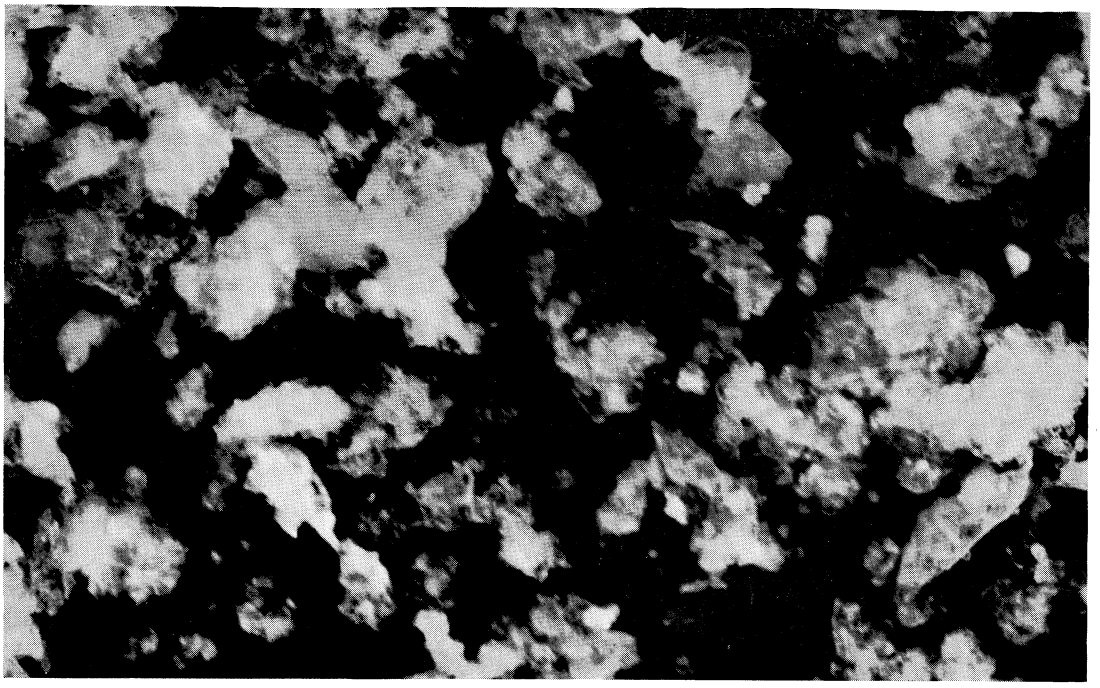


Fig. 3.—Vitamin A palmitate, 40×.

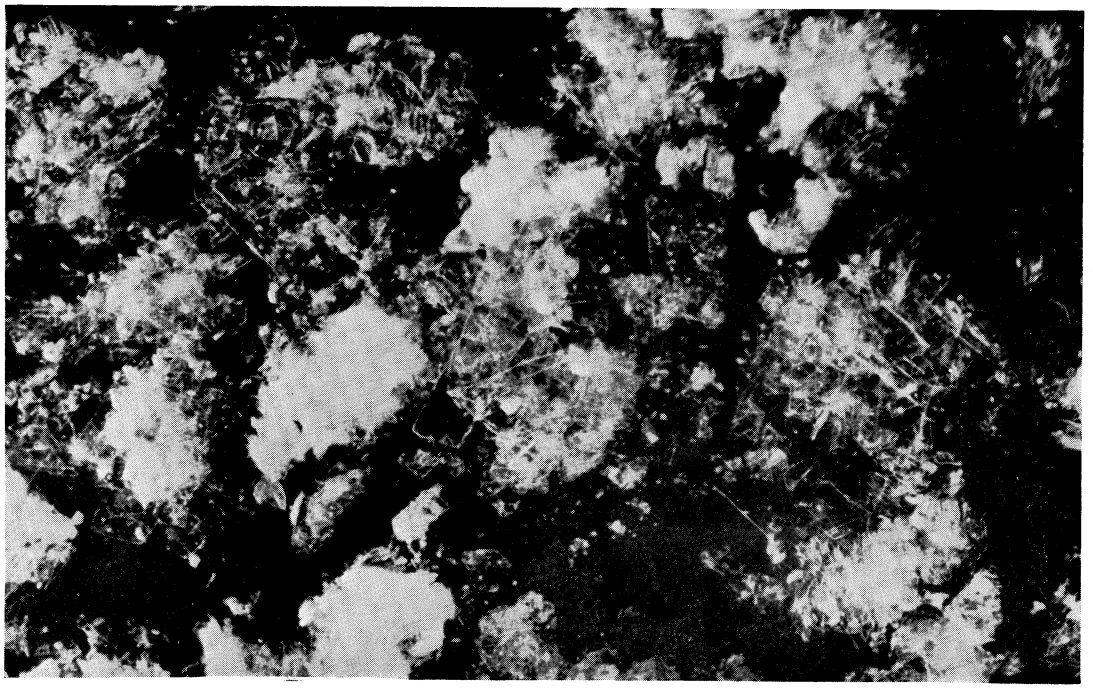


Fig. 4.—Vitamin A β-naphthoate, 24×.

tion coefficients of vitamin A calculated from the extinction coefficients of the esters are also reported. On an equivalent basis vitamin A acetate had a greater $E^{1\%}_{1\,cm.}$ (620 mμ) value than the other vitamin A esters prepared. The equivalent extinction coefficient of the acetate at 620 mμ was also greater than that of free vitamin A.

The method used to determine the $E^{1\%}_{1\,cm.}$ (620 mμ) values has been described.[4]

Biological Potency.—The crystalline aliphatic esters of vitamin A had substantially the same equivalent biological potency as crystalline vitamin A (Table III). The conversion factors of the esters (biological potency/$E^{1\%}_{1\,cm.}$ 328 mμ) were also substantially the same as that of vitamin A. The high conversion factor of di-vitamin A succinate was partly due to the low equivalent extinction coefficient of vitamin A in this ester. The factor for vitamin A β-naphthoate was significantly higher than that of the aliphatic esters. The reason for this is not yet clear.

This finding that certain aliphatic esters of vitamin A have the same equivalent biological potency as vitamin A agrees with the work of Braude, *et al.*[8] These workers found that a natural vitamin A ester concentrate prepared by the molecular distillation of a fish liver oil had the same conversion factor as a vitamin A concentrate prepared by the molecular distillation of a saponified fish liver oil. However, the conversion factor of the vitamin A esters in undistilled fish liver oils has usually been greater than that of the free vitamin A prepared from the oils by saponification.[9] This difference was probably due to the presence of impurities in the oils which absorbed at 328 mμ but which had lower biological potencies than vitamin A. Baxter and Robeson[4] and Braude, *et al.*,[8] review what is known of these substances.

At present it is difficult to compare conversion factors measured in different laboratories because the bioassay procedures are not sufficiently uniform. These procedures may not give the same potency for a pure vitamin A compound. Thus, the biological potency of vitamin A β-naphthoate determined in this Laboratory (four assays gave a mean of 3,440,000 U. S. P. XI units per g.) was over 50% higher than the value found by Underhill and Coward (2,225,000 I. U. per g.).[10] It is in establishing such uniform bioassay procedures in different laboratories that we believe the new crystalline esters should be most useful.

(8) Braude, Foot, Henry, Kon, Thompson and Mead, *Biochem. J.*, **35**, 693 (1941).

(9) Emmett and Bird, *J. Biol. Chem.*, **119**, xxxi (1937); Hickman, *J. Biol. Chem.*, **128**, xliii (1939); Moll and Reid, *Hoppe-Seyl. Z.*, **260**, 9 (1939).

(10) Underhill and Coward, *Biochem. J.*, **33**, 594 (1939).

TABLE III

COMPARISON OF BIOLOGICAL POTENCY OF VITAMIN A ESTERS AND VITAMIN A

Vitamin A	No. assays	Total no. of rats	Mean biological potency (U. S. P. XI units/g. × 10^{-6})	Equiv. biological potency of vitamin A (U. S. P. XI units/g. × 10^{-6})	Conversion factor: biological potency / $E^{1\%}_{1\,cm.}$ (328 mμ)
Acetate	9	90	3.52	4.04 ± 0.23	2350 ± 133
Palmitate	8	80	2.31	4.23 ± .31	2520 ± 183
Succinate	1	24	3.14	3.59	2630
β-Naphthoate	4	40	3.44	5.29 ± .24	3160 ± 145
Alcohol	8	160	4.30[4]	4.30 ± .39	2460 ± 227

The biological potencies assigned to the vitamin A esters in this paper are provisional values which may be changed slightly in the forthcoming paper by Harris in which the assays are described in detail. H. J. Cannon of the Laboratory of Vitamin Technology, Chicago, independently performed biological assays on solutions of the crystalline compounds (except di-vitamin A succinate) in refined cottonseed oil. These solutions were identified only by code numbers. The biological potencies calculated from his results lay, in each case, within the standard deviations found by Harris.

Experimental

Vitamin A Acetate.—Crystalline vitamin A (4.5 g., 0.016 mole) was dissolved in a mixture of ethylene chloride (25 cc.) and pyridine (5 cc.) and cooled to 10°. A solution of acetyl chloride (1.4 g., 0.018 mole) in ethylene chloride (25 cc.) was slowly added. After standing for two hours at room temperature, protected from light, the mixture was poured into 0.5 *N* aqueous sulfuric acid and extracted with ether. The extract was successively washed with 0.5 *N* sulfuric acid, water, 10% potassium carbonate solution, and water. After distillation of ether under reduced pressure, the residue (5.0 g.) was crystallized from methyl alcohol (50 cc.) at 5°. Recrystallization gave pale yellow prismatic crystals of vitamin A acetate which were filtered and dried under suction in a funnel of the type previously described.[4] The yield was 75% of the theoretical. The acetate melted at 57–58° and had an elimination maximum of 132.5° from petroleum constant yield oil compared with 121° for the standard reference dye, Celanthrene Red.

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.48; H, 9.76. Found: C, 80.34; H, 9.86.

Vitamin A Palmitate.—Vitamin A (3.5 g., 0.012 mole) was dissolved in a mixture of ethylene chloride (35 cc.) and pyridine (5.0 cc.) and cooled to −15°. Palmityl chloride (3.7 g., 0.013 mole) was added slowly with shaking. After standing for three hours at room temperature, the reaction mixture was extracted as for vita-

min A acetate, except that after the carbonate washes the ether solution was washed three times with 0.5 *N* sodium hydroxide. After removal of ether the palmitate was obtained as a yellow oil (6.02 g.). This oil was dissolved in petroleum ether (100 cc., b. p. 30–65°) and extracted five times with 83% ethyl alcohol to remove unesterified vitamin A. The recovered palmitate (5.1 g., $E^{1\%}_{1\,cm.}$ 328 mμ = 861) still contained traces of palmitic acid (acid value = 5). This was removed by crystallization from propylene oxide (165 cc.) at −30° for two hours. The acid was filtered (0.19 g.) and the filtrate was cooled slowly, by lagging to −30°. In eighteen hours vitamin A palmitate crystallized as thin yellow plates which were filtered and dried under vacuum. The yield (3.1 g.) was 48% of the theoretical. After recrystallization from propylene oxide the palmitate had m. p. 27–28°. Its elimination maximum from glyceride constant yield oil was 213° (Celanthrene Red 126°).

Anal. Calcd. for $C_{36}H_{60}O_2$: C, 82.45; H, 11.45. Found: C, 82.11; H, 11.52.

The preparation of crystalline vitamin A palmitate was troublesome because the ester frequently separated in amorphous form. This form appeared to be more soluble in propylene oxide than the crystals and separated from solution more slowly. Decomposition of vitamin A during esterification did not cause the formation of amorphous palmitate. It separated frequently from crude preparations with high $E^{1\%}_{1\,cm.}$ (328 mμ) values.

To prevent the formation of amorphous palmitate certain changes in the preparative method were made. Pyridine was replaced by quinoline; ethylene chloride was replaced by chloroform. The esterification was performed in a system from which oxygen was rigorously excluded. The solutions were both rapidly cooled and slowly cooled during the crystallization step. However, these changes were ineffective.

It was then thought that the amorphous ester might be a geometrical isomer of the crystalline ester. Therefore, catalysts known to isomerize carotenoids were employed. Solutions of the amorphous ester in propylene oxide were treated with traces of iodine and organic bases. The solutions were exposed to sunlight. Unsuccessful attempts were then made to crystallize the ester samples. At present the experimental conditions necessary to ensure the preparation of crystalline palmitate are not known.

Di-vitamin A Succinate.—Vitamin A (2 g., 0.007 mole) was dissolved in a mixture of ethylene chloride (10 cc.) and pyridine (2 cc.) and cooled to 0°. A solution of succinyl chloride (0.55 g., 0.0035 mole) in ethylene chloride (10 cc.) was slowly added, with shaking, and the mixture was allowed to stand one hour at room temperature. The extraction was performed as for vitamin A acetate.

The crude product, a red oil (2.4 g.) was crystallized from ethyl formate (10 cc.), then recrystallized from ethyl formate (15 cc.), at −35°. The crystals were yellow prisms, m. p. 76–77°. The yield was 46% of the theoretical. The elimination maximum was above 250° from glyceride constant yield oil.

Anal. Calcd. for $C_{44}H_{62}O_4$: C, 80.73; H. 9.48. Found: C, 80.26; H, 9.50.

Vitamin A β-Naphthoate.—This was obtained by a procedure which gave a better yield than that reported by Mead.[3] Vitamin A (4.5 g., 0.016 mole) was dissolved in ethylene dichloride (25 cc.) and pyridine (5 cc.). β-Naphthoyl chloride (m. p. 51–52°, 3 g., 0.016 mole) in ethylene dichloride (25 cc.) was added at 25° and the mixture was allowed to stand for four hours at room temperature. The ester was extracted as for vitamin A palmitate. It consisted of a viscous yellow oil (7 g.). This was crystallized from absolute ethyl alcohol (150 cc.) at 5° (yield 58% of theoretical). The ester consisted of delicate, yellow plates which melted at 73–74°. After one recrystallization the m. p. was 74–75°. Repeated crystallizations did not raise the m. p. further.

Anal. Calcd. for $C_{31}H_{36}O_2$: C, 84.53; H, 8.18. Found: C, 84.90; H, 8.13.

Summary

1. Three crystalline esters of vitamin A have been prepared by the esterification of crystalline vitamin A. These esters are: vitamin A acetate, vitamin A palmitate, and di-vitamin A succinate.

2. The extinction coefficients of the esters at 328 mμ and of the antimony trichloride blue colors at 620 mμ have been determined.

3. The biological potency of the esters, adjusted for differences in the molecular weights, was the same as that of crystalline vitamin A.

4. Vitamin A acetate was the most resistant of the crystalline preparations to atmospheric oxidation. It appears to be the most stable crystalline ester of vitamin A yet prepared.

ROCHESTER, NEW YORK RECEIVED MAY 27, 1942

[CONTRIBUTION NO. 27 FROM THE LABORATORIES OF DISTILLATION PRODUCTS, INC.]

Crystalline Vitamin A[1]

BY JAMES G. BAXTER AND CHARLES D. ROBESON

The Holmes and Corbet Crystals

Holmes and Corbet[2] crystallized the vitamin A in ishinagi liver oil from methyl alcohol as yellow needles, melting at 7.5–8°. The authors[3] crystallized the vitamin A in ling cod and other fish liver oils from ethyl formate as yellow prisms, melting at 63–64° (hereafter called 64° crystals) (Fig. 1). Because the Holmes and Corbet crystals had different properties from ours we have prepared and examined specimens of the crystals melting at 7° (hereafter called 7° crystals).[4] This examination indicated that the 7° crystals are not pure vitamin A, but contain methyl alcohol. Crystalline vitamin A melts at 64°. The evidence for these conclusions and certain properties of crystalline vitamin A are given in this paper.

The 7° crystals were prepared from the liver oil of the California jewfish (*Stereolepis gigas*). This oil is similar to the liver oil of the Japanese ishinagi (*Stereolepis ishinagi*), used by Holmes and Corbet. The method of isolation was similar to that of Holmes and Corbet except that the vitamin A esters were concentrated by molecular distillation of the fish liver oil prior to saponification and crystallization from methyl alcohol.

The moist crystals were dried at a temperature gradually rising from −30 to −5° in a system continuously evacuated by a high vacuum condensation pump (limiting vacuum = 0.001 mm.). The rate of drying was determined by measuring the vapor pressure in the system with a Pirani type gage. The pressure decreased steadily during six hours to a value of 0.008 mm., then remained substantially constant for sixteen hours at −5°. The crystals were then examined. They were needle-like in structure (Fig. 2), resembling those of Holmes and Corbet, but melted less sharply at 7–10°.

The following observations were made:

(1) The 7° crystals retained methyl alcohol. This was determined by drying a sample in a stream of nitrogen at 50° and finding the loss in weight. The percentage of alcohol found (10%) corresponded to one mole of methyl alcohol per mole of vitamin A. Since, however, the samples used in the determination were small, this percentage was considered to be only approximate. The 64° crystals lost no weight when they were similarly dried.

(2) The 64 and 7° crystals were interconvertible. When the 7° crystals were cooled in ethyl formate solution, 64° crystals separated. When a solution of the 64° crystals in methyl alcohol was cooled 7° crystals were deposited.

(3) The 64 and 7° crystals gave the same crystalline vitamin A acetate (m. p. 57–58°) and β-naphthoate (m. p. 74–75°). Also, the extinction coefficient of the 7° crystals ($E^{1\%}_{1cm.}$ 328 mμ = 1720, corrected for methyl alcohol present) was nearly the same as that of the 64° crystals ($E^{1\%}_{1cm.}$ 328 mμ = 1750).

It was concluded from these data that the 64° crystals represent crystalline vitamin A. The 7° crystals, which appeared to be similar to those made by Holmes and Corbet, were vitamin A containing methyl alcohol.

Evidence was noted indicating that the methyl alcohol in the 7° crystals was not merely entrained: (1) Most of the alcohol in the moist 7° crystals, as previously mentioned, was removed readily under high vacuum but the last 10% could not be removed in this way. (2) The 7° crystals had a different crystalline structure than crystalline vitamin A (when the latter was crystallized from methyl alcohol) and they separated from solution more rapidly and in greater yield (see next section). (3) Specimens of the 7° crystals prepared independently by Holmes and Corbet,[2] by Mead[5] and by us melted at substantially the same temperature, and hence probably contained similar quantities of methyl alcohol, although they were crystallized and dried by different procedures. It seems improbable that this would have occurred if the methyl alcohol had merely been held by entrainment.

The question as to whether the 7° crystals represent a true molecular compound containing

(1) Presented in part before the Division of Biological Chemistry of the American Chemical Society, Atlantic City meeting, September, 1941.

(2) Holmes and Corbet, THIS JOURNAL, **59**, 2042 (1937).

(3) Baxter and Robeson, *Science*, **92**, 203 (1940).

(4) At the Atlantic City meeting the 64 and 7° crystals were identified as α- and β-vitamin A. This nomenclature has been discarded.

(5) Mead, *Biochem. J.*, **33**, 589 (1939).

TABLE I

CRYSTALLIZATION OF VITAMIN A CONCENTRATE ($E^{1\%}_{1cm.}$ 328 mμ = 1550) FROM METHYL ALCOHOL, ETHYL FORMATE, PROPYLENE OXIDE AND PETROLEUM ETHER (B. P. 30–65°)

Concentration of vitamin A (g./100 cc. solution) = 20%.

Crystn.	Solvent	Seeded with cryst.-	Type of crystal separating	Crystn. temp., in deg.	% yield of vit. A[a]
1	MeOH	Vit. A	Vit. A	−35	18
2	MeOH	Vit. A (MeOH)	Vit. A (MeOH)	−35	62
3	MeOH	Vit. A (MeOH) or no seeding	Vit. A (MeOH)	−70	81
4	Et. Form.	Vit. A, vit. A (Et. Form.[b]) or no seeding	Vit. A	−35	40
5	Et. Form.	Vit. A	Vit. A[c]	−70	74
6	Et. Form.	Vit. A (Et. Form.) or no seeding	Vit. A (Et. Form.)	−70	60
7	Prop. ox.	Vit. A	No crystn.	−35	..
8	Prop. ox.	No seeding	Vit. A	−70	20
9	Pet. eth.	No seeding	Vit. A	−35	20
10	Pet. eth.	No seeding	Vit. A	−70	45

[a] Yield figures obtained after evaporating solvent from crystals in stream of nitrogen at 50°. [b] These seed crystals dissolved. [c] The solution was crystallized, but not filtered, at −35 and −55° before being crystallized and filtered at −70°.

fixed proportions of vitamin A and methyl alcohol was not examined.

Crystallization of Vitamin A.—In the further study of the affinity of vitamin A for various solvents, a rich concentrate ($E^{1\%}_{1cm.}$ 328 mμ = 1550) was crystallized from methyl alcohol, ethyl formate, petroleum ether (b. p. 30–65°), and propylene oxide, at temperatures of approximately −35 and −70°. The solutions were usually seeded to prevent supersaturation and were allowed to crystallize for as long as two weeks, in certain cases, to attain equilibrium. The nature of the crystals formed and the yields obtained are shown in Table I.

These experiments indicated that vitamin A has an affinity for ethyl formate as well as for methyl alcohol. In the table the notations "vitamin A (MeOH)" and "vitamin A (Et Form.)" mean that the designated crystals contained methyl alcohol and ethyl formate which could not be removed completely under high vacuum without melting the crystals. The notation does not imply that a molecular compound existed nor that a molecular proportion of solvent was retained by the crystals.

Vitamin A (MeOH) separated in Crystallizations (Crystns.) 2 and 3, *i. e.*, when a 20% solution of a vitamin A concentrate in methyl alcohol was cooled to −35° and seeded with vitamin A (MeOH) crystals, or cooled to −70° without seeding. In Crystn. 1, vitamin A separated. Thus, either vitamin A or vitamin A (MeOH) could be crystallized from methyl alcohol.

Vitamin A (Et Form.) crystallized from ethyl formate at −70° (Crystn. 6) unless the solution was cooled gradually to −70° in the presence of vitamin A crystals. Then vitamin A crystallized (Crystn. 5). Only vitamin A could be crystallized from ethyl formate at −35° (Crystn. 4).

Since vitamin A (Et Form.), like vitamin A (MeOH), separated from solution more rapidly than vitamin A, concentrates from distilled and saponified fish liver oils were first crystallized in this form at −70° to remove the bulk of the impurities in the non-saponifiable matter. Vitamin A was then obtained by recrystallizing the concentrate from ethyl formate at −35°.

Vitamin A (Et Form.) was only briefly examined. Even after filtration under pressure the preparations contained as much as 80% adsorbed and entrained ethyl formate. After fifteen hours of continuous evacuation at −35° (final vapor pressure = 0.009 mm.) one sample melted at −4 to 2° and contained 12% ethyl formate. Another preparation contained 10% ethyl formate and melted at 7–10°. The percentages are again only approximate.

Solvent-free vitamin A crystallized from propylene oxide or petroleum ether (Crystns. 7–10). Thus, it appears that only the more polar solvents have an affinity for vitamin A. The hydroxyl group of the vitamin is evidently responsible for this property because esters of vitamin A, such as the acetate, crystallized from methyl alcohol or ethyl formate without solvent of crystallization.



Fig. 1.—Crystalline vitamin A, m. p. 63–64°, × 14. (Photomicrographs, Figs. 1 and 2, courtesy of R. P. Loveland, Eastman Kodak Company, Research Laboratories.)



Fig. 2.—Crystals of vitamin A(MeOH), m. p. 7–10°, ×48.

Properties of Crystalline Vitamin A

Extinction Coefficient at 328 mμ and 622 mμ.—Nine recent preparations of crystalline vitamin A have had an average extinction coefficient at the absorption maximum of 1750 ± 21 in absolute ethyl alcohol[6] (unless otherwise stated all extinction coefficients reported in this paper were determined in this solvent). One of these preparations had an extinction coefficient at the absorption maximum of 1780 (average of 3 determinations) (Fig. 3). Dr. F. P. Zscheile and R. L. Henry of Purdue University kindly assayed this latter preparation and also obtained the value 1780 at the maximum. They have recently reported spectrographic data for other preparations of crystalline vitamin A.[7]

The spectrographic measurements did not support the value of $E^{1\%}_{1cm.}$ 325 mμ = 1880 for pure vitamin A, suggested as the probable value by Morton.[8]

The position of the absorption maximum of vitamin A varied from 326–328 mμ in ethyl alcohol with our instrument. Zscheile and Henry, using an instrument capable of greater precision, found the maximum in ethyl alcohol to be at 324 mμ. Thus, the wave length now assigned to the vitamin A maximum (328 mμ) may be incorrect. It has, however, seemed advisable to determine the extinction coefficients reported in this paper at the absorption maximum and to report them as at 328 mμ unless the maximum lay outside the range 326–328 mμ.

In petroleum ether (b. p. 30–65°) and ethyl formate the average extinction coefficients of vitamin A at 328 mμ were 1760 and 1715, respectively. These values were not considered significantly different from that in ethyl alcohol. In cyclohexane and chloroform the extinction coefficients were 1550 and 1260 at 328 mμ and 333 mμ, respectively. These values seemed to be significantly lower than the value in ethyl alcohol.

We believe that certain solvents such as cyclohexane are able to repress the absorption of vitamin A. The suggestion of Adamson and Evers[9] that the extinction coefficient of vitamin A is higher in ethyl alcohol than in cyclohexane because complex formation occurs in the former does not seem probable in view of the high extinction coefficient of vitamin A in petroleum ether.

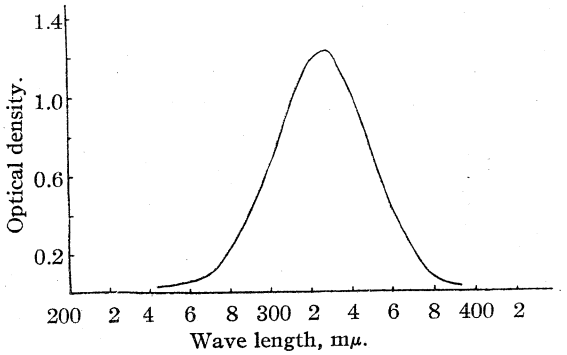


Fig. 3.—Spectrophotometric curve of crystalline vitamin A in ethyl alcohol ($E^{1\%}_{1cm.}$ 328 mμ = 1780).

The extinction coefficient of solutions of vitamin A in ethyl alcohol was unchanged after two days of storage in amber bottles at room temperature. Thus, we were unable to confirm the observation of Darby, quoted by Holmes and Corbet,[2] that the extinction coefficient of highly purified vitamin A preparations rapidly decreases in ethyl alcohol solution. The solutions in ethyl alcohol were stable also to radiation from the spark used with the spectrograph even when exposures of 160 sec., four times the normal exposure, were given. Zscheile and Henry reported a similar finding.[7] However, the extinction coefficient of solutions of vitamin A in cyclohexane and chloroform did decrease from 2 to 6% during storage for twenty-four hours at room temperature.

The extinction coefficient of the antimony trichloride blue color of vitamin A at 622 mμ was 4800. This is the average of five determinations on vitamin A with $E^{1\%}_{1cm.}$ 328 mμ = 1750 and agrees well with the value 4700 previously reported[3] from measurements on other vitamin A preparations. In a typical determination 1 cc. of a vitamin A solution in chloroform (0.001576 g./100 cc.) was treated with 10 cc. of a chloroform solution of antimony trichloride (saturated at 20°). The percentage transmission at 622 mμ of the transitory blue color was measured within three seconds with a Hardy recording spectrophotometer.[10]

From our work the value $E^{1\%}_{1cm.}$ 617 mμ = 6000, suggested as being probable by Morton,[8] appears to be too high.

(6) Mr. G. Wait and assistants of this Laboratory made the spectrographic measurements using a Hilger quartz spectrograph, model E-498, with a Spekker ultraviolet photometer. The light source was a tungsten–steel spark.

(7) Zscheile and Henry, *Ind. Eng. Chem., Anal. Ed.*, **14**, 422 (1942).

(8) Morton, *Ann. Rev. Biochem.*, **XI**, 368 (1942).

(9) Adamson and Evers, *Analyst*, **66**, 106 (1941).

(10) We are indebted to Mr. E. Richardson, Eastman Kodak Company Research Laboratories, for measuring the absorption spectra.

The "L" Value.—Vitamin A can be assayed rapidly by measuring the intensity of its antimony trichloride blue color with certain photoelectric colorimeters, such as the Evelyn. This instrument uses sharply filtered rather than monochromatic light. Therefore, the results are expressed in terms of a quantity L rather than E. L is analogous to E, the extinction, and the L value ($L^{1\%}_{1cm.}$ 622 mμ) is analogous to $E^{1\%}_{1cm.}$ 622 mμ. Dann and Evelyn[11] found that L was proportional to the vitamin A concentration for galvanometer readings (G) between 20 and 70. Thus, in this range the L value was nearly constant. Koehn and Sherman,[12] however, found that L was not proportional to the vitamin A concentration over this range and the L value was consequently not constant. In these experiments pure vitamin A was not used. Both groups of workers used the non-saponifiable matter from fish liver oils, possibly containing oxidized vitamin A.

The relation between L and the vitamin A concentration is of practical as well as theoretical interest. For this reason the L value of crystalline vitamin A was measured at concentrations corresponding to galvanometer readings from 20–70 (Table IIa). The L value of crystalline vitamin A acetate was measured in the same way to determine the effect of esterification on the L value of vitamin A (Table IIb).

TABLE II

VARIATION OF THE L VALUE ($L^{1\%}_{1cm.}$ 622 mμ) WITH CONCENTRATION OF (A) VITAMIN A AND (B) VITAMIN A ACETATE

Concn. (g./100 cc. × 10^4)	Galvanometer reading, average, cor.	$L^{1\%}_{1cm.}$ 622 mμ
a. Vitamin A ($E^{1\%}_{1cm.}$ 328 mμ = 1740)		
1.73	74^2	3880
2.60	64^0	3920
3.46	55^2	3875
4.33	47^3	3895
5.19	41^3	3840
6.06	36^2	3800
6.93	31^0	3860
7.79	28^0	3730
8.66	24^2	3705
9.35	21^3	3725
10.39	18^1	3735
b. Vitamin A acetate ($E^{1\%}_{1cm.}$ 328 mμ = 1470)		
1.63	77^1	3600
2.61	66^2	3565
3.26	59^2	3635
4.89	46^2	3565
5.22	44^2	3540
6.52	36^0	3575
8.15	28^2	3510
9.78	22^3	3455
11.41	17^3	3455
13.04	14^2	3375

The procedure was similar to that of Dann and Evelyn. Samples of vitamin A (0.0433 g.) and vitamin A acetate (0.0815 g.) were dissolved in chloroform (50 cc.) to prepare stock solutions. From 1–9 cc. of these stock solutions were further diluted to give solutions with the desired vitamin A concentration. Portions of these solutions (1 cc.) were treated with 10 cc. of a solution of antimony trichloride in chloroform, saturated at 20°. Duplicate readings were taken at each dilution (maximum deviation = 1 (G) unit) and the values of G were averaged.

A linear relation did not exist between L and the concentration of vitamin A or vitamin A acetate for galvanometer readings between 20 and 70. A nearly linear relation did exist between G = 30–70. In this range vitamin A ($E^{1\%}_{1cm.}$ 328 mμ = 1740) had an average L value of 3865 ± 39. Vitamin A acetate ($E^{1\%}_{1cm.}$ 328 mμ = 1470) had an average L value of 3570 ± 40.

From the standard deviations it was calculated that 21 out of 22 observations of the L value of vitamin A or vitamin A acetate would lie within ± 2.2% of the average value, for galvanometer readings taken between G = 30–70. This error was doubled if the range G = 20–70 was used.

Our purest vitamin A ($E^{1\%}_{1cm.}$ 328 mμ = 1780) had an L value of 3990. The equivalent L value of vitamin A calculated from the L value of vitamin A acetate was 4090. It thus appears that the L value of vitamin A is about 4000 and that the blue color of one ester of vitamin A had a greater equivalent absorption than vitamin A itself.

The following relations were determined between the extinction coefficients of vitamin A ($E^{1\%}_{1cm.}$ 328 mμ = 1740) and vitamin A acetate ($E^{1\%}_{1cm.}$ 328 mμ = 1470) and the average L values

Vitamin A: $E^{1\%}_{1cm.}$ 328 mμ = L value × (0.45 ± 0.005).

Vitamin A acetate: $E^{1\%}_{1cm.}$ 328 mμ = L value × (0.41 ± 0.005)

The value for the conversion factor of vitamin A lies between the value of 0.41 ± 0.05 reported by Dann and Evelyn and the value 0.50 ± 0.01 reported by McFarland and Sutherland.[13]

Other Physical and Chemical Constants.—The *molecular weight* of vitamin A, determined

(11) Dann and Evelyn, *Biochem. J.*, **32**, 1008 (1938).

(12) Koehn and Sherman, *J. Biol. Chem.*, **132**, 527 (1940).

(13) McFarland and Sutherland, *Can. J. Research*, **16**, 421 (1938).

by a micro modification of the Menzies–Wright ebullioscopic method in ethyl alcohol, was 263.[14] The calculated value for $C_{20}H_{30}O$ was 286. The *index of refraction* was $n^{22}D$ 1.6410. In this determination the refractive indices of 20–70% solutions of vitamin A in refined mineral oil were measured with an Abbe refractometer. These indices when plotted against the vitamin A concentration gave a straight line which could be accurately extrapolated to 100% vitamin A. The *acetyl value*, determined by the method of West, Hoaglund and Curtis,[15] was 149. The calculated value was 150 mg. CH_3CO per gram. The *iodine value* determined by the method of von Mikusch and Frazier[16] was 390. The theoretical value was 444. A 500% excess of 0.4 *N* Hanus solution was used for a reaction period of three hours at 0°.[17] The *elimination maximum* was 125°, one degree below that of the reference dye, Celanthrene Red, added to the solution before distillation. Glyceride constant yield oil was used.[18]

Biological Potency

Crystalline vitamin A was found to have a provisional biological potency of 4,300,000 U. S. P. XI units per gram. This value is about 30% higher than that suggested as being probable by Morton.[8] The factor for converting the average extinction coefficient at 328 mμ of the preparations bioassayed to U. S. P. XI units was 2460.

This conversion factor of 2460 is higher than the value of 2000 widely accepted as the conversion factor of vitamin A in fish liver oils. If confirmed, it means that fish liver oils contain substances (or a substance) absorbing at 328 mμ which are either biologically less active than crystalline vitamin A or are biologically inactive.

Baxter, *et al.*,[19] have reported evidence tending to show that these substances may have vitamin A activity. However, we have not been successful in separating them from vitamin A by chromatographic adsorption. Robinson[20] has suggested that these substances absorbing at 328 mμ are oxidized vitamin A which has no biological activity. His experimental results, however, do not appear to establish this explanation. A significant discrepancy did not appear between spectrographic and biological assays made on his oxidized vitamin A preparations until the 328 mμ band of vitamin A had been badly deformed and shifted toward the ultraviolet.

The value of 4,300,000 U. S. P. XI units per gram for crystalline vitamin A was obtained as the average of eight biological assays (a total of 160 rats used) made by Dr. P. L. Harris of this Laboratory. They will be reported in detail elsewhere. Vitamin A was also assayed by H. J. Cannon of the Laboratory of Vitamin Technology, Chicago. From his results an average biological potency of 4,700,000 U. S. P. XI units per gram was calculated. For the 7° crystals Harris found a biological potency of 3,900,000 U. S. P. XI units per gram, corrected for the methyl alcohol present. Only two assays were performed, however, so the biological potency was not established as accurately as for vitamin A itself.

Experimental

Preparation of Crystalline Vitamin A

A. Distillation of Fish Liver Oils.—Cryst. vitamin A was prepared from shark liver ($E^{1\%}_{1cm.}$ 328 mμ = 100), ling cod liver ($E^{1\%}_{1cm.}$ 328 mμ = 129), California jewfish liver ($E^{1\%}_{1cm.}$ 328 mμ = 317) and halibut viscera ($E^{1\%}_{1cm.}$ 328 mμ = 72), oils.

A cyclic molecular still, similar to that described by Hickman[18] was used. The vitamin A esters distilled from 180–220° at a pressure of 0.003 mm. The distillates were light yellow oils without fishy taste or odor. Fractions with an extinction coefficient at 328 mμ of 400 or greater were combined for saponification. From 50–70% of the initial vitamin A was obtained at this potency.

B. Saponification.—A vitamin A ester concentrate (67 g., $E^{1\%}_{1cm.}$ 328 mμ = 539) from distilled ling cod liver oil was saturated with nitrogen by bubbling commercial gas through it for ten minutes. Then 190 cc. of 2 *N* alcoholic potassium hydroxide, similarly saturated with nitrogen, was added. Saponification was effected by refluxing the mixture for thirty minutes in an atmosphere of nitrogen. The mixture was then diluted with freshly boiled and cooled water and extracted with reagent grade ethyl ether. The extract was washed with 10% aqueous potassium carbonate, with water, and dried. The ether was distilled under reduced pressure.

The free vitamin A concentrate (28.6 g., $E^{1\%}_{1cm.}$ 328 mμ = 1260) was a red viscous oil which could be directly crystallized from ethyl formate. However, vitamin A of greater purity was obtained by first distilling the saponified concentrate.

C. Redistillation.—The saponified concentrate from (B) was dissolved in two volumes of corn oil residue and

(14) We wish to thank Dr. L. T. Hallett, Eastman Kodak Company Research Laboratories, for the microanalysis.

(15) West, Hoaglund, and Curtis, *J. Biol. Chem.*, **104**, 627 (1934).

(16) von Mikusch and Frazier, *Ind. Eng. Chem., Anal. Ed.*, **13**, 782 (1941).

(17) The determination was kindly done by Mr. E. S. Barnitz of this Laboratory.

(18) Hickman, *Ind. Eng. Chem.*, **29**, 968 (1937); Embree, *ibid.*, **29**, 975 (1937).

(19) Baxter, Harris, Hickman and Robeson, *J. Biol. Chem.*, **141**, 991 (1941).

(20) Robinson, *Biochem. J.*, **32**, 807 (1938).

distilled in a cyclic molecular still. Fractions were taken at 10°-intervals from 90–160° with two cycles at each temperature. Vitamin A distilled principally from 105–135° as an odorless, orange oil. The distillate was viscous and the condenser wall had to be warmed to cause the distillate to flow into the receiver. Fractions with an extinction coefficient of 1400 or greater were combined for crystallization (17.5 g., $E^{1\%}_{1cm.}$ 328 mμ = 1440).

D. Crystallization of Vitamin A (Ethyl Formate).—The vitamin A concentrate from (C) was dissolved in ethyl formate (70 cc.), cooled to −35° for eighteen hours, seeded with cholesterol and then cooled to −55° for eight hours. The solids which separated (1.1 g.) were filtered in a Büchner funnel cooled with dry-ice. The filtrate deposited no solids when cooled at −70° for eighteen hours so the flask was scratched at intervals to promote crystallization. In three hours crystallization began and was complete in three days. The crystals were filtered and washed in a modified Büchner funnel, cooled with dry-ice (see Filtration and Drying). Much entrained solvent was pressed out with dental dam. After distillation of ethyl formate under reduced pressure a vitamin A concentrate was obtained (9.2 g., $E^{1\%}_{1cm.}$ 328 mμ = 1670).

E. Crystalline Vitamin A.—The vitamin A concentrate from (D) was dissolved in ethyl formate (40 cc.) and stored at −35° for eighteen hours during which time the flask was repeatedly scratched. Vitamin A began to separate in large prismatic crystals during this period and crystallization was allowed to continue for an additional twenty-four hours. The crystals were filtered in the modified Büchner funnel and dried.

The first crop of crystals weighed 1.67 g. By concentrating the filtrate and seeding it at −35° an additional 1.06 g. was obtained. The yield was further increased by 1.32 g. by cooling the filtrate from the second crop to −70° for five days and recrystallizing the vitamin A at −35°. The average $E^{1\%}_{1cm.}$ 328 mμ value of the three crops of crystals was 1720. Thus, the yield of crystalline vitamin A was approximately 15% of that present in the fish liver oil. After two crystallizations from ethyl formate vitamin A melted at 63–64° and had $E^{1\%}_{1cm.}$ 328 mμ = 1750.

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.84; H, 10.56. Found: C, 83.90, 83.70; H, 10.30, 10.40.[14]

An alternative crystallization procedure gave an over-all yield of 25%. The solution of (D) in ethyl formate (40 cc.) was crystallized at −35, −55, and finally at −70°. The crystals were not filtered until crystallization was completed at −70°. Under these conditions vitamin A and not vitamin A (ethyl formate) separated. The extinction coefficient of the crystals at 328 mμ was 1710 but more small crystals with inferior keeping quality were present than when the other procedure was used.

Vitamin A was sealed in glass ampoules, under vacuum, and stored at −35°. Under these conditions the extinction coefficient and the biological potency were unchanged after four to six months.

Filtration and Drying.—A modified Büchner funnel was constructed to filter vitamin A under nitrogen pressure. A circular steel ring, 0.5″ wide, was provided for the mouth of the funnel (75 mm. inside diameter). This was held in place by tie rods connected to a similar steel ring fitted to the throat of the funnel. A steel cover was provided with a hose connection to admit nitrogen. A pressure-tight union between ring and cover was obtained with a rubber gasket and six bolts attached to the periphery of the metal ring. These bolts fitted through holes in the cover. Excess solvent in the crystals was removed by pressure from a piece of dental dam fitted between gasket and cover. The funnel was cooled by a removable insulated jacket filled with dry-ice.

To dry the crystals the cover was tightened and the funnel was evacuated by connecting its outlet to an oil pump. Evacuation for fifteen to twenty hours at a temperature gradually rising from −60 to 5° was usually necessary. Filtrations and drying were done in a cold room at 5°.

Refrigeration.—Three temperatures were used most frequently, −35, −55, and −70°. An ice-cream cooling cabinet maintained a temperature of −35° ± 5°. A wooden box insulated with cork, and cooled with dry-ice served to keep a temperature near −55°. Vessels were cooled to −70 ± 10° by packing them in powdered dry-ice and storing them in the insulated cabinet.

Solvents.—Eastman Kodak Co. ethyl formate was filtered through anhydrous potassium carbonate to remove formic acid and was then fractionally distilled. Solvents such as propylene oxide, petroleum ether (b. p. 30–65°), and methyl alcohol were Eastman grade and were used without further purification.

Summary

Crystalline vitamin A has been isolated from shark liver, ling cod liver, California jewfish liver and halibut viscera oils as yellow prisms, melting at 63–64°. Evidence was obtained indicating that the crystalline vitamin A of Holmes and Corbet (m. p. 7.5–8°) contained methyl alcohol.

Crystalline vitamin A had a provisional biological potency of 4,300,000 U. S. P. XI units per gram. Its conversion factor, 2460, was higher than the conversion factor of vitamin A in fish liver oils.

The extinction coefficient of crystalline vitamin A at 328 mμ was 1780. The extinction coefficient of the vitamin A antimony trichloride blue color at 622 mμ was 4800. The L value ($L^{1\%}_{1cm.}$ 622 mμ), measured with an Evelyn photoelectric colorimeter, was 3990. L was a nearly linear function of the vitamin A concentration for galvanometer readings (G) between 30 and 70.

The molecular weight, the elimination maximum, the index of refraction, the acetyl value, and the iodine value of crystalline vitamin A were determined. These confirmed the formula for vitamin A proposed by Karrer.

ROCHESTER, NEW YORK RECEIVED APRIL 24, 1942

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

The Nitration of Lepidine and 2-Chlorolepidine

BY STANLEY E. KRAHLER[1] AND ALFRED BURGER

In the course of an investigation of quinoline derivatives of potential antimalarial activity, certain aminolepidines were prepared from the corresponding nitro compounds.[2] It was found that the nitration of 2-chlorolepidine yielded two isomeric mono nitro derivatives in a ratio of 1:6. The isomer formed in smaller amount was identified as 6-nitro-2-chlorolepidine, while the major reaction product was postulated to be 5-nitro-2-chlorolepidine. The 8-position was ruled out for the nitro group because the chloro-2-hydroxy- and chloro-2-chlorolepidine prepared from our nitro product differed from the 8-chloro-2-hydroxy- and the 2,8-dichlorolepidine, respectively, as reported by Kermack and Muir.[3] The data furnished by the British authors did not seem to call for re-investigation since their preparation of 8-chloro-2-hydroxylepidine from *o*-chloroacetoacetanilide, and the melting point of their product, had been confirmed by Monti and Cirelli.[4]

Shortly after the publication of our experiments, Johnson and Hamilton[5] reported that the compound obtained by cyclization of *o*-chloroacetoacetanilide could also be prepared from the major nitration product of 2-chlorolepidine. The melting point of their product checked that of the compound which we had regarded as 5-chloro-2-hydroxylepidine. Likewise, the melting point of the 2,8-dichlorolepidine of Johnson and Hamilton did not agree with that observed by Kermack and Muir for their dichloro compound, but with that of the substance to which we had assigned the structure of 2,5-dichlorolepidine.

In the nitration of lepidine the nitro group enters position 8 since the corresponding aminolepidine can be derived from 8-nitro-2-chlorolepidine by reduction.[5a]

We repeated Johnson and Hamilton's ring closure using commercial *o*-chloroacetoacetanilide, and corroborated the results of these authors. A mixture melting point of the 8-chloro-2-hydroxylepidine obtained by this procedure exhibited no depression with a sample of our chloro-2-hydroxylepidine, and thereby established the structure of our nitro derivative as 8-nitro-2-chlorolepidine.

The position of the nitro group has now been confirmed by degradation to a well-known nitroquinoline. For this purpose, 8-nitrolepidine was converted to 8-nitroquinoline-4-aldehyde by the method of Koenigs,[6] and the aldehyde was oxidized to 8-nitrocinchoninic acid. This acid was decarboxylated to 8-nitroquinoline, which was identified by mixture melting point with a sample prepared from *o*-nitroaniline by the Skraup synthesis. Moreover, 5-nitrocinchoninic acid prepared by nitration of cinchoninic acid[7] depressed the melting point of our 8-nitroquinoline-4-carboxylic acid.

It seemed probable that Kermack and Muir, and Monti and Cirelli, had obtained the isomeric 8-chloro-4-hydroxyquinaldine in their ring closures. A support was given to this assumption by recent studies of Jacini,[8] who showed that in the preparation of acetoacetanilide derivatives by the method of Fierz-David and Ziegler,[9] elimination of one molecule of water rather than of ethanol may occur with the formation of ethyl β-arylaminocrotonates. This method had been used by Monti in the synthesis of compounds interpreted by her as 2-hydroxylepidine derivatives.

8-Chloro-4-hydroxyquinaldine as described by Hughes and Lions[10] melts at 220°. We repeated the synthesis of these investigators, and obtained a compound melting at 229–230°. Chlorination of this derivative yielded 4,8-dichloroquinaldine; the structure of this compound was proved by degradation to quinaldine. The dichloro derivative reacted with piperidine to furnish 8-chloro-4-piperidinoquinaldine; with sodium methoxide it yielded 8-chloro-4-methoxyquinaldine. The melting points of these compounds are listed in the following table and compared with those of the supposedly isomeric lepidine derivatives of Kermack and Muir.

(1) Eli Lilly Research Fellow, 1940–1942.
(2) Krahler and Burger, THIS JOURNAL, **63**, 2367 (1941).
(3) Kermack and Muir, *J. Chem. Soc.*, 300 (1933).
(4) Monti and Cirelli, *Gazz. chim. ital.*, **66**, 723 (1936).
(5) (a) Johnson and Hamilton, THIS JOURNAL, **63**, 2864 (1941); (b) **63**, 2867 (1941).
(6) Koenigs, *Ber.*, **31**, 2364 (1898).
(7) Koenigs and Lossow, *ibid.*, **32**, 717 (1899).
(8) Jacini, *Gazz. chim. ital.*, **71**, 53 (1941).
(9) Fierz-David and Ziegler, *Helv. Chim. Acta*, **11**, 776 (1928).
(10) Hughes and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 458 (1938); *Chem. Abs.*, **33**, 611 (1939).

Derivatives of quinaldine	M. p., °C.	Kermack and Muir's postulated derivatives of lepidine	M. p., °C.
8-Chloro-4-hydroxy-	229–230	8-Chloro-2-hydroxy-	230
4,8-Dichloro-	87–88	2,8-Dichloro-	87–88
8-Chloro-4-piperidino--picrate	124–125 161–163	8-Chloro-2-piperidino--picrate	125–126 159
8-Chloro-4-methoxy-	122–124	8-Chloro-2-methoxy-	122

Only 2-hydroxylepidine could be isolated from the reaction mixture when 2-chlorolepidine was oxidized with selenium dioxide. Bromination of 2-chlorolepidine yielded small amounts of 4-(dibromomethyl)-2-hydroxylepidine; this compound could not be hydrolyzed to 2-hydroxyquinoline-4-aldehyde.

In an experiment designed to synthesize 2-lepidylmalonic acid, sodium diethyl malonate was condensed with 2-chlorolepidine in carefully dried ethanol solution. The reaction product was found to be 2-ethoxylepidine instead; sodium ethoxide had competed with sodium diethylmalonate in the condensation.

Experimental

8-Nitroquinoline-4-aldehyde.—Several attempts were made to oxidize 8-nitrolepidine to the aldehyde with selenium dioxide according to the direction of Johnson and Hamilton,[5a] but more reproducible results were obtained by the method of Koenigs.[6] Bromination of 8-nitrolepidine gave 8-nitro-4-(dibromomethyl)-quinoline in 89% yield, m. p. 111.5–112.5°. The hydrolysis of the dibromomethyl group was effected by dissolving equal parts of the compound and of silver nitrate in five parts of 60% acetic acid and heating the mixture on a steam-bath for four hours. A small amount of hydrochloric acid was added to complete the precipitation of silver halides. The solution was filtered, made alkaline with solid sodium carbonate, and the precipitated aldehyde was isolated. The yield of crude colorless product of m. p. 163–173° was 97%; the compound could be used in the following oxidation without further purification.

8-Nitroquinoline-4-carboxylic Acid.—One and seven-tenths grams of the crude aldehyde, dissolved in 50 cc. of acetone, was oxidized by dropwise addition of 17.75 cc. of a 5% potassium permanganate solution at 40°. The precipitated manganese dioxide was brought into solution by adding some water saturated with sulfur dioxide, the acetone boiled off, and the volume of the solution maintained constant by dilution with water. 8-Nitrocinchoninic acid crystallized as glittering yellow needles, m. p. 253–254° (dec.). The yield was 1.3 g. (71%).

Anal. Calcd. for $C_{10}H_6N_2O_4$: N, 12.84. Found: N, 12.55.

8-Nitroquinoline.—Three-tenths gram of 8-nitrocinchoninic acid, mixed with an equal amount of copper bronze, was heated gently at 100 mm. pressure until the rapid decarboxylation had subsided. The reaction product was distilled out under 20 mm. pressure, and the oily distillate crystallized on cooling. Sublimation at 70° and 2 mm. yielded yellow crystals, m. p. 86–89°. A mixture melting point with an authentic sample of 8-nitroquinoline (m. p. 88–90°) showed no depression.

Attempted Preparation of 2-Chloroquinoline-4-aldehyde.—To a boiling solution of 2.2 g. of 2-chlorolepidine and 4.4 g. of anhydrous sodium acetate in 35 cc. of glacial acetic acid was added a solution of 4.2 g. of bromine in 20 cc. of glacial acetic acid. Decolorization occurred after thirty minutes of boiling. The solution was cooled, poured into ice-water, and the precipitated solid extracted four times with ether. The insoluble material was recrystallized from boiling ethanol. The almost colorless needles melted at 307–308° (dec.), the yield was 0.5 g. (12%). The compound proved to be **4-(dibromomethyl)-2-hydroxyquinoline.**

Anal. Calcd. for $C_{10}H_7Br_2NO$: C, 37.86; H, 2.23. Found: C, 38.06; H, 2.65.

Hydrolysis to 2-hydroxyquinoline-4-aldehyde was unsuccessful. This is in accord with the observation[5a] that 2-hydroxy-4-(bromomethyl)-quinoline resists hydrolysis when refluxed with 80% acetic acid.

The oily residue from the combined ether extracts of the high-melting 2-hydroxy-4-(dibromomethyl)-quinoline was hydrolyzed with silver nitrate in acetic acid solution. The oily reaction product gave a pronounced aldehyde test but did not crystallize and yielded no crystalline derivatives.

8-Chloro-4-hydroxyquinaldine.—Ten grams of *o*-chloroaniline was dissolved in 10 g. of ethyl acetoacetate, one drop of 17% hydrochloric acid was added, and the mixture was allowed to stand over sulfuric acid in an evacuated desiccator for twenty-four hours. The oily yellow ethyl β-(*o*-chlorophenyl)-aminocrotonate was dropped with stirring into 100 cc. of dry paraffin oil preheated to 240°. When all the ester had been added, the temperature was maintained at 240° for five minutes. The clear yellow solution was allowed to cool; crystallization set in at 150°. The mixture was diluted with ligroin, the product was filtered and recrystallized from dilute ethanol. The colorless crystals melted at 229–230°; the yield was 4.4 g. (29%).

Anal. Calcd. for $C_{10}H_8ClNO$: C, 62.03; H, 4.17. Found: C, 62.10; H, 4.79.

4,8-Dichloroquinaldine.—A mixture of 1.4 g. of 8-chloro-4-hydroxyquinaldine and 5 cc. of phosphorus oxychloride was heated on a steam-bath until all the material had gone into solution. This chlorination proceeded more rapidly than the corresponding reaction with 2-hydroxylepidine. The mixture was poured into ice-water and made ammoniacal. An oily precipitate appeared, and solidified on scratching. Recrystallization from dilute methanol, and sublimation at 70° and 2 mm. yielded 1.3 g. (85%) of colorless needles, m. p. 87–88°.

Anal. Calcd. for $C_{10}H_7Cl_2N$: C, 56.63; H, 3.33. Found: C, 56.62; H, 4.30.

One-half gram of the dichloro compound was mixed with 3 g. of zinc dust, and heated slowly in a small distilling flask. A few drops of a clear oil distilled from the mixture. The picrate, prepared from the distillate and recrystallized from boiling ethanol, appeared as yellow needles, m. p. 188–190° (dec.). A mixture melting point with quinaldine picrate (m. p. 192–194°) showed no depression.

8-Chloro-4-piperidinoquinaldine.—A mixture of 0.6 g. of 4,8-dichloroquinaldine and 5 cc. of piperidine was re-

fluxed for four hours, poured into water, the precipitated piperidino derivative was filtered and recrystallized three times from dilute methanol. The compound appeared as lustrous colorless plates; m. p. 124–125°.

Anal. Calcd. for $C_{15}H_{17}ClN_2$: C, 69.09; H, 6.57. Found: C, 69.26; H, 7.41.[11]

The **picrate** crystallized from ethanol as yellow needles, m. p. 161–163°.

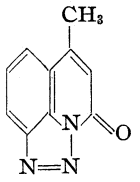
8-Chloro-4-methoxyquinaldine.—A solution of 0.043 g. of sodium in 2 cc. of methanol was added to a solution of 0.4 g. of 4,8-dichloroquinaldine in 30 cc. of methanol, and the mixture was refluxed for twelve hours. The reaction product was precipitated as an almost colorless solid by dilution with water, and purified by fractional sublimation at 90° and 3 mm. The small colorless plates melted at 122–124°.

Anal. Calcd. for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85. Found: C, 64.30; H, 5.39.

2-Chlorolepidine and Sodium Diethyl Malonate.—A solution of 9 g. of diethyl malonate in 10 cc. of absolute ethanol was refluxed with a solution of 1.3 g. of sodium in 30 cc. of absolute ethanol for five minutes; 10 g. of 2-chlorolepidine in 10 cc. of absolute ethanol was added, and the mixture boiled for fifty hours. The separated sodium chloride was filtered, 7.6 g. of potassium hydroxide was added, and the alkaline mixture refluxed for four hours to complete hydrolysis of the ester. Neutralization with dilute acetic acid precipitated an oil which crystallized on cooling. It was recrystallized from dilute alcohol and appeared as colorless needles, m. p. 49–50°. Analysis showed it to be 2-ethoxylepidine.[12]

Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.97; H, 7.00. Found: C, 76.33; H, 6.91.

2-Oxo-4-methylquinoline-1,8-diazoimide.—The method of preparation of this diazoimide which we had interpreted[2] as 5-hydroxy-3-pyrido-[4,3,2-*de*]-cinnoline, has now been improved. A hot solution of 8-amino-2-hydroxylepidine



in 21 cc. of 10% hydrochloric acid was cooled, and the suspension of the finely divided hydrochloride was diazotized with sodium nitrite solution. The diazoimide separated as a brown amorphous precipitate. It was filtered, suspended in hot water, and the mixture heated on a steam-bath for one hour. The tan solid was filtered; the yield was 1.0 g. (47.5%); m. p. 236–237.5° (dec.).

The diazoimide could be recrystallized from boiling ethanol without decomposition, in contrast to other diazoimides (aryl azides)[13] which decompose under these conditions with the loss of one molecule of nitrogen. However, when our diazoimide was boiled in ethanol solution with "darco" a strong odor of acetaldehyde was noted, and 2-hydroxylepidine crystallized on dilution with water. It was identified by a melting point and a mixture melting point with an authentic sample.

Summary

1. The structure of the lepidine derivatives substituted in position 8 prepared by Johnson and Hamilton has been confirmed. These compounds are identical with those previously interpreted by us as the isomeric 5-substituted derivatives of lepidine.

2. The compound described by us as 5-hydroxy-3-pyrido-[4,3,2-*de*]-cinnoline is therefore 2-oxo-4-methylquinoline-1,8-diazoimide.

3. The 8-chloro derivatives of lepidine reported by Kermack and Muir apparently are 8-chloro derivatives of quinaldine.

(11) The values for hydrogen for our quinaldine derivatives ran high due to weather conditions. The daily test microanalyses of known compounds showed the same tendency.

(12) Knorr, *Ann.*, **236**, 69 (1886).

(13) Sah and Wen-Hou Yin, *Rec. trav. chim.*, **59**, 238 (1940).

CHARLOTTESVILLE, VA. RECEIVED JUNE 24, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

The Synthesis of Phenolic Glycosides

BY THOMAS H. BEMBRY AND GARFIELD POWELL[1]

In the course of work in this Laboratory on derivatives of tetrahydrocannabinol, we had occasion to attempt the preparation of the glucoside. The method of Helferich and Schmitz-Hillebrecht,[2] employing zinc chloride or *p*-toluenesulfonic acid as catalyst in a fused mixture of phenol and sugar pentaacetate, was first used. It was not possible in the case of the difficultly accessible phenol, tetrahydrocannabinol, to use the large excess ordinarily employed in this procedure, and poor results were obtained when equimolar quantities of the reactants were used.

On the other hand, we found that tetrahydrocannabinol and a number of other phenols condense smoothly with fully acetylated sugars in benzene solution in the presence of moist phosphorus oxychloride, giving high yields of acetyl-

(1) We are indebted to Smith, Kline and French Laboratories, and one of us (T. H. B.) to the Julius Rosenwald Fund for generous grants to support this work.

(2) Helferich and Schmitz-Hillebrecht, *Ber.*, **66**, 378 (1933).

ated β-glycosides based on the amount of phenol used. We believe that this method gives distinct promise of general usefulness for the preparation of the phenolic glycosides.

The present work describes the application of the method to the preparation of the glycosides of a number of representative phenols, using various fully acetylated sugars. The preparation of the glucoside of tetrahydrocannabinol will be described elsewhere.

Experimental

Pure phosphorus oxychloride appeared to be unsatisfactory as a catalyst, and we used as a standard a reagent made by the addition of 1% by volume of distilled water to a redistilled analytical reagent grade of the material.

Procedure

A solution of phenol (1 mole), the fully acetylated sugar (1 mole), and the phosphorus oxychloride reagent ($^1/_3$ mole) in dry benzene was heated under reflux for three hours. After cooling, the reaction mixture was shaken with ice water, and the benzene layer was separated, washed with dilute sodium hydroxide solution, then with water, and then dried over calcium chloride. After evaporation of the solvent under reduced pressure, the residue was crystallized from an appropriate solvent, usually 95% ethanol.

In this way we prepared tetraacetyl-phenol-β-*d*-glucoside[2,3] (44%), m. p. 125–126° (cor.), $[\alpha]^{26}D$ −23° ($CHCl_3$), from phenol and β-pentaacetyl glucose; tetraacetyl-phenol-β-*d*-galactoside[2,4] (44%), m. p. 123–124° (cor.), $[\alpha]^{21}D$ −26° (C_6H_6), from phenol and β-pentaacetylgalactose; triacetylphenol-β-*d*-xyloside[2] (57%), m. p. 147–148° (cor.), $[\alpha]^{22}D$ −52° ($CHCl_3$), from phenol and tetraacetylxylose; tetraacetyl-α-naphthol-β-*d*-glucoside[3,5] (58%), m. p. 178–179° (cor.), $[\alpha]^{22}D$ −72° ($CHCl_3$), from α-naphthol and β-pentaacetyl glucose; and the new tetraacetyl-(*o*-hydroxydiphenyl)-β-*d*-glucoside[6] (35%), long white needles form 95% ethanol, m. p. 155–156° (cor.), $[\alpha]^{22}D$ −56° ($CHCl_3$), from *o*-hydroxydiphenyl and β-pentaacetylglucose.

Anal.[7] Calcd. for $C_{26}H_{28}O_{10}$: C, 62.40; H, 5.60. Found: C, 62.56; H, 5.59.

The latter derivative was deacetylated by the method of Zemplén[8] to give *o*-diphenyl-β-*d*-glucoside (90%) as shining needles from water, m. p. 76–77° (cor.), $[\alpha]^{25}D$ −42° (EtOH).

Anal.[7] Calcd. for $C_{18}H_{20}O_6$: C, 65.06; H, 6.02. Found: C, 64.81; H, 6.07.

For the preparation of tetraacetyl-phenol-β-*d*-fructoside,[2] m. p. 129–130° (cor.), $[\alpha]^{22}D$ −147° ($CHCl_3$), it was found that the reaction mixture darkened less and a somewhat better yield (33%) was obtained if (1) the benzene solution of the reactants was allowed to stand at room temperature for twenty-four hours, rather than being heated under reflux for three hours as in the general procedure, and (2) the benzene extract was washed with bicarbonate rather than sodium hydroxide.

As a further check on the identity of the known glycosides, quantitative carbon–hydrogen determinations were run[7] on all samples; satisfactory agreement with theory was obtained in each case.

Summary

A method for the condensation of phenols with the fully acetylated sugars in the presence of phosphorus oxychloride in benzene solution to form glycosides of phenols has been described. The physical constants of *o*-diphenyl-β-*d*-glucoside are reported.

NEW YORK, N. Y. RECEIVED MARCH 30, 1942

(3) Fisher and Mechel, *Ber.*, **49**, 2813 (1916); Carter, *ibid.*, **63**, 586 (1930); Montgomery, Richtmyer and Hudson, THIS JOURNAL, **64**, 690 (1942).

(4) Fisher and Armstrong, *Ber.*, **35**, 833 (1902).

(5) Drouin, *Bull. soc. chim.*, **13**, 5 (1895).

(6) These substances were assigned the β-configuration on the basis of the analogy with the other cases, in which the configuration was established by comparison with authentic samples prepared by other methods.

(7) We are indebted to Mr. Saul Gottlieb for carrying out these analyses.

(8) Zemplén, *Ber.*, **62**, 1613 (1929).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

Friedel–Crafts Acylations of Some Sterically Hindered Alkylbenzenes

BY G. F. HENNION AND S. F. DEC. MCLEESE[1]

Introduction

The Friedel–Crafts ketone synthesis has been applied to but few *s*-alkylbenzenes; there are no reports of such reactions with *p*-di-*s*-alkyl derivatives. Since the latter are sterically hindered with respect to the available ortho positions, have tertiary hydrogen in the side chains, which also are susceptible to rearrangement, migration and displacement in the presence of aluminum chloride, it was thought of interest to study the course of their reactions with acetyl and benzoyl chlorides. A variety of these hydrocarbons was available from previous investigations.[2]

We were especially interested in the possibility of acylating within the side chains since these contain labile hydrogen which might react in preference to hindered hydrogen of the ring. This was not observed, however, and it appears now that 1,4-di-*s*-alkylbenzenes substitute normally in the 2-position. Mono-*s*-alkylbenzenes react in the 4-position as expected. Reactions of *t*-butylbenzene, *p*-*s*-butyltoluene and *p*-di-*t*-butylbenzene were studied also to permit comparisons of the products with those obtained from the other hydrocarbons. An anomalous reaction was observed only with *p*-di-*t*-butylbenzene, which lost one butyl group, giving *p*-*t*-butylacetophenone in 72% yield.

In order to establish structures for the various ketones, it was necessary to oxidize them to known or identifiable benzene-carboxylic acids. With sodium dichromate–sulfuric acid–acetic acid mixture the alkyl and dialkylacetophenones gave terephthalic acid. Oxidation of dialkylacetophenones with dilute nitric acid yielded the corresponding 4-alkylisophthalic acids, thus proving that the previous dichromate oxidations had completely removed the acetyl group in each case. Nitric acid converted *p*-*s*-alkylacetophenones to *p*-*s*-alkylbenzoic acids. In further confirmation of the assigned structures, 2,5-di-*s*-butylacetophenone was degraded to trimellitic acid by oxidation with chromic acid followed by heating with nitric acid in a sealed tube. The *p*-alkylbenzophenones and 2,5-dialkylbenzophenones were readily converted to *p*-benzoylbenzoic acid and benzoylterephthalic acid, respectively.

The non-identity of *p*-*s*-butylacetophenone and the *p*-*t*-compound, coupled with the established identity of *p*-*s*-butylbenzoic acid with an authentic sample, serves to show that the *s*-alkyl groups are not altered in structure under the conditions of the experiments.

The various ketones are described in Table I and some of the oxidation products in Table II. These list the new compounds only. It is to be noted (Table I) that there is considerable exaltation in the molecular refractions, characteristic of compounds of this type.

TABLE I

CONSTANTS, YIELDS AND ANALYTICAL DATA FOR KETONES

Compound	B. p. °C.	Mm.	$n^{20}D$	d^{20}_4	Yield, %	Mol. wt. Calcd.	Mol. wt. Obsd.	*MR* Calcd.	*MR* Obsd.	% Carbon Calcd.	% Carbon Obsd.	% Hydrogen Calcd.	% Hydrogen Obsd.
p-*s*-Butylacetophenone	134–135	11	1.5195	0.9631	74	176	172	54.03	55.51	81.81	81.75	9.09	9.11
p-*s*-Amylacetophenone	144–145	11	1.5150	.9555	58	190	185	58.64	59.96	82.11	82.18	9.47	9.72
p-*s*-Octylacetophenone	134–135	3	1.5078	.9333	68	232	227	72.50	74.08	82.76	83.15	10.34	10.37
2-Methyl-5-*s*-butylacetophenone	132–133	11	1.5180	.9588	85	190	188	58.64	60.05	82.11	81.98	9.47	9.42
2,5-Di-*s*-butylacetophenone	148–149	14	1.5056	.9316	80	232	230	72.50	73.94	82.76	82.91	10.34	10.11
2,5-Di-*s*-amylacetophenone	126–127	3	1.5052	.9278	65	260	254	81.73	83.15	83.08	83.02	10.77	10.76
p-*s*-Butylbenzophenone	188	9	1.5760	1.0359	88	238	238	73.52	76.03	85.71	85.52	7.56	7.80
p-*s*-Amylbenzophenone	188–190	5	1.5672	1.0205	60	252	249	78.13	80.69	85.72	85.76	7.94	7.82
p-*s*-Octylbenzophenone	212–214	5	1.5540	0.9981	73	294	287	91.99	94.40	85.71	85.80	8.84	8.78
p-*s*-Dodecylbenzophenone	243–245	4	1.5392	.9689	45	350	344	110.46	113.19	85.71	85.62	9.71	9.70
2,5-Di-*s*-butylbenzophenone	155	3	1.5540	.9968	60	294	284	91.99	94.51	85.71	85.60	8.84	8.86

TABLE II

OXIDATION PRODUCTS

Compound	M. p., °C.	Neutral. equivalent Calcd.	Neutral. equivalent Obsd.
4-*s*-Butylbenzoic acid	91– 92	178	176
4-*s*-Amylbenzoic acid	103–104	192	189.3
4-*s*-Butylisophthalic acid	237–238	111	112
4-*s*-Amylisophthalic acid	230–231	118	120.7

Experimental

Acetophenones.—These were prepared in 0.2- to 0.8-mole quantities after the manner described in "Organic

(1) Present address, Webster College, St. Louis, Mo.

(2) Hennion, *et al.*, THIS JOURNAL, **62**, 1145 (1940); **63**, 2603 (1941).

Syntheses."[3] The monoalkylbenzenes reacted even at −10°; with the dialkylbenzenes it was necessary to heat to the reflux temperature of carbon disulfide for several hours. Products were fractionated through a 40-cm. column to constant n_D. *p-t*-Butylacetophenone from *t*-butylbenzene had b. p. 133–134° (11 mm.); $n^{20}D$ 1.5199; d^{20} 0.9642; from *p*-di-*t*-butylbenzene, b. p. 134° (11 mm.); $n^{20}D$ 1.5195; d^{20} 0.9635. The two semicarbazones had identical m. p. and mixed m. p., 220–221° (uncor.).

Benzophenones.—The method of Gattermann and Wieland[4] was used. Products are semi-viscous, slightly yellow liquids. They were distilled twice from glass wool in a low side-arm Claisen flask, followed by fractionation by means of a horizontal flask molecular still.[5]

Oxidations with Dichromate.—Two-gram samples of alkyl- and dialkylacetophenones were heated at 65–75° with 32 g. of sodium dichromate in 60 cc. of acetic acid containing 44 g. of sulfuric acid. After diluting with water and standing overnight, the terephthalic acid was filtered, washed and dried. Neutralization equivalent, calcd., 83; obs. 83.5. Dimethyl ester, m. p. and mixed m. p., 139–140°.

Oxidation of Monoalkylacetophenones with Nitric Acid.—A 6-g. sample was refluxed with 600 cc. of dilute nitric acid (d. 1.09) for from eight to forty-eight hours. Terephthalic acid was removed from the hot solution and the *p-s*-alkylbenzoic acid allowed to crystallize.[6] The latter was purified by heating for four hours in 15 cc. of acetic acid containing 4 g. of tin and 1 g. of zinc dust and a little hydrochloric acid, to remove nitrated impurities. Several crystallizations from dilute alcohol then gave pure products.

Oxidation of Dialkylacetophenones with Nitric Acid.—Six-gram samples were boiled with 600 cc. of nitric acid (d. 1.09) for several days and the products purified as described above.

Trimellitic Acid.—An 11.6-g. sample of di-*s*-butylacetophenone was oxidized with 75 g. of chromic acid (added in 1-g. portions over a period of thirty-five hours) in 170 g. of acetic acid. The solution was poured into ice-water and extracted three times with ether. The extract was distilled, yielding a solid residue which could not be purified. Two grams of this material was heated with 10 cc. of 1:2 nitric acid in a sealed tube for twenty-four hours. After the terephthalic acid was separated, trimellitic acid crystallized on cooling. It is very soluble in water; neutralization equivalent, calcd., 70; obs., 76.

Oxidation of Benzophenones.—When boiled with dilute nitric acid, *p-s*-butyl- and *p-s*-amylbenzophenone gave *p*-benzoylbenzoic acid, m. p. and mixed m. p. 192–193° (cor.). The *s*-octyl and *s*-dodecyl derivatives were not appreciably affected in this manner. Oxidation of 3-g. samples was accomplished by heating for sixteen hours with 20 g. of potassium dichromate in 90 g. of water containing 30 g. of sulfuric acid. 2,5-Di-*s*-butylbenzophenone was oxidized with dichromate–sulfuric acid–acetic acid mixture at 40°: benzoylterephthalic acid, m. p. 283° (cor.); neutralization equivalent, calcd., 135; obs., 137.

Ketone Derivatives.—Monoalkylacetophenones yielded semicarbazones in the usual manner. Prolonged heating was required to derivatize the dialkyl compounds. The new acetophenone semicarbazones with their melting points are: *p-s*-butyl, 190–191°; *p-s*-amyl, 173–174°; *p-s*-octyl, 144–145°; 2-methyl-5-*s*-butyl, 114–115°; 2,5-di-*s*-butyl, 160–161°; 2,5-di-*s*-amyl, 149–150°. Semicarbazones could not be obtained from the benzophenones.

Summary

1. *s*-Alkyl and *p*-di-*s*-alkylbenzenes react with acetyl and benzoyl chlorides in the presence of aluminum chloride without disturbance of the alkyl groups.

2. When *p*-di-*t*-butylbenzene reacted with acetyl chloride one *t*-butyl group was displaced by acetyl.

3. Structures of the various ketones were proved by oxidation.

4. A number of new substituted acetophenones, benzophenones and benzene carboxylic acids are reported and described.

NOTRE DAME, INDIANA RECEIVED JULY 17, 1942

(3) "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1934, Vol. XIV, p. 1.

(4) "Laboratory Methods of Organic Chemistry," The Macmillan Co., New York, N. Y., 24th ed., 1938, p. 343.

(5) Morton, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1938, p. 120.

(6) *p-s*-Octylacetophenone gave only terephthalic acid.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

The Preparation and Alkylation of 1,4-Dimesityl-3-methyl-1,2,4-butanetrione Enol

BY ROBERT E. LUTZ AND DANIEL H. TERRY[1]

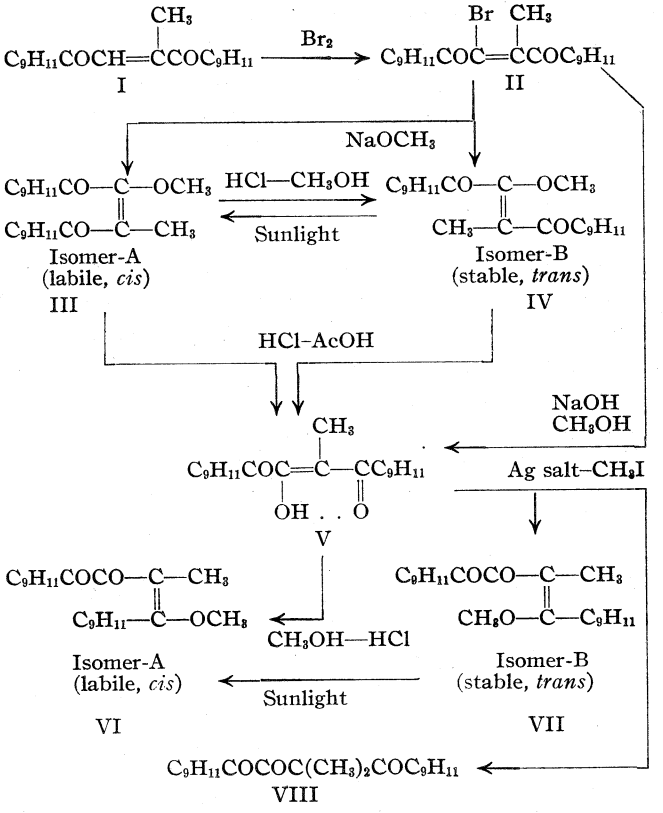
The substitution of halogen, alkyl, phenyl or benzoyl on the 3-carbon of 1,4-diphenyl-1,2,4-butanetrione enol promotes cyclization and stabilizes the hydroxyfuranone form. The effect of these groups on the keto–enol tautomerism is obscured because of the cyclization. On the other hand, the 1,4-dimesityl compound and its bromo derivative[2] do not cyclize because of the excessive steric hindrance, and in these types the keto–enol reactions can be investigated without this complication. It seemed desirable to study a few more examples of this type, and the present report deals with the preparation and alkylation of the 3-methyl derivative.

The 3-methyl triketone enol (V) was first obtained as a minor product in the alkylation of the silver salt of 1,4-dimesityl-1,2,4-butanetrione enol.[3] A better method of preparation has now been devised which also demonstrates the structure of the product. This synthesis started from dimesitoylmethylethylene (I) which was made from mesaconyl chloride by the Friedel–Crafts reaction. Bromination gave *cis*-bromodimesitoylmethylethylene (II).[4] The bromo compound reacted with sodium methoxide to give two enol methyl ethers which from their mode of formation must be the *cis*- and *trans*-isomers (III and IV). Acid hydrolysis of these ethers, or alkali hydrolysis of the bromo unsaturated diketone itself (II), gave the desired triketone enol (V) in good yield.

The triketone enol (V) is yellow in color, gives a red color with ferric chloride and reacts rapidly with bromine and with diazomethane. It is strongly acidic as is shown by its solubility in sodium carbonate and it gives an unstable brilliant yellow silver salt. It shows no tendency to cyclize to a hydroxyfuranone.

The methylation with diazomethane gave four isomeric compounds. Two of these proved to be the *cis*- and *trans*-2-methyl ethers (III and IV) which were obtained as mentioned above by the action of sodium methoxide on the bromo unsaturated diketone (II). One was assigned the *cis*-configuration (III) on the basis of its instability and conversion by means of methanolic hydrogen chloride into the other which was stable and therefore was assumed to be *trans* (IV). The inversion in the opposite direction from *trans* to *cis* was accomplished by exposure to sunlight in pure methanol.

The other two of the four isomeric methylation products were shown also to be enol ethers by the facile acid hydrolysis to the enol (V). By difference they must be the structurally isomeric *cis*- and *trans*-4-methyl ethers (VI and VII). The *cis–trans* relationship was confirmed by the inversion of one (the stable) into the other (the labile) by the action of sunlight; unfortunately, inversion in the opposite direction was not accomplished. We are assuming tentatively that the labile form



(1) du Pont Fellow, 1939–1940. Present location, Jackson Laboratory, du Pont de Nemours Co., Wilmington, Del.

(2) (a) Lutz and Wood, THIS JOURNAL, **60**, 705 (1938); (b) Lutz and Terry, *J. Org. Chem.*, **7**, 274 (1942).

(3) Lutz and Terry, *ibid*, **7**, 320 (1942).

(4) Lutz and Terry, THIS JOURNAL, **64**, 2426 (1942).

is that one which has the mesityl and mesitylglyoxyl groups on the same side of the molecule, namely, VI.

One striking fact was observed in this series, namely, that the enol (V) reacted readily and quantitatively with methanolic hydrogen chloride to give the *labile* 4-methyl ether (VI). This type of reaction does not take place with dimesitylbutanetrione enol itself (the diphenyl analogs all give the alkoxyfuranones under these conditions). There is analogy for direct etherification of a strongly acidic enolic hydroxyl in the case of hydroxynaphthoquinone, where etherification to 2-methoxy-*p*-naphthoquinone takes place under these conditions.[5] In the case in hand it is perhaps surprising that the labile 4-methyl ether should be the one formed.

The formation of all of the four possible isomeric ethers in the reaction between the enol (V) and diazomethane calls to mind the formation of three of the four possible isomeric ethers in the similar methylation of the dimesitylbutanetrione enol itself.[3] It is clear from these results that there is no simple stereochemical relation between the products of methylation and the presumably chelated enols from which they were made.

Alkylation of the silver salt of the enol (V) was of interest because it was expected to produce results closer to those obtained in the case of dimesitylbutanetrione silver enolate than to those obtained in the case of the diphenyl analog. The dimesityl triketone silver enolate underwent chiefly oxygen-alkylation at the 4-oxygen whereas the diphenyl analog was found to undergo mainly carbon-alkylation. The results in the present case were approximately as predicted. Dimesitylmethylbutanetrione silver enolate reacted with methyl iodide to give a mixture of carbon and oxygen-alkyl derivatives. The carbon-alkyl derivative (VIII) was obtained in a yield of 30%. The oxygen-alkyl derivative was obtained in 65% yield and was the expected 4-enol methyl ether, but it was the stable stereoisomer-B (VII).

In summary of the alkylation results it may be said that diazomethane reacts with the enol to give all four 2- and 4-enol ethers; methanolic hydrogen chloride gives the labile 4-enol ether; and the silver salt with methyl iodide gives the stable 4-enol ether along with a lesser but sizeable yield of the carbon-alkyl derivative. The marked tendency to react at the 4-oxygen is noteworthy.

(5) Fieser, THIS JOURNAL, **48**, 2922 (1926).

Experimental

1,4-Dimesityl-3-methyl-1,2,4-butanetrione Enol (V).—A suspension of 4.5 g. of the *cis*-2-enol methyl ether (III) in 40 cc. of concd. acetic acid, 10 cc. of concd. hydrochloric acid and 5 cc. of water was stirred vigorously at room temperature for three hours. The solution became bright yellow, and 4.25 g. (98%) of bright yellow needles separated (m. p. 120–122°). When the reaction mixture was refluxed the yields were smaller and a larger amount of non-crystalline material formed. Repeated crystallizations from methanol brought the melting point to 124.5–125°.

Anal. Calcd. for $C_{23}H_{26}O_3$: C, 78.86; H, 7.5. Found: C, 78.40, 78.81; H, 7.23; 7.39.

Alternative preparations are as follows.

(a) A suspension of 1.5 g. of the *cis*-bromo unsaturated diketone (II) in 75 cc. of 90% methanol and 1.5 g. of sodium hydroxide was refluxed for ten minutes after solution was complete. The purple solution was acidified with dilute hydrochloric acid, diluted with water and extracted several times with ether. The ether extract was shaken four times with 25-cc. portions of 5% sodium hydroxide. Acidification of the alkaline solution and extraction with ether removed the enol which was isolated as a partly crystallized residue upon evaporation of the solvent. Crystallization from ethanol gave 0.8 g. (64%).

In a similar experiment using 80% methanol and refluxing for one hour, largely non-crystalline material was obtained along with a 30% (by weight) yield of a colorless solid which upon repeated crystallization from ethyl acetate melted at 234° (it contained no halogen). *Anal.* C, 81.98; 81.73; H, 6.90; 6.77. This compound has not been investigated.

(b) The action of methyl iodide on the dimesitylbutanetrione silver enolate in isopropyl ether (refluxing for two hours) gave the carbon-methyl derivative (V) in 7% yield.

(c) Hydrolysis of the *cis*-2-enol methyl ether by means of saturated methanolic hydrogen chloride gave the enol (V) in 81% yield.

The enol (V) gave a deep maroon color with alcoholic ferric chloride. It is soluble in aqueous sodium carbonate.

The sodium enolate did not crystallize from a methanol solution. It proved to be quite soluble in water and alcohol, in contrast to the sodium salt of the parent dimesitylbutanetrione enol. **The silver salt** (bright yellow) was precipitated from an aqueous or methanolic solution of the sodium salt by the addition of silver nitrate; it darkened rapidly on standing and was black within twenty minutes.

Hydroxylamine in pyridine or in methanol was without action, as also was semicarbazide and 2,4-dinitrophenylhydrazine in ethanol.

Methylation by Diazomethane.—Two grams of the enol (V) was added to 50 cc. of ether containing 0.4 g. of diazomethane. After the vigorous reaction subsided the solution was allowed to stand overnight and was washed with dilute hydrochloric acid and with water. Upon evaporation of the ether in a current of dry air, an oil was obtained from which digestion with ethanol produced a crystalline precipitate (0.72 g. or 44%) which proved to be the main product, the 2-enol methyl ether-A (*cis*) (III) (described under this

compound). A second fraction (0.18 g., 9%) was then obtained and shown to be the *trans*-2-enol methyl ether (IV) (described under that compound). Upon standing the filtrate deposited a third compound (yield 15%) which was found to be the *cis*-4-enol methyl ether (VI) (described under that compound). Careful manipulation of the residues produced a fourth and more soluble isomer in a 30% yield. This was obtained from 90% ethanol and was shown to be the 4-enol methyl ether-B (*trans*) (VII) (described under that compound).

Alkylation of the Silver Enolate with Methyl Iodide.—A methanol solution of 1.2 g. of the enol (V) and one equivalent of sodium methoxide was treated with 3.5 cc. of methyl iodide. The mixture was stirred mechanically and maintained at 0°. An aqueous solution (65 cc.) of 2% silver nitrate was added slowly and stirring was continued for three hours while the mixture was allowed to come to room temperature. The mixture was then heated on a water-bath at 60° for one hour, filtered from silver iodide, diluted with water and extracted with ether. The ether solution was shaken three times with 20-cc. portions of 10% sodium hydroxide which removed the unchanged enol present (0.34 g. was recovered). Evaporation of the ether gave a bright yellow solid which was washed with methanol; yield 0.58 g. (65%). This proved to be the 4-enol methyl ether-B (*trans*) (VII). From the methanol solution 0.3 g. (37%) of bright yellow crystals of the dimethyltriketone (VIII) was isolated (see that compound).

***cis*-1,4-Dimesityl-3-methyl-1,2,4-butanetrione 2-Enol Methyl Ether (III).**—This compound was obtained as described under the methylation of the enol with diazomethane (yield 44%). It was obtained in better yield as follows.

A mixture of 2.5 g. of *cis*-bromodimesitoylmethylethylene (II) and 50 cc. of methanol containing 2 g. of dissolved sodium was stirred for two hours at room temperature. The colored solution was concentrated and diluted with water slowly; 0.22 g. (12%) of pale yellow crystals separated and was identified as the *trans*-2-enol methyl ether-B (described below). Further concentration of the filtrate produced 1.08 g. (58%) of a more soluble and colorless product. This was recrystallized repeatedly from methanol and melted at 134.5–135°. This latter compound was obtained in almost quantitative yield by exposing a methanol solution of the *trans*-isomer-B (V) to the action of sunlight for eight hours.

Anal. Calcd. for $C_{24}H_{28}O_3$: C, 79.12; H, 7.74; OCH_3, 8.5. Found: C, 78.93; H, 7.63; OCH_3, 8.79, 8.44.

Hydrolysis of 4 g. in a mixture of concd. acetic acid, 10 cc. of concd. hydrochloric acid and 5 cc. of water, at room temperature (three hours) or under refluxing for fifteen minutes, gave nearly quantitative yields of the enol (V).

The enol ether (III) was recovered unchanged after (a) exposure to sunlight for six hours in chloroform containing a trace of iodine; and (b) treatment with alcoholic sodium acetate under reflux for seven hours.

Treatment of 0.5 g. of the compound for five days with saturated methanolic hydrogen chloride gave two crystalline fractions. The first (0.3 g.) was the *trans*-isomer-B (IV), and the second (0.15 g.) the enol (V).

***trans*-1,4-Dimesityl-3-methyl-1,2,4-butanetrione 2-Enol Methyl Ether-B (IV).**—This compound was obtained as described above in 12% yield by the action of sodium methoxide on the *cis*-bromo unsaturated diketone (II), and in 9% yield by the action of diazomethane on the enol (V). It was obtained also in 60% yield by the action of saturated methanolic hydrogen chloride on the *cis*-isomer-A (III) at room temperature for five days (as described above). The *trans*-isomer-B was purified by repeated crystallizations from ligroin, 85% methanol, and methanol; pale yellow crystals of m. p. 156.5–157°.

Anal. Calcd. for $C_{24}H_{28}O_3$: OCH_3, 8.52. Found: OCH_3, 8.48.

Hydrolysis of 0.5 g. by a mixture of 10 cc. of concd. acetic acid, 3 cc. of concd. hydrochloric acid and 2 cc. of water at room temperature for three hours gave 0.3 g. (6%) of nearly pure enol (V).

***cis*-(?)-1,4-Dimesityl-3-methyl-1,2,4-butanetrione 4-Enol Methyl Ether-A (VI).**—A solution of 0.45 g. of the enol (V) in saturated methanolic hydrogen chloride was allowed to stand for five days at room temperature. Evaporation in an air stream gave 0.44 g. (92%) of product which was crystallized repeatedly from methanol and obtained as colorless prisms of m. p. 142°.

Anal. Calcd. for $C_{24}H_{28}O_3$: C, 79.12; H, 7.74; OCH_3, 8.52. Found: C, 78.25; H, 7.99; OCH_3, 8.33.

This compound was obtained also in 15% yield in the methylation of the enol with diazomethane, as described above. It was also obtained by the action of sunlight for seven hours on a methanol solution of the *trans*-isomer-B (VII).

Hydrolysis of 0.25 g. by 25 cc. of concd. acetic acid, 4 cc. of concd. hydrochloric acid and 3 cc. of water under reflux for fifteen hours gave 0.2 g. (83%) of nearly pure enol (V). Treatment of the ether (VI) with methanolic potassium hydroxide under reflux for five hours was without effect. This ether was not changed by exposure to sunlight for six hours in chloroform containing a trace of iodine.

***trans*-(?)-1,4-Dimesityl-3-methyl-1,2,4-butanetrione 4-Enol Methyl Ether-B (VII).**—This isomer was prepared as described above by the action of methyl iodide on the silver enolate and also by the action of diazomethane on the enol. Upon repeated crystallization from methanol it was obtained as pale yellow needles of m. p. 119.5–120°.

Anal. Calcd. for $C_{24}H_{28}O_3$: C, 79.12; H, 7.74; OCH_3, 8.52. Found: C, 78.57; H, 8.09; OCH_3, 8.79.

Hydrolysis of 0.25 g. in the concd. acetic–hydrochloric acid–water mixture (refluxing for one and one-half hours) gave 0.21 g. (81%) of nearly pure enol (V). The compound was recovered unchanged after treatment with (a) methanolic potassium hydroxide (refluxing for ten hours) and (b) saturated methanolic hydrogen chloride (for three days at room temperature).

1,4-Dimesityl-3,3-dimethylbutanetrione-1,2,4 (VIII).—This bright yellow compound was obtained as described above in the methylation of the silver enolate of (V) by methyl iodide. Repeated crystallizations from ethanol brought the melting point to 132.5–133°.

Anal. Calcd. for $C_{24}H_{28}O_3$: C, 79.12; H,7 .74; OCH_3, 0. Found: C, 79.28, 79.41; H, 7.60, 7.85; OCH_3, 0.

The compound was recovered unchanged when treated with (a) the concd. acetic–hydrochloric acid–water mixture

(refluxing for thirty minutes) and (b) hydroxylamine in methanol (refluxing for ten hours).

Summary

1,4-Dimesityl-3-methyl-1,2,4-butanetrione enol has been synthesized from mesaconyl chloride.

Methylation with diazomethane gave all of the four possible methyl ethers. The *cis–trans* 2-enol methyl ethers were made in another way by the action of sodium methoxide on bromodimesitoylethylene. The configurations were determined by interconversions and relative stability. The labile 4-enol methyl ether was obtained in a second way by acid catalytic methylation of the enol; and the stable 4-enol methyl ether, along with the carbon-methyl derivative, was obtained by alkylation of the silver enolate.

CHARLOTTESVILLE, VA. RECEIVED JULY 6, 1942

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

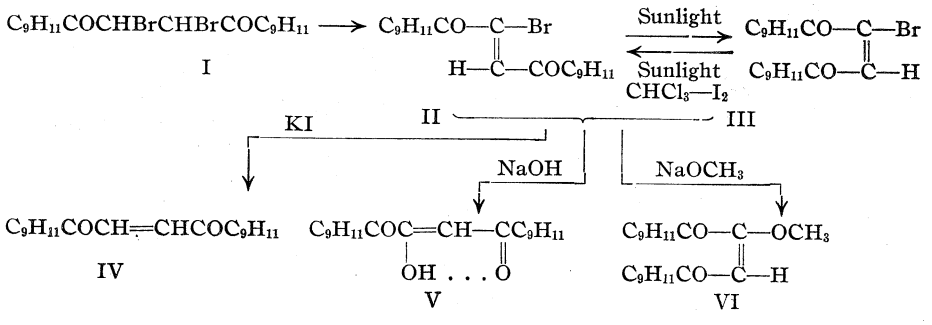
The Stereoisomeric Bromo 1,4-Dimesityl Unsaturated 1,4-Diketones

BY ROBERT E. LUTZ AND DANIEL H. TERRY[1]

This report deals with the preparation of some halogen derivatives which were made in connection with the work on 1,4-dimesityl and 1,4-dimesityl-3-methyl 1,2,4-butanetrione enols.

The 1,4-Dimesityl Series

The yellow *trans*-bromodimesitoylethylene (II) is made easily from dimesitoylethylene dibromide (I).[2] It is converted by the action of sunlight into a colorless isomer which, therefore, must be the *cis*-isomer (III). Conversion back into the *trans*-isomer was brought about by the action of sunlight on a chloroform solution containing a trace of iodine as a catalyst.



Both *cis*- and *trans*-isomers react with methanolic potassium hydroxide to give the triketone enol (V) and with sodium methoxide to give the *cis*-2-enol ether (VI). In the latter reaction no consistent stereochemical orientation is involved. 1,4-Addition probably occurs, but the intermediate 4-enolates, while theoretically capable of existing and maintaining individual configurations, would hardly be expected to do so during this reaction under alkaline conditions.[3]

The action of potassium iodide on the bromo unsaturated diketones in both cases gave *trans*-dimesitoylethylene (IV), a somewhat surprising reaction which must be attributed to the fact that these compounds contain the conjugated α-bromoketone system. The halogen in the corresponding dimesitylmethyl series is not reducible under the same conditions, however, due perhaps to an increase in the total steric hindrance by the substituted methyl group.

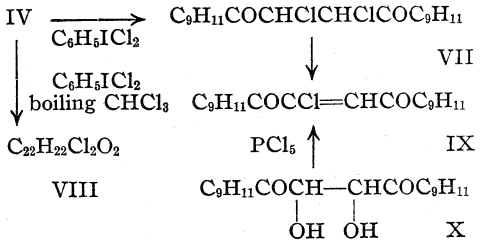
Chlorination of dimesitoylethylene (IV) was carried out to verify certain compounds and reactions which had been previously reported.[2,4] Phenyl iodochloride in cold chloroform converted the unsaturated diketone into the dichloride (VII) which had previously been isolated in extremely small amounts when free chlorine was used.[2] This dichloride when subjected to the action of boiling ethanol lost hydrogen chloride and gave the yellow *trans*-dimesitoylchloroethylene (IX) which can be made by the action of hydrochloric acid on dimesitoylethylene oxide[4] and by the action of phosphorus pentachloride on dimesitoylglycol (X).

(1) du Pont Fellow, 1939–1940; present location, Jackson Laboratory, E. I. du Pont de Nemours & Co., Wilmington, Del.

(2) Lutz, THIS JOURNAL, **48**, 2905 (1926).

(3) *Cf.* the facile rearrangement of the labile 4-enol ether [Lutz and Terry, *J. Org. Chem.*, **7**, 320 (1942)].

(4) Lutz and Wood, THIS JOURNAL, **60**, 229 (1938).

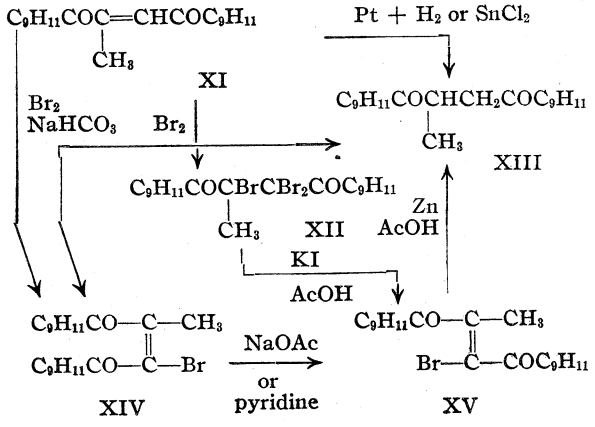


When dimesitoylethylene was treated with phenyl iodochloride in boiling chloroform, a dichloro unsaturated diketone (VIII) was obtained which was shown to involve nuclear substitution, by the resistance toward reduction by zinc and acetic acid of at least one of the halogens. This compound evidently is a derivative of IX.

The 1,4-Dimesityl-3-methyl Series

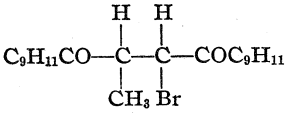
The unsaturated diketone of this series (XI) does not give a stable dibromide but reacts slowly in chloroform solution to give what appears to be the *cis*-bromo unsaturated diketone (XIV), along with two other products, the saturated diketone (XIII) and a tribromo compound which is believed to be XII. Possibly the unstable dibromide and hydrobromide are involved and, in the presence of hydrogen bromide generated during the reaction, act as α-bromoketones to give up bromine and simultaneously to undergo reduction.[5]

In order to avoid complications due to secondary bromination the same reaction was carried out in the presence of an excess of powdered sodium bicarbonate to remove hydrogen bromide. Under these conditions the *cis*-bromo unsaturated diketone was obtained relatively free from by-products and in good yield.



The structure of the *cis*-bromo unsaturated diketone (XIV) was proved by analysis and by the facile rearrangement under the influence of sodium acetate or pyridine into a stable isomer which consequently must be the *trans*-form (XV). The *trans*-compound was then reduced by means of zinc and acetic acid to the saturated diketone (XIII) which was obtained also by direct reduction of the unsaturated diketone (XI).

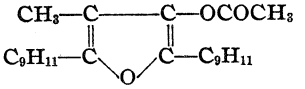
The conversion of the *trans*-unsaturated diketone (XI) to the labile *cis*-bromo unsaturated diketone (XIV) by bromination presumably involves the intermediate formation of an unstable dibromide. Obviously, in view of the production of the *labile*-stereoisomer under these circumstances this transformation is best interpreted as a *trans*-addition of bromine to give an unstable dibromide of the configuration (XVI), followed by *trans*-elimination of hydrogen bromide.



XVI

The structure of the tribromo derivative (XII) was deduced from analysis and the conversion by means of potassium iodide into the *trans*-bromo unsaturated diketone (XV).

Incidental to this work the acetoxyfuran (XVII) was made from the unsaturated diketone (XI). When the usual combination, acetic anhydride and sulfuric acid, was employed, there was produced a sulfur containing compound of empirical formula $C_{23}H_{26}O_5S$; however, when acetyl chloride was substituted for acetic anhydride, as was done in the case of dimesitoylethylene itself, the acetoxyfuran was then obtained without difficulty.



XVII

Experimental

The 1,4-Dimesityl Series

***trans*-2-Bromo-1,4-dimesityl-2-butanedione-1,4 (1,2-dimesitoylbromoethylene) (II).**—The best preparation has previously been reported.[6] The bromo compound has now been obtained in other ways as follows:

(a) A suspension of 5 g. of the dibromide of dimesitoylethylene (I) and 1.5 g. of sodium benzoate in 75 cc. of absolute ethanol was refluxed for one and one-half hours. On cooling 0.85 g. of unchanged material separated. On diluting the filtrate with water 3.5 g. (84%) of crude products separated.

(b) A mixture of 5 g. of dibromide (I), 3 g. of freshly prepared silver benzoate, and 50 cc. of isopropyl ether was

(5) *Cf.* Couper and Lutz, *J. Org. Chem.*, **7**, 79 (1942).

(6) Conant and Lutz, THIS JOURNAL, **47**, 881 (1925).

refluxed for eight hours and filtered. Evaporation gave 2.8 g. (55%) of II.

(c) A solution of 0.2 g. of the *cis*-isomer (III) in chloroform to which a crystal of iodine had been added, was exposed to sunlight for six hours; 0.05 g. of pure *trans*-isomer (II) was recovered and identified.

The following experiments were performed on the *trans*-compound (II):

(a) Treatment of 2.0 g. in 70% ethanol with 1 g. of potassium hydroxide under refluxing for one hour gave 1.6 g. (94%) of nearly pure enol (V).

(b) Treatment with a 30:5:3 concd. acetic acid–concd. hydrochloric acid–water mixture under refluxing for two hours was without result.

(c) Exposure of a solution of one gram in ethanol to sunlight for eight hours gave 0.8 g. of the *cis*-isomer.

(d) A solution of 0.15 g. in concd. acetic acid with potassium iodide reacted slowly on standing. Iodine was liberated. Upon diluting with water 0.1 g. of dimesitoylethylene separated and was identified.

(e) Acetic anhydride and a small amount of concd. sulfuric acid at 100° for five minutes was without action.

(f) A solution of sodium methoxide was added under stirring to a methanol solution of 0.75 g. of II and the reaction was allowed to continue at room temperature for thirty minutes. Dilution with water gave 0.57 g. (62%) of nearly pure product which was recrystallized and identified as the *cis*-2-enol methyl ether (VI).

***cis*-2-Bromo-1,4-dimesityl-2-butenedione-1,4 (1,2-dimesitoylbromoethylene) (III).**—An ethanol solution of 1 g. of the *trans*-isomer (II) was bleached by exposure for eight hours to sunlight. Upon evaporation and crystallization 0.8 g. of colorless *cis*-isomer was isolated. After repeated crystallization from 70% ethanol it melted at 88–89°.

Anal. Calcd. for $C_{22}H_{23}BrO_2$: C, 66.2; H, 5.8. Found: C, 66.2; H, 6.1.

The action of 0.2 g. of **potassium hydroxide** in 30 cc. of 70% methanol on 0.3 g. of III (refluxing for one hour) gave 0.23 g. (92%) of nearly pure enol (V).

Potassium iodide in cond. acetic acid at 75° converted this compound in good yield into dimesitoylethylene.

Acetic anhydride and a trace of concd. sulfuric acid at 100° for five minutes was without effect.

Sodium methoxide in methanol acting on 0.15 g. of III at room temperature for thirty minutes gave 0.11 g. (83%) of nearly pure *cis*-2-enol methyl ether (VI).

2,3-Dichloro-1,4-dimesitylbutanedione-1,4 (Dimesitoylethylene dichloride) (VII).—A solution of 2 g. of the *trans*-unsaturated diketone (IV) in 50 cc. of dry chloroform was treated with 1.8 g. of phenyliodochloride; the mixture was allowed to stand in a glass-stoppered flask for five days at room temperature, with occasional shaking. Evaporation of the resulting solution gave a colorless solid residue which was washed with ethanol; yield 0.94 g. (39%). Repeated crystallization from ethyl acetate brought the melting point to 209° (decomp.) (*cf.* ref. 2).

Anal. Calcd. for $C_{22}H_{24}Cl_2O_2$: C, 67.52; H, 6.18; Cl, 18.12. Found: C, 67.51, 66.52; H, 6.16, 5.71; Cl, 18.04.

***trans*-2-Chloro-1,4-dimesityl-2-butenedione-1,4 (Dimesitoylchloroethylene) (IX).**—The compound has been reported previously.[4] It may be obtained also as follows:

(a) A solution of 0.2 g. of the dichloro saturated diketone (VII) in 25 cc. of ethanol was refluxed for eight hours. The yellow solution was evaporated and 0.17 g. (95%) of nearly pure product was obtained. It was recrystallized and identified by mixture melting point with a sample prepared previously.[4]

(b) A solution of 0.3 g. of dimesitoylethylene glycol (X) in dry chloroform was treated with 0.2 g. of phosphorus pentachloride. A vigorous reaction took place with evolution of hydrogen chloride. The chloroform was evaporated, water added and the organic material was extracted with ether. Upon evaporation and crystallization of the residual oil from ethanol 0.2 g. of the chloro unsaturated diketone was obtained in nearly pure condition. It was identified by mixture melting point.

A Dichlorodimesitoylethylene (VIII).—A mixture of 10 g. of dimesitoylethylene, 8.6 g. of phenyliodochloride and 50 cc. of dry chloroform was refluxed for three hours. Concentration under reduced pressure gave 0.4 g. of bright yellow solid which was purified by repeated crystallization from ethyl acetate; yellow needles; m. p. 209.5–210°.

Anal. Calcd. for $C_{22}H_{22}Cl_2O_2$: C, 67.84; H, 5.65. Found: C, 68.06, 68.08; H, 5.67, 5.44.

Reduction of a small sample by zinc dust and concd. acetic acid gave a new chlorine containing compound of m. p. 166–167° which was not purified or investigated further. This sufficed to show that at least one of the chlorines of VIII was in a mesityl nucleus.

The 1,4-Dimesityl-2-methyl Series

***trans*-1,4-Dimesityl-2-methyl-2-butenedione-1,4 (1,2-Dimesitoylmethylethylene) (XI).**—The following modification of the earlier procedure[7] was used. Thirty grams of mesaconyl chloride was added dropwise over two hours to a well-stirred mixture of 120 cc. of carbon disulfide, 60 g. of finely ground anhydrous aluminum chloride and 48 g. of mesitylene. The mixture was then warmed on a water-bath for twenty minutes and poured into ice and hydrochloric acid. The carbon disulfide layer was separated and distilled, and the residue crystallized from ethanol; yield 54.6 g. (91%) melting at 88–90°. Recrystallized material melting at 96° was used in succeeding experiments.

The action of sunlight (two days) on a methanol solution was without result. Bromination according to the earlier method[8] gave much non-crystalline material and small yields of solids which were mixtures. Attempts to isolate a dibromo compound failed and it appeared likely that this desired compound was unstable and easily converted into the unsaturated bromo diketone through loss of hydrogen bromide. A typical experiment is as follows: a chloroform solution (15 cc.) of 7.2 g. of bromine was added dropwise with mechanical stirring to a solution of 15 g. of (XI) in 20 cc. of chloroform at −10°. Copious evolution of hydrogen bromide was observed and the color of bromine was discharged slowly. After the addition the mixture was allowed to stand for fifteen minutes and was evaporated under reduced pressure. The solid which appeared was washed with petroleum ether and filtered (18 g. melting at 124–126°). A portion of this (0.5 g.) upon

(7) Lutz and Taylor, THIS JOURNAL, **55**, 1168 (1933).

(8) Taylor, Dissertation, University of Virginia, 1932.

distillation in the vacuum oven at 130° gave a crystalline deposit on the cold-finger condenser of 0.3 g. (m. p. 140–142°) which was identified as the *cis*-bromo unsaturated diketone (XIV). The residue from this distillation was crystallized from ethanol and gave 0.15 g. of colorless solid of m. p. 180–182°. This is described below as tribromodimesitylbutanedione (XII). Concentration of the petroleum ether washings of the crude product (above) gave an oil which contained little halogen. This material was finally induced to crystallize by vacuum distillation at 135° onto a cold-finger condenser, followed by manipulation and seeding of the distillate. This product (0.33 g.) melted at 58–60° and was identified as the saturated diketone (XIII).

Chlorination attempts, using phenyl iodochloride, were unsuccessful.

1,4-Dimesityl-2-methylbutanedione-1,4 (XIII).—A solution of 3 g. of the unsaturated diketone (XI) in 100 cc. of ethanol was hydrogenated using 0.15 g. of platinum oxide. One molecule was absorbed rapidly. Two drops of piperidine were added and the mixture was allowed to stand for six hours under hydrogen. Filtration and evaporation gave an oil, which, upon vacuum distillation onto a cold-finger condenser and manipulation in solvents, was finally induced to crystallize. Upon repeated recrystallization from ethanol it melted at 60.5°.

Anal. Calcd. for $C_{23}H_{28}O_2$: C, 82.14; H, 8.33. Found: C, 81.72; H, 8.49.

This same compound was obtained by reduction of the unsaturated diketone (XI) by means of stannous chloride in a 3:1 mixture of concd. acetic and hydrochloric acids, and also by reduction of the *trans*-bromo unsaturated diketone (XV) by means of zinc and concd. acetic acid.

Attempts to obtain a crystalline furan through the use of hydriodic acid (sp. gr. 1.7), or refluxing acetic acid continuously saturated with hydrogen chloride, were without success. The use of acetic anhydride and sulfuric acid led to a compound of m. p. 102–103° (crystallized from ligroin) which was shown not to be the furan by analyses. This was not studied further.

2,2,3-Tribromo-1,4-dimesityl-3-methylbutanedione-1,4 (XII).—The crude material obtained as described above was partially purified by vacuum evaporation of the impurities consisting of compounds containing less halogen, and was further purified by repeated crystallization from an ethanol–ethyl acetate mixture; m. p. 188°.

Anal. Calcd. for $C_{23}H_{25}O_2Br_3$: C, 48.17; H, 4.36. Found: C, 47.85; H, 4.42.

This compound was isolated in several experiments from mixtures obtained by brominations followed by manipulations in which sodium methoxide was used. This compound did not react and remained as an insoluble residue.

Reduction of the tribromo compound (0.15 g.) in concd. acetic acid by potassium iodide (warming to 70° and then allowing to cool slowly on standing for three hours) gave 0.06 g. of nearly pure *trans*-bromo unsaturated diketone (XV) which was purified by crystallization from ethanol and identified.

***cis*-2-Bromo-1,4-dimesityl-3-methyl-2-butenedione-1,4 (XIV).**—A chloroform solution of 4.8 g. of bromine was added dropwise to a mechanically stirred solution of 10 g. of the unsaturated diketone (XI) in chloroform containing 1 g. of suspended powdered sodium bicarbonate. The temperature was maintained at 0°. The color of bromine disappeared within twenty minutes after the last addition. This solution was then washed in succession with aqueous sodium bisulfite and with water. Upon evaporation and crystallization of the residue from petroleum ether, 7.8 g. of fine colorless needles was obtained (77.7%). Repeated crystallizations from ethanol–ethyl acetate mixtures brought the melting point to 143.5–144°. From the filtrates 1.4 g. of starting material was recovered.

Anal. Calcd. for $C_{23}H_{25}O_2Br$: Br, 19.37. Found: Br, 19.55.

***trans*-2-Bromo-1,4-dimesityl-3-methyl-2-butenedione-1,4 (XV).**—A mixture of 3 g. of the *cis*-isomer (XIV), 3 g. of sodium acetate and 50 cc. of 95% ethanol was refluxed for two hours. Upon cooling and diluting with water 2.05 g. of product separated (m. p. 168–169°). Alternate crystallizations from ethanol and from ethyl acetate raised the melting point to 171–171.5°.

Anal. Calcd. for $C_{23}H_{25}O_2Br$: C, 66.85; H, 6.10. Found: C, 67.14; H, 6.14.

This compound was obtained also when sodium benzoate was substituted for sodium acetate; and it was obtained when a mixture of the *cis*-isomer and isopropyl ether and freshly precipitated silver benzoate was refluxed for twelve hours. The same transformation was effected by the action of a 1:1 mixture of pyridine and water under refluxing for one hour.

Reduction of 0.5 g. of XV by 25 cc. of concd. acetic acid and 1 g. of zinc dust under stirring for ninety minutes at room temperature gave an oil which finally was induced to crystallize after distillation in the vacuum oven at 133°. The yield was 0.16 g. and the m. p. 57–59°; it was identified by mixture melting point as the saturated diketone (XIII).

3-Acetoxy-2,5-dimesityl-4-methylfuran (XVII).—Two drops of concd. sulfuric acid were added to a suspension of 1.5 g. of dimesitoylmethylethylene (XI) in 10 cc. of acetyl chloride. The suspended solid dissolved immediately with darkening. After warming for five minutes the mixture was hydrolyzed with ice-water and neutralized with sodium carbonate. Extraction with ether and subsequent evaporation gave 0.52 g. of almost pure product. Repeated crystallization from ethanol raised the melting point to 88°. Some starting material was recovered from the residual oils.

Anal. Calcd. for $C_{25}H_{28}O_3$: C, 79.84; H, 7.49. Found: C, 79.57; H, 7.75.

When acetic anhydride was used instead of acetyl chloride in the above experiment only unchanged material was obtained.

Summary

trans-Bromodimesitoylethylene has been converted into a *cis*-form. Reactions of the stereoisomers have been studied.

The chlorination of dimesitoylethylene with phenyliodochloride gave the monochloro derivative in good yield.

Bromination of dimesitoylmethylethylene gave a *cis*-monobromo derivative from which the *trans*-isomer was made by inversion. The use of sodium bicarbonate in preventing secondary reactions during bromination is described.

CHARLOTTESVILLE, VA. RECEIVED JULY 6, 1942

[CONTRIBUTION FROM NICHOLS LABORATORY, NEW YORK UNIVERSITY]

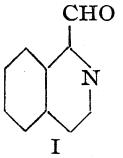
Condensation Reactions of Isoquinaldaldehyde

BY ROBERT S. BARROWS AND H. G. LINDWALL

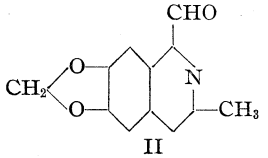
The successful use of lepidine as a source of cinchoninaldehyde[1] suggested that 1-methylisoquinoline might similarly be oxidized through the action of selenium dioxide to yield isoquinaldaldehyde (I). The method of Späth,[2] with modification, was used for the preparation of 1-methylisoquinoline. The modification involved the substitution of Raney nickel for platinized asbestos in the dehydrogenation of 1-methyl-3,4-dihydroisoquinoline. The 1-methylisoquinoline thus obtained was characterized by the preparation of several known derivatives.

The oxidation of 1-methylisoquinoline by selenium dioxide was carried out in dioxane solution with vigorous stirring; an excess of selenium dioxide was avoided. The product (I), which is volatile with steam, reacts with Tollens reagent, gives a sodium bisulfite addition product, and forms an oxime, a phenylhydrazone and a semicarbazone. The aldehyde (I) formed no hydrate.

A similar oxidation of 1,3-dimethyl-6,7-methylenedioxy-isoquinoline was carried out. The product, an aldehyde, formed a monoxime, and is tentatively assigned the structure 3-methyl-6,7-methylenedioxy-isoquinaldaldehyde (II).



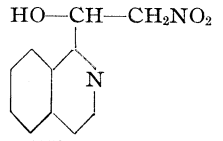
I



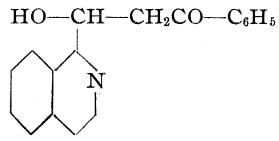
II

The condensation reactions of compound I with a series of "active methylene" compounds were studied. Condensation with nitromethane was accomplished readily to yield α-nitro-β-hydroxy-β-(isoquinolyl-1)-ethane (III).

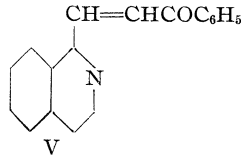
Initial attempts at condensation with acetophenone gave a mixture of products; with varied conditions, however, either IV, V, or VI could be obtained as the principal product. If the condensation of equimolecular quantities of isoquinaldaldehyde and acetophenone was carried out in the presence of sodium hydroxide for a short period of time, IV was obtained, but if longer time was allowed or if sodium ethylate was used, compound V resulted. With an excess of acetophenone and either sodium hydroxide or sodium ethylate, VI was the principal product.



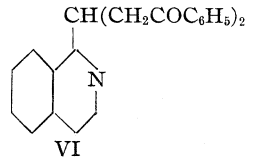
III



IV

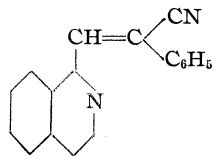


V

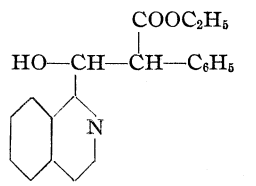


VI

No product could be obtained from isoquinaldaldehyde and phenylacetic acid under conditions of the Perkin condensation, but two derivatives of phenylacetic acid were condensed under other conditions. Phenylacetonitrile and compound I yielded VII in the presence of diethylamine or sodium ethylate; ethyl phenylacetate and I gave VIII when sodium ethylate was used as the catalyst.



VII



VIII

Experimental

1-Methylisoquinoline.—To 1-methyl-3,4-dihydroisoquinoline (15 g.) was added an excess of Raney nickel and the mixture was heated under reflux for fifteen to twenty minutes or until the temperature of the mixture had reached 248° (the boiling point of 1-methylisoquinoline); yield, 70–75%; boiling point 124–126° (at 10 mm.). **Melting points of derivatives:** picrate, 230–232°; sul-

(1) Kwartler and Lindwall, THIS JOURNAL, **59**, 524 (1937).

(2) Späth, Berger and Kuntara, *Ber.*, **63**, 134 (1930); Späth and Polgar, *Monatsh.*, **51**, 190 (1929).

fate, 246–248°; hydrochloride 200–205°; chloroplatinate, 233–234°; methiodide, 208°.

Isoquinaldaldehyde (I).—To a solution of 1-methylisoquinoline (10 g.) in dioxane (17 cc.) was added, drop by drop, a solution of selenium dioxide (8.9 g.) in dioxane (90 cc.); the solutions were mixed over a period of one-half hour with agitation and gentle warming. The final mixture was then heated, with agitation, on the steam-bath for three hours. At the end of this time the solution was cooled and the precipitated selenium was removed; the bulk of the dioxane was removed under diminished pressure; the residual material was then steam distilled. The product (I) crystallized from the distillate after several hours at ice-box temperature; long white needles, m. p. 55–55.5°; yield, 42%. The product reduces Tollens reagent and forms a bisulfite addition product slowly. It is soluble in acetone, ligroin, benzene, but it is only slightly soluble in water.

Anal. Calcd. for $C_{10}H_7NO$: C, 76.49; H, 4.46; N, 8.92. Found: C, 76.40; H, 4.80; N, 8.90.

Semicarbazone of I.—Yellow plates from ethyl alcohol; m. p. 195–197°.

Anal. Calcd. for $C_{11}H_{10}N_4O$: N, 26.17. Found: N, 25.95, 26.41.

Oxime of I.—White needles from 50% ethyl alcohol; m. p. 171–172°.

Anal. Calcd. for $C_{10}H_8N_2O$: N, 16.27. Found: N, 16.01.

Phenylhydrazone of I.—Yellow needles from ethyl alcohol; m. p. 174–175°.

Anal. Calcd. for $C_{16}H_{13}N_3$: N, 17.00. Found: N, 17.19.

3-Methyl-6,7-methylenedioxy-isoquinaldaldehyde (II).—To a solution of 2.2 g. of 1,3-dimethyl-6,7-methylenedioxy-isoquinoline in 20 cc. of dioxane was added, drop by drop, a solution of 1.3 g. of selenium dioxide in 20 cc. of dioxane. The mixture was stirred and warmed gently during the addition which required one-half hour. One and one-half hours of further heating on the steam-bath were allowed. The precipitated selenium was filtered from the hot mixture and the filtrate was steam-distilled. When the bulk of the dioxane had been removed in the course of this distillation, the product (II) began to separate from the residue; yield, 34% after crystallization from toluene. Light yellow needles from ethyl alcohol; m. p. 186.5–188.5°. The product (II) reduces Tollens reagent.

Anal. Calcd. for $C_{12}H_9NO_3$: N, 6.51. Found: N, 6.64.

Oxime of II.—Needles from 50% ethyl alcohol; m. p. 215–216°.

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: N, 12.17. Found: N, 11.90.

α-Nitro-β-hydroxy-β-(isoquinolyl-1)-ethane (III).—To a mixture of 0.3 g. of nitromethane and 0.32 g. of I was added diethylamine (2 drops). The solution, which became warm, was cooled and allowed to stand for two hours. A small amount of water was then added and an oil separated. Vigorous scratching caused the oil to solidify. The crude product (III) was dried on a porous tile; crude yield, 71%. The product may be crystallized from ligroin but heating in solvents causes apparent gradual decomposition; m. p. 106–107°, approx.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: N, 12.84; Found: N, 12.75.

β-Hydroxy-β-(isoquinolyl-1)-propiophenone (IV).—A few small pieces of ice were added to a solution of 0.2 g. of I and 0.17 g. of acetophenone in 8 cc. of ethyl alcohol. Then 15 cc. of 10% sodium hydroxide solution was added slowly. The solution soon became milky and after fifteen to twenty minutes a yellow crystalline product (IV) appeared; recrystallized from ethyl alcohol; m. p. 114.5–115°; yield, 85%.

Anal. Calcd. for $C_{18}H_{15}NO_2$: N, 5.05. Found: N, 4.76.

β-(Isoquinolyl-1)-acrylophenone (V). Method A.—Compound I (0.25 g.) was dissolved in 15 cc. of ethyl alcohol, and to this solution was added an excess of acetophenone (0.38 g.) and a small amount of ice. After then adding 6 cc. of 10% sodium hydroxide solution, the mixture was allowed to stand for one hour at room temperature. At the end of this time the product had appeared as fine yellow needles; yield, 60%; recrystallized from ethyl alcohol, m. p. 144–146°. **Method B.**—Equimolecular amounts of I (0.5 g.) and acetophenone (0.33 g.) were dissolved in 2 cc. of absolute alcohol and to this was added 5 drops of a solution of sodium ethylate in alcohol (0.05 g. of sodium per 1 cc.). At first the solution became warm and turned green but after standing the color changed to yellow and finally solidified to a crystalline mass. Treatment with bone black and crystallization from alcohol gave light yellow needles, m. p. 145.5–146°; yield 77%. A melting point determination when mixed with the product of method A showed no depression.

Anal. Calcd. for $C_{18}H_{13}NO$: C, 83.38; H, 5.04; N, 5.40. Found: C, 83.32, 83.23; H, 5.14, 4.99; N, 5.50, 5.44.

Bis-acetophenonyl-(isoquinolyl-1)-methane (VI).—Compound I (0.25 g.) and acetophenone (0.35 g.) were dissolved in 2 cc. of absolute ethyl alcohol and to this solution was added 0.5 cc. of a solution of sodium ethylate in alcohol (0.05 g. of sodium per 1 cc.). The product (VI) was removed by filtration after twenty hours. White plates from alcohol, m. p. 133–133.5°; yield, 42%. A small amount of VI was also obtained from the residual liquid after the removal of compound V in method "A" above.

Anal. Calcd. for $C_{16}H_{21}NO_2$: C, 80.90; H, 5.73; N, 3.69; mol. wt., 277. Found: C, 81.26; H, 5.57; N, 3.68, 3.84; mol. wt. (micro-cryoscopic, with camphor), 264.

α-Phenyl-β-(isoquinolyl-1)-acrylonitrile (VII).—A solution was prepared consisting of 0.4 g. of phenylacetonitrile 0.5 g. of isoquinaldaldehyde and 1 cc. of absolute ethyl alcohol. To this was added a small amount of sodium ethylate solution (three drops of solution containing 0.05 g. of sodium per 1 cc. of ethyl alcohol). After cooling and scratching the product separated as light yellow needles; recrystallized from ethyl alcohol, m. p. 96.5–97°; yield, 92%.

Anal. Calcd. for $C_{18}H_{12}N_2$: C, 84.36; H, 5.13; N, 10.93. Found: C, 84.44; H, 4.83; N, 10.94.

Ethyl Ester of α-Phenyl-β-hydroxy-β-(isoquinolyl-1)-propionic Acid (VIII).—Compound VIII was prepared by a method similar to that used in the preparation of VII.

employing ethyl phenylacetate with isoquinaldaldehyde; recrystallized from ethyl alcohol as white needles, m. p. 134.5–135.5°; yield, 45%.

Anal. Calcd. for $C_{20}H_{19}NO_3$: C, 74.72; H, 5.98; N, 4.36. Found: C, 74.46; H, 5.61; N, 4.47.

Summary

1. 1-Methylisoquinoline and 1,3-dimethyl-6,7-methylenedioxyisoquinoline are oxidized by selenium dioxide to yield isoquinaldaldehyde and 3-methyl-6,7-methylenedioxy-isoquinaldaldehyde, respectively.

2. Isoquinaldaldehyde has been found to undergo condensation reactions with nitromethane, acetophenone, phenylacetonitrile and ethyl phenylacetate.

NEW YORK, N. Y. RECEIVED JULY 17, 1942

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Amino Ketones. I. Synthesis of Amino Alcohols and 1,3-Diamino Compounds from β-Amino Ketones

BY NORMAN H. CROMWELL, Q. T. WILES[1] AND O. C. SCHROEDER[2]

Although many previous investigations[3] have been concerned with the addition of various amines to α,β-unsaturated ketones, few studies have been made with the resulting β-amino ketones.

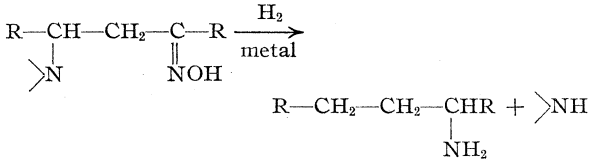
It seemed of interest to attempt the preparation of certain amino alcohols and the corresponding 1,3-diamino compounds of possible pharmacological value from such β-amino ketones by the application of certain known reactions.

The present investigation deals with the addition of certain amines to benzalacetone and benzalacetophenone and the conversion of the products to amino alcohols and 1,3-diamino compounds.

It has been found that both morpholine and piperidine add readily to benzalacetone to give, respectively, β-morpholinobenzylacetone (I) and β-piperidinobenzylacetone (II), isolated as the hydrochlorides. The preparation of β-amino ketones using high boiling, water soluble amines is best accomplished in water insoluble solvents. This allows the removal of the excess reactant amine by water washing. Conversely, the preparation of β-amino ketones from water insoluble amines such as aniline is easiest to manipulate in a water soluble solvent such as alcohol.

The oximes (III) and (IV) of the amino ketones (I) and (II) were prepared in good yields but it was necessary to take certain precautions to obtain these results. The best yields were obtained when the reaction medium was strongly basic. It was necessary that the amino ketone hydrochloride be added only after the hydroxylamine was available in the reaction medium to react immediately with the amino ketone before it could decompose to the α,β-unsaturated ketone. These amino ketoximes were amphoteric. The oximes (XIII) and (XIV), respectively, of β-morpholinobenzylacetophenone[3f] and of β-anilinobenzylacetophenone[3a] were also prepared.

Attempts to reduce these various amino ketoximes with catalytic hydrogen to the corresponding 1,3-diamino compounds were not successful. In all cases the following reaction was noted



The oximes (III) and (IV) however, were reduced in fair yields to the 1,3-diamino compounds (V) and (VI) using sodium and alcohol according to the method of Kohn.[4] The benzamides (VII) and (VIII) of these diamines were also prepared.

In order to obtain possible ephedrine-like amino alcohols the β-amino ketones (I) and (II) were reduced with sodium amalgam according to the method of Kohn.[5] These amino ketone hydrochlorides were not stable to catalytic hydrogenation though various conditions were employed.

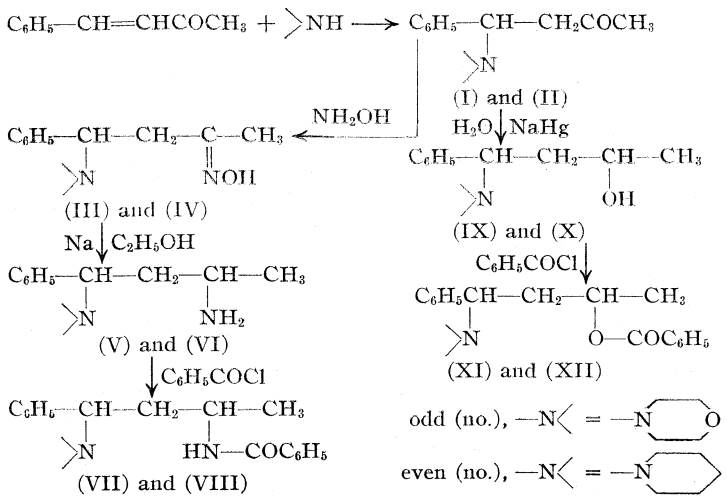
(1) Present address: Shell Development Co., Emeryville, Calif.

(2) Present address: E. I. du Pont de Nemours and Co., Charleston, W. Va.

(3) (a) Tambor and Wildi, *Ber.*, **31**, 352 (1898); (b) Smith and Adkins, THIS JOURNAL, **60**, 407 (1938); (c) Georgi and Schwyzer, *J. prakt. Chem.*, **86**, 273 (1912); (d) Kohn and Morgenstern, *Monatsh.*, **24**, 773 (1903); **28**, 479 (1907); (e) Pollard and Stewart, THIS JOURNAL, **58**, 1980 (1936); (f) **59**, 2006, 2702 (1937); (g) Macovski and Silberg, *J. prakt. Chem.*, **137**, 131 (1933); (h) Jones and Kerner, *J. Chem. Soc.*, 363 (1933).

(4) Kohn, *Monatsh.*, **29**, 519 (1908).

(5) Kohn, *ibid.*, **28**, 423 (1907).



The benzoates (XI) and (XII), isolated as the hydrochlorides, were prepared from the corresponding am no alcohols.

The studies of these reactions and products are being continued and extended.

Experimental[6]

β-Morpholino- and β-Piperidino-benzylacetones.—Benzalacetone (10 g., 0.068 mole) dissolved in petroleum ether (35 ml., b. p. 88–100°) was refluxed for fourteen hours with an excess (0.10 mole) of the corresponding amine. The mixtures were then allowed to stand in the ice chest for two days. Ether was added to dissolve any precipitated oil and the mixtures completely extracted with several portions of water to remove excess amine. The dry ether–petroleum ether solutions were then treated with dry hydrogen chloride to precipitate the white hydrochlorides (I) and (II). The hydrochloride (I) was recrystallized from methanol–dry ether mixtures while the hydrochloride (II) was recrystallized from ethanol–dry ether solutions. Both of these hydrochlorides decomposed to give benzalacetone when water solutions of them were warmed.

Amino Ketoximes, (III) and (IV).—To a cooled solution ot potassium hydroxide (48 g., 0.84 mole) in methanol (200 to 300 ml.) hydroxylamine hydrochloride (14.4 g., 0.20 mole) dissolved in water (30 ml.) was added. To this solution the corresponding β-amino ketone hydrochloride (0.044 mole) in methanol (25 ml.) was added. The reaction mixtures were allowed to stand at room temperature for two days. The precipitated potassium chloride was then removed and most of the methyl alcohol evaporated *in vacuo*. The remaining water solutions were cooled in an ice-bath and slowly neutralized with dilute hydrochloric acid. The oily solid which separated was extracted in each case with 50 ml. of ether. The impure products were obtained by evaporation of these solutions.

The products were recrystallized from petroleum ether (b. p. 35–40°)–ether solutions. Although two isomeric forms seemed to be present here, only the higher melting ones were isolated. Both of these amino ketoximes were soluble in dilute hydrochloric acid and in dilute potassium hydroxide solutions. These two substances were unstable to heat, especially in acid solutions.

Attempts to reduce these amino ketoximes to the diamines (V) and (VI) using catalytic methods were not successful. Using fifteen hundred pounds of hydrogen with Raney nickel at 40°, ethanol solutions of (III) and (IV) gave only 4-phenyl-2-aminobutane, isolated as its hydrochloride, m. p. 142°,[7] and morpholine and piperidine, respectively. Results of the same nature were obtained using pressures of fifty pounds of hydrogen and Raney nickel catalyst. In one experiment a little concd. ammonium hydroxide was added to the reduction mixture but still only these decomposition products could be isolated.

4-Phenyl-4-morpholino-2-aminobutane and 4-Phenyl-4-piperidino-2-aminobutane.—The corresponding amino ketoxime (10 g.) was dissolved in 80 ml. of ethanol and heated under reflux. Over a period of two hours 12 g. of sodium was added a piece at a time. Enough ethanol (80 cc.) was added from time to time to dissolve the sodium. The mixture was cooled and 12 ml. of water added to destroy the sodium ethoxide. The solution was cooled to 0° and neutralized with dilute hydrochloric acid. The salt was filtered off and the alcohol removed by vacuum distillation. To the thick residue, strong sodium hydroxide (50%) was added to precipitate the free base as an oil which was removed by extraction with ether. The ether solution was washed well with saturated salt solution, dried and evaporated.

The products were distilled under vacuum with an efficient pump. In each of these preparations some decomposition took place to give 4-phenyl-2-aminobutane. The formation of the diamine (VI) was also accompanied by the formation of a very high boiling, glassy-like product which was soluble in dilute hydrochloric acid but was not identified.

Both of the water-clear diamines (V) and (VI) were only slightly soluble in water but were readily soluble in dilute hydrochloric acid.

Benzamides.—The benzamides (VII) and (VIII) were prepared from the diamines (V) and (VI) by treating cooled ether solutions of them with one equivalent of benzoyl chloride. The precipitated hydrochlorides were hydrolyzed with dilute sodium bicarbonate solutions to give the benzamides. These products were recrystallized from dilute alcohol solutions. Both of these compounds were soluble in dilute hydrochloric acid solutions.

4-Phenyl-4-morpholinobutanol-2 and 4-Phenyl-4-piperidinobutanol-2.—Attempts to reduce the amino ketone hydrochlorides (I) and (II) with hydrogen and noble metal catalysts gave only very low yields of the desired amino alcohols. Decomposition, with the loss of morpholine or piperidine, respectively, occurred; the β-piperidinobenzylacetone was the least stable.

(6) Micro Dumas analyses for nitrogen and semi-micro analyses for carbon and hydrogen by the Analytical Laboratory, Department of Chemistry, University of Nebraska, under the supervision of H. Armin Pagel.

(7) Harries and Osa, *Ber.*, **36**, 2997 (1903).

TABLE I

ANALYTICAL AND PHYSICAL DATA FOR AMINO KETONES AND DERIVATIVES

Compound	Cpd. no.	Yield, %	M. p., °C.	Percentage composition: Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
β-Anilinobenzyl acetophenone oxime	(XIV)	67	131	79.71	6.37	8.86	79.49	6.39	8.68
β-Morpholinobenzyl-acetone hydrochloride[b]	(I)	63	152			5.19			5.20
acetone oxime	(III)	50	107	67.71	8.12		67.49	8.28	
acetophenone oxime	(XIII)	57	178	73.51	7.14	9.02	73.62	7.33	8.75
4-Phenyl-4-morpholino-2-aminobutane	(V)	37	130[a]	71.72	9.46	11.95	71.37	9.59	11.82
2-benzamidobutane	(VII)	55	158	74.52	7.74		74.50	7.72	
butanol-2 hydrochloride	(IX)	40	156	61.86	8.15		61.78	8.26	
butanol-2 benzoate hydrochloride	(XI)	30	236	67.10	6.97		66.84	7.02	
4-Phenyl-4-piperidino-2-aminobutane	(VI)	30	112[a]			12.06			11.77
2-benzamidobutane	(VIII)	50	144	78.53	8.40	8.32	78.46	8.49	8.19
butanol-2	(X)	50	137[a]	77.21	9.93	6.00	76.92	9.81	5.88
butanol-2 benzoate hydrochloride	(XII)	55	217	70.67	7.55		70.61	7.66	
β-Piperidinobenzyl-acetone hydrochloride[c]	(II)	70	158	67.27	8.28		67.28	8.48	
acetone oxime	(IV)	60	105	73.13	9.00		72.95	8.91	

[a] B. p., at 1 mm. [b] Calcd.: Cl, 13.14. Found: Cl, 13.12. [c] Calcd.: Cl, 13.24. Found: Cl, 13.47.

Reduction was accomplished with sodium amalgam (3%). The corresponding amino ketone hydrochloride (10 g.) was dissolved in 100 ml. of water and cooled to −3°. To these solutions, over a period of one hour, sodium amalgam (190 g., 3%) was added in small portions. It was necessary to add small amounts of acid from time to time to keep the solution just acid (19 ml. of concd. hydrochloric acid and 50 ml. of water).

The acid solution was decanted from the mercury and made strongly basic with concd. sodium hydroxide (50%) to precipitate the free base. The amino alcohol (IX) was isolated and identified as its hydrochloride by passing dry hydrogen chloride into ether solutions of the base. The hydrochloride of the amino alcohol (X) was too hygroscopic to analyze, so the free base was vacuum distilled to give a water-white, thick oil which was readily soluble in dilute hydrochloric acid but only slightly water soluble.

4-Phenyl-4-morpholinobutanol-2 Benzoate Hydrochloride.—To 4.5 g. of the amino alcohol hydrochloride (IX) was added 16 g. of benzoyl chloride. This mixture was heated at 115° for two hours. The red oily mixture was cooled and mixed with dry ether to give a gummy precipitate. The gummy hydrochloride was dissolved in water and color removed from the solution with activated charcoal. The colorless solution was cooled and neutralized with strong sodium hydroxide. The precipitated oil was dissolved in ether and converted to the hydrochloride with dry hydrogen chloride. This product was recrystallized several times from alcohol (95%)–ether mixtures to give white needles (XI).

4-Phenyl-4-piperidinobutanol-2 Benzoate Hydrochloride.—To 0.80 g. of the amino alcohol (X) dissolved in 6 ml. of dry ether 0.48 g. of benzoyl chloride was added slowly. The white solid precipitate that formed immediately was recrystallized several times from a mixture of dry ether, ethyl acetate and ethanol to give white needles (XII).

β-Morpholinobenzylacetophenone Oxime (XIII).—The β-morpholinobenzylacetophenone for this experiment was prepared in 95% yields according to the method of Pollard and Stewart.[3f] This β-amino ketone (20.0 g.) was added to a mixture of 9.4 g. of hydroxylamine hydrochloride, 14.0 g. of sodium acetate, 30 ml. of water, and 200 ml. of methyl alcohol. This mixture was heated to boiling with shaking for ten minutes and then allowed to stand at room temperature for one day. The white precipitate was filtered off and washed with two portions of 50% methyl alcohol–water solution and then water, and the product dried, wt. 12 g., m. p. 178°. Recrystallization from 50% mixtures of chloroform and methanol did not change the melting point. This product was only slightly soluble in dilute sodium hydroxide, but was readily soluble in dilute hydrochloric acid.

Attempts to reduce this amino ketoxime with sodium and alcohol were not successful. The amino ketoxime was recovered unchanged.

β-Anilinobenzylacetophenone Oxime (XIV).—β-Anilinobenzylacetophenone for this experiment was prepared in good yield by the method of Tambor and Wildi.[3a] This amino ketone (10 g., 0.033 mole) was added to a mixture of hydroxylamine hydrochloride (11.4 g., 0.165 mole), potassium hydroxide (33 g., 0.60 mole) and 300 ml. of methanol and the mixture refluxed for fifty minutes. The reaction mixture was cooled and water added to give a white precipitate. Recrystallization of this product from methanol gave 7 g. of flaky white crystals. This product was not soluble in fifty, ten or five per cent. solutions of potassium hydroxide. It was also insoluble in 5% hydrochloric acid but dissolved in the concd. acid.

Summary

1. Two new β-aminobenzylacetones have been prepared and procedures for preparing oximes of β-amino ketones discussed.

2. General methods for preparing β-amino alcohols and 1,3-diamino compounds from α,β-unsaturated ketones have been investigated.

3. Two new amino alcohols with their corresponding benzoates and two new 1,3-diamines with their corresponding benzamides have been prepared.

LINCOLN, NEBRASKA RECEIVED MARCH 27, 1942

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Studies on D-Galactosan <1,5>β<1,6>

BY RAYMOND M. HANN AND C. S. HUDSON

The hexose anhydride, D-galactosan <1,5>β-<1,6>, was first synthesized by Micheel[1] by the action of hot aqueous barium hydroxide upon 2,3,4,6 - tetraacetyl - D - galactopyranosido - trimethyl-ammonium bromide; the over-all yield of the anhydride, based on the crystalline acetobromo-D-galactose employed, was 38%. Micheel also reported that he obtained a small amount of the same anhydride by the pyrolysis of β-D-galactose at temperatures of 270 to 360° and a pressure of 3 millimeters.[2] The <1,5><1,6> structure was assigned by Micheel on the basis that acetobromo-D-galactose contains the 1,5 ring and that the 1,6 ring is probably more stable than the 1,3 and 1,4 rings; the <1,5><1,6> structure was also the only probable one containing two adjacent hydroxyl groups in the *cis*-position, which seemed necessary in order to account for the ready formation of a monoacetone compound (m. p. 151–152°; $[\alpha]^{20}D$ −73.3° in chloroform). These inferences of Micheel were proved to be correct by the work of McCreath and Smith[3]; they isolated as a by-product in the preparation of 1,2:3,4-diacetone galactose a monoacetone galactosan agreeing in physical properties with the one described by Micheel, and by methylation they converted it to a sirupy monomethyl-monoacetone-D-galactosan, which, upon hydrolysis with strong acid, formed the known crystalline 2-methyl-D-galactopyranose[4]; the monomethyl-monoacetone-D-galactosan, upon selective mild acid hydrolysis and subsequent methylation, formed a crystalline trimethyl-D-galactosan, which, upon complete acid hydrolysis, yielded crystalline 2,3,4-trimethyl-galactopyranose monohydrate. The ring structure of the parent galactosan is therefore <1,5><1 6> and the β-configuration is assigned to the 1,6 ring, as first proposed by Micheel because the space formula indicates a high probability for this configuration. The monoacetone derivative is accordingly 3,4-isopropylidene-D-galactosan <1,5>β<1,6>, as originally inferred by Micheel.

Recently we[5] have found that the pyrolysis of α-lactose monohydrate, under the experimental conditions previously used for the preparation of D-mannosan <1,5>β<1,6> from vegetable ivory, yields a distillate containing both levoglucosan and D-galactosan <1,5>β<1,6>. The anhydrides are readily separable through the fact that the galactosan, but not the glucosan, condenses with acetone; average yields of 12.3 g. of levoglucosan and 20.7 g. of 3,4-isopropylidene-D-galactosan <1,5>β<1,6> have been obtained by the pyrolysis of a 200-g. charge of lactose monohydrate; economy in price of starting material, simplicity and speed of experimental procedures, and the relatively high yields of the desired products, thus combine to make this procedure of pyrolysis an excellent method for obtaining an abundant supply of these two sugar anhydrides at relatively low cost. In the case of the galactosan, such a result is of special importance; the galactosan and its acetone derivative are now inexpensive and readily accessible substances, suit-

(1) Micheel, *Ber.*, **62**, 687 (1929).

(2) Ordinary galactose is the α-form; we have shown (THIS JOURNAL, **63**, 2241 (1941)) that its pyrolysis gives good yields of D-galactosan <1,5>β<1,6>. We find that the yield of levoglucosan (D-glucosan <1,5>β<1,6>) is independent of the form of anhydrous glucose (α or β) that is pyrolyzed. The melting of such α- or β-forms establishes equilibrium between them, as may be inferred from an old record by C. Tanret (*Bull. soc. chim.*, [3] **13**, 734 (1895)). We have repeated his experiment under more precise control. The glassy melts which were obtained by heating samples of pure α- and β-D-glucose at 170° for fifteen minutes were cooled and then dissolved in water at 20°; the specific rotations after seven minutes were essentially alike (+53 and +50), representing the equilibrium rotation of glucose.

(3) McCreath and Smith, *J. Chem. Soc.*, 387 (1939).

(4) Oldham and Bell, THIS JOURNAL, **60**, 323 (1938).

(5) Hann and Hudson, *ibid.*, **63**, 1484 (1941).

able for synthetic studies in the preparation of new compound sugars possessing a linkage at the second carbon atom of galactose.

Although the structure of D-galactosan<1,5>-β<1,6> has been firmly established through the methylation studies of McCreath and Smith, it seemed desirable to seek confirmation of it by application of the periodate methods previously employed in this Laboratory in studies on D-glucosan (levoglucosan),[6] D-altrosan,[7] and D-mannosan.[8] It was found that the oxidation of the anhydride by per-iodic acid or sodium metaperiodate proceeded with the reduction of two molecular equivalents of the oxidant and the generation of a molecular equivalent each of formic acid and L′-oxy-D-methylene-diglycolic aldehyde; the latter compound, upon further oxidation with bromine water in the presence of strontium carbonate, formed strontium L′-oxy-D-methylene-diglycolate, the same crystalline salt that had been obtained previously from D-glucosan, D-altrosan and D-mannosan. This result proves that the same structure and β<1,6> configuration are common to the four hexose anhydrides; the galactosan is therefore D-galactosan<1,5>β<1,6>, and the conclusions of the previous investigators are confirmed by this independent method.

The present investigation has been extended to include the preparation of several new derivatives of D-galactosan<1,5>β<1,6>; by customary procedures 3,4-isopropylidene-D-galactosan<1,5>β<1,6> has been converted into its 2-substituted acetyl, benzoyl and tosyl derivatives, all of which are crystalline; by selective mild acid hydrolysis the isopropylidene group of these compounds is removed and, although the 2-acetyl-D-galactosan<1,5>β<1,6> could not be crystallized, it was possible to crystallize 2-benzoyl- and 2-tosyl-D-galactosan<1,5>β<1,6>; migration of the acyl groups does not appear to occur under the experimental conditions of the hydrolysis since the monobenzoate, upon treatment with acetone and anhydrous copper sulfate, regenerates 2-benzoyl-3,4-isopropylidene-D-galactosan<1,5>β<1,6> in high yield. The 2-benzoyl-D-galactosan<1,5>β<1,6> yielded by suitable reactions, crystalline 3,4-diacetyl and 3,4-ditosyl derivatives; by treatment with benzoyl chloride, it formed a crystalline 2,3,4-tribenzoyl-D-galactosan<1,5>β<1,6>, which was identical with the tribenzoate obtained by direct benzoylation of D-galactosan<1,5>β<1,6>. The 2-tosyl-D-galactosan<1,5>β<1,6> is a compound of particular interest, since studies now in progress indicate that upon detosylation it forms a compound (m. p. 132–133°; $[\alpha]^{20}D$ −84° in water), which gives correct carbon and hydrogen analyses for an anhydro-D-galactosan<1,5>β<1,6>; its behavior thus parallels that of 4-tosyl-D-mannosan<1,5>β<1,6>, which is known[9] to form an anhydro-D-mannosan<1,5>β<1,6>, presumably 3,4-anhydro-D-talosan<1,5>β<1,6>, upon detosylation.

We express our appreciation to Dr. A. T. Ness for performing the microchemical analyses in connection with this study.

Experimental

D-Glucosan<1,5>β<1,6> and 3,4-Isopropylidene-D-galactosan<1,5>β<1,6> from α-Lactose Monohydrate.—Three successive charges of 75, 65 and 60 g. of α-lactose monohydrate were pyrolyzed in the apparatus and under the experimental condition specified[8] for the preparation of D-mannosan<1,5>β<1,6> from vegetable ivory. The combined pyrolysates, a dark colored sirup, was dissolved in 200 cc. of water and the solution, after clarification by filtration through a layer of 45 g. of decolorizing carbon on a Büchner funnel of 171 mm. diameter, was concentrated *in vacuo* to a thick sirup; a solution of the sirup in 75 cc. of acetone was poured in a thin stream into an additional 325 cc. of acetone, and, after decantation from a small amount of precipitated gum, the acetone solution was agitated with 40 g. of anhydrous copper sulfate for twenty-four hours; the copper sulfate was removed by filtration and the filtrate was concentrated *in vacuo* to a magma of the consistency of honey; the magma was thinned with 25 cc. of isopropyl alcohol and the crystalline product (24.0 g.), which was mainly 3,4-isopropylidene-D-galactosan<1,5>β<1,6>, was separated by filtration and preserved for final purification as described later in this paragraph. The filtrate was concentrated *in vacuo* to remove the isopropyl alcohol, and the resulting sirup was transferred to a crystallizing dish with the aid of 20 cc. of warm acetone; crystallization, which occurred spontaneously as the solution cooled, was allowed to progress for twenty-four hours in the refrigerator and the precipitate (13.6 g.), which was nearly all levoglucosan, was then separated by filtration. The further purification of the products was conducted as follows: the levoglucosan fraction was refluxed for ten minutes with 5 parts of chloroform, in which 3,4-isopropylidene-D-galactosan<1,5>β<1,6> is readily soluble and levoglucosan practically insoluble, and the crystalline levoglucosan was removed by filtration; to the chloroform filtrate the 3,4-isopropylidene-D-galactosan<1,5>β<1,6> fraction previously isolated and additional chloroform to maintain a volume of 5 cc. of solvent for each gram of solid were added and the mixture was refluxed for ten

(6) Jackson and Hudson, THIS JOURNAL, **62**, 958 (1940).
(7) Richtmyer and Hudson, *ibid.*, **62**, 961 (1940).
(8) Knauf, Hann and Hudson, *ibid.*, **63**, 1447 (1941).
(9) Hann and Hudson, *ibid.*, **64**, 925 (1942).

minutes, and then allowed to stand for several hours at room temperature; the levoglucosan was removed by filtration and the 3,4-isopropylidene-D-galactosan <1,5>β<1,6> was recovered by concentration of the chloroform filtrate. The average yield of levoglucosan from 200 g. of lactose monohydrate was 12.3 g. (13%) and that of 3,4-isopropylidene-D-galactosan <1,5>β<1,6> was 20.7 g. (18%). The latter compound may be crystallized from 3 parts of water or 5 parts of ethyl acetate; it melted at 151–152° and showed a specific rotation[10] of −72.9° in chloroform (*c*, 0.87). Micheel[1] records a melting point of 151–152° and a specific rotation of −73.3° in chloroform (*c*, 1.4), and McCreath and Smith[3] record the same melting point and a specific rotation $[\alpha]^{19}D$ of −72.5° in chloroform (*c*, 1.7) for 3,4-isopropylidene-D-galactosan <1,5>β<1,6>.

Anal. Calcd. for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.41; H, 6.88.

2-Acetyl-3,4-isopropylidene-D-galactosan<1,5>β-<1,6>.—A solution of 2.0 g. of 3,4-isopropylidene-D-galactosan <1,5>β<1,6> in a mixture of 10 cc. of pyridine and 10 cc. of acetic anhydride was allowed to stand overnight at room temperature and then poured upon crushed ice. The crystalline acetyl derivative (2.0 g.; 83%) which separated was recrystallized from 50 parts of boiling water and obtained as colorless plates, which melted at 136–137° and had a specific rotation of −51.4° in chloroform (*c*, 0.88).

Anal. Calcd. for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60; CH_3CO, 17.6. Found: C, 54.36; H, 6.49; CH_3CO, 17.5.

2-Benzoyl-3,4-isopropylidene-D-galactosan<1,5>β<1,6>.—To an ice-cold solution of 3.0 g. of 3,4-isopropylidene-D-galactosan <1,5>β<1,6> in 10 cc. of pyridine, benzoyl chloride (1.9 cc.; 1.1 molecular equivalents) was added dropwise; the reaction mixture was allowed to stand overnight at room temperature and then poured upon crushed ice to precipitate the crystalline benzoyl derivative. The yield was 3.7 g. (82%). The substance deposited from its solution in 5 parts of alcohol in fine needles which melted at 119–120° and exhibited a specific rotation of +6.3° in chloroform (*c*, 0.84).

Anal. Calcd. for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92; C_6H_5CO, 34.3. Found: C, 62.96; H, 5.92; C_6H_5CO, 34.7.

2-Tosyl-3,4-isopropylidene-D-galactosan<1,5>β<1,6>.—This compound was obtained in quantitative yield by the action of *p*-toluene-sulfonyl chloride (1.4 g.; 1.5 molecular equivalents) on a solution of 1.0 g. of 3,4-isopropylidene-D-galactosan <1,5>β<1,6> in 6 cc. of pyridine. It was recrystallized from 8 parts of alcohol in the form of quadrilateral plates, which melted at 118–119° and showed a specific rotation of −63.7° in chloroform (*c*, 0.92).

Anal. Calcd. for $C_{16}H_{20}O_7S$: C, 53.92; H, 5.66. Found: C, 53.85; H, 5.61.

D-Galactosan<1,5>β<1,6> from 3,4-Isopropylidene-D-galactosan<1,5>β<1,6>.—A solution of 20.0 g. of 3,4-isopropylidene-D-galactosan <1,5>β<1,6> in 220 cc. of 0.1 *N* hydrochloric acid was allowed to stand for twenty-four hours at 20°, during which period the specific rotation reached a constant value of −17.9°, equivalent to a rotation of −22.4° for D-galactosan <1,5>β<1,6>. The solution, which was devoid of reducing power (negative Fehling test), was treated with silver carbonate to remove the hydrochloric acid and then concentrated *in vacuo* to dryness. The yield of D-galactosan <1,5>β<1,6> was 14.5 g. (91%) and this material required no further purification for use in synthetic work. After recrystallization to constant physical properties from 5 parts of alcohol, it melted at 223–224° and showed a specific rotation of −22.0° in water (*c*, 1.96). Micheel[1] records a melting point of 220–221° and a specific rotation $[\alpha]^{21}D$ of −21.9° in water (*c*, 2.14).

Anal. Calcd. for $C_6H_{10}O_5$: C, 44.44; H, 6.22. Found: C, 44.51; H, 6.28.

Per-iodic Acid Oxidation of D-Galactosan<1,5>β-<1,6>.—A solution of 5.6199 g. of D-galactosan<1,5>β-<1,6> in 75 cc. of water was cooled in an ice-bath and 122 cc. of 0.625 *M* aqueous per-iodic acid (2.2 molecular equivalents) was gradually added. The oxidation was allowed to proceed at 20° for twenty-four hours and the volume was adjusted to 250 cc. by the addition of water. The titration of a 5-cc. aliquot for excess per-iodic acid revealed that 2.02 molecular equivalents of oxidizing agent had been reduced. The specific rotation of the oxidation product, calculated as L′-oxy-D-methylene-diglycolic dialdehyde, was −13.9°. This value is in good agreement with those reported for the per-iodic acid oxidation of levoglucosan,[6] D-altrosan <1,5>β<1,6>[7] and D-mannosan <1,5>β-<1,6>,[8] namely, −15.0°, −14.5° and −14.9°, and −14.2°, respectively. The sirupy aldehyde was isolated and further oxidized by bromine water in the presence of strontium carbonate in the usual way; crystalline strontium L′-oxy-D-methylene-diglycolate pentahydrate was obtained in a yield of 4.7 g. (38%). This salt, after two recrystallizations from water, gave a specific rotation of +27.7° (*c*, 0.6), a value near that of +28.1° recorded by Richtmyer and Hudson for the same salt obtained from D-altrosan <1,5>β<1,6>. When 0.5731 g. of the pentahydrate was dissolved in 25 cc. of *N* hydrochloric acid the specific rotation of the resulting solution of free L′-oxy-D-methylene-diglycolic acid was +7.9°, in close agreement with the values of +8.0°,[6] +7.9°,[7] and +7.8°[8] previously reported.

Anal. Calcd. for $C_5H_4O_6Sr \cdot 5H_2O$: C, 17.78; H, 1.19; Sr, 25.94; H_2O, 26.67. Found: C, 17.67; H, 1.16; Sr, 25.90; H_2O, 26.45.

Sodium Metaperiodate Oxidation of D-Galactosan<1,5>β<1,6>.—To an ice-cold solution of 0.5900 g. of D-galactosan <1,5>β<1,6> in 25 cc. of water, 20 cc. of 0.546 *M* aqueous sodium periodate (3.00 molecular equivalents) was added and the oxidation reaction allowed to proceed at 20° for twenty-four hours. The volume was adjusted to 50 cc. with water and a 5-cc. aliquot, upon analysis, indicated the consumption of 2.00 molecular equivalents of the periodate during the oxidation; the titration of a further 10-cc. aliquot with 0.1 *N* sodium hydroxide, using methyl red as an indicator, consumed 7.15 cc. of alkali, equivalent to the production of 0.98 molecular equivalent of formic acid as a product of the oxidation. D-Galactosan <1,5>β<1,6> would be expected to reduce

(10) All of the crystalline compounds described in the experimental part were recrystallized to constant melting point (cor.) and specific rotation $[\alpha]^{20}D$; *c* is the concentration in grams in 100 cc. of solution; the tube length was 4 dm.

two equivalents of periodate and form one equivalent of formic acid.

2,3,4-Tribenzoyl-D-galactosan<1,5>β<1,6>.—A solution of 1.0 g. of D-galactosan <1,5>β<1,6> in 10 cc. of pyridine was cooled in an ice–salt bath and 2.35 cc. (3.3 molecular equivalents) of benzoyl chloride was added dropwise. The reaction mixture was allowed to stand at room temperature for twenty-four hours and poured upon crushed ice; the crystallization of the thick sirup which precipitated was difficult but was finally attained by the alternate addition and slow evaporation of small amounts of methyl alcohol. The tribenzoate deposited from its solution in 20 parts of methyl alcohol in the form of glistening prisms, which melted at 89–90° and showed a specific rotation of +84.8° in chloroform (*c*, 1.05).

Anal. Calcd. for $C_{27}H_{22}O_8$: C, 68.35; H, 4.67; C_6H_5CO, 66.5. Found: C, 68.41; H, 4.63; C_6H_5CO, 66.2.

2,3,4-Tritosyl-D-galactosan<1,5>β<1,6>.—To an ice-cold solution of 2.0 g. of D-galactosan <1,5>β<1,6> in 20 cc. of pyridine, 7.8 g. of tosyl chloride (3.3 molecular equivalents) was added and the reaction mixture allowed to stand for twenty-four hours at room temperature. The gum which separated upon addition of the pyridine solution to water gradually crystallized over a period of two weeks and yielded 6.3 g. of a granular powder. By fractional crystallization, first from aqueous acetic acid and finally from alcohol, a yield of 2.0 g. (26%) of tritosyl-D-galactosan <1,5>β<1,6> was separated from the mixture of partially tosylated galactosans. The tritosyl compound deposited from its solution in 4 parts of alcohol in the form of small needles which melted at 103–104° (cor.) and showed a specific rotation of −51.1° in chloroform (*c*, 1.26). These constants were not changed by further recrystallization.

Anal. Calcd. for $C_{27}H_{28}O_{11}S_3$: C, 51.91; H, 4.52; S, 15.40. Found: C, 51.76; H, 4.70; S, 15.31.

2-Benzoyl-D-galactosan<1,5>β<1,6>.—A solution of 2.5 g. of 2-benzoyl-3,4-isopropylidene-D-galactosan <1,5>-β<1,6> in 25 cc. of 20% acetic acid was refluxed for two and one-half hours; upon cooling, the solution deposited 1.5 g. (68%) of 2-benzoyl-D-galactosan. The benzoate was recrystallized from 5 parts of alcohol or 15 parts of 20% acetic acid; it formed prisms which melted at 164–165° and had a specific rotation of +47.2° in chloroform (*c*, 0.8). The presence of other monobenzoylated-D-galactosans in the product, as a result of a conceivable acyl migration, would seem to be excluded, since (as described in the following paragraph) a nearly quantitative yield of authentic 2-benzoyl-3,4-isopropylidene-D-galactosan <1,5>β<1,6> may be obtained from it by treatment with acetone and anhydrous copper sulfate. Upon further benzoylation, the 2-benzoyl-galactosan yields the 2,3,4-tribenzoyl-D-galactosan <1,5>β<1,6> previously described.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30; C_6H_5CO, 39.5. Found: C, 58.68; H, 5.23; C_6H_5CO, 39.2.

2-Benzoyl-3,4-isopropylidene-D-galactosan<1,5>β<1,6> from 2-Benzoyl-D-galactosan<1,5>β<1,6>.—A solution of 1.0 g. of the 2-benzoyl-D-galactosan <1,5>β<1,6> in 25 cc. of acetone was refluxed with 5.0 g. of anhydrous copper sulfate for three hours. The copper sulfate was separated by filtration and the filtrate was concentrated to a dry crystalline residue. The reaction product was recrystallized from 5 cc. of alcohol and gave a yield of 1.0 g. (91%) of 2-benzoyl-3,4-isopropylidene-D-galactosan <1,5>β<1,6>, identical in melting point and specific rotation with the substance obtained by direct benzoylation of 3,4-isopropylidene-D-galactosan <1,5>β<1,6>. A mixed melting point showed no depression.

2-Benzoyl-3,4-diacetyl-D-galactosan<1,5>β<1,6>.—A solution of 1.0 g. of 2-benzoyl-D-galactosan <1,5>β<1,6> in a mixture of 10 cc. of pyridine and 10 cc. of acetic anhydride was allowed to stand at room temperature for eighteen hours and then poured upon crushed ice. The precipitated 2-benzoyl-3,4-diacetyl-D-galactosan (1.3 g., quantitative) was separated by filtration and recrystallized from 10 parts of alcohol. It formed needles which melted at 103–104° and rotated +85.4° in chloroform (*c*, 0.9).

Anal. Calcd. for $C_{17}H_{18}O_8$: C, 58.28; H, 5.18. Found: C, 58.48; H, 5.13.

2-Benzoyl-3,4-ditosyl-D-galactosan<1,5>β<1,6>.—This substance was obtained by tosylation of the monobenzoyl-D-galactosan <1,5>β<1,6> by the usual method; recrystallized from 5 parts of alcohol, it was obtained in prisms which melted at 119–120° and rotated +78.0° in chloroform (*c*, 0.8).

Anal. Calcd. for $C_{27}H_{26}O_{10}S_2$: C, 56.42; H, 4.55; S, 11.16. Found: C, 56.43; H, 4.56; S, 11.07.

Summary

The pyrolysis of α-lactose monohydrate under reduced pressure forms a sirup from which, after condensation with acetone, yields of 13% of levoglucosan and 17.5% of 3,4-isopropylidene-D-galactosan <1,5>β<1,6> were obtained. Selective mild acid hydrolysis converts the latter compound into the known D-galactosan <1,5>β<1,6>. Confirmation of the ring structure and configuration of the galactosan was obtained by periodate oxidative procedures. A number of new derivatives of 3,4-isopropylidene-D-galactosan <1,5>β<1,6> and of D-galactosan <1,5>β<1,6> have been prepared and described.

BETHESDA, MD. RECEIVED JULY 31, 1942

[CONTRIBUTION NO. 867 FROM THE KODAK RESEARCH LABORATORIES]

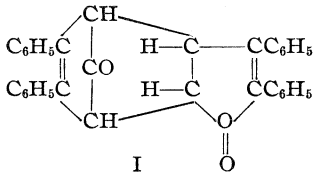
The Behavior of Certain Carbonyl Bridge Compounds with Alkaline Hydrogen Peroxide

BY C. F. H. ALLEN AND J. W. GATES, JR.

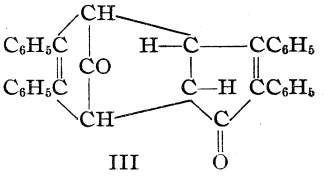
Some time ago[1] it was shown that when the bimolecular product I, that results from treatment of anhydroacetonebenzil with acidic dehydrating agents, was treated with chromium trioxide in acetic acid, poor and varying yields of an isomer were obtained. This new substance also lost carbon monoxide on heating, to give an indanone II having two phenyl groups on the same carbon atom. It was furthermore concluded that the isomerism was due to space relations. Since many new facts about the reactions of the bimolecular product are now available,[2] as a result of which the structure has been slightly modified,[2b] it was necessary to re-examine the "oxidation product" isomer III. During the course of this work degradation and synthesis established the correctness of the structure previously assigned to the indanone.

When the bimolecular product I is stirred at room temperature with a cold alkaline solution of hydrogen peroxide, a peroxide IV is formed; this contains four extra atoms of oxygen. It loses this oxygen almost explosively when heated, but seems stable at room temperature. Upon treatment with hydrogen bromide, bromine is liberated and the bimolecular product regenerated. It likewise liberates iodine from potassium iodide in acetic acid. When it is dissolved in acetic acid, oxygen is evolved and the "oxidation product" isomer III, previously secured with difficulty by means of chromic acid, was formed. These reactions are practically quantitative.

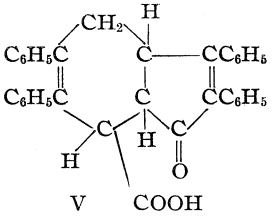
Both isomers I and III give the same derivatives; thus, with alkaline reagents the acid V results, phenylmagnesium bromide gives the same carbinol, and in the Grignard machine both show one active hydrogen and one addition. The only difference is in the results of pyrolysis: both lose carbon monoxide, but one gives the indanone II and the other its isomer VI, by way of two intermediate isomeric unsaturated ketones.[2] Since the same derivatives are obtained from both, the only difference being the result of pyrolysis, the difference between the isomers must be of a spatial nature. That is, the position of the hydrogens on the bond common to the two rings appears to be the significant factor, and, as concluded in the earlier paper,[1] the two substances are presumably geometrical isomers, as represented in I and III.



I



III



V

The above formulas differ from those previously assigned[1] only in the interchange of the angular phenyl group and one hydrogen atom at the other end of an allylic system. The fact that both give the same derivatives is explained on the basis of catalysis by acidic or basic substances present in all reactions. The only reaction carried out in the absence of a possible catalyst is the heating, and this leads quantitatively to a different product in each instance. The previous suggestion that the bimolecular product was a mixture has been abandoned,[2] but the reasons[1] for assigning it a *cis*-configuration I are retained.

The indanone II, in which the grouping —CH_2-CO— had been proved previously, has now been degraded to a lactone VII and to a hydrocarbon XI, both of which have been synthesized by reactions that leave no doubt as to their structures. The synthesis from the known keto acid VIII also establishes the position of the side chain.

The diketone IX resulting from the action of

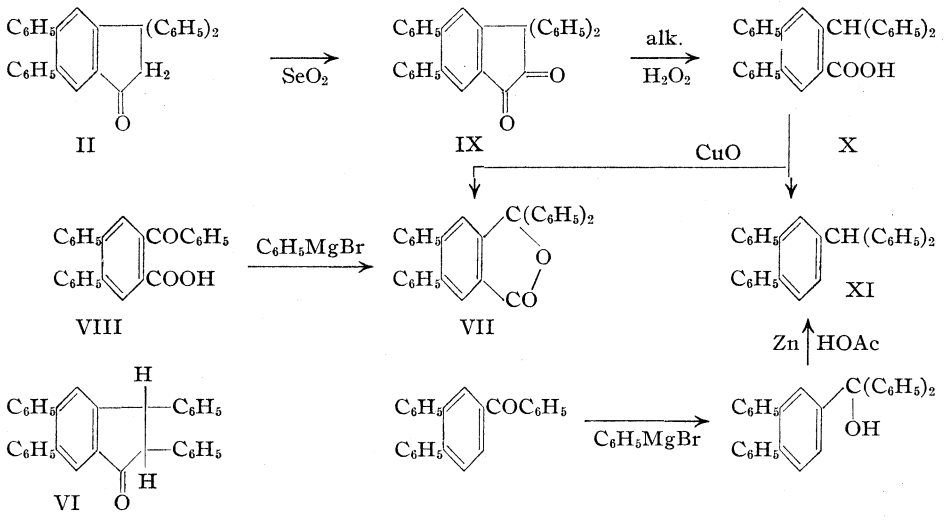
(1) Allen and Rudoff, *Can. J. Res.*, **B15**, 321 (1937).

(2) Allen and Gates, THIS JOURNAL, **64**, (a) 2120 (1942); (b) **64**, 2123 (1942).

selenium dioxide on the indanone is readily cleaved by alkaline hydrogen peroxide to the acid X. When the latter is treated under decarboxylating conditions with copper carbonate (or oxide), a portion loses the carboxyl group and gives the triphenylmethane derivative XI; this was synthesized, as shown in the outline, from 3,4-diphenylbenzophenone. The remainder of the product is the lactone VII, evidently formed by oxidation of the triphenylmethane hydrogen atom of X to hydroxyl, followed by closing of the lactone ring. The interrelation and lactone synthesis are shown in the chart.

CHART I

DEGRADATION OF THE INDANONE II; SYNTHESIS OF TWO PRODUCTS

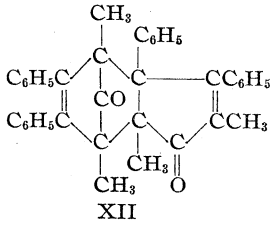


It is obvious that there has been a 1,2-shift of a phenyl group during the decarbonylation of the bimolecular product isomer III; this rearrangement must have been due to the heating. It has been shown previously that there was no rearrangement during the decarbonylation of the isomer I, by accomplishing the removal of the bridge carbonyl by the action of sodium methoxide at the boiling point of methanol[2a] and securing the same end-product in both reactions, the indanone VI; the phenyl groups are linked to the same carbon atoms in I and in VI.

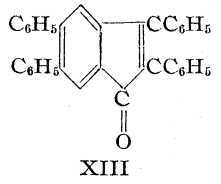
The behavior of the indandione IX toward alkaline hydrogen peroxide is similar to that of the simpler 3,3-diphenylindandione-1,2, as described by Gagnon[3] but neither of these is in agreement with the results of Koelsch.[4] In the work described in this paper, all variations of experimental procedure always gave the same product, but the yields were much improved by the use of Gagnon's technique; the intermediate aroylformic acid was not isolated.

The indandione IX gives a quinoxaline with *o*-phenylenediamine, instead of the anil[1]; the last molecule of water is held very tenaciously. This observation may account for the disagreement reported on the quinoxaline of 3,3-diphenylindandione-1,2.[3,4] The diketone IX also gives a crystalline glycol XVIII with excess phenylmagnesium bromide.

Evidence as to the structure of the peroxide is not decisive. A homologous bimolecular product XII[5] that has no hydrogen in the positions *alpha* to the carbonyl group does not give a peroxide; neither does it show active hydrogen in the Grignard machine. Thus these two anomalous properties must be related in some way to the carbonyl bridge and adjacent hydrogen. The most obvious relation is that of an enol, and such has already been suggested[2b] to account for the active hydrogen. It is also well established that highly substituted enols are capable of forming peroxides.[6] These, however, have but two atoms of oxygen, whereas the bimolecular product peroxide has four.



XII



XIII

The isomer III does not form a peroxide; this suggests that the space relations also have an influence upon its formation.

During the preparation of the isomeric bimolecular product III by the action of chromic acid,[1]

(3) Gagnon, Hudon, Cantin and Ganas, *Trans. Roy. Soc. Can.*, (III) **33**, 47 (1939).

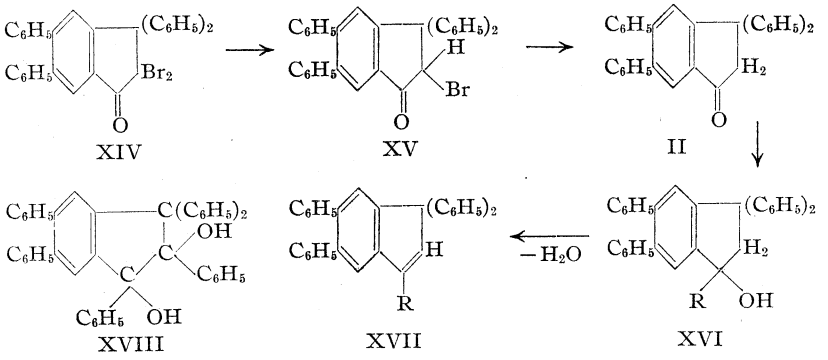
(4) Koelsch and LeClaire, *J. Org. Chem.*, **6**, 532 (1941).

(5) Allen and VanAllan, THIS JOURNAL, **64**, 1260 (1942).

(6) Kohler and Mydans, *ibid.*, **54**, 4667 (1932).

substances of varying melting points resulted, all of which, upon analysis, were found to contain varying amounts of oxygen, and which gave no depression of melting point on admixture; upon heating, they all gave the indanone II practically quantitatively. This suggests that they were a single substance plus oxygen; the maximum value, plus four oxygen atoms, was only obtained by the use of alkaline hydrogen peroxide. A variety of products, which will be described in detail in a later paper, resulted when tetraphenylindenone, XIII, was treated with alkaline hydrogen peroxide. A true peroxide appears to be formed primarily, however.

The proof of the —CH_2CO— group in the rearranged indanone II previously proved in several ways has received confirmation in this paper through stepwise reduction of the dibromo substitution product XIV by means of the Grignard reagent. This is characteristic of α-haloketones[7]; one halogen is removed at a time, so the monobromoketone XV can be isolated as an intermediate during the process.



The indanone II gave carbinols XVI with Grignard reagents. On dehydration these gave hydrocarbons XVII. These are isomeric with other hydrocarbons[2] of which the structures are still in doubt, obtained from closely related carbinols; however, the non-identity shows that in the others there must be a different arrangement of phenyl groups around the indene ring.

Experimental

The Peroxide IV.—In a solution of 500 cc. of alcohol, 50 cc. of water and 8 g. of sodium hydroxide, was suspended 42 g. of bimolecular product I; to this was added 50 cc. of 16% hydrogen peroxide with vigorous stirring and the temperature kept below 30° for two hours. Then it was chilled externally by ice, filtered, rinsed with a little methanol, and air-dried. The yield was 40–42 g. It softens about 80°, gradually decomposing up to 200°.

Anal. Calcd. for $C_{34}H_{24}O_6$: C, 77.8; H, 4.5. Found: C, 77.3; H, 4.5.

The peroxide liberates the halogen from potassium iodide or hydrogen bromide in acetic acid, with regeneration of the bimolecular product, but if an acetic acid solution is heated to boiling, the solid dissolves with evolution of gas, and on cooling, the isomeric indenone III separates in rods which melt at 215°.

Anal. Calcd. for $C_{34}H_{24}O_2$: C, 87.9; H, 5.2. Found: C, 87.9; H, 5.1.

This melting point was not lowered on admixture with samples of widely varying melting points from chromic acid oxidation; these specimens melted with decomposition all the way up to 264° and contained fractional amounts of oxygen not corresponding with exactly one or two equivalents. Regardless of the melting point, each gave the same indanone II on decarbonylation and loss of oxygen.

The isomeric bimolecular product III no longer forms a peroxide; on heating at 260–270°, 3,3,5,6-tetraphenylindanone-1 II is formed practically quantitatively. It also gave the acid V with alcoholic potash, confirmed by conversion to its methyl ester, and the same phenyl carbinol[2b] with phenylmagnesium bromide and decomposition by iced ammonium chloride and corresponding hydrocarbon[2b] on dehydration above 300°.

The Quinoxaline of the Diketone IX.—This was obtained as previously described,[1] but recrystallized from benzene–ligroin. Before analysis it was dried at 100° *in vacuo* over phosphorus pentoxide for nineteen hours.

Anal. Calcd. for $C_{39}H_{26}N_2$: C, 89.7; H, 5.0. Found: C, 89.6; H, 5.2.

Cleavage of the Diketone IX.—To a suspension of 27 g. of the diketone[1] in 600 cc. of alcohol was added a solution of 12 g. of sodium hydroxide in 75 cc. of water; after cooling in ice and stirring for a half hour all had dissolved. Then 75 cc. of 16% hydrogen peroxide was added and after an additional two hours the solution was diluted with 600 cc. of water, filtered and the filtrate acidified with acetic acid. After extracting with chloroform and appropriate manipulation, 16 g. (61%) of the acid X, (4,5-diphenyl-2-benzhydrylbenzoic acid) m. p. 258–259°, was collected. The yield by this variation in procedure is much better than when sodium peroxide is used.[1] The acid dissolves in *dilute* alkali only.

Anal. Calcd. for $C_{32}H_{24}O_2$: C, 87.3; H, 5.5. Found: C, 87.5; H, 5.5.

The methyl ester, prepared in the usual manner, separates in rods from benzene–methanol; m. p. 165°.

Anal. Calcd. for $C_{33}H_{26}O_2$: C, 87.2; H, 5.7. Found: C, 87.5; H, 5.5.

The Lactone VII (3,4-Diphenyl-diphenylphthalide). (a) Synthesis.—This was accomplished by treatment of

(7) Kohler and Tishler, THIS JOURNAL, **54**, 1594 (1932); **57**, 217 (1935).

TABLE I

PROPERTIES OF CARBINOLS AND HYDROCARBONS

Substance	M. p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
XVI, R = C_6H_5	233–234 d.[a]	$C_{39}H_{30}O$	91.1	5.8	91.0	5.9
XVII, R = CH_3	180[a]	$C_{34}H_{26}$	94.0	6.0	93.6	6.0
XVII, R = C_6H_5	227[a]	$C_{39}H_{28}$	94.4	5.6	94.1	5.6
XVII, R = α-$C_{10}H_7$	244[b]	$C_{43}H_{30}$	94.5	5.5	94.2	5.6
XVIII	159[c]	$C_{45}H_{34}O_2$	89.1	5.6	88.9	5.7

[a] Prisms. [b] Needles. [c] Tiny rods.

2-benzoyl-4,5-diphenylbenzoic acid VIII[8] with phenylmagnesium bromide, decomposing the complex with ammonium chloride, and recrystallizing from acetic acid. It forms rods; m. p. 180°.

Anal. Calcd. for $C_{32}H_{22}O_2$: C, 87.7; H, 5.0. Found: C, 87.7; H, 4.9.

(b) **From the Acid X.**—An intimate mixture of 15 g. of the acid and 2 g. of copper carbonate was heated at 260–265° for a half hour, and the cooled melt extracted with hot benzene; it was filtered from metallic copper and diluted with ligroin. The lactone was deposited in a yield of 20%. From the filtrate 3,4-diphenylbenzhydrylbenzene XI crystallized in a 30% yield. It forms needles and rods from acetic acid, m. p. 143°.

Anal. Calcd. for $C_{31}H_{24}$: C, 93.9; H, 6.1. Found: C, 93.9; H, 6.0.

The hydrocarbon XI was also synthesized from 3,4-diphenylbenzophenone and phenylmagnesium bromide; the oily carbinol was reduced by zinc and acetic acid.

The lactone is unaffected by bromine, acetyl chloride and chromic acid. It is reduced to the acid X by zinc and acetic acid.

2-Bromo-3,3,5,6-tetraphenylindenone, XV, was obtained when the dibromoketone XIV[1] was treated with excess phenylmagnesium bromide in the usual manner. It separates in needles from benzene, m. p. 240°. The yield was 60%. Repetition of the treatment on this bromoketone gave the indanone II.

(8) Allen, A. C. Bell, A. Bell and VanAllan, THIS JOURNAL, **62**, 656 (1940).

Anal. Calcd. for $C_{33}H_{23}OBr$: C, 76.9; H, 4.5; Br, 15.5. Found: C, 76.7; H, 4.4; Br, 15.4.

The carbinols, XVI, were secured by the usual procedure, decomposing the organometallic complex with ammonium chloride. The corresponding hydrocarbons XVII were produced by refluxing 4 g. of the carbinols in 50 cc. of 2% sulfuric acid in acetic acid for a half hour. Their properties are collected in Table I.

The glycol, 1,2,3,3,5,6-hexaphenylindandiol-1,2,XVIII, was prepared from the diketone IX and an excess of phenylmagnesium bromide in butyl ether for six hours at 100°.

Summary

The bimolecular product, formed by the action of acidic dehydrating agents on anhydracetonebenzil, forms a peroxide, upon treatment with alkaline hydrogen peroxide. This substance loses its oxygen and gives an isomer in acetic acid solution. The isomer affords a previously described indanone on decarbonylation.

The indanone has been degraded to known products, the syntheses of two of which are described. It has also been converted into a carbinol and hydrocarbon isomeric with some closely related substances.

ROCHESTER, N. Y. RECEIVED JULY 6, 1942

[CONTRIBUTION FROM THE NICHOLS CHEMISTRY LABORATORY OF NEW YORK UNIVERSITY]

Deamination of 5-Amino-8-nitroisoquinoline[1]

BY BERTRAM KEILIN AND W. E. CASS[2]

In an attempt to prepare 8-nitroisoquinoline, 5-acetylaminoisoquinoline[3] was nitrated and the resulting acetylaminonitroisoquinoline hydrolyzed to an aminonitroisoquinoline. When the aminonitroisoquinoline was diazotized in hydrochloric acid solution and treated with hypophosphorous acid,[4] there was obtained 8-chloroisoquinoline, identified by analysis and by comparison with a known sample of 8-chloroisoquinoline.[5]

In the preceding diazotization-deamination, the nitro group was displaced by chlorine, nitrous acid being evolved. This displacement of the nitro group possibly occurred during diazotization,

(1) Constructed, in part, from the B.A. research paper of Bertram Keilin, New York University, University College, 1942.

(2) Present address: Research Laboratory, General Electric Company, Schenectady, New York.

(3) Craig and Cass, THIS JOURNAL, **64**, 783 (1942).

(4) Adams and Kornblum, *ibid.*, **63**, 188 (1941).

(5) Pomeranz, *Monatsh.*, **18**, 1 (1897), prepared, but did not analyze, 8-chloroisoquinoline by ring closure of *o*-chlorobenzalaminoacetal.

because it was noted that an excess of nitrous acid was always present in the diazotized solution, even when less than the theoretical amount of sodium nitrite had been added. Since the replacement of the nitro group by chlorine resulted in the formation of 8-chloroisoquinoline, the structure, 5-amino-8-nitroisoquinoline, was assigned to the starting material. Other examples of the displacement of a nitro group, labilized by the diazonium group, have been observed in the case of dinitroanisidines[6] and 1-nitro-2-aminonaphthalene.[7]

Several further attempts to prepare 8-nitroisoquinoline from 5-amino-8-nitroisoquinoline were made without success. Diazotization in dilute or concentrated sulfuric acid and deamination with alcohol or hypophosphorous acid failed to lead to 8-nitroisoquinoline. The use of acetic and sulfuric acids as a diazotization medium[8] and alcohol deamination likewise failed, possibly as a result of the low solubility of 5-amino-8-nitroisoquinoline in glacial acetic acid.

Experimental

All melting points are corrected.

5-Acetylamino-8-nitroisoquinoline.—Finely powdered and thoroughly dried 5-acetylaminoisoquinoline[9] (18.6 g., 0.1 mole) was added slowly with mechanical stirring to 100 cc. of concentrated sulfuric acid maintained at 0–10°. When all of the acetylaminoisoquinoline had dissolved, a cool solution of 11.1 g. (0.11 mole) of potassium nitrate in 40 cc. of concentrated sulfuric acid was added with constant stirring during the course of forty-five minutes, the mixture being maintained at 15–20°. After the addition of the potassium nitrate–sulfuric acid was complete, the reaction mixture was allowed to stand at 15–20° for an additional forty-five minutes and then poured onto excess cracked ice. The acid solution was neutralized with ammonium hydroxide, more ice being added as necessary to keep the solution cool. The precipitated crude product was filtered and recrystallized from alcohol, using decolorizing charcoal, as yellow-brown needles; yield, 11.2 g; m. p. 225–227°. By concentration of the mother liquor, an additional 5.2 g. of substance of m. p. 224–226° was recovered, making the total yield 16.4 g. (71%). Further recrystallizations from alcohol gave yellow needle clusters of m. p. 226–228°.

Anal. Calcd. for $C_{11}H_9O_3N_3$: C, 57.14; H, 3.92; N, 18.18. Found: C, 57.3; H, 3.8; N, 18.1.

5-Amino-8-nitroisoquinoline Hydrochloride.—A solution of 15 g. of 5-acetylamino-8-nitroisoquinoline in 150 cc. of 20% hydrochloric acid was boiled under reflux for twenty-five minutes. The reaction mixture was cooled and the orange-red crystalline precipitate filtered. This substance proved to be the monohydrate of 5-amino-8-nitroisoquinoline hydrochloride. The crude yield was 15.6 g. (97%). The substance was recrystallized from water plus a small amount of hydrochloric acid as orange needles, m. p. 288–290° (dec.). On standing in a vacuum desiccator over sulfuric acid, the product became orange-red in color and lost its water of hydration. (This color change was also observed during the melting point determination for the hydrated salt.) The anhydrous salt melted at 289–291° (dec.).

Anal. Calcd. for $C_9H_8O_2N_3Cl \cdot H_2O$: H_2O, 7.39. Found: H_2O, 7.3, 7.4. Calcd. for $C_9H_8O_2N_3Cl$: N, 18.63; Cl, 15.71. Found: N, 18.5; Cl, 15.7.

5-Amino-8-nitroisoquinoline.—Neutralization of a hot aqueous solution of the preceding hydrochloride with ammonium hydroxide caused the formation of a voluminous precipitate of the free base in nearly quantitative yield. The substance crystallized from alcohol as orange needles, m. p. 268–270° (dec.).

Anal. Calcd. for $C_9H_7O_2N_3$: C, 57.14; H, 3.73; N, 22.22. Found: C, 57.3; H, 3.7; N, 22.1.

Treatment of 5-amino-8-nitroisoquinoline with warm dilute hydrochloric acid caused the formation of the hydrate of its hydrochloride salt (m. p. 288–290° (dec.)). Likewise the substance, heated with acetic anhydride, was transformed into 5-acetylamino-8-nitroisoquinoline (m. p. 226–228°).

8-Chloroisoquinoline.—A suspension of 4.88 g. (0.02 mole) of the hydrate of 5-amino-8-nitroisoquinoline hydrochloride in 30 cc. of concentrated hydrochloric acid was cooled to −10–0° and, with stirring, a solution of 1.3 g. (0.019 mole) of sodium nitrite in 10 cc. of water was slowly added. As diazotization proceeded, the color of the solution lightened and the suspended aminonitroisoquinoline hydrochloride dissolved. A starch–iodide test for nitrous acid was at all times positive. After the addition of the nitrite, the solution was stirred and cooled for five minutes and then 20 cc. of ice-cold 50% hypophosphorous acid was added. Nitrogen and some oxides of nitrogen were evolved. The reaction mixture was allowed to stand in an icebox six hours, then overnight at room temperature and finally was poured on ice and made basic with 20% sodium hydroxide solution. Steam distillation of the mixture separated a colorless oil which, on standing in the icebox, crystallized in long fine needles. The crude yield was 2.3 g. (70%); m. p. 54–55°. The substance crystallized from petroleum ether as small, white prisms of m. p. 55.5–56.5° (Pomeranz[5] reported m. p. 55°). The substance showed no depression in a mixed melting point with a sample of 8-chloroisoquinoline, prepared by ring closure, described below.

Anal. Calcd. for C_9H_6NCl: C, 66.07; H, 3.70; N, 8.56; Cl, 21.67. Found: C, 66.0; H, 3.6; N, 8.5; Cl, 21.2.

Picrate.—Recrystallized from alcohol as hair-fine yellow needles; m. p. 189.5–191.5°. No depression was observed

(6) Meldola and Eyre, *J. Chem. Soc.*, **79**, 1076 (1901); **81**, 988 (1902).

(7) Morgan, *ibid.*, **81**, 1376 (1902).

(8) Hodgson and Walker, *ibid.*, 1620 (1933).

(9) In the preparation of large amounts of 5-acetylaminoisoquinoline,[3] it was observed that this substance, recrystallized from dilute alcohol, lost its crystalline appearance on standing in a vacuum desiccator over sulfuric acid. Analysis indicated that the substance crystallized as a hemi-hydrate. *Anal.* Calcd. for $C_{11}H_{10}ON_2 \cdot {}^1/_2H_2O$: H_2O, 4.62. Found: H_2O, 4.6.

in a mixed melting point with the picrate of 8-chloroisoquinoline prepared by ring closure.

Anal. Calcd. for $C_{15}H_9O_7N_4Cl$: N, 14.27. Found: N, 14.0.

o-Chlorobenzalaminoacetal.—Equimolar amounts of *o*-chlorobenzaldehyde and aminoacetal[10] were heated in an oil-bath at 110° until the liberated water was driven off. The product, distilled under reduced pressure, was obtained as an almost colorless oil in 95% yield; b. p. 114–117° (2 mm.) (oil-bath at 150–160°).

Anal. Calcd. for $C_{13}H_{18}O_2NCl$: C, 61.05; H, 7.10; N, 5.48. Found: C, 60.7; H, 7.0; N, 5.3.

8-Chloroisoquinoline.—The method of Tyson,[11] using sulfuric acid and phosphorus pentoxide, was employed for the ring closure of *o*-chlorobenzalaminoacetal. The method of working up the product, however, was modified as follows. The cooled sulfuric acid reaction mixture (from 20 g. of *o*-chlorobenzalaminoacetal) was poured on ice and made basic with ammonium hydroxide. The basic solution was extracted with three 200-cc. portions of ether. The combined ether extracts were then extracted with 100 cc. of 6 *N* hydrochloric acid. The hydrochloric acid solution was evaporated to dryness on the steam-bath, made basic with potassium carbonate solution and steam distilled. There was obtained 8-chloroisoquinoline of m. p. 55–56° in 9% yield. The picrate crystallized from alcohol as very fine yellow needles of m. p. 189.5–191.5°.

(10) Cass, THIS JOURNAL, **64**, 785 (1942).
(11) Tyson, *ibid.*, **61**, 183 (1939).

Summary

1. The preparation of 5-amino-8-nitroisoquinoline has been described.

2. Deamination of 5-amino-8-nitroisoquinoline in hydrochloric acid has been shown to yield 8-chloroisoquinoline.

NEW YORK, N. Y. RECEIVED JULY 28, 1942

[CONTRIBUTION FROM THE NICHOLS CHEMISTRY LABORATORY OF NEW YORK UNIVERSITY]

2-Phenyloxazole; *para*-Substituted Derivatives[1]

BY JEROME J. ROSENBAUM AND W. E. CASS[2]

In an extension of previously reported work[3] on the synthesis of ortho-substituted derivatives of 2-phenyloxazole, *p*-nitrobenzalaminoacetal was treated with sulfuric acid and phosphorus pentoxide. The product isolated from this reaction proved to be 2-(*p*-nitrophenyl)-oxazole. Oxidation of this substance yielded *p*-nitrobenzamide. By reduction of the nitro group there was obtained 2-(*p*-aminophenyl)-oxazole, from which several derivatives were prepared. Deamination of 2-(*p*-aminophenyl)-oxazole resulted in the formation of 2-phenyloxazole, identical with the substance obtained by the deamination of 2-(*o*-aminophenyl)-oxazole.[3] Nitration of 2-phenyloxazole resulted in the formation of 2-(*p*-nitrophenyl)-oxazole.

The preparation of 2-(*p*-nitrophenyl)-oxazole was also accomplished by treatment of *p*-nitrobenzoylaminoacetal with sulfuric acid and phosphorus pentoxide. Unlike the case of the corresponding ortho derivative,[3] this alternate method of preparation gave 2-(*p*-nitrophenyl)-oxazole in yields comparable to those obtained from *p*-nitrobenzalaminoacetal.

(1) Constructed, in part, from the B.A. research paper of Jerome J. Rosenbaum, New York University, University College, June, 1942.
(2) Present address: Research Laboratory, General Electric Company, Schenectady, New York.
(3) Cass, THIS JOURNAL, **64**, 785 (1942).

Pharmacological tests on 2-(*p*-sulfanilamidophenyl)-oxazole were carried out by the Merck Institute for Therapeutic Research, Rahway, New Jersey. In staphylococcal infections in mice, this compound was not particularly effective in comparison with sulfathiazole. In streptococcal infections, although some activity was shown, the compound was not as effective as sulfanilamide.

Experimental

All melting points are corrected.

***p*-Nitrobenzalaminoacetal.**—Equimolar amounts of *p*-nitrobenzaldehyde and aminoacetal[3] were heated in an oil-bath at 110–120° until the liberated water was driven off. The reaction mixture was allowed to cool somewhat and twice its volume of dry ether was added. Cooling of the ether solution with dry-ice resulted in the precipitation of *p*-nitrobenzalaminoacetal in 80–87% yield. Further recrystallization from ether gave white plates of m. p. 56–57°, b. p. 165–168° (2 mm.) (oil-bath 200–210°).

Anal. Calcd. for $C_{13}H_{18}O_4N_2$: C, 58.62; H, 6.81; N, 10.52. Found: C, 58.7; H, 6.5; N, 10.6.

2-(*p*-Nitrophenyl)-oxazole from *p*-Nitrobenzalaminoacetal.—The reaction of *p*-nitrobenzalaminoacetal with sulfuric acid and phosphorus pentoxide was carried out following the method used in the preparation of 2-(*o*-nitrophenyl)-oxazole.[3] The crude product, however, was not purified by steam distillation but by recrystallization from alcohol, using decolorizing charcoal. 2-(*p*-Nitrophenyl)-oxazole was thus obtained as yellowish needles in 40% yield, m. p. 163.5–164.5°.

Anal. Calcd. for $C_9H_6O_3N_2$: C, 56.85; H, 3.18; N, 14.73. Found: C, 56.8; H, 3.3; N, 14.6.

2-(*p*-Nitrophenyl)-oxazole was weakly basic, dissolving in concentrated hydrochloric or sulfuric acid, but reprecipitating on dilution of the solution with water. The substance could be recrystallized from benzene as stout yellowish needles. A test for the nitro group was positive. Steam distilled, the substance passed over as small white crystals, which, however, crystallized from benzene as yellowish needles.

Oxidation of 2-(*p*-nitrophenyl)-oxazole was carried out using potassium permanganate or bromine water as previously described for the oxidation of 2-(*o*-nitrophenyl)-oxazole.[3] In each case the product of oxidation, recrystallized from water plus a small amount of ammonium hydroxide, was identified as *p*-nitrobenzamide by a mixed melting point determination with an authentic sample of *p*-nitrobenzamide (m. p. 199–202°).

2-(*p*-Nitrophenyl)-oxazole from *p*-Nitrobenzoylaminoacetal.—*p*-Nitrobenzoylaminoacetal[4] (10.8 g., 0.038 mole) was added slowly with constant stirring to 70 cc. of concentrated sulfuric acid cooled to −5°. This cold solution was allowed to drop during eight minutes onto a mixture of 25 g. of phosphorus pentoxide and 6 cc. of sulfuric acid in a flask fitted with an efficient reflux condenser and maintained at 180–190° in an oil-bath. The flask was occasionally shaken and, after the addition was complete, the reaction mixture was allowed to stand twenty-five minutes at 180–190°. After cooling, the reaction mixture was poured on ice and made basic with ammonium hydroxide. The crude product was filtered and recrystallized from alcohol, using decolorizing charcoal. There was obtained 3.3 g. (45%) of product as almost white needles of m. p. 163.5–164.5°. This substance showed no depression in a mixed melting point determination with 2-(*p*-nitrophenyl)-oxazole prepared from *p*-nitrobenzalaminoacetal.

2-(*p*-Aminophenyl)-oxazole.—Hydrogenation of a suspension of 2-(*p*-nitrophenyl)-oxazole in absolute ethanol was carried out, using Raney nickel, as previously described for the corresponding ortho derivative.[3] After filtration of the catalyst and evaporation of the alcohol under reduced pressure, the crude product (obtained in nearly quantitative yield) was recrystallized several times from benzene as white needles of m. p. 121–123°.

Anal. Calcd. for $C_9H_8ON_2$: C, 67.49; H, 5.04; N, 17.49. Found: C, 67.5; H, 5.0; N, 17.5.

The reduction of 2-(*p*-nitrophenyl)-oxazole was also carried out using stannous chloride. A solution of 5 g. (0.0263 mole) of the nitro compound in 22.5 cc. of concentrated hydrochloric acid was added to 18.5 g. (0.0812 mole) of stannous chloride dissolved in 22.5 cc. of concentrated hydrochloric acid. The reaction mixture was warmed on the steam-bath and then, with cooling, made strongly basic with 33% sodium hydroxide solution. The precipitated crude product was obtained in 92% yield.

Unlike the corresponding ortho derivative,[3] 2-(*p*-aminophenyl)-oxazole in alcohol solution did not show fluorescence in daylight. In ultraviolet light, however, a bluish fluorescence was observed.

(4) Löb, *Ber.*, **27**, 3093 (1894).

Derivatives of 2-(*p*-Aminophenyl)-oxazole.—The picrate and the acetyl, benzoyl and acetylsulfanilyl derivatives of 2-(*p*-aminophenyl)-oxazole were prepared as previously described for the corresponding ortho derivatives,[3] essentially the same yields being obtained. These derivatives are listed in Table I.

TABLE I

2-(—)-oxazole	M. p., °C.	*Anal.* Calcd.	N, % Found
p-Aminophenyl, picrate[a,c]	182.5–184 (dec.) $C_{15}H_{11}O_8N_5$	17.99	18.0
p-Acetylaminophenyl[a,d]	191.5–192.5 $C_{11}H_{10}O_2N_2$	13.86	13.9
p-Benzoylaminophenyl[a,e]	163.5–164.5 $C_{16}H_{12}O_2N_2$	10.60	10.7
p-(N^4-Acetylsulfanilamido)-phenyl[b,d]	226.5–228 $C_{17}H_{15}O_4N_3S$	11.76	11.7

[a] Recrystallized from 50% alcohol. [b] Recrystallized from absolute alcohol. [c] Yellow needles. [d] Needles. [e] Plates or prisms.

2-(*p*-Sulfanilamidophenyl)-oxazole.—Hydrolysis of 2-(*p*-(N^4-acetylsulfanilamido)-phenyl)-oxazole was effected by boiling the substance under reflux with ten times its weight of 12% hydrochloric acid for thirty minutes. By neutralization of the solution with ammonium hydroxide the product was precipitated in 95% yield. The substance was recrystallized from 50% alcohol, using decolorizing charcoal, as small plates; m. p. 191.5–192.5°.

Anal. Calcd. for $C_{15}H_{13}O_3N_3S$: C, 57.13; H, 4.16; N, 13.33. Found: C, 57.2; H, 4.1; N, 13.2.

2-Phenyloxazole.—Deamination of 2-(*p*-aminophenyl)-oxazole, as described previously for the corresponding ortho derivative,[3] resulted in the formation of 2-phenyloxazole (b. p. 226–228°) in 34% yield. The picrate (m. p. 115–116°) prepared from this substance showed no depression in a mixed melting point with the picrate of 2-phenyloxazole previously prepared.[3]

Nitration of 2-Phenyloxazole.—To 0.2 g. of 2-phenyloxazole in 5 cc. of concentrated sulfuric acid was added 0.2 g. (excess) of potassium nitrate. The mixture was stirred until the potassium nitrate was dissolved, allowed to stand one hour at room temperature and then warmed to 70° for ten minutes. Ice was added and the mixture neutralized with ammonium hydroxide. The crude yield was 0.2 g. (77%); however, the product was impure as was shown by its low melting point (below 100°). Recrystallization from alcohol followed by recrystallization from benzene and ligroin gave a small amount of yellowish needles of m. p. 162.5–164°. No depression was observed in a mixed melting point with 2-(*p*-nitrophenyl)-oxazole prepared from *p*-nitrobenzalaminoacetal.

Summary

1. Certain para-substituted derivatives of 2-phenyloxazole have been prepared.

2. Pharmacological tests on 2-(*p*-sulfanilamidophenyl)-oxazole have been reported.

NEW YORK, N. Y. RECEIVED JULY 28, 1942

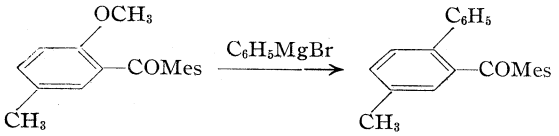
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

ortho Alkylation and Arylation of Mesityl Aryl Ketones

BY REYNOLD C. FUSON AND S. B. SPECK

The action of aryl Grignard reagents on mesityl aryl ketones[1] and aryl mesitoates[2] has been shown to bring about *ortho* arylation. The change evidently involves 1,4 addition followed by oxidation of the addition product, although the manner in which the latter transformation occurs has not been determined. It amounts to the elimination of a molecule of hydrogen from the dihydrobenzenoid compound or its enol form.

A method has now been discovered whereby the arylation can be effected smoothly and in high yields. It consists simply in the use of mesityl *o*-methoxyaryl ketones. An example is the conversion of 2-methoxy-5-methylbenzoylmesitylene (I) to 2-phenyl-5-methylbenzoylmesitylene (II) by the action of phenylmagnesium bromide.



I II

The reaction proceeded readily and in good yield at room temperature.

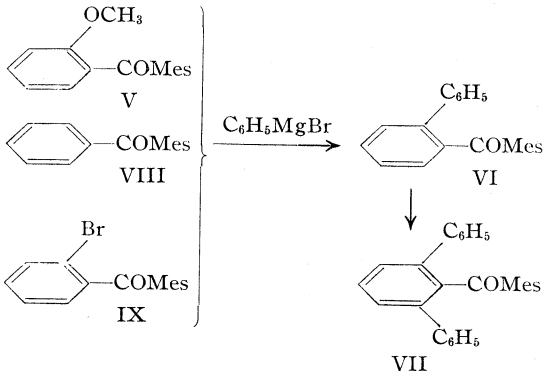
ortho-Alkylation could be effected also. When ethylmagnesium bromide was used the product was 2-ethyl-5-methylbenzoylmesitylene (III).



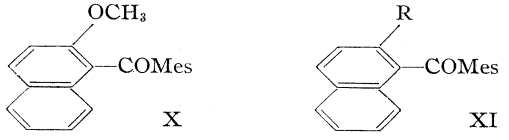
III IV

As was to be expected, phenylmagnesium bromide at higher temperatures brought about diphenylation to produce 2,6-diphenyl-3-methylbenzoylmesitylene (IV).

Similar results were obtained with 2-methoxybenzoylmesitylene (V). One or two phenyl groups could be introduced, the products being VI and VII, respectively. The monophenyl derivative (VI) had been obtained, though in lower yield, by the action of phenylmagnesium bromide on benzoylmesitylene (VIII).[1] It is significant that the 2-bromo derivative (IX) yielded the diphenylated ketone, VII. Presumably, this transformation involves the monophenyl ketone (VI) as an intermediate.

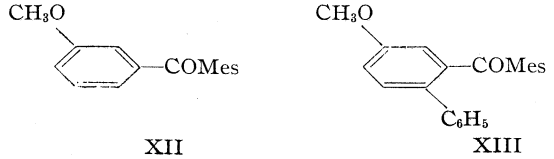


The conversion of the methoxyl compound (V) to the monophenyl ketone takes place much more readily than the introduction of the second phenyl group, *i. e.*, the transformation of VI to VII. The two processes are evidently dissimilar in nature. In order to simplify the study of the replacement of methoxyl groups, the investigation was extended to 1-mesitoyl-2-methoxynaphthalene (X) which has no second *ortho* position. This ketone reacted smoothly with phenylmagnesium bromide to yield 1-mesitoyl-2-phenylnaphthalene (XI, R = C_6H_5).



In a similar manner methyl, ethyl, *n*-butyl and α-naphthyl groups were introduced by use of the appropriate Grignard reagents. The yields varied from 56 to 80%.

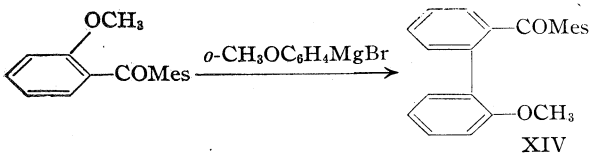
An attempt to replace a methoxyl group in a meta position was unsuccessful. 3-Methoxybenzoylmesitylene (XII) reacted with phenylmagnesium bromide to yield a methoxy compound, which probably has the structure represented by XIII.



(1) Fuson, Armstrong and Speck, *J. Org. Chem.*, **7**, 297 (1942).
(2) Fuson, Bottorff and Speck, THIS JOURNAL, **64**, 1450 (1942).

This is in contrast to the action of phenylmagnesium bromide on V, the ortho isomer of XII, to produce *o*-phenylbenzoylmesitylene (VI).

The new reaction served to establish the structure of 2-(2-methoxyphenyl)-benzoylmesitylene (XIV) reported previously.[2] It was found possible to obtain it by condensing 2-methoxybenzoylmesitylene with *o*-methoxyphenylmagnesium bromide.



XIV

The new method for introducing alkyl and aryl radicals into an aromatic ring appears to depend on 1,4 addition of the Grignard reagent followed by the elimination of the elements of methanol. The ether is a vinylog of methyl mesitoate and would, therefore, be expected to react with the Grignard reagent in an analogous manner. This suggests also the alternate possibility that the replacement of the methoxyl group might be the result of simple metathesis.

Experimental[3]

1-Mesitoyl-2-methoxynaphthalene (X).—A solution of 76 g. of mesitoyl chloride in 90 cc. of carbon disulfide was added slowly to a mixture of 75 g. of β-naphthyl methyl ether, 63 g. of aluminum chloride and 150 cc. of carbon disulfide. The mixture was stirred at room temperature for about twelve hours and then treated with an ice–hydrochloric acid mixture. The organic layer was separated and washed with dilute sodium hydroxide solution and water. The solvent was removed by evaporation, and the solid product, 1-mesitoyl-2-methoxynaphthalene, was recrystallized from ethanol. The yield of 1-mesitoyl-2-methoxynaphthalene was 65 g. The ketone crystallized from alcohol in yellow plates; m. p. 109–110°.

Anal. Calcd. for $C_{21}H_{21}O_2$: C, 82.57; H, 6.95. Found: C, 82.97; H, 6.49.

2-Methoxy-5-methylbenzoylmesitylene (I).—This compound was prepared by the Friedel–Crafts method in a manner similar to the foregoing. From 36.6 g. of 4-methylanisole and 54.6 g. of mesitoyl chloride was obtained 54 g. of the methoxy ketone. It crystallized from ethanol as light green needles; m. p. 103°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.55; H, 7.52. Found: C, 80.63; H, 7.44.

***m*-Methoxybenzoylmesitylene.**—This ketone was prepared from *m*-methoxybenzoyl chloride and mesitylene by the Friedel–Crafts method. The yield was 58% of the theoretical. The compound separated from ethanol as colorless crystals; m. p. 76°.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.29; H, 7.10. Found: C, 80.15; H, 7.36.

***o*-Methoxybenzoylmesitylene (V).**—The Grignard reagent prepared from 14 g. of magnesium and 85 g. of *o*-bromoanisole in 250 cc. of dry ether was added slowly, with stirring, to a solution of 72 g. of mesitoyl chloride in 200 cc. of dry ether. Heat was generated and a white precipitate formed. The mixture became semi-solid when all the reagent had been added. It was decomposed with dilute acid and washed with successive portions of water, dilute sodium hydroxide, and more water. The solvent was removed by evaporation and the residue crystallized from alcohol. The yield was 30 g. of *o*-methoxybenzoylmesitylene, which separated from ethanol in light yellow-green crystals; m. p. 112–113°.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.29; H, 7.10. Found: C, 80.15; H, 7.23.

Action of Grignard Reagents on Mesityl *o*-Methoxyaryl Ketones.—The experimental procedures for the reactions are very similar and can be indicated by a detailed description of two representative procedures.

2-Methoxy-5-methylbenzoylmesitylene and Phenylmagnesium Bromide.—A solution of 13.4 g. of 2-methoxy-5-methylbenzoylmesitylene in 60 cc. of dry benzene was added slowly to the reagent prepared from 3 g. of magnesium and 16.0 g. of bromobenzene in 30 cc. of dry ether and the mixture was heated under reflux for eight hours. The temperature remained at about 60°. The color of the solution changed successively to green, deep blue and, finally, dark red. The reaction mixture was treated with cold dilute hydrochloric acid. The organic layer was washed with dilute acid and water and the solvent removed by evaporation. The viscous red oil was distilled under reduced pressure. About 3.5 g. of a solid was isolated from a fraction of the distillate. This substance crystallized from alcohol in colorless needles. It had the composition of 2,6-diphenyl-3-methylbenzoylmesitylene (IV).

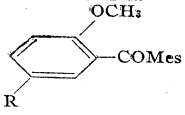
Table I lists this and five other condensations that were carried out in a similar manner with 2-methoxybenzoylmesitylene and 2-methoxy-5-methylbenzoylmesitylene. Yields, melting points and analytical data are given for the products.

1-Mesitoyl-2-methoxynaphthalene and Ethylmagnesium Bromide.—A solution of 7.6 g. of 1-mesitoyl-2-methoxynaphthalene in 25 cc. of dry ether was added over a period of ten minutes to the reagent prepared from 1.2 g. of magnesium and 4.2 g. of ethyl bromide in 30 cc. of dry ether and 20 cc. of dry benzene. The stirring was continued for an additional fifteen minutes. The color of the reaction mixture became pale green and later changed to orange-red. A large amount of a white precipitate formed. The mixture was treated with an ice–hydrochloric acid mixture and the organic layer washed with water. The solvent was removed by evaporation and the solid residue taken up with alcohol and allowed to crystallize. A yield of 6 g. of 1-mesitoyl-2-ethylnaphthalene was obtained. This substance separated from aqueous alcohol in colorless crystals.

This and four other condensations are shown in Table II. Melting points, yields and analytical data are given for the products.

(3) Micronalyses by Miss Margaret McCarthy and Miss Theta Spoor.

TABLE I

Reactants: R in formula  Grignard reagent	Temp. of reaction, °C.	Product[a]: Substituted benzoylmesitylene	M. p., °C.	Yield, %	Analyses, %: Calcd. C	Calcd. H	Found C	Found H
H C_6H_5MgBr	30	2-Phenyl-[1]	89	35	...	..	...	..
H C_6H_5MgBr	60	2,6-Diphenyl-[b]	162	20	89.32	6.43	89.74	6.44
H o-$CH_3OC_6H_4MgBr$	60	2-(2-Methoxyphenyl)-[2]	94	47	...	..	...	..
CH_3 C_6H_5MgBr	30	2-Phenyl-5-methyl-	73	18	87.84	7.07	87.82	7.20
CH_3 C_6H_5MgBr	60	2,6-Diphenyl-5-methyl-	131	20	89.18	6.71	89.50	6.87
CH_3 C_2H_5MgBr	30	2-Ethyl-5-methyl-	58	28	85.65	8.34	85.77	7.93

[a] The products were purified by recrystallization from ethanol. [b] This compound was obtained in 2.5% yield by the action of phenylmagnesium bromide on *o*-bromobenzoylmesitylene. It was also formed in traces by the condensation of phenylmagnesium bromide with 2-phenylbenzoylmesitylene.

TABLE II

REACTIONS OF 1-MESITOYL-2-METHOXYNAPHTHALENE

Grignard reagent	Temp. of the reaction, °C.	Product: Substituted 1-mesitoyl-naphthalene	M. p., °C.	Yield, %	Analyses, %: Calcd. C	Calcd. H	Found C	Found H
C_6H_5MgBr	60	2-Phenyl-[a]	136	59	89.09	6.34	88.64	6.35
α-$C_{10}H_7MgBr$	30	2-α-Naphthyl-[2,b]	181	76				
CH_3MgI	30	2-Methyl-[a,c]	67	56	87.47	7.01	87.56	7.17
C_2H_5MgBr	30	2-Ethyl-[a]	90	80	87.36	7.34	87.47	7.21
n-C_4H_9MgBr	30	2-n-Butyl-[a]	73	55	87.22	7.93	86.96	7.79

[a] Recrystallized from ethanol. [b] Recrystallized from a mixture of benzene and ethanol. [c] 1-Mesitoyl-2-methylnaphthalene was prepared also from 2-methyl-1-naphthoyl chloride and mesitylene by the Friedel–Crafts method and by the condensation of 2-methyl-1-naphthoyl chloride with mesitylmagnesium bromide. These syntheses were carried out by Mr. B. C. McKusick.

Action of Phenylmagnesium Bromide on *m*-Methoxybenzoylmesitylene.—A solution of 6.4 g. of *m*-methoxybenzoylmesitylene in 50 cc. of dry benzene was added to a solution of Grignard reagent prepared from 1.5 g. of magnesium, 8.0 g. of bromobenzene and 25 cc. of dry ether. The mixture was heated for eight hours under reflux, during which time it developed a red-brown color. Decomposition in the usual manner and distillation of the product yielded 0.5 g. of a solid that, after recrystallization from petroleum ether (b. p. 60–120°), melted at 194–195° (cor.). It was probably 2-phenyl-5-methoxybenzoylmesitylene.

Anal. Calcd. for $C_{23}H_{22}O_2$: C, 83.59; H, 6.72. Found: C, 83.59; H, 7.02.

Summary

It has been found that when 2-methoxyaryl mesityl ketones are treated with a Grignard reagent the methoxyl group is smoothly replaced by the hydrocarbon radical of the Grignard reagent. The reaction occurs with either alkyl or aryl Grignard reagents.

URBANA, ILLINOIS RECEIVED JUNE 29, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE STATE COLLEGE OF WASHINGTON]

The Bromination of 4-Phenylphenyl Chloroacetate

BY STEWART E. HAZLET, LEE C. HENSLEY AND HERMAN JASS

Earlier work[1] on the bromination of 4-phenylphenyl acetate and benzoate in the presence of iron as a catalyst showed that the acetyloxy radical caused 2-orientation while the larger benzoyloxy group promoted 4′-orientation in the biphenyl nucleus. A study has now been made of the corresponding ester of chloroacetic acid in order to see whether the spatial or other possible influence of this intermediate-sized radical were large enough to inhibit 2-orientation. The results in carbon tetrachloride and 1,1,2-trichloroethane show that the chloroacetyloxy group had a steric effect, *i. e.*, caused the bromine to enter the 4′-position. Abnormal results were found, however, when the reaction was carried out in acetic acid.

Experimental Part

4-Phenylphenyl Chloroacetate.—Seventy-eight grams of 4-phenylphenol was dissolved in a solution containing 63 ml. of pyridine and 126 ml. of 1,4-dioxane; the solution was cooled to 5°, and 52 ml. of chloroacetyl chloride was added in small portions. The mixture was allowed to stand overnight, and it was then gradually warmed to 115° and heated at that temperature for three and one-half hours. Again it was allowed to stand overnight at room temperature. The ester was extracted from the reaction mixture with three 50-ml. portions of boiling benzene. The combined extracts were washed with water, with 10% hydrochloric acid and 5% sodium hydroxide solutions, and finally with water, and then dried with anhydrous sodium sulfate in the presence of Norite. A yield of 82.8 g. (73.2%) was obtained after removal of the benzene by distillation. After two recrystallizations from ethanol, the product, colorless needles, melted at 116–117°. The compound was also purified by distillation; b. p. 185° (3 mm.). The melting point of the distillate was 116–117°.

Anal. Calcd. for $C_{14}H_{11}O_2Cl$: Cl, 14.4. Found: Cl, 14.3.

4-Phenylphenyl Bromoacetate.—This compound was prepared in 75.7% yield by a method essentially the same as that used for the preparation of the analogous chloro compound. The product was purified by recrystallization from ethanol and by distillation; b. p. 185° (3 mm.) and m. p. 112–112.5°. It was in the form of colorless needles, almost identical with 4-phenylphenyl chloroacetate. It is interesting to note that this bromoacetate and the corresponding chloroacetate, when mixed, melt without depression.

Anal. Calcd. for $C_{14}H_{11}O_2Br$: Br, 27.5. Found: Br, 27.6.

Chloroacetates of Bromophenylphenols.—By treatment of the appropriate phenols with one and one-half to two equivalents of chloroacetyl chloride in the presence of a little more than enough dry pyridine to combine with all of the hydrogen chloride liberated and usually in the presence of 1,4-dioxane, the esters shown in Table I were obtained.

TABLE I

CHLOROACETATES OF THE BROMOPHENYLPHENOLS

Phenol used	Yield, %	Solvent	Crystal form, colorless	M. p., °C.	Formula	Analyses, % Cl + Br Calcd.	Found
2-Bromo-4-phenyl-[2]	46	Ligroin (70–90°)	Short, hexagonal prisms	60.5–62	$C_{14}H_{10}O_2ClBr$	35.5	35.5
2,6-Dibromo-4-phenyl-[2]	67.5	Ligroin (70–90°)	Needles	83 – 84	$C_{14}H_9O_2ClBr_2$	48.3	48.3
4-(4-Bromophenyl)-[3]	45.5	Ethanol	Platelets	140 –141.5	$C_{14}H_{10}O_2ClBr$	35.5	35.5

Bromination of 4-Phenylphenyl Chloroacetate in Glacial Acetic Acid ("Analytical Reagent").—(A) Fifteen grams of 4-phenylphenyl chloroacetate was dissolved in 110 ml. of glacial acetic acid ("analytical reagent"). The solution was heated to 100°, a trace of iron powder was added, and 4.1 ml. of bromine dissolved in 25 ml. of glacial acetic acid was introduced dropwise over a period of thirty minutes. Mechanical stirring, which had been provided, was continued for six hours while the mixture was heated at 118° (±2°). After standing overnight at room temperature, the dark red reaction mixture was poured into 600 ml. of water, and extraction with three 70-ml. portions of benzene followed. The combined benzene extracts were washed with 5% sodium hydroxide solution and water and dried with anhydrous sodium sulfate in the presence of Norite; the material in this solution constituted *Fraction A-I*. The alkaline solution, mentioned above, was acidified and extracted with benzene—*Fraction A-II*.

(B) A second bromination was carried out in the same manner as described above, but the reaction mixture was not poured into water, and the major portion of the acetic acid was removed by distillation under reduced pressure. The residue was dissolved in ether, and the solution was shaken with solid sodium bisulfite and allowed to stand overnight with this reagent in the presence of Norite. After filtering, the ether was removed by distillation. The

(1) For the last paper on substitutions in esters containing diphenyl groups see Hazlet and Kornberg, THIS JOURNAL, **63**, 1890 (1941).

(2) Hazlet, Alliger and Tiede, *ibid.*, **61**, 1447 (1939).

(3) Bell and Robinson, *J. Chem. Soc.*, 1127 (1927); Hazlet, THIS JOURNAL, **59**, 1087 (1937).

residue was next distilled at low pressure. *Fraction B-I* distilled at 80–82° (5 mm.); *Fraction B-II* was collected at 137° (2 mm.); no other material distilled at this pressure up to 160° where the distillation was stopped.

The compounds isolated from these various fractions are represented below in Table II; only very small amounts of purified products were obtained.

TABLE II

Fraction	Compound	M. p., °C.[a]
A-I	4-Phenylphenyl chloroacetate	111.5–112.5
A-II[b]	4-Phenylphenol	154 –158
	2,6-Dibromo-4-phenylphenol	85 – 86
B-I	Chloroacetic acid	45 – 48
B-II	4-Phenylphenyl acetate	83 – 85

[a] Identification by means of a mixed melting point determination with an authentic sample was made in each case. [b] Separated by fractional crystallization.

Bromination of 4-Phenylphenyl Chloroacetate in Specially Treated Glacial Acetic Acid.—Ten grams of 4-phenylphenyl chloroacetate was dissolved in 30 ml. of acetic acid which had been freshly distilled from phosphorus pentoxide. A trace of iron powder and then 3.3 ml. of bromine were added. The reaction mixture was stirred and heated at 115–120° for ten hours. The acetic acid was removed by distillation at reduced pressure, and the residue solidified on cooling. After one crystallization from 70–90° ligroin, the product was obtained as colorless, granular crystals; 8.25 g. (70% yield). Ethanol was used for recrystallizations, and colorless needles resulted; m. p. 110–111.5°. Qualitative analysis (sodium fusion method) gave a test for bromine.

Anal. Calcd. for $C_{14}H_{11}O_2Br$: Br, 27.5. Found: Br, 27.5.

When the product was mixed with 4-phenylphenyl bromoacetate, a melting point of 111–112.5° was observed.

Hydrolysis of 4-Phenylphenyl Bromoacetate.—To further prove the identity of the material assumed to be 4-phenylphenyl bromoacetate, a sample of the product obtained by the bromination of 4-phenylphenyl chloroacetate in specially treated glacial acetic acid was hydrolyzed. When the phenol which was obtained (m. p. 159–161°) was mixed with a carefully purified sample of 4-phenylphenol there was no softening below 161°, and the mixture melted between 161.5 and 163°. Thus its identity as 4-phenylphenol was established.

Bromination of 4-Phenylphenyl Chloroacetate in Carbon Tetrachloride.—Four and eight-tenths grams of the chloroacetate was dissolved in carbon tetrachloride, a trace of powdered iron was added, the mixture was heated to 75°, and 1.2 ml. of bromine was added dropwise with stirring. After the mixture had been heated for four hours at 70 to 80°, it was poured into water and extracted first with ether and then with chloroform. From the ether solution there was obtained 0.8 g. of product; m. p. 139–141°. The chloroform extract yielded 0.8 g. of product; m. p. 139.5–141.5°. The total yield was 1.6 g. (26%). Because mixtures of the two samples melted without depression, they were combined and recrystallized from ethanol; needles were obtained, m. p. 141–142.8°. This compound was shown to be 4-(4-bromophenyl)-phenyl chloroacetate; a mixture of it and 4-(4-bromophenyl)-phenyl chloroacetate, prepared as described in a previous paragraph, melted without depression.

Hydrolysis of 4-(4-Bromophenyl)-phenyl Chloroacetate.—A small amount of the reaction product obtained by the bromination of 4-phenylphenyl chloroacetate in carbon tetrachloride solution was hydrolyzed, and the crude phenolic product was dissolved in pyridine and converted to 4-(4-bromophenyl)-phenyl benzoate as described previously.[2] The product, after crystallization from methanol, melted at 191° and there was no depression when mixed with a known sample of the benzoate.

Bromination of 4-Phenylphenyl Chloroacetate in 1,1,2-Trichloroethane.—The procedure for this bromination was the same as that carried out in carbon tetrachloride as described above except that after the reaction had been carried out in 1,1,2-trichloroethane, the mixture was washed with water, and then the solvent was removed by distillation. The yield of crude product was nearly quantitative but, after recrystallizations from ethanol, the needles which melted at 141–142.5° represented only a 60% yield of 4-(4-bromophenyl)-phenyl chloroacetate.

Summary

1. The bromination of 4-phenylphenyl chloroacetate in different solvents led to a variety of products: (a) glacial acetic acid ("analytical reagent")—4-phenylphenyl chloroacetate, 4-phenylphenyl acetate, 2,6-dibromo-4-phenylphenol, 4-phenylphenol and chloroacetic acid; (b) specially treated glacial acetic acid—4-phenylphenyl bromoacetate; (c) carbon tetrachloride—4-(4-bromophenyl)-phenyl chloroacetate; (d) 1,1,2 - trichloroethane—4 - (4 - bromophenyl) - phenyl chloroacetate.

2. The behavior in carbon tetrachloride and 1,1,2-trichloroethane in part confirms the earlier suggestion that steric effects may determine the positions taken by substituents entering an ester molecule of the type represented.

3. Several related compounds which had not been reported previously have been prepared and some of their properties reported.

PULLMAN, WASHINGTON RECEIVED JULY 18 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Physiologically Active Phenethylamines Containing a Tertiary Hydroxyl

BY C. M. SUTER AND ARTHUR W. WESTON[1]

It has been found that the introduction of an alkyl group into the *beta* position of phenethylamines[2] or α-methylphenethylamines[3] lowers the toxicity without appreciably affecting the physiological action. The extension of this study to include the effect of alkylating the carbon atom bearing the hydroxyl in amines of the type $C_6H_5CH(OH)CH(R)NHR$ (R is H or CH_3) seemed of interest.

Despite the great number of ephedrine derivatives that have been prepared, only one reference[4] to the desired alkylephedrines, $C_6H_5C(OH)(R)CH(CH_3)NHCH_3$ (R is CH_3 or C_2H_5), was found. A report on the vasoconstricting action of these compounds was also included. Similarly, only the methyl derivatives of *nor*ephedrine, $C_6H_5C(OH)(CH_3)CH(CH_3)NH_2$,[5] and of its isomer $C_6H_5C(OH)(CH_3)CH_2NHCH_3$ (I)[6,7] have been described. Of the other possible series of amines, $C_6H_5C(OH)RCH_2NH_2$(II), the methyl,[4,8,9,10] ethyl,[4,10] butyl,[11] and cyclohexyl[11] compounds have been prepared and some preliminary pharmacological data reported.[4,11] More recently the 2,5-dimethoxy derivatives of I and II[12] have been synthesized.

In the present investigation representatives of three series of amines containing a tertiary hydroxyl in which the *beta* group is alkyl, alkenyl, or cycloalkyl have been prepared and some preliminary data on their toxicity and other pharmacological properties obtained.[13] All these compounds were synthesized by the reaction of a suitable Grignard reagent upon the aminoketone hydrochlorides. This method of preparing hydroxyamines has been used by other investigators.[4,5,11,12,14] Although some of the compounds contained two asymmetric carbon atoms only one racemic modification was formed. This behavior also occurs in the reaction between amino ketones and aryl Grignard reagents[15] and has been attributed to the effect of the adjacent carbon atom bearing the amino group.

$$C_6H_5COCH(R)NHR'\cdot HCl \xrightarrow[\text{then } H_2O]{R''MgX} C_6H_5C(OH)(R'')CH(R)NHR'$$

The hydroxyamines were not isolated but were converted directly into their hydrochlorides and purified by crystallization. The yields were very good. The reaction of *t*-butylmagnesium chloride upon α-methylaminopropiophenone gave a mixture of amines whose hydrochlorides could not be separated readily. Apparently both reduction and addition had taken place.[16]

The toxicities[13] of the amine hydrochlorides were determined on white mice by the method outlined earlier.[17] The results are listed in the last three columns of Table I. For comparison purposes 2-amino-1-phenyl-1-propanol and ephedrine are included.

Preliminary data obtained from investigating the effect of these compounds on rabbits, dogs and guinea pigs indicate that in general their pressor activity is similar to that of ephedrine and phenylpropanolamine although the effect may be more transient. Tachyphylaxis was noted in all tests with these compounds. In accordance with the previous observations[2,3] the presence of an alkyl group *beta* to the amino group greatly reduces the toxicity without apparently impairing the activity.

Three of the *nor*ephedrine derivatives, the *n*-butyl, *n*-hexyl, and cyclohexyl compounds, were examined for surface anesthesia on the rabbit's cornea.[18] Some anesthesia was produced by the *n*-butyl and cyclohexyl compounds in 3% solution but this was accompanied by a marked irritation which was particularly pronounced in the *n*-butyl

(1) Sharp and Dohme Research Associate, 1938–1940.
(2) Weston, Ruddy and Suter, unpublished work.
(3) Suter and Weston, THIS JOURNAL, **64**, 533 (1942).
(4) Lévy and Sergent-Montsaratt, *Paris Médical*, **21**, 148 (1931).
(5) Mills and Grigor, *J. Chem. Soc.*, 1568 (1934).
(6) Tiffeneau, *Ann. chim. phys.*, [8] **10**, 145 (1907).
(7) Fourneau, *J. pharm. chim.*, [6] **20**, 481 (1904).
(8) Fourneau, *ibid.*, [7] **2**, 337 (1909).
(9) Jacobs and Heidelberger, *J. Biol. Chem.*, **21**, 436 (1915).
(10) Tiffeneau and Cahnmann, *Bull. soc. chim.*, [5] **2**, 1876 (1935).
(11) Kanao and Shinozuka, *J. Pharm. Soc. Japan*, **50**, 1152 (1930); *C. A.*, **25**, 1636 (1931).
(12) Baltzly and Buck, THIS JOURNAL, **62**, 161 (1940).
(13) We are grateful to Dr. Paul H. Mattis and Mr. Albert R. Latvin of Sharp and Dohme for permission to include a summary of their experiments on the toxicity and pressor activity of these compounds.
(14) Tiffeneau, Oryekhov and Roger, *Bull. soc. chim.*, [4] **49**, 1757 (1931).
(15) Tiffeneau, Lévy and Ditz, *ibid.*, [5] **2**, 1848 (1935).
(16) Kharasch and Weinhouse, *J. Org. Chem.*, **1**, 209 (1936).
(17) Suter and Weston, THIS JOURNAL, **63**, 602 (1941).
(18) We are grateful to Mr. Harry Robinson of Sharp and Dohme for a report of these tests.

TABLE I

PROPERTIES OF AMINE HYDROCHLORIDES

Amine	Yield, %	M. p., °C. (cor.)	Solvent	Formula	Cl, % Calcd.	Cl, % Found[h]	Toxicity LD_0	Toxicity LD_{50}	Toxicity LD_{100}
$C_6H_5C(OH)(C_2H_5)CH_2NH_2$[a]	73	180 –181	Dioxane	$C_{10}H_{16}ONCl$	17.59	17.66	400	630	900
$C_6H_5C(OH)(C_4H_9\text{-}n)CH_2NH_2$[b]	78	151 –152	Dioxane	$C_{12}H_{20}ONCl$	15.44	15.49	200	310	600
$C_6H_5C(OH)(CH_3)CH(NH_2)CH_3$[c]	63	239 –239.5[d]	Abs. alc.	$C_{10}H_{16}ONCl$	17.59	17.69	600	850	1100
$C_6H_5C(OH)(C_2H_5)CH(NH_2)CH_3$	93	220.5–222[d]	Acetone–alc.	$C_{11}H_{18}ONCl$	16.44	16.47	200	350	450
$C_6H_5C(OH)(C_4H_9\text{-}n)CH(NH_2)CH_3$	85	213 –216[d]	Bz–pet. ether	$C_{13}H_{22}ONCl$	14.55	14.53	200	315	450
$C_6H_5C(OH)(C_6H_{13}\text{-}n)CH(NH_2)CH_3$	81	193 –200[d]	EtOAc–pet. ether	$C_{15}H_{26}ONCl$	13.05	12.94	300	375	450
$C_6H_5C(OH)(C_6H_{11}\text{-cyclo})CH(NH_2)CH_3$	57	261 –263[d,e]	Alc.–dioxane	$C_{15}H_{24}ONCl$	13.14	13.11	200	275	350
$C_6H_5C(OH)(CH_3)CH(NHCH_3)CH_3$[f]	75	234 –235	Abs. alc.	$C_{11}H_{18}ONCl$	16.44	16.44	900	1100	1400
$C_6H_5C(OH)(C_2H_5)CH(NHCH_3)CH_3$[g]	95	197.5–198.5[d]	Abs. alc.–ether	$C_{12}H_{20}ONCl$	15.44	15.44	400	525	600
$C_6H_5C(OH)(C_3H_7\text{-}n)CH(NHCH_3)CH_3$	91	182.5–183.5[d]	Chloroform	$C_{13}H_{22}ONCl$	14.55	14.25	200	310	400
$C_6H_5C(OH)(C_4H_9\text{-}n)CH(NHCH_3)CH_3$	88	149 –150	Acetone	$C_{14}H_{24}ONCl$	13.75	13.75	200	325	500
$C_6H_5C(OH)(C_3H_5)CH(NHCH_3)CH_3$[i]	90	166.5–167.8	Abs. alc.–ether	$C_{13}H_{20}ONCl$	14.67	14.88	300	550	700
$C_6H_5CHOHCHNH_2CH_3$							100	490	900
$C_6H_5CHOHCH(NHCH_3)CH_3$							200	390	700

[a] Previously prepared by reduction of oxime, m. p. 183.5° (cor.) ref. 10; ref. 4, m. p. 184–186°. [b] Ref. 11, m. p. 151–152°. [c] Ref. 5, m. p. 244°. [d] Melted with decomposition. [e] This material forms a dihydrate which retained water of crystallization even after two hours at 100° and 40 mm. After drying at 140° for nine hours the solvent was lost but was regained when exposed to the air for a day. *Anal.* Calcd. for $C_{15}H_{24}ONCl\cdot 2H_2O$: H_2O, 11.78. Found: H_2O, 12.46. [f] Ref. 4, m. p. 245–248°. [g] Ref. 4, m. p. 192°. [h] Since the agreement between our m. p. values and those given in the literature was not always entirely satisfactory, analyses for previously known compounds are included. The disagreement probably occurs because the "melting points" are decomposition temperatures and hence vary with the rate of heating. [i] The allylmagnesium bromide was prepared according to the procedure of Gilman and McGlumphy, *Bull. soc. chim.*, **43**, 1322 (1928).

and *n*-hexyl compounds and was evident even in 1% solutions. Because of this undesirable effect only preliminary tests were made.

Experimental

Aminoketone Hydrochlorides.—The ω-aminoacetophenone hydrochloride was prepared by hydrolysis of the product obtained from phenacyl bromide and hexamethylenetetramine.[19] α-Aminopropiophenone hydrochloride was obtained by reduction of the corresponding isonitroso compound[20] with stannous chloride[21] while the N-methyl derivative was obtained by the action of methylamine upon α-bromopropiophenone.[22]

Reaction of Aminoketone Hydrochlorides with Grignard Reagents.—The preparation of β-ethyl*nor*ephedrine is described as a typical example. A Grignard reagent was prepared from 5.3 g. (0.24 mole) of magnesium and a slight excess of ethyl bromide so that no unused magnesium remained. To the ether solution was added at 0° with stirring 10 g. (0.054 mole) of α-aminopropiophenone hydrochloride. Stirring was continued for several hours and the mixture was allowed to stand overnight.[23] A two-layer system formed. After hydrolysis with ice and dilute sulfuric acid the ether layer was removed and evaporated to dryness but left no residue. The aqueous layer was made alkaline, the amine extracted with ether, the ether layer dried over sodium sulfate and made acid with hydrogen chloride gas. The weight of air-dried material, m. p. 210–212° (dec.), was 10.8 g. or 93% of the theoretical amount. Crystallization from an acetone–alcohol mixture gave 8.8 g., m. p. 219–221° (dec.). Further crystallization raised the m. p. only slightly to 220.5–222° (dec.). Essential data for this and other similar compounds are listed in Table I. All melting points are corrected. The yields given are for the crude products.

(19) Slotta and Heller, *Ber.*, **63B**, 1027 (1930); Mannich and Hahn, *ibid.*, **44**, 1548 (1911).

(20) Hartung and Crossley, *Org. Syn.*, **16**, 44 (1936).

(21) Behr-Bregawski, *Ber.*, **30**, 1521 (1897).

(22) Hyde, Browning and Adams, THIS JOURNAL, **50**, 2287 (1928).

(23) This was unnecessary as there was little evidence of reaction after a few hours of stirring. In the case of the higher alkyl Grignards, however, it was sometimes necessary to reflux the mixture as unreacted solid remained after the addition.

Summary

1. Twelve β-hydroxyphenethylamine derivatives in which the hydroxyl group is tertiary have been prepared by the action of aliphatic Grignard reagents upon aminoalkyl phenyl ketone hydrochlorides. Seven of the amines are new compounds.

2. Toxicity data of these amines toward white mice indicate that they are less toxic than the corresponding hydroxy amines having no *beta* alkyl group.

3. A preliminary report on other pharmacological properties of these compounds has been made.

EVANSTON, ILLINOIS RECEIVED APRIL 11, 1942

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH, DIVISION OF ORGANIC CHEMISTRY]

On the Epimeric 7-Hydroxycholesterols

BY O. WINTERSTEINER AND WILLIAM L. RUIGH

It has been shown recently that 7(α)- and 7(β)-hydroxycholesterol as well as the corresponding ketone, 7-ketocholesterol, are formed from cholesterol by autoxidation in aqueous colloidal solution.[1,2] In connection with studies on the mechanism of this reaction it seemed of interest to determine whether the reduction of the ketone acetate with aluminum isopropylate, which is the customary method for preparing 7(α)-hydroxycholesterol,[3] also yields the 7(β)-epimer, as it does in the case of 7-ketoepicholesterol.[4] 7(β)-Hydroxycholesterol has been so far accessible only by permanganate oxidation of cholesteryl acid phthalate,[5] a method which in our hands has given a yield of only 10% or less.

At first we searched for the 7(β)-diol in the resinous mother liquor material remaining after separation of the crystalline portion of the hydrolyzed reduction product which according to Windaus, *et al.*,[3] should be essentially 7(α)-hydroxycholesterol. We were unable to isolate the desired compound from such fractions, which instead yielded two other substances to be described later. We therefore turned our attention to the crystalline fraction which is obtained by precipitating the ethereal solution of the crude hydrolyzed reduction product with petroleum ether. These crystalline products, with melting points at 165–174°, were consistently found to be levorotatory ($[\alpha]_D$ −11 to −16°), which was surprising in view of the fact that the dibenzoate and the 7-monobenzoate[6] of the 7(α)-diol have specific rotations of +104 and +94°, respectively. "7-Hydroxycholesterol," presumed to be the α-epimer, has so far been described only in a patent by Windaus and Schenk.[7] According to these authors it melts at about 178°, but the specific rotation was not given. We found that fractions rich in 7(β)-hydroxycholesterol could indeed be obtained from the crude crystalline preparations by using a comparatively large amount of hot methanol for recrystallization. Further purification yielded substantial quantities of the levorotatory 7(β)-diol. The identity of the compound was confirmed by the preparation of the dibenzoate.

Recrystallization of the crude diol mixture from ether or acetone yielded a mass of fine long needles, m. p. 174–176°, answering the description of Windaus and Schenk[7] for 7(α)-hydroxycholesterol, but retaining the levorotation of the starting preparation. Further recrystallization from small volumes of methanol did not change these properties. On benzoylation of this material 7(α)-hydroxycholesterol dibenzoate was obtained as the sole product in 67% yield, proving that the mixture consisted preponderantly of the 7(α)-epimer. There remained to be re-investigated the claim of Windaus and Schenk that hydrolysis of the dibenzoate yields again the substance melting at 178°. Our hydrolysis product was a gelatinous mass with a specific rotation of +4.6°, which proved to be much more difficult to crystallize than the epimeric mixture. It eventually yielded a small amount of needles melting at 178.5° and possessing a specific rotation of +7.2°. Benzoylation of the amorphous product resulted in the formation of the dibenzoate in almost theoretical yield. Acetylation in pyridine yielded quantitatively the higher melting (m. p. 107°) of the two forms of the diacetate mentioned in the patent of Windaus and Schenk. We conclude that 7(α)-hydroxycholesterol is a slightly dextrorotatory substance which is much more soluble in organic solvents than the 7(β)-epimer and cannot be as readily obtained in crystalline form. The presence of small amounts of the 7(β)-epimer evidently improves its capacity to crystallize, probably due to the formation of mixed crystals. From the specific rotations it appears that the crude crystalline diol mixtures contain up to 20% of the 7(β)-epimer. In regard to the over-all yield of the latter compound from cholesterol the route *via* 7-ketocholesterol is inferior to the oxidative method of Barr, *et al.*; it is of practical value only if the α-epimer is also desired.

The differences between the specific rotations of 7(α)- and 7(β)-hydroxycholesterol (Δ = 98°), and especially of the corresponding dibenzoates

(1) Wintersteiner and Bergström, *J. Biol. Chem.*, **137**, 785 (1941).
(2) Bergström and Wintersteiner, *ibid.*, **141**, 597 (1941).
(3) Windaus, Lettre and Schenk, *Ann.*, **520**, 98 (1935).
(4) Windaus and Naggatz, *ibid.*, **542**, 204 (1939).
(5) Barr, Heilbron, Parry and Spring, *J. Chem. Soc.*, 1437 (1936).
(6) Wintersteiner and Ruigh, THIS JOURNAL, **64**, 1177 (1942).
(7) Windaus and Schenk, U. S. Patent 2,098,985 (1937).

(Δ = 201°) and diacetates (Δ = 227°) are unusually large for epimers and indicate a marked deflection of valency angles of carbon atom 7 in one or both epimeric forms. It seemed of interest to determine whether this factor influences the speed of ester hydrolysis at C_7, relative to that at C_3, in the two epimeric dibenzoates. 7(α)-Benzoxycholesteryl benzoate on hydrolysis with cold methanolic sodium ethylate solution yields almost quantitatively the 7-monoester.[6]

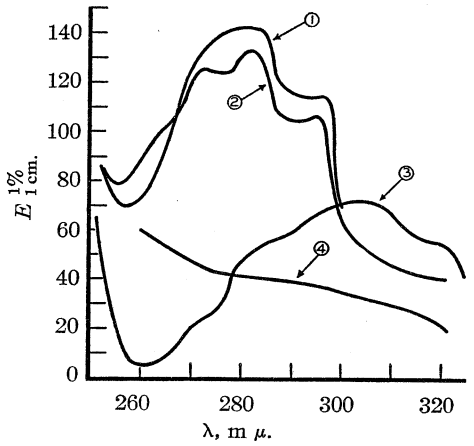


Fig. 1.—Absorption curves in ether solution of crude products formed from: ①, 7(α)-benzoxycholesterol, boiling dimethylaniline[6]; ②, 7(α)-benzoxycholesterol, pyrolysis[6]; ③, 7(β)-benzoxycholesterol, pyrolysis; ④, 7(β)-benzoxycholesterol, boiling dimethylaniline.

When the 7-epimeric dibenzoate was subjected to the same treatment, the result was similar in that a monobenzoate was the sole hydrolysis product. The method used for ascertaining the position of the benzoxy group in the 7(α)-monobenzoate, namely, conversion into 7-dehydrocholesterol, gave inconclusive results, but proof that the new monoester was likewise a 7-benzoate was adduced by reductive removal of the benzoxy group. Extending the observation of Barr, *et al.*,[5] that 7(β)-hydroxycholesterol on catalytic reduction yields cholestanol, we found that the dibenzoates of both 7(α)- and 7(β)-hydroxycholesterol are reduced under similar conditions to β-cholestanyl benzoate. When applied to the new monobenzoate the reaction yielded β-cholestanol, while from a mixed ester, the acid succinate-benzoate, β-cholestanyl acid succinate was obtained.

It is thus clear that stereochemical factors do not play a role in the relative inertness of the ester linkage at C_7 toward alkaline hydrolyzing agents. However, the ease with which benzoic acid can be cleaved from the two epimeric 7-monobenzoates, either by pyrolysis or by treatment with high-boiling amines, to form 7-dehydrocholesterol is definitely influenced by the configuration at C_7. This is illustrated in Fig. 1, which shows the absorption spectra of the crude products obtained by these reactions. The 7(α)-monobenzoate in both reactions yielded products containing 50% or more dehydrosterol, as measured by the extinction at 283 mμ.[6] In contrast, the 7(β)-monobenzoate on pyrolysis gave rise preferentially to a compound with a maximum at 305 mμ, which is probably identical with the cholestatriene obtained under similar conditions by Windaus and Naggatz[4] from 7(α)-benzoxyepicholesteryl benzoate and by Eckhardt[8] from 7(α)-hydroxycholesteryl benzoate. The reaction product obtained from the 7(β)-monobenzoate by boiling with dimethylaniline gave an uncharacteristic curve without any clearly differentiated maxima. Further fractionation with digitonin showed that a small amount of 7-dehydrocholesterol was present. We also found that by lowering the pressure during the pyrolysis from 1 to about 0.01 mm., some dehydrosterol was formed in addition to the entity absorbing at 305 mμ. Quite analogous results were obtained in both reactions with the two 7-epimeric dibenzoates. These findings justify the conclusion that 7(β)-hydroxycholesterol is greatly inferior to the 7(α)-epimer as a starting product for the preparation of 7-dehydrocholesterol.

Spectrographic examination of the non-crystallizable portion of the reduction product revealed the presence of two light-absorbing entities, with maxima around 240 and 280 mμ, respectively. The absorption at 240 mμ is not merely due to unchanged 7-ketocholesterol, since after treatment of the mixture with Girard's reagent it was found to be associated for the most part with the non-ketonic fraction. From one batch of reduced material a crystalline compound of the composition $(C_{27}H_{44})_2O$ was isolated, the spectrum of which exhibited a high, sharply defined maximum at 243 mμ. This substance was dextrorotatory ($[\alpha]_D$ +92°), and gave an intense Lifschütz color reaction. These properties are compatible with the structure either of a di-$\Delta^{4,6}$-cholestadienyl-3-ether or a di-$\Delta^{3,5}$-cholestadienyl-7-ether. A decision between these alternative structures cannot be made on the basis of the rotation rule which

(8) Eckhardt, *Ber.*, **71**, 461 (1938).

in general permits to distinguish between Δ^4- and Δ^5-compounds containing only one ethylenic bond.[9] $\Delta^{4,6}$-Cholestadiene[10] obeys this rule by being dextrorotatory, but $\Delta^{4,6}$-cholestadienol-3(β) and its esters are levorotatory.[11] On the other hand, in the yet undescribed $\Delta^{3,5}$-cholestadienol-7, and especially in its esters and ethers, the sign of rotation might well depend, as in the 7-hydroxycholesterols, on the configuration of C_7.

The dicholestadienyl ether is undoubtedly only an incidental by-product formed in small amounts, the isolation of which was facilitated by its comparative stability. We have spectroscopic and other evidence that the parent alcohol is likewise present among the reduction products, but repeated attempts to effect its isolation were unsuccessful.

The compound absorbing in the region around 280 mμ was not, as might have been supposed, $\Delta^{3,5}$-cholestadienone-7, but was identified as the epimeric $\Delta^{4,6}$-cholestadienone-3. The formation of the 3-ketone from 7-ketocholesteryl acetate by the action of aluminum isopropylate is obviously preceded by ester hydrolysis, which is known to occur under these conditions.[7] The mechanism of the subsequent oxidation at C_3 probably follows the same pattern as the dismutation of dehydroisoandrosterone to testosterone described by Oppenauer,[12] with the 7-keto group in the present case functioning as the hydrogen acceptor. Migration of the double bond from the 5–6 to the 4–5 position, followed by dehydration of the 7-hydroxy group, could then occur under the tendency to establish a triply conjugated system. Alternatively, the precursor may be 7(β)-hydroxycholesterol, which is capable of rearranging into Δ^6-cholestenediol-3(β),5[2]; the latter compound is known to yield $\Delta^{4,6}$-cholestadienone-3 on oxidation with acetone and aluminum phenolate.[13]

Experimental

7(β)-Hydroxycholesterol.—Twenty-five grams of 7-ketocholesteryl acetate was reduced with isopropyl alcohol (500 cc.) and aluminum isopropylate (43 g.) in the usual manner.[3] The mixture was poured into 3 liters of 2% aqueous potassium hydroxide solution, allowed to stand for two hours at room temperature, and extracted with ether. The washed and dried ether solution was evaporated to 75 cc. On addition of 300 cc. of pentane, a precipitate of fluffy needles formed on standing (7.8 g., $[\alpha]_D$ −15.5°, 1.80% in chloroform). Recrystallization from methanol (70 cc.) yielded 1.27 g. of material with an $[\alpha]_D$ −70.6°, 1.0% in chloroform. After three more crystallizations from methanol, 577 mg. of 7(β)-hydroxycholesterol, m. p. 184–185°, $[\alpha]_D$ −84° (0.99% in chloroform) was obtained. The melting point of a mixture with a preparation obtained by the procedure of Barr, *et al.*,[5] showed no depression.

The results obtained on another batch of reduced 7-ketocholesteryl acetate were similar. The crude crystalline diol mixtures (m. p. 173–174°, $[\alpha]_D$ −14.3°, 1.33% in chloroform) did not materially change its properties on recrystallization from acetone, or from a small volume of methanol. Recrystallization from a larger amount of the latter solvent yielded 7(β)-hydroxycholesterol, m. p. 177–178.5°, $[\alpha]^{23}_D$ −87.6° (0.96% in chloroform).[14] The preparation lost 3.4% of solvent on drying *in vacuo* at 100° for one hour.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.52; H, 11.52. Found: C, 80.74; H, 11.73.

One hundred milligrams was benzoylated with pyridine and benzoyl chloride. The resulting product melted at 151–152.5°. The melting point of a mixture with authentic 7(β)-benzoxycholesteryl benzoate, m. p. 151–152.5°[15] showed no depression ($[\alpha]^{23}_D$ −107.5° (0.66% in chloroform)).

Anal. Calcd. for $C_{41}H_{54}O_4$: C, 80.60; H, 8.92. Found: C, 80.94; H, 9.01.

7(α)-Hydroxycholesterol.—Five grams of 7(α)-benzoxycholesteryl benzoate was refluxed in 100 cc. of 5% methanolic potassium hydroxide solution for six hours. The hydrolysis product, recovered by ether extraction, was a white amorphous mass melting at 167–170°, $[\alpha]_D$ +4.6° (0.85% in chloroform). Five hundred milligrams was treated with various solvents, and finally a small amount of needles, m. p. 177–178.5°, was obtained from ether. On recrystallization from the same solvent, the melting point became less sharp (55 mg., m. p. 169–177°, $[\alpha]_D$ +7.2° (1.0% in chloroform)). 250 mg. of the amorphous preparation yielded on re-benzoylation 327 mg. of crude dibenzoate, m. p. 169.5–170.5° (85%). On acetylation in pyridine, a *diacetate* melting at 105–106° was obtained in theoretical yield; on recrystallization from ether–methanol the compound separated as blunt prisms, m. p. 106–107°, $[\alpha]^{27}_D$ +51.8° (1.1% in chloroform).

(9) Stavely and Bergmann, *J. Org. Chem.*, **1**, 575 (1937).

(10) Eck, Van Peursem and Hollingsworth, THIS JOURNAL, **61**, 171 (1939).

(11) Petrow, *J. Chem. Soc.*, 66 (1940); Spring and Swain, *ibid.*, 320 (1941).

(12) Oppenauer, *Acta Brevia Neerland. Physiol. Pharmacal, Microbiol.*, **7**, 176 (1937); *Rec. trav. chim.*, **56**, 137 (1937).

(13) Bergström and Wintersteiner, *J. Biol. Chem.*, **143**, 503 (1942).

(14) 7(β)-Hydroxycholesterol, m. p. 186° contains 1 mole of methanol of crystallization; the methanol-free form melts at 154–157° and forms mixed crystals of intermediate melting points and methanol content with the high-melting modification (*cf.* Wintersteiner and Ritzmann, *J. Biol. Chem.*, **136**, 697 (1940)). The specific rotation is, therefore, a better criterion of purity than the melting point, which may show erratic changes on recrystallization if the more stable low-melting modification is once present. The highest specific rotation observed for the methanol-containing form was −91.2° (*loc. cit.*). Barr, *et al.*, gave −86.4°, which is closer to the values found in the present work.

(15) The melting point of this preparation had been previously reported as 155–157° (Wintersteiner and Ritzmann, ref. 14). The higher value is incorrect and was traced to a standardized thermometer which had become defective.

Anal. Calcd. for $C_{31}H_{50}O_4$: C, 76.48; H, 10.36. Found: C, 76.29; H, 10.27.

7(β)-Benzoxycholesterol.—To one gram of 7(β)-benzoxycholesteryl benzoate in 20 cc. of benzene was added a solution of sodium methylate (0.66 g.) in absolute methanol (33 cc.). The mixture was allowed to stand at 25° for seventeen hours. The hydrolysis product was recovered by ether extraction. The oily ether residue was dissolved in a few cc. of warm ether. On standing in the refrigerator, the solution deposited crystals, the amount of which increased on addition of 30 cc. of pentane. Another crop was obtained from the mother liquor material by repetition of this process. Altogether 744 mg. (90%) of 7(β)-benzoxycholesterol was recovered in form of fine needles, which melted at 145–146°, $[\alpha]^{26}D$ −201° (1.04% in chloroform). It is not precipitated by digitonin in 90% ethanol, a behavior also shown by the 7(α)-monobenzoate.

Anal. Calcd. for $C_{34}H_{50}O_3$: C, 80.58; H, 9.95. Found: C, 80.15; H, 9.95.

The absorption spectrum in alcohol confirmed the presence of only one benzoxy group: $\epsilon_{231\ m\mu}$ = 12,500, $\epsilon_{272\ m\mu}$ = 705. 7(β)-Hydroxycholesterol dibenzoate, $\epsilon_{231\ m\mu}$ = 28,000, $\epsilon_{272\ m\mu}$ = 1480.

Benzoylation in pyridine yielded the diester, 7(β)-benzoxycholesteryl benzoate, m. p. 150–151.5°.

The monoester (101 mg.) dissolved in acid-free ethanol (15 cc.) was shaken with palladium black (51 mg.) in a hydrogen atmosphere. The hydrogen uptake was extremely slow, and shaking had to be continued for several days for completion of the reaction. After filtering and evaporation of the solvent the reaction product was taken up in ether, and the latter extracted with sodium carbonate solution, from which was recovered 17.6 mg. of benzoic acid, m. p. 121°. The material recovered from the ether phase was purified by means of digitonin. Decomposition of the digitonide (253 mg.) yielded a crystalline product which after two recrystallizations from ethanol melted at 139.5–140° and did not depress the melting point of authentic β-cholestanol, m. p. 140.5°. The acetate prepared from this material melted at 108.5–109.5°, as did a mixture with authentic β-cholestanyl acetate of the same melting point.

7(β)-Benzoxycholesteryl 3,5-Dinitrobenzoate.—The mixed ester was prepared in the usual manner. It crystallized from benzene–alcohol as needles, m. p. 178.5–179.5°; $[\alpha]^{23}D$ −88.2° (1.0% in chloroform).

Anal. Calcd. for $C_{41}H_{52}O_8N_2$: C, 70.26; H, 7.48; N, 4.00. Found: C, 70.59; H, 7.84; N, 4.24.

7(β)-Benzoxycholesteryl Acid Succinate.—A solution of 70 mg. of the monoester and 300 mg. of succinic anhydride in 3 cc. of pyridine was refluxed for two hours. The acid ester was recovered in the usual way by extraction from ether with potassium carbonate solution, acidification and transfer into ether (73.4 mg.). Recrystallization of the ether residue from methanol yielded small needles melting at 150–151°.

Anal. Calcd. for $C_{38}H_{54}O_6$: C, 75.20; H, 8.97. Found: C, 75.20; H, 8.98.

Ninety-one mg. of 7(β)-benzoxycholesteryl acid succinate was hydrogenated for seventeen hours in a mixture of ethanol (5 cc.) and glacial acetic (3 cc.) with palladium black (45 mg.). The crystalline portion of the reaction product (32 mg.) was recrystallized once from methanol and formed plates melting at 165–167°, $[\alpha]^{26}D$ +13.0° (0.61% in chloroform). An authentic sample of β-cholestanyl acid succinate of the same melting point had an $[\alpha]^{26}D$ of +13.2°. The melting point of the mixture showed no depression.

Dicholestadienyl Ether.—The mother liquor of the crystalline diol mixture from the reduction of 40 g. of 7-ketocholesterol was concentrated to a sirup, which was acetylated in pyridine and chromatographed in pentane solution according to the scheme described in a previous paper.[2] About 5 g. of material passed into the first washings with pentane. When dissolved in a small volume of warm benzene–ethanol 1:2 it deposited a crystalline product (600 mg., m. p. 150–160°). Several crystallizations from ethyl acetate yielded rosets of small needles melting at 158–160°, $[\alpha]D$ +90.6° (0.90% in chloroform). The compound is readily soluble in ether, benzene and hexane, sparingly soluble in ethyl acetate, and practically insoluble in methanol and ethanol. It remained unchanged on boiling in 5% methanolic potassium hydroxide solution, and was not adsorbed from hexane solution by aluminum oxide. Its chromogenic potency in the Lifschütz reaction is about equal to that of 7(β)-hydroxycholesterol.

Anal. Calcd. for $C_{54}H_{88}O$: C, 86.10; H, 11.78; mol. wt., 752.7. Found: C, 86.29, 86.25; H, 11.58, 11.84; mol. wt. (Rast), 663.

The absorption spectrum of the compound shows a high and very narrow band (indicative of the presence of two identical chromophoric groups) at 243 mμ, ε = 54,000 (in ether). The curve shows an inflection at about 249 mμ (ε = 48,000). These properties are in accord with the spectrographic data for $\Delta^{4,6}$-cholestadienyl-3-acetate, $\epsilon_{239\ m\mu}$ = 26,000[11] and of $\Delta^{4,6,22}$-ergostatrienyl acetate, $\epsilon_{240\ m\mu}$ = 27,000.[16]

On hydrogenation in ethyl acetate solution with platinum oxide as catalyst, 2 moles of hydrogen was consumed per sterol residue. No crystalline products could be obtained from the reaction product. It failed to be adsorbed on aluminum oxide, and was purified by precipitation from ether solution with acetone (m. p. 148–162°, $[\alpha]D$ +44°, Lifschütz reaction negative). The analysis indicated the composition $C_{27}H_{46-48}O_{1/2}$. Obviously, a mixture of isomeric reduced ethers had been formed.

$\Delta^{4,6}$-Cholestadienone-3.—In the hope to effect a separation of the dicholestadienyl ether by its insolubility in methanol, 12.7 g. of pentane-soluble mother liquor material from another reduction batch was dissolved in 50 g. of hot methanol. The oil which separated on cooling (2.9 g.) was dissolved in hexane and chromatographed on aluminum oxide in the usual manner. The fractions eluted with benzene–hexane 1:4, together 460 mg., were crystalline, and on recrystallization from 90% alcohol yielded heavy plates melting at 80–81°, which gave no depression of the melting point on admixture of $\Delta^{4,6}$-cholestadienone-3, m. p. 80–81°, prepared by the method of Dane, Wang and Schulte.[17]

Anal. Calcd. for $C_{27}H_{42}O$: C, 84.65; H, 11.07. Found: C, 84.45; H, 11.18.

(16) Güntzel, *Ber.*, **72**, 1317 (1939).

(17) Dane, Wang and Schulte, *Z. physiol. Chem.*, **245**, 80 (1937).

The semicarbazone melted at 228–229°; the mixture with an authentic sample showed no depression.

The ultraviolet absorption properties of the ketone ($\epsilon_{285\ m\mu}$ = 26,000, in ethanol) and of the semicarbazone ($\epsilon_{305\ m\mu}$ = 46,000, in dioxane) closely agreed with those of the authentic preparations.[13]

We are indebted to Dr. N. H. Coy of the Vitamin Laboratory of E. R. Squibb and Sons for the spectrographic measurements, and to Miss Mildred Moore for able technical assistance.

The microanalyses were carried out by J. F. Alicino, Fordham University.

Summary

The crystalline, levorotatory product obtained by reduction of 7-ketocholesteryl acetate with aluminum isopropylate is a mixture of 7(α)- and 7(β)-hydroxycholesterol containing up to 20% of the latter epimer. Free 7(α)-hydroxycholesterol, in contradistinction to its esters, is only slightly dextrorotatory. It cannot be as readily obtained in crystalline form as the β-epimer or the epimeric mixture.

7(β)-Benzoxycholesteryl benzoate on hydrolysis with sodium methylate in the cold yields quantitatively 7(β)-benzoxycholesterol. The position of the benzoxy group was proved by its reductive removal, since the monoester, unlike its epimer, 7(α)-benzoxycholesterol, is not amenable to conversion into 7-dehydrocholesterol.

Two by-products of the reduction of 7-ketocholesteryl acetate, a dicholestadienyl ether and $\Delta^{4,6}$-cholestadienone-3, have been isolated. Possible mechanisms for the formation of the latter compound are discussed.

NEW BRUNSWICK, N. J. RECEIVED JULY 1, 1942

[CONTRIBUTION FROM RÖHM AND HAAS COMPANY, INC., AND RESINOUS PRODUCTS & CHEMICAL CO.]

The Chemistry of Acrylonitrile. I. Cyanoethylation of Active Methylene Groups

BY HERMAN ALEXANDER BRUSON

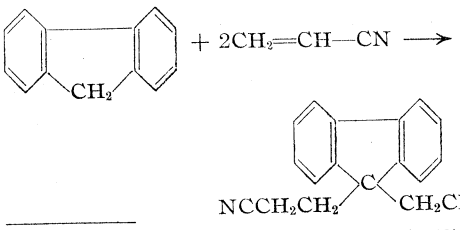
The reactions of acrylonitrile with amines,[1] phenols,[2] hydrogen sulfide,[3] butadiene[4] and halogens[5] have been described almost exclusively in the patent literature. Concerning the chemical behavior of acrylonitrile with other types of compounds, very little is known.

Because of its extremely reactive double bond, acrylonitrile condenses readily with a variety of organic compounds having labile hydrogen atoms or active methylene groups. These reactions occur in the presence of small quantities of alkaline condensing agents and are of the Michael type. The unique property of acrylonitrile in this respect is that it seeks out every available reactive hydrogen atom and by direct addition introduces the $-CH_2-CH_2-CN$ group in place thereof.

A powerful alkaline catalyst which is effective for promoting the cyanoethylation of many types of organic compounds is trimethylbenzylammonium hydroxide which is employed in the form of an aqueous 40% solution known as "Triton B" (Trade Mark). In some cases sodium or potassium methylate, 30% methanolic potassium hydroxide, or even aqueous 40% sodium hydroxide are effective, but the solubility of "Triton B" and its high degree of alkalinity renders it particularly effective where the other alkalies either fail to initiate the reaction at all or to give good yields.

In this paper, the condensation of acrylonitrile with compounds having the reactive methylene or methenyl grouping $C{=}C{-}\underset{|}{C}H{-}C{=}C$ in a carbocycle is described.[6] Such a grouping is present in fluorene, indene, cyclopentadiene, anthrone, the fulvenes and many of their substituted derivatives.

In the presence of a catalytic amount of "Triton B," acrylonitrile readily condenses with fluorene to yield *bis*-9,9-(β-cyanoethyl)-fluorene (I).



(I)

(1) British Patent 404,744 (1934), 457,621 (1936), I. G. Farbenindustrie; Hoffmann and Jacobi, U. S. Patents 1,992,615 (1935), 2,017,537 (1935).

(2) German Patent 670,357 (1939); Langley and Adams, THIS JOURNAL, **44**, 2326 (1922).

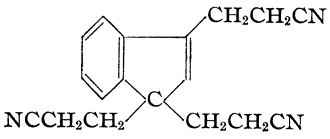
(3) German Patent 669,961 (1939); U. S. Patent 2,163,176.

(4) Wolfe, U. S. Patent 2,217,632 (1940).

(5) Long, U. S. Patent 2,231,363 (1941); Lichty, U. S. Patent 2,231,838 (1941); D'Ianni, U. S. Patent 2,231,360 (1941).

(6) See also Bruson, U. S. Patent 2,280,058 (1942).

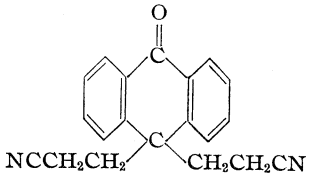
Indene likewise adds acrylonitrile in the presence of "Triton B" to yield a liquid di-cyanoethylation product and crystalline tris-(β-cyanoethyl)-indene very probably, (II) even when 1:1



(II)

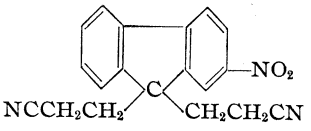
molecular proportions of the reactants are employed.

Anthrone similarly adds two moles of acrylonitrile to form meso-bis-(β-cyanoethyl)-anthrone (III).



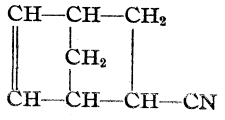
(III)

These reactions take place at room temperature with evolution of heat. In order to prevent excessive polymerization of the acrylonitrile and to allow the condensation to proceed smoothly to completion, resort to cooling and the use of inert solvents such as dioxane or tertiary butanol have been found helpful, particularly if the reactive methylene compound is a high melting solid. In dioxane solution for example, 2-nitro-fluorene condenses readily with acrylonitrile in the presence of "Triton B" to form *bis*-9,9-(β-cyanoethyl)-2-nitro-fluorene (IV) almost quantitatively.



(IV)

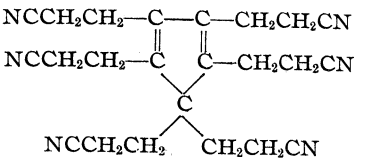
The reaction of acrylonitrile with cyclopentadiene was of particular interest because in the absence of a catalyst, a Diels–Alder adduct (V)



(V)

is formed by 1,4-addition. This adduct is a colorless, relatively low boiling liquid and forms spontaneously and almost quantitatively with considerable evolution of heat when the two components are mixed in equimolecular proportions.

However, in the presence of "Triton B" as the catalyst, the formation of the Diels–Alder type of adduct is so far repressed that each of the six hydrogen atoms in the cyclopentadiene molecule adds to acrylonitrile to form a crystalline hexacyanoethylation product (VI) melting at 203°,

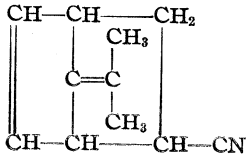


(VI)

accompanied by a mixture of lower poly-cyanoethylation products of cyclopentadiene, boiling much higher than the Diels–Alder adduct.

This unexpected reaction of cyclopentadiene can best be explained by a resonating system of double bonds making all the methylene and methenyl hydrogen atoms equally active, or by a mechanism involving a shift of the residual methylene hydrogen atom to a contiguous carbon atom as soon as the first cyanoethyl group is introduced, thus forming new reactive methylene groups successively around the cycle as each cyanoethyl group enters. When the resonating system is interrupted as for example by dimerization of the cyclopentadiene or by adduct formation with the loss of a double bond, then acrylonitrile no longer can add to the methenyl groups remaining. Neither dicyclopentadiene nor the adduct (V) reacted with acrylonitrile in the presence of Triton B. The peculiar shifting of a hydrogen atom in the cyclopentadiene nucleus has already been pointed out by Ziegler and Crössmann[7] to explain the activity of various fulvenes.

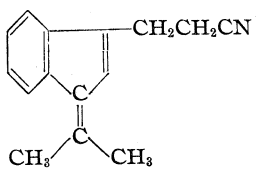
In order to test the activity of a resonating fulvene system toward acrylonitrile, dimethylfulvene was treated with acrylonitrile in the absence and in the presence of Triton B. In the former case, the expected crystalline Diels–Alder type adduct (VII) was isolated, but in the presence of Triton B higher cyanoethylation products of dimethyl-



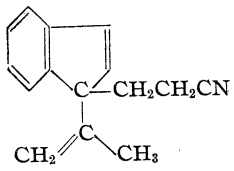
(VII)

fulvene were obtained in impure form. However, ω,ω-dimethylbenzofulvene[8] reacted with acrylonitrile in the presence of Triton B to yield a crystalline cyanoethylation product, corresponding to the formula VIII-A or VIII-B, whereas without the Triton B only resinous adducts were obtained.

(7) Ziegler and Crössmann, *Ann.*, **511**, 89 (1934).
(8) Thiele and Merck, *ibid.*, **415**, 260 (1918).



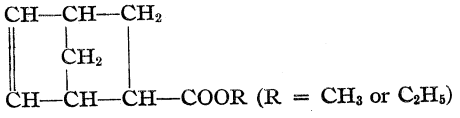
(VIII-A)



(VIII-B)

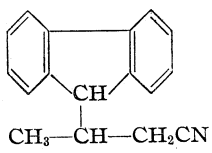
The pure poly-cyanoethylation products I, II, III and VI were each converted into their respective polycarboxylic acids IX, X, XI and XII by alkaline hydrolysis.

Attempts to replace acrylonitrile by acrylic esters such as methyl acrylate or ethyl acrylate in the above experiments so as to obtain the corresponding poly-(carbalkoxy-ethyl) derivatives were unsuccessful. Cyclopentadiene and the acrylic esters gave only the Diels–Alder type adducts (XIII) regardless of whether Triton B was used as the catalyst or not.



(XIII)

Crotononitrile reacted in the presence of Triton B with indene or cyclopentadiene to give poorly-defined, resinous cyano-alkylation products. With fluorene, however, a crystalline cyano-alkylation product, XIV, was obtained.



(XIV)

Not only does acrylonitrile cyanoethylate each available hydrogen atom of carbocylic compounds of the types described above, but also each reactive hydrogen atom of a methyl, methylene, or methenyl group which is contiguous to a nitro or carbonyl group as in the nitro-paraffins or ketones; furthermore as in the reactive methylene groups of malonic esters, malonamides, cyanacetic esters, cyanacetamides, benzyl cyanides, benzyl sulfonamides, α,β-unsaturated nitriles and amides. These will be described in later papers.

Experimental

(I) **Bis-9,9-(β-cyanoethyl)-fluorene.**—Acrylonitrile (111.3 g.) was added dropwise during the course of one hour to a rapidly stirred solution consisting of 166 g. of fluorene, 500 g. of dioxane, and 5 g. of aqueous 40% trimethylbenzylammonium hydroxide. The reaction temperature was maintained between 30 and 40° by occasional cooling with ice-water. The mixture was then stirred for three hours longer at room temperature to complete the condensation. At the end of this time, the dark brown solution obtained was neutralized with dilute hydrochloric acid and, without interrupting the stirring, 800 cc. of water was added to precipitate the product in granular form. The precipitate was filtered off and air dried; crude yield 250 g. Upon recrystallization once from 500 g. of ethanol, the product separated as yellowish crystals m. p. 118–119°; yield 201 g. or 74%. One more recrystallization from ethanol using Norite gave the pure compound as colorless needles m. p. 121°. *Anal.* Calcd. for $C_{19}H_{16}N_2$: C, 83.78; H, 5.92; N, 10.29. Found: C, 84.03; H, 5.76; N, 10.33. It is readily soluble in benzene, chloroform, acetone, ethyl acetate or dioxane at 25°. It is insoluble in ether, and is only slightly soluble in cold methanol or ethanol, but dissolves readily on heating.

(II) **Tris-1,1,3-(β-cyanoethyl)-indene.**—To a mixture of 69.5 g. of indene (0.6 mole), 100 g. of dioxane, and 4 g. of aqueous 40% trimethylbenzylammonium hydroxide there was added dropwise during two hours 95.4 g. of acrylonitrile (1.8 mole) while the reaction mixture was stirred and cooled to 25–30°. After the addition, the dark solution was stirred at room temperature for an hour and then acidified to litmus with dilute hydrochloric acid. The mixture was shaken with an equal volume of ethylene dichloride and a little water. The aqueous layer was discarded, and the ethylene dichloride layer washed with water and then evaporated to dryness under reduced pressure on a steam-bath. The residue was a dark red, viscous oil weighing 147 g. Upon distillation in high vacuum, two main fractions were obtained as follows

I. 210–220° (2 mm.) 18 g. pale yellow oil
II. 280–290° (1 mm.) 58 g. viscous reddish oil

Fraction I analyzed 12.76% N, corresponding to di-(β-cyanoethyl)-indene, $C_{15}H_{14}N_2$ (calcd.: N, 12.61).

Fraction II crystallized on standing. Upon recrystallization from ethanol using "Norite" for decolorizing, it separated in colorless crystals, m. p. 65°.

Anal. Calcd. for $C_{18}H_{17}N_3$: C, 78.50; H, 6.23; N, 15.26. Found: C, 78.80; H, 6.09; N, 15.39.

(III) **Meso-bis-(β-cyanoethyl)-anthrone.**—Acrylonitrile (15.9 g.) was added dropwise during thirty minutes to a stirred solution consisting of 29.1 g. of anthrone, 100 g. of dioxane and 3 g. of aqueous 40% trimethylbenzylammonium hydroxide while the reaction mixture was maintained at 40°. A deep red solution resulted. This was stirred for one hour longer at 35° and then allowed to stand eighteen hours. The mixture was then acidified with dilute hydrochloric acid whereupon the red color disappeared. The crystalline product was filtered off, washed and dried; yield 40 g. After crystallization from glycol monoethyl ether ("Cellosolve"), it formed colorless prisms, m. p. 215°. *Anal.* Calcd. for $C_{20}H_{16}N_2O$: C, 79.92; H, 5.37; N, 9.32. Found: C, 80.36; H, 5.45; N, 9.49.

(IV) **Bis-9,9-(β-cyanoethyl)-2-nitro-fluorene.**—To a solution of 20 g. of 2-nitrofluorene, 150 g. of dioxane and 2 g. of aqueous 40% trimethylbenzylammonium hydroxide there was added dropwise during twenty minutes 10.6 g. of acrylonitrile, while the reaction mixture was stirred and cooled to 35–40°. The mixture was then stirred for two hours longer and finally neutralized with dilute hydrochloric acid. The crystalline product was filtered off,

washed and dried; yield 21 g. Upon recrystallization from glycol monoethyl ether it formed yellow needles, m. p. 236–237°. *Anal.* Calcd. for $C_{19}H_{15}N_3O_2$: C, 71.90; H, 4.77; N, 13.12. Found: C, 72.40; H, 4.80; N, 13.09.

(V) **3-Cyano-1,4-endomethylene-cyclohexene-5.**—To 33 g. of cyclopentadiene in a flask under a reflux condenser, there was added 26.5 g. of acrylonitrile. After standing for about ten minutes the mixture became warm and began to boil. The exothermal reaction lasted for about a half hour. The mixture was allowed to stand for four hours thereafter and then distilled in vacuum at 11 mm. A colorless oil came over at 80–85° (11 mm.), yield 49.5 g.; $n^{25}D$ 1.4876; d^{25}_{25} 1.0066. *Anal.* Calcd. for C_8H_9N: N, 11.76. Found: N, 11.70. It crystallizes in an ice-bath but is liquid at room temperature.

(VI) **Hexa-(β-cyanoethyl)-cyclopentadiene.**—Acrylonitrile (106 g.) was added dropwise during two hours to a stirred, cooled mixture of 66 g. of cyclopentadiene, 100 g. of dioxane, and 4 g. of aqueous 40% trimethylbenzylammonium hydroxide while the reaction temperature was maintained at 20–25°. The mixture was stirred three hours longer at 20°, then neutralized with dilute hydrochloric acid. During the condensation the mixture became almost black but bleached to a yellow color on the addition of the acid. The crystalline product was filtered off. It was a tan-colored powder; yield 34 g. Upon recrystallization from glycol monomethyl ether it separated in colorless needles, m. p. 203°. *Anal.* Calcd. for $C_{23}H_{24}N_6$: C, 71.84; H, 6.30; N, 21.86. Found: C, 71.80; H, 6.26; N, 21.93.

The original filtrate was washed with water, dried and distilled in vacuum. Only a small amount boiled below 90° at 11 mm. The bulk distilled from 100 to 280° (1 mm.) with some decomposition and considerable residue but a clean fractionation was not accomplished.

(VII) **3-Cyano-1,4-endo-isobutenylidene-cyclohexene-5.**—A mixture of 50 g. of dimethylfulvene and 25 g. of acrylonitrile was gently heated on a water-bath under reflux for several hours until no further refluxing occurred. The viscous reddish product was distilled in vacuum at 1 mm. At 95–100° (1 mm.) an amber-colored oil came over which gradually crystallized; yield 35 g. Upon recrystallization from petroleum ether using Norite for decolorization, the product was obtained as colorless crystals, m. p. 87°. Calcd. for $C_{11}H_{13}N$: C, 82.96; H, 8.24; N, 8.80. Found: C, 83.20; H, 8.03; N, 8.90.

VIII-A or VIII-B. Cyanoethylated Dimethylbenzofulvene.—To a solution of 44 g. ω,ω-dimethylbenzofulvene, 44 g. of dioxane and 3 g. of Triton B, acrylonitrile (15 g.) was added dropwise while stirring at 25–35°. The mixture was stirred for four hours after the exothermal reaction had ceased, and then neutralized with dilute hydrochloric acid, taken up in ethylene dichloride, and washed and dried *in vacuo* at 100°. The residual oil weighing 61 g. was distilled in vacuum at 1 mm. The main fraction came over at 180–230° (1 mm.) and solidified in the receiver; yield 13 g. Upon recrystallization from methanol the product was obtained as yellow crystals, m. p. 121°. Calcd. for $C_{15}H_{15}N$: C, 86.07; H, 7.23; N, 6.69. Found: C, 85.90; H, 7.11; N, 6.64.

(IX) **Bis-9,9-(β-carboxy-ethyl)-fluorene.**—A mixture of 16 g. of sodium hydroxide, 400 cc. of water and 40 g. of (I) was boiled under reflux with rapid stirring, for twelve hours. The solution was bleached with charcoal, cooled, filtered, and the filtrate acidified hot with hydrochloric acid. The white precipitate (yield 41 g. air-dried) was recrystallized from ethanol. It separated in colorless crystals, m. p. 273–274°. *Anal.* Calcd. for $C_{19}H_{18}O_4$: C, 73.51; H, 5.85. Found: C, 73.70; H, 5.83.

(X) **Tris-1,1,3-(β-carboxy-ethyl)-indene.**—A mixture of 23 g. of potassium hydroxide, 225 cc. of water and 27 g. of (II) was stirred and boiled under reflux for three hours. The clear solution was bleached with charcoal, filtered and acidified with hydrochloric acid. The product separated as a resinous solid which became crystalline after being dissolved in hot water and allowed to separate slowly on cooling. After several recrystallizations from hot water, the melting point remained unchanged at 161–162°. *Anal.* Calcd. for $C_{18}H_{20}O_6$: C, 65.03; H, 6.07. Found: C, 64.80; H, 5.97.

(XI) **Bis-meso-(β-carboxy-ethyl)-anthrone.**—A mixture of 12 g. of sodium hydroxide, 120 cc. of water, 70 cc. of ethanol, and 27 g. of (III) was stirred rapidly and boiled under reflux for seven hours. The solution was cooled, filtered, and the filtrate acidified with hydrochloric acid. The product separated as an oil which rapidly solidified; yield 27 g. Upon recrystallization from dilute ethanol (75% H_2O + 25% ethanol) it separated in colorless flakes which sinter at 220° and decompose at 230°. *Anal.* Calcd. for $C_{20}H_{18}O_5$: C, 70.97; H, 5.36. Found: C, 71.10; H, 5.41.

(XII) **Hexa-(β-carboxy-ethyl)-cyclopentadiene.**—A mixture of 140 g. of sodium hydroxide, 1000 cc. of water and 184 g. of (VI) was boiled under reflux for eighteen hours. The dark solution was treated with Norite, filtered, and the filtrate acidified with concd. hydrochloric acid (350 g.) and cooled to 5°. The white crystalline precipitate was filtered off, washed on the filter with 200 cc. of ice-water and dried in an oven at 60°; yield 199 g. of crude acid containing 0.09% ash. It may be purified by recrystallization from four times its weight of water by chilling the solution to 5°. The purified analytical sample formed colorless crystals, m. p. 180–181°. It is readily soluble in alcohol and in warm water. *Anal.* Calcd. for $C_{23}H_{30}O_{12}$: C, 55.39; H, 6.07. Found: C, 55.40; H, 5.93.

(XIII) **3-Carbomethoxy-1,4-endomethylene-cyclohexene-5.**—A mixture of 33 g. of cyclopentadiene and 43 g. of methyl acrylate was placed in a flask under a reflux condenser. After standing for about thirty minutes the mixture began to boil. After boiling had ceased, the mixture was allowed to stand for twenty-four hours and was then distilled under reduced pressure. The product came over at 71–73° (8 mm.) as a colorless oil of strong characteristic valerian odor; yield 64 g. or 84%; $n^{25}D$ 1.4745; d^{25}_{25} 1.0543. *Anal.* Calcd. for $C_9H_{12}O_2$: iodine no., 167. Found: 170.

The corresponding ethyl ester (XIII, R is C_2H_5) was prepared in the same manner as above from ethyl acrylate and cyclopentadiene. It is a colorless oil of b. p. 84–85° (10 mm.), $n^{25}D$ 1.4675; d^{25}_{25} 1.0268. *Anal.* Calcd. for $C_{10}H_{14}O_2$: saponification no., 338. Found: 338. It is also formed in 85% yield instead of the expected poly-(carbethoxy-ethyl) derivative when ethyl acrylate is added to cyclopentadiene containing "Triton B."

(XIV) 9-(β-Cyano-isopropyl)-fluorene.—To a stirred solution of 83 g. of fluorene, 250 g. of dioxane, and 10 g. of "Triton B," there was added dropwise 67 g. of allyl cyanide during the course of one hour while the exothermal reaction was maintained at 38–47° by intermittent cooling. The mixture was then heated at 45–50° for six hours longer, cooled, rendered acid to congo red indicator with dilute hydrochloric acid, taken up in its own volume of ethylene dichloride and washed thoroughly with water. The ethylene dichloride layer was evaporated to dryness and the residual dark oil distilled in vacuum. After a small forerun of unchanged fluorene, the main fraction boiled between 190° and 220° (1–2 mm.) and weighed 60 g. It formed a yellow balsam which gradually solidified to a crystalline mass. After recrystallization from methanol, the pure product was obtained as colorless crystals melting at 92–93°. *Anal.* Calcd. for $C_{17}H_{15}N$: C, 87.50; H, 6.49; N, 6.00. Found: C, 87.51; H, 6.38; N, 6.07.

The same product is obtained by using crotononitrile in place of allyl cyanide.

Acknowledgment.—The analyses of the above products were performed by Mr. C. W. Nash, and much of the experimental work was done by Mr. Thomas Riener of these Laboratories.

Summary

1. Acrylonitrile condenses in the presence of strong bases, notably aqueous trimethylbenzylammonium hydroxide ("Triton B") as a catalyst, with reactive carbocyclic methylene or methenyl compounds such as fluorene, indene, anthrone, cyclopentadiene and fulvenes to replace each reactive hydrogen atom by a β-cyanoethyl radical.

2. The preparation and properties of bis-(β-cyanoethyl)-fluorene, tris-(β-cyanoethyl)-indene, bis-(β-cyanoethyl)-anthrone, hexa-(β-cyanoethyl)-cyclopentadiene, and the corresponding carboxylic acids obtained therefrom by hydrolysis are described, as well as the cyanoethylation product of dimethylbenzofulvene and certain Diels–Alder type adducts of acrylonitrile and acrylic esters.

3. Allyl cyanide or crotononitrile condensed with fluorene to a 9-(β-cyano-isopropyl)-fluorene.

PHILADELPHIA, PA. RECEIVED JULY 23, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

The Rearrangement of 1,1,3,3,5,5-Hexamethylcyclohexatriol-2,4,6 to Hexamethylbenzene

BY ERLE B. AYRES AND CHARLES R. HAUSER

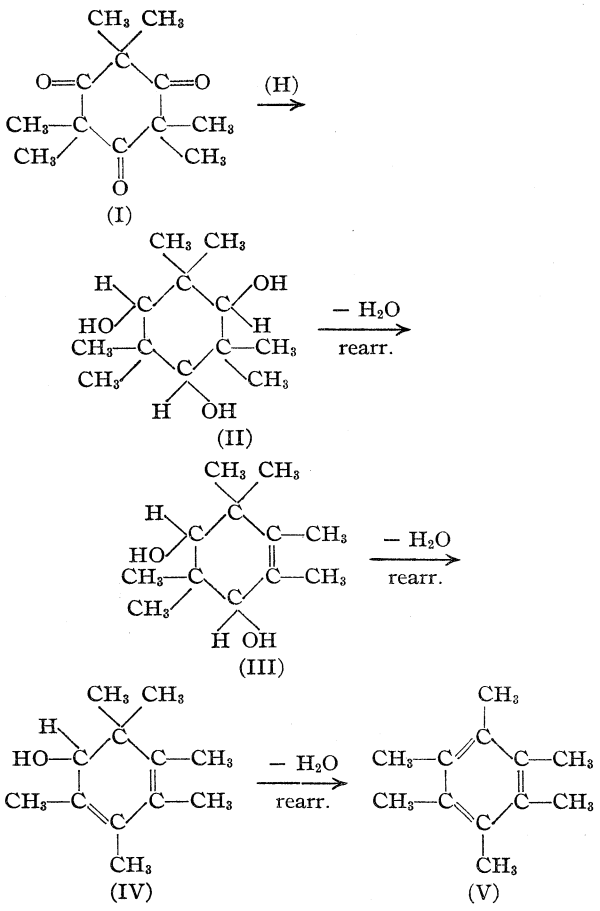
In another investigation in this Laboratory a method was developed for the synthesis of hexamethylcyclohexatrione-1,3,5 (I) in an over-all yield of approximately 25% starting with ethyl isobutyrate and isobutyryl chloride.[1] It seemed possible that the cyclohexatrione (I) might be reduced to the triple neopentyl system, 1,1,3,3,5,5-hexamethylcyclohexatriol-2,4,6 (II), which might be made to undergo a triple dehydration and rearrangement to form hexamethylbenzene (V). This transformation, which represents a new route from an aliphatic to an aromatic compound, has been realized.

The cyclohexatrione (I) was reduced catalytically[2] in good yield to the cyclohexatriol (II), which was probably a mixture of two stereoisomers; in one of the isomers the three hydroxyl groups are arranged on one side of the ring, and in the other, two hydroxyl groups are on one side and the third hydroxyl on the opposite side of the ring. In the present study no attempt has been made to separate the two isomers after a substance was obtained the melting point of which was not raised by further recrystallization. The cyclohexatriol was dissolved in sulfuric acid, giving a colored mixture from which practically pure hexamethylbenzene in approximately 20% yield was extracted with ligroin. Other products were present in the sulfuric acid layer but were not identified in the present investigation. The rearrangement was also carried out in warm phosphoric acid, but the yield of hexamethylbenzene was very low. Treatment of the cyclohexatriol with thionyl chloride gave only tarry material from which no hexamethylbenzene could be isolated.

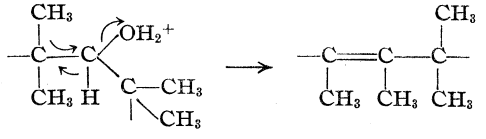
The conversion of the hexamethylcyclohexatriol (II) to hexamethylbenzene (V) probably involves

(1) The methods are described by Hudson and Hauser (THIS JOURNAL, **61**, 3567 (1939). Better yields were subsequently obtained (Hudson, Ph.D. Thesis, Duke University (1941)) as follows: for ethyl isobutyryl isobutyrate, 74%; for ethyl 2,2,4,4,6-pentamethyl-3,5-diketoheptanoate, 72%; for hexamethylcyclohexatrione-1,3,5, 52%.

(2) The authors are indebted to Dr. Homer Adkins of the University of Wisconsin for carrying out this reduction.



three separate reactions,[3] each consisting of the removal of a hydroxyl group (as a molecule of water from the oxonium ion formed by the addition of a proton to the hydroxyl), the shift of a methyl group with its attached electron pair, and the loss of a proton to form a double bond,[4] thus[5]



It is obvious that the monodehydration of (II) can give only one cyclic product (III). Of the hydroxyl groups in (III), the one in the α-position to the double bond might be preferentially lost because of the possibility of allylic resonance in the resulting carbonium ion. Shift of a methyl group would give (IV), which contains conjugated double bonds. The third rearrangement should follow only the course giving hexamethylbenzene. In view of the several side reactions that one might expect to occur in the conversion of (II) to (V), it is not surprising that the yield of hexamethylbenzene is only 20%.

Experimental

1,1,3,3,5,5-Hexamethylcyclohexatriol-2,4,6.—This substance was prepared by the reduction[2] of hexamethylcyclohexatrione-1,3,5 (15.3 g.) over copper chromite for five hours at 200 atm. at 200°. The triketone took up approximately three molecular equivalents of hydrogen. An alcoholic suspension of the reduction product yielded on filtering 7.0 g. of silky white crystals, m. p. 242–246° after some softening at 170°. Evaporation of the filtrate yielded 7.7 g. of slightly gummy solid; total yield of crude product, 14.7 g. (93%). After several recrystallizations from alcohol or, better, from acetone, the crystals melted at 251.0–251.5°. The substance could also be purified by sublimation.

Anal.[6] Calcd. for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.85; H, 11.03.

Dehydration and Rearrangement of 1,1,3,3,5,5-Hexamethylcyclohexatriol-2,4,6.—To 15 cc. of ice-cold concentrated sulfuric acid was added 1.00 g. of 1,1,3,3,5,5-hexamethylcyclohexatriol-2,4,6. The color of the mixture became pale yellow and then reddish to red-brown during two hours. At one point there seemed to be very little suspended material; then the quantity of fine white platelets appeared to increase. After standing for two days at room temperature, the mixture was extracted with purified ligroin (b. p. 54–64°). After washing, drying and removing the ligroin under partial pressure, there was left an oil which solidified completely to 0.15 g. (19.4%) of white crystalline solid, m. p. 164–165°; a mixed melting point with a sample of Eastman Kodak hexamethylbenzene (m. p. 164–165°) was the same. The sulfuric acid layer was poured over crushed ice and the oily mixture extracted with ether. Upon washing the ether with sodium bicarbonate solution, drying and evaporation, there remained a trace of unidentified material.

In another experiment, 1,1,3,3,5,5-hexamethylcyclohexatriol-2,4,6 (1.00 g.) was warmed over a steam-bath with 85% phosphoric acid. From a ligroin extract of the mixture was obtained a very small amount of impure hexamethylbenzene and small amounts of solids which decomposed at about 200° and were perhaps phosphoric esters. An experiment carried out using thionyl chloride yielded only tarry material.

Summary

1,1,3,3,5,5-Hexamethylcyclohexatriol-2,4,6 on treatment with sulfuric acid undergoes partly a triple dehydration and rearrangement of the neopentyl type, yielding hexamethylbenzene.

DURHAM, NORTH CAROLINA RECEIVED JULY 18, 1942

(3) Although it would appear improbable that the three dehydrations and rearrangements take place simultaneously, the possibility is not entirely excluded; the triply charged oxonium ion required could probably be formed in low concentration, and such a reaction would involve considerable driving force in forming the aromatic ring.

(4) See especially Whitmore, THIS JOURNAL, **54**, 3274 (1932).

(5) Whitmore and Stahly, *ibid.*, **55**, 4153 (1933), found that di-*t*-butylcarbinol, which is analogous to the section of (II) represented above, yields the expected olefin only under mild conditions; instead, a tertiary butyl group is eliminated as a carbonium ion. It is possible that this type of reaction occurs also with compound (II).

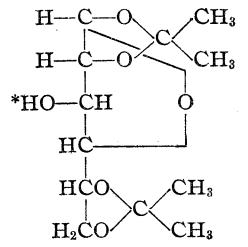
(6) Microanalysis by Saul Gottlieb, Columbia University, New York, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 271]

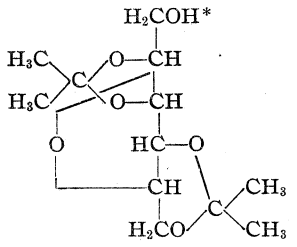
The Rates of Reaction of Diacetone Glucose, Diacetone Galactose and Diacetone Sorbose with *p*-Toluenesulfonyl Chloride in Pyridine Solution[1]

BY ROBERT C. HOCKETT AND MASON L. DOWNING

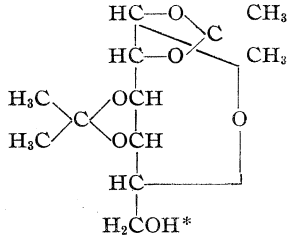
In a previous publication[2] the "selective" action of triphenylchloromethane upon primary alcohols in pyridine solution as compared with the action of this chloride upon secondary alcohols, was interpreted as a difference in the rates of reaction of such alcohols under the conditions employed. This view was supported by direct rate measurements by polarimetric means upon the reactions between trityl chloride[3] and the diisopropylidene derivatives of D-glucose, L-sorbose and D-galactose, respectively, in pyridine solution. All these compounds reacted when an eight to one molecular proportion of the chloride was used, the reactions were pseudounimolecular, and the times of half-change were in the ratio 226:6.6:1 in the order of their names.



Diisopropylidene D-glucose (secondary)



Diisopropylidene L-sorbose (primary)



Diisopropylidene D-galactose (primary)

On account of an apparent tendency among chemists to regard triphenylchloromethane as a quite peculiar or exceptional reagent, we thought it worth while to extend the study to an investigation of the rates of reaction of *p*-toluenesulfonyl chloride with the same sugar derivatives under the same conditions.[4] Such a study has yielded results which are compared with the previous ones below.

TABLE I

Substance	Rate constant (hours and dec. logs) Trityl (21°)	Rate constant (hours and dec. logs) Tosyl (23 ± 2°)	Times of half-change, hours Trityl (21°)	Times of half-change, hours Tosyl (23 ± 2°)
Diacetone glucose	0.00016	0.0149	1880.0	20.20
Diacetone sorbose	0.0055	0.5160	54.7	0.583
Diacetone galactose	0.036	1.038	8.3	0.272

1.00 g. substance in 50.0 pyridine solution 8:1 ratio of chloride; 2-dm. tube. $K = \frac{1}{t} \log_{10} \frac{\alpha_0 - \alpha_\infty}{\alpha_t - \alpha_\infty}$.

The obvious conclusions are two: *p*-toluenesulfonyl chloride reacts faster with all the substances than does trityl chloride under the same conditions; the velocity ratios are of the same order of magnitude for the three substances in their reactions with either chloride. The rate ratio for the diacetone glucose and diacetone sorbose is 34.7/1 in the reaction with trityl chloride and 34.4/1 in the reaction with *p*-toluenesulfonyl chloride. Thus the latter appears to be equally "selective." More strictly speaking, the selectivity is a characteristic of the alcohols rather than of the halides.

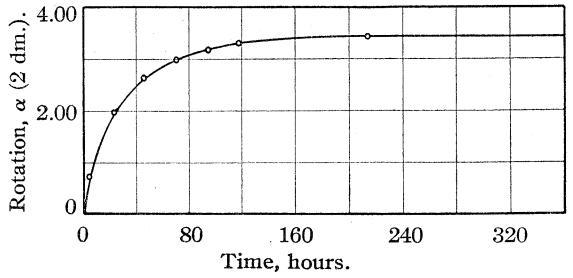


Fig. 1.—Diacetone-glucose and tosyl chloride at 23 ± 2°.

Much evidence is accumulating which tends to show that benzoyl chloride, acetic anhydride and other agents show much the same kind of selection.[5]

An extension of these measurements to other temperatures is in progress.

We express our indebtedness to Hoffmann-La Roche, Inc., of Nutley, N. J., for a quantity of diacetone-L-sorbose.

(1) This paper is taken from a thesis submitted by Mason L. Downing in partial fulfillment of the requirements for the Degree of Bachelor of Science in June, 1941.

(2) Hockett, Fletcher and Ames, THIS JOURNAL, **63**, 2516 (1941).

(3) "Trityl chloride" has become a widely accepted abbreviation for triphenylchloromethane.

(4) *Cf.* Compton, THIS JOURNAL, **60**, 395 (1938).

(5) Cramer, Hockett and Purves, *ibid.*, **61**, 3463 (1939); Brigl and Grüner, *Ber.*, **65**, 641 (1932).

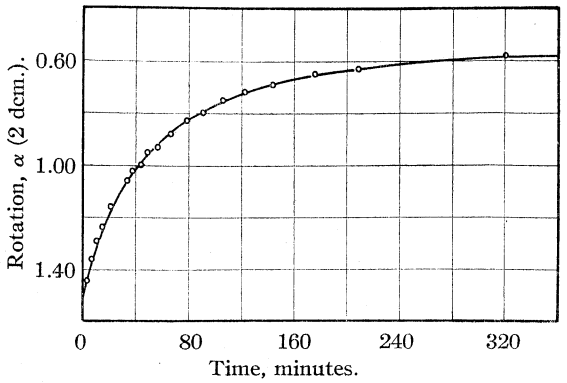


Fig. 2.—Diacetone-sorbose and tosyl chloride at 23 ± 2°.

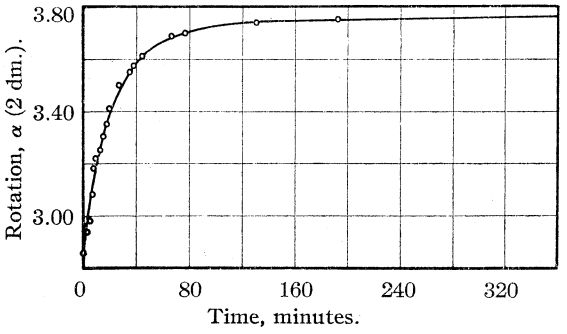


Fig. 3.—Diacetone-galactose and tosyl chloride at 23 ± 2°.

Experimental

1,2;5,6-Diisopropylidene-D-glucofuranose.—A sample of this substance obtained from the Corn Products Refining Co., contained a considerable amount of monoacetone glucose. It was dissolved in water and extracted three times with very small portions of benzene to remove colored impurities. After a treatment with decolorizing carbon, the colorless aqueous solution was extracted five times with chloroform; the extract was dried with sodium sulfate, filtered, and concentrated to crystallization. The product after a recrystallization from benzene and drying, melted from 109.5–110° (cor.) and rotated[6] −17.6° (*c*, 2.040; H_2O).

1,2;3,4-Diisopropylidene-D-galactopyranose.—This was prepared exactly as described previously.[2]

2,3;4,6-Diisopropylidene-L-sorbofuranose.—The dark-brown distillate supplied by Hoffmann-LaRoche was dissolved in ether and most of the coloring matter was removed by extractions with 20% KOH solution and then by carbon treatment. Almost colorless crystals were obtained when the dried ether extract was evaporated. A final recrystallization from petroleum ether (b. p. 30–60°) yielded white crystals melting from 77.5–78.5°.

Toluenesulfonyl Chloride.—Eastman Kodak Co. product melting 68.5–69.0° (cor.) was employed.

Pyridine.—A colorless fraction dried over KOH and boiling at 115.3–115.5° was used.

The Rate Measurements.—The method described for the case of triphenylchloromethane was duplicated.[2] The reactions took place in a constant-temperature room at 23 ± 2°.

Summary

1. The rates of reaction of *p*-toluenesulfonyl chloride with diacetone glucose, diacetone sorbose and diacetone galactose at a molar ratio of 8 to 1 in pyridine solution, have been measured polarimetrically.

2. The reactions were pseudounimolecular and gave times of half-change in the ratio 74.2: 2.1: 1 in the order named.

3. The "selectivity" of *p*-toluenesulfonyl chloride toward primary hydroxyl groups as compared with secondary ones is of the same order as the "selectivity" of triphenylchloromethane.

(6) Specific rotation of the D line of sodium at 24°.

CAMBRIDGE, MASS. RECEIVED AUGUST 11, 1942

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

Solubilities of Orthanilamide, Metanilamide and Sulfanilamide[1a]

BY R. H. KIENLE AND J. M. SAYWARD[1b]

In connection with a broad program of research on chemotherapeutic agents of the sulfanilamide type, a study of certain physical chemical properties of sulfanilamide and its therapeutically inactive isomers was undertaken. Any distinction found between the active para compound and the inactive ortho and meta isomers might contribute to the explanation of the therapeutic activity of sulfanilamide.

(1a) Presented at the 103rd meeting of the American Chemical Society, Memphis, Tenn., April, 1942.

(1b) **Present address:** Stamford Research Laboratories, American Cyanamid Company, Stamford, Connecticut.

The present paper reports on the water-solubilities of the three sulfanilamide isomers. The results led to dilatometry and manometric drying of the solid phase of sulfanilamide. Microscopical and X-ray investigation of the three isomers is expected to be published at a later date by our Laboratories. Solubilities were also determined at 37° in buffered solutions.

Experimental

Materials.—Sulfanilamide (U. S. P.) from plant production was recrystallized from alcohol and from hot water.

Orthanilamide was synthesized by standard methods

from *o*-nitrochlorobenzene by oxidizing the disulfide, amidating and reducing. The product was recrystallized repeatedly from hot water (using traces of hydrosulfite to prevent discoloration), once from diluted alcohol, and once from cold diluted acetone.

Metanilamide was prepared from nitrobenzene by converting to the sulfonyl chloride, amidating and reducing. It was recrystallized repeatedly from hot water (also using hydrosulfite), from hot alcohol and from hot diluted acetone.

Titration with nitrite indicated that the products were 100.0 ± 0.3% pure. Elementary analyses and mixed melting point determinations with materials furnished by Dr. E. H. Northey[2] confirmed these values.

Buffered solutions used in measuring solubility at various *p*H values are listed with their ionic strengths (calculated from dissociation constants) in Table III.

Determination of Solubilities.—Half-filled bottles containing excess solid were rotated, usually overnight, in a water thermostat controlled to ±0.02° by an all-glass mercury–toluene regulator. Equilibrium was approached usually from above and during twelve hours or more (overnight); exceptions are indicated in Table I and Fig. 1. It will also be noted that approach toward equilibrium from below and shorter runs in general gave equivalent results. Sampling was accomplished by forcing the solution, with air pressure, through a glass wool immersion filter into a 15–25-cc. pycnometer immersed in the bath. The pycnometer (resembling a pipet bulb) was closed by two stopcocks, cleaned, dried, cooled and weighed, after which the contents were flushed into a volumetric flask. Duplicate aliquots were acidified (10 cc. of concentrated hydrochloric acid per 25-cc. sample), iced below 15°, and titrated with *N*/25 sodium nitrite to first blue on starch–iodide paper.

TABLE I

Temp., °C.	Solubilities, g./100 g. Orthanilamide S	Orthanilamide 2σ	Metanilamide S	Metanilamide 2σ	Sulfanilamide S	Sulfanilamide 2σ
23.0	0.65		1.14		0.64	
					.64	
24.0	.67		1.21		.69	
26.0	.75		1.34		.77	
27.0					.82[b]	±0.012
					.82[b,a]	
					.82	
					.83	
28.0	.82		1.48	±0.018	.87	
	.82		1.49		.87	
30.5	.91				1.01	
31.7					1.08	
					1.08[a]	
33.0	1.01		1.89		1.19	
34.0	1.05				1.26	
					1.27[a]	±0.015
					1.27	
35.5	1.11		2.19		1.37	
37.0	1.20	±0.024	2.37	±0.031	1.47	±0.010
	1.20		2.36[a]		1.47	
	1.20[a]		2.35[a]		1.47[a]	
	1.18[b]		2.34[b]		1.47[a]	
					1.46[b]	
37.05	1.19					
39.0			2.58		1.61	
					1.61	
42.0	1.46		3.01		1.84	
46.0	1.70		3.70		2.21	
50.0	2.00[b]		4.58[b]		2.68[b]	

[a] Equilibrium approached from below. [b] Duration less than twelve hours.

(2) Observed melting points for experimental, Northey's, and mixed samples: orthanilamide, 155.2, 155.3, 154.8; metanilamide, 142.1, 141.9, 142.1; sulfanilamide, 165.9, 165.8, 166.0.

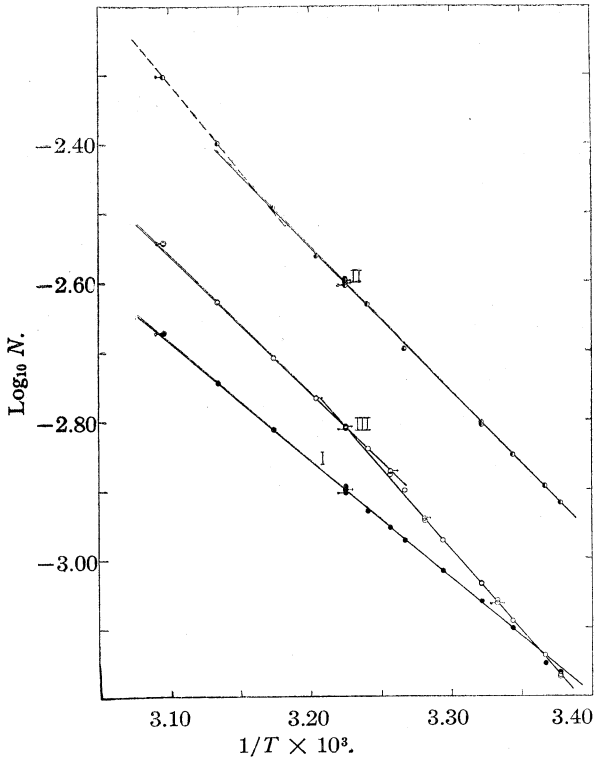


Fig. 1.—Solubility of sulfanilamide isomers in water; I, ●, orthanilamide; II, ◐, metanilamide; III, ○, sulfanilamide; ○–+ equilibrium approached from below; ●–○, duration of experiment less than twelve hours.

In buffered solutions at 37° the solubility was determined by drawing the sample directly into a volumetric pipet, yielding results on a volume basis.

Accuracy of the experimental results, based on the estimated error in weighing and in titration, is taken to be about ±0.01 g./100 g. of solution. This corresponds to ±0.012 × 10^{-3} in mole fraction (±0.0024 in log *N*); these limits are indicated by the size of the circles in Fig. 1. The precision of the results has been calculated in those cases where several determinations were carried out at one temperature. Values of 2 σ vary from 0.01 to 0.03 g./100 g.—see Table I. The consistency with which the experimental points fall on straight lines in the log *N versus* 1/*T* plot, Fig. 1, is also indicative of the degree of reproducibility.

Dilatometry.—The dilatometers were of the Bouyoucos type, 100-ml. capacity, with ground stoppers. They were suspended with capillaries immersed in a glass thermostat controlled to ±0.1°. They were charged with about 35 g. of sulfanilamide hydrate crystals (large plates formed from a 1.75% solution by slow cooling below 40°) suspended in toluene or Solvesso No. 2. Readings of the capillary level were taken periodically until essentially con-

stant at each temperature. Above 37° this required many hours.

Manometric Drying.[3]—The apparatus consisted of a mercury manometer, cold trap and vacuum pump connected to a flask in a thermostat at 21°. In the flask was placed a thin layer of ground-up, wet crystals prepared as for dilatometry. During evacuation, pressures were read at intervals (four minutes after closing the connection to the pump). After a definite fall in pressure a sample of the crystals was removed and analyzed both by drying at 110° and by titrating with nitrite.

Results

Solubilities of orthanilamide, metanilamide and sulfanilamide, as directly determined by weight in the temperature range 23–50°, are given in Table I. Values of 2 σ were calculated where duplicate data made this possible.

Solubilities by volume do not differ from values on the weight basis by more than 0.01 g./100 cc. This follows as, over the range 23–50°, the densities of the solutions varied only as follows: orthanilamide, 0.999 to 0.995; metanilamide, 1.000 to 1.001; sulfanilamide, 0.999 to 0.996 g./100 cc.

The experimental aqueous solubility data are plotted in Fig. 1, using $\log_{10} N$ and $1/T$ as coordinates. The discontinuity in the curve for sulfanilamide indicates a phase transition, which was confirmed by dilatometry (see below) as well as by the microscopical and X-ray investigations. Manometric drying, reported below, has shown the transition to involve a monohydrate.

A possible discontinuity at about 43° in the case of metanilamide is also shown. Dashes have been used for the higher temperature line, because only two points determine it, and the 50° point is perhaps unreliable since equilibrium was approached during only 3.3 hours. If the dashed line is correct, the main portion of the curve represents a metastable equilibrium, for it corresponds to higher solubilities than would the extension of the dashed line. (In the microscopical work, various modifications of the anhydrous solid phases of all three isomers were observed. In preparing crystals for this examination it appeared that a transformation for metanilamide may occur near 43°.)

Equations expressing the relation of temperature and solubility, in terms of mole fraction, have been derived from the straight lines of Fig. 1. The general equation is

$$\log N = a(1/T) + b \qquad (1)$$

where N is mole fraction and T is degrees absolute. Values of the constants, a and b, are given in Table II. Solubility as g./100 g. of solution may be derived from mole fraction by the relation

$$S = (17{,}214N)/(18.02 + 154N) \qquad (2)$$

Differential heats of solution have been calculated from the lines of Fig. 1, using the Schröder equation

$$\log N_2 - \log N_1 = \frac{\Delta H}{4.575}\left(\frac{1}{T_1} - \frac{1}{T_2}\right) \qquad (3)$$

where ΔH is heat of solution in calories per mole, values for which appear in Table II. Taking the heat of transition as the difference between the heats of solution of the two forms, the heat absorbed by the hydrate → anhydrous transition of sulfanilamide at 37° is 1810 cal./mole.

TABLE II

Compound	Heat of solution, cal./mole	Constants for solubility equation a	b
Orthanilamide	7,820	−1710	2.615
Metanilamide	9,570	−2091	4.156
Sulfanilamide (< 37°)	10,860	−2373	4.844
Sulfanilamide (> 37°)	9,050	−1978	3.570

Qualitative independent evidence of the transition of sulfanilamide, indicated by the solubility data, was sought in a dilatometric investigation. Such was found, there being a distinct increase in volume, evidenced by a discontinuity in the temperature–volume curve, which occurred within 2–4° above 37°. Suspended or negligible rate of transformation close to the transition point accounts for the higher temperature observed in these experiments. Figure 2 portrays the curves obtained from two such experiments.

It had been noticed early that platy sulfanilamide crystals grown at ordinary temperatures changed when exposed to air (or to alcohol or acetone), becoming opalescent, even at room temperature. This change could be forestalled in a saturated or a controlled humidity (such as over 18% sulfuric acid). Crystals rinsed with alcohol gave evidence of water content in rough moisture determinations. Manometric dehydration was undertaken to determine the composition of the hydrate thus indicated.

Hydrate existence of orthanilamide or metanilamide had not been indicated either by change in appearance or by weight loss on drying, so manometric drying was not carried out in these cases.

In Fig. 3 is a graph of observed vapor pressure as wet crystals of sulfanilamide hydrate were

(3) These measurements were carried out by Drs. W. L. Seaman and J. J. Freeman, of the Calco Laboratories, to whom grateful acknowledgment is made.

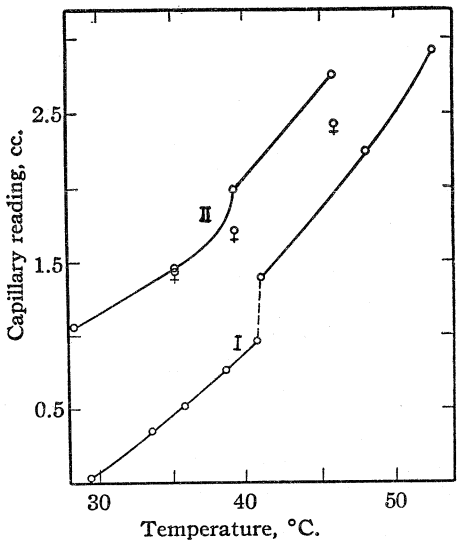


Fig. 2.—Dilatometry of sulfanilamide monohydrate: O, final readings; ♀, non-equilibrium points one hour after temperature change (Curve II).

dried at 21°, plotted against time. The first plateau, of course, corresponds to saturated solution wetting the crystals. After a sudden fall in pressure, another step occurs; crystals removed from the system at this point analyzed 9.4% water by drying and 9.1% by titration; theory for the monohydrate is 9.4%. Such a determination was carried out on two samples, from separate preparations of crystals, with the same results. Further dehydration, during which the temperature was raised to 30° and alcohol–carbon dioxide used on the cold trap, reduced the pressure to a few tenths of a millimeter. Drying at 110° of a sample removed at this point showed only 0.5% loss in weight.

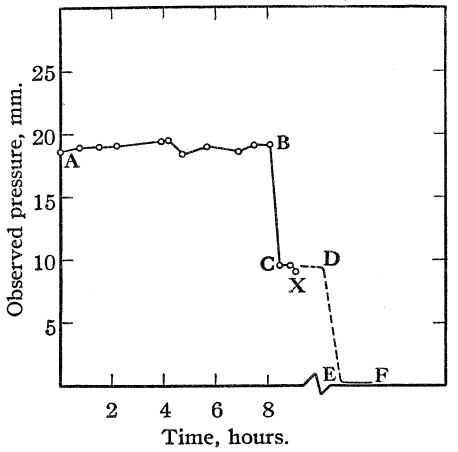


Fig. 3.—Manometric drying of sulfanilamide monohydrate: A-B, wet crystals; C-D, monohydrate; E-F, anhydrous solid; sample removed at X contained 9.4% of water; A-B and C-D at 21°, E-F at 30°.

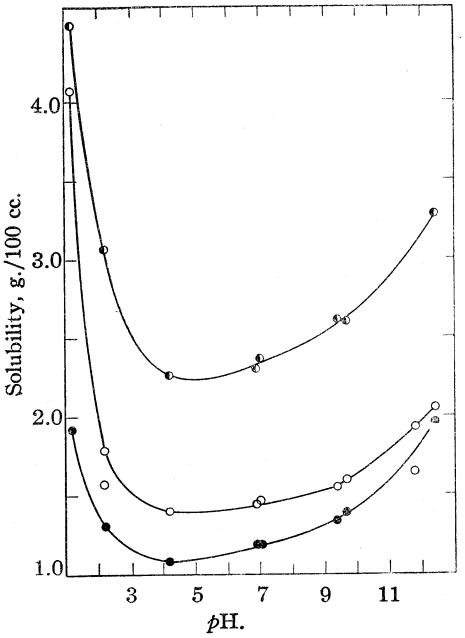


Fig. 4.—Solubility of sulfanilamide isomers in buffer solutions at 37°: ●, orthanilamide; ◐, metanilamide; O, sulfanilamide.

Solubility data at 37° in buffered solutions of various *p*H values appear in Table III. Figure 4 shows solubility to be minimum at *p*H 4.5–5.0. Solubility increases markedly above *p*H 9 and below *p*H 3. Sulfanilamide shows an especially great increase below *p*H 2. Different buffers of the same *p*H may give different results (Table III); the curves in Fig. 4 were drawn for corresponding buffers for the three isomers.

TABLE III

SOLUBILITY AND *p*H AT 37.0°

*p*H	Components	Ionic strength	Solubility, g./100 cc. Orth-anil-amide	Met-anil-amide	Sulf-anil-amide
1.2	KCl	0.12	1.92	4.48	4.07
2.2	KCl	.06	..	..	1.57
2.2	Phthalate	.05	1.31	3.07	1.79
4.2	Phosphate–citric acid	.84	1.08	2.26	1.40
6.9	Phosphate	.03	1.19	2.30	1.44
(5.7)	Distilled water	..	1.19	2.36	1.47
9.4	Boric acid–KCl	.08	1.34	2.61	1.55
9.7	Boric acid–KCl	.09	1.39	2.60	1.60
11.8	Glycine	.11	..	..	1.93
11.8	Citrate	.40	..	..	1.65
12.4	Borate	.23	1.96	3.28	2.05

Discussion

Several types of sulfanilamide crystals have been noted by Van Zyp.[4] Undoubtedly one of these

(4) Van Zyp, *Pharm. Weekblad*, **75**, 585 (1938).

is the hydrate form, but neither composition nor temperature conditions of formation were specified.

Polymorphism of sulfanilamide has been described by Watanabe,[5] working in Japan. By means of X-ray study three forms of the solid were defined. The crystals studied were all obtained from alcohol; hence Watanabe could not have obtained the hydrate which is the main feature of this investigation.

Since 37° is body temperature, the sulfanilamide hydrate or transition thereof may hypothetically bear some relation to therapeutic activity, perhaps as a water carrier in biological coupled reactions or as an energy transfer mechanism.

The behavior in buffers bears out the hypothesis that sulfanilamide and its isomers may behave as ampholytes, with minimum solubility at an "isoelectric point" (pH 4.5–5.0 at 37°). The solubility increase for sulfanilamide at pH 1.2 appears to be exceptionally large.

The similarity of "isoelectric point" of sulfanilamide with that of blood serum proteins may be involved in therapeutic activity.

(5) Watanabe, *Naturwissenschaften*, **29**, 116 (1941); *Chem. Abs.*, **36**, 695 (1942).

The authors are indebted to Dr. G. L. M. Christopher for help rendered in the preparation of this paper and to Dr. M. L. Crossley for the encouragement to carry through this type of investigation.

Summary

1. The aqueous solubilities of orthanilamide, metanilamide and sulfanilamide have been determined in the range 23–50°.

2. Heats of solution calculated from the solubility data are: orthanilamide 7820; metanilamide 9570; sulfanilamide below 37°, 10,860, above 37°, 9050 cal./mole.

3. The discontinuity in the solubility curve of sulfanilamide at 37° represents a transition, confirmed by dilatometry, and shown by analysis to involve a monohydrate.

4. Solubilities in buffered solutions of pH 1.2 to 12.4 at 37° exhibit a minimum for all three isomers at pH 4.5–5.0, with striking increase above pH 9 and below pH 3, especially for sulfanilamide below pH 2.

BOUND BROOK, NEW JERSEY RECEIVED MAY 7, 1942

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

Reactions in Solutions Containing O_3, H_2O_2, H^+ and Br^-. The Specific Rate of the Reaction $O_3 + Br^- \longrightarrow$

BY HENRY TAUBE

When ozone and bromide ion are mixed in acid solution, the net reaction

$$O_3 + 2H^+ + 2Br^- = O_2 + Br_2 + H_2O$$

takes place so rapidly that a direct measure of the specific rate is not possible. In the present paper, experiments on the measurement of this specific rate by an indirect method are reported. The system studied contained acid, O_3, Br^- at a relatively low concentration and H_2O_2. Hydrogen peroxide possesses the properties that at low (Br^-), it rapidly reduces bromine to Br^-,[1] that the reaction with Br^- under the present conditions is negligibly slow, and that the direct interaction with ozone is also slow.[2] The net reaction which takes place in this mixture is

$$H_2O_2 + O_3 = 2O_2 + H_2O \qquad (A)$$

It has been shown[2] that this reaction is accelerated by Br^-, and that the catalytic decomposition of ozone

$$2O_3 = 3O_2 \qquad (B)$$

which accompanies reaction A in a mixture of H_2O_2, O_3 and acid is suppressed by low concentrations of Br^-.

The experiments consisted of a study of the variation of the rate of A with (O_3), (H_2O_2), (H^+) and (Br^-). Analysis of the data showed that three distinct paths are available for reaction A. Mechanisms for these paths, consistent with the data, and with other work in this field are proposed.

Experimental

Acid solutions of O_3 at 0° were prepared as described[2]; redistilled water was used for the most part. Merck's inhibitor free Superoxol was used to make up the solution of H_2O_2. A stock supply of sodium perchlorate solution was prepared by neutralizing perchloric acid with C. P. sodium carbonate.

(1) Bray and Livingston, THIS JOURNAL, **50**, 1663 (1928).
(2) Taube and Bray, *ibid.*, **62**, 3357–3373 (1940).

The method of handling the solutions was the same as that described in the earlier article. Usually nine cells were filled for a single experiment; these were placed in an ice-bath shielded from light and analyzed at intervals. The time of emptying, less than one-tenth minute, was small compared to the shortest interval between successive quenchings, one and one-half minutes.

The rates were obtained by plotting the values of (O_3) or (H_2O_2) against time in minutes, and measuring the slopes at intervals on the curve. Each experiment yields values of the rates for a fairly wide range of (O_3) and (H_2O_2); for each experiment a table was computed listing corresponding values of time, (H_2O_2), (O_3), rates and suitable functions of these variables. The system is not nearly as sensitive to traces of impurities as it is in the absence of Br^- and results were reproducible.

All experiments were carried out at 0°. Except where otherwise stated, the ionic strength was maintained at 0.20 by the addition of sodium perchlorate solution. The units used throughout are: concentration in moles per liter and time, t, in minutes.

In all experiments for which rate data are presented, (H^+) and (Br^-) were sufficiently high to eliminate reaction B almost completely, so that $\Delta(H_2O_2) = \Delta(O_3)$. For the analysis in most cases the cell content was forced into an acidified solution of sodium bromide, and potassium iodide and ammonium molybdate solutions were then added. After the hydrogen peroxide had reacted completely with the iodide ion, the total iodine (equivalent to the sum of the ozone and hydrogen peroxide) was determined. One cell in each run was allowed to proceed to completion, and the final concentration of the reagent in excess then determined. This permitted the concentration of hydrogen peroxide and ozone at any time to be calculated from the corresponding value of their sum. Orienting experiments showed that this method gave the same results as the method of separate analysis.[2]

In most of the experiments, (Br^-) added was small compared to (H_2O_2) or (O_3); when (Br_2) was appreciable, appropriate corrections were made in calculating the concentration of ozone and hydrogen peroxide.

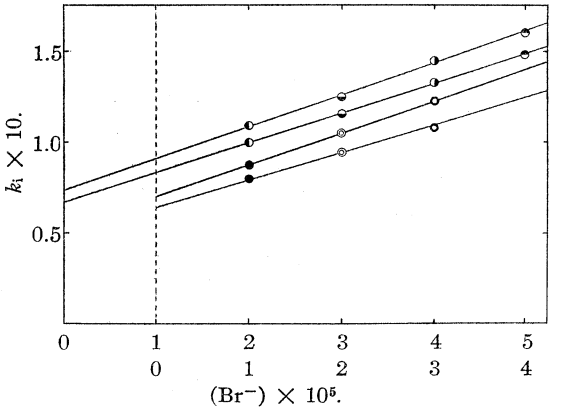


Fig. 1.—Variation of k_i with (Br^-); $\mu = 0.20$: $(H_2O_2) = 12.5 \times 10^{-4}$ M. The lower row of values for the abscissa refers to lines 3 and 4, the lines being numbered from top to bottom. Points represented by the same symbol are results of the same experiment; the upper one always is a result later in an experiment after (O_3) has decreased to the designated value. To eliminate (H_2O_2) as a variable, the data were corrected to the recorded value of (H_2O_2) using the law of variation with (H_2O_2) demonstrated in Fig. 2; the maximum correction was about 6%.

line	$(O_3) \times 10^4$	$(H^+) \times 10^3$	slope
1	2	1.16	1750
2	3	1.16	1600
3	1	2.60	1750
4	2	2.60	1520

Results

Figure 1 presents data on the variation of the rate of reaction A with (Br^-) at low values of (H^+) and at low values of the ratio $(O_3)/(H_2O_2)$. The specific rate k_i, which is plotted as ordinate, is defined by

$$-d(H_2O_2)/dt = -d(O_3)/dt = k_i(O_3)$$

For each line in the figure, the only variable is the concentration of Br^-. The results show that the rate law consists of at least two terms. One of these varies directly with (Br^-); its value is given by the slope of the straight lines through points of constant (H^+), (H_2O_2) and (O_3) and varying (Br^-). The slopes of the lines (*cf.* table under Fig. 1) are nearly constant and independent of (H^+). The slight variation as (O_3) decreases and time increases is discussed in connection with Fig. 2. The other term represented by the intercept on the vertical axis is independent of (Br^-); the variation of this term with (H^+) over a wide range is discussed below.

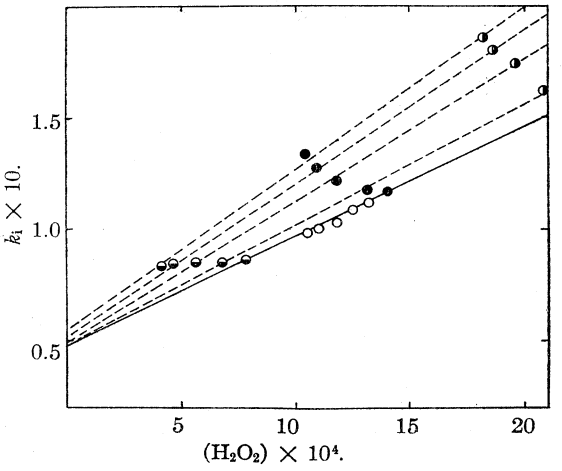


Fig. 2.—Variation of k_i with (H_2O_2), at 3×10^{-5} M Br^-, 1.16×10^{-2} M $HClO_4$, $\mu = 0.20$. All points from one experiment are distinguished by the same symbol. The open circles distinguish an experiment in which the method of handling the solutions was changed (see text). Numbering the lines from top to bottom: for line 1, $(O)_3 = 0.5 \times 10^{-4}$ M; for 2, 1.0×10^{-4} M; 3, 2×10^{-4} M; 4, 3.25×10^{-4} M; 5, 4.2×10^{-4} M.

Figure 2 shows the variation of k_i with (H_2O_2) at 1.16×10^{-3} M $HClO_4$, 3×10^{-5} M Br^- and low values of the ratio $(O_3)/(H_2O_2)$. Along each line, the only variable is (H_2O_2); from line to line, (O_3) differs. It is again apparent that there are at least two terms in the rate law. The peroxide independent term, which is represented by the finite limiting value of $k_i = 0.048 \pm 0.002$ at zero peroxide, can be identified with the bromide dependent term of Fig. 1. This follows since the coefficient obtained by dividing the value of the intercept by the concentration of $Br^-(0.048/3 \times 10^{-5}) = 1600$ is the same as the slope of the lines in Fig. 1. The peroxide dependent part of the rate law then corresponds to the (Br^-) independent term of Fig. 1.

The experiment in Fig. 2 represented by the open circles was an experiment in which five cells were rapidly and consecutively filled. During the experiment, the ozone concentration fell to one-third of its initial value; these points are seen to fall in line with the initial points in the other experiments and prove that k_i is independent of (O_3) (*i. e.*, rate is proportional to (O_3)) for these conditions. In all the other experiments, the process of filling the cells was interrupted to make analyses. This probably occasioned a loss of ozone from the main body of the solution and the variation of k_1, *ca.* 40% for an 8-fold variation in (O_3), with (O_3) shown by the lines through these points is therefore mainly due to this cause; these results have been included for the sake of completeness, but the lower line is taken as the best representation of the rate of reaction for these conditions.

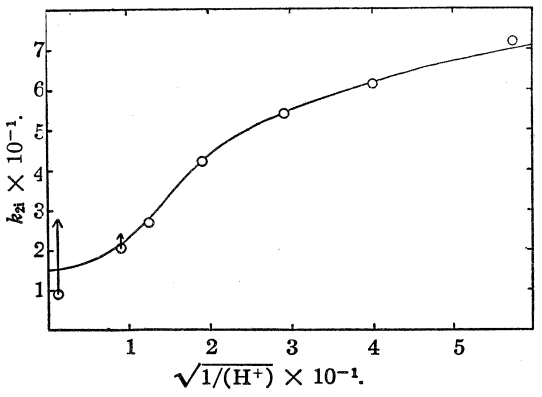


Fig. 3.—The variation of k_{2i} with (H^+); $\mu = 0.2$. $(O_3) = 3.0 \times 10^{-4}$ M, H_2O_2 = *ca.* 14.0×10^{-4} M for the series. $(Br^-) = 2 \times 10^{-5}$ M except in the two experiments at lowest H^+ where it was 5×10^{-5} M. In the two experiments at high (H^+), the bottom of the arrow is the value if the maximum correction for path III is applied; top is the value if no correction for path III is applied (see text).

The results of Figs. 1 and 2 may be summarized by the equation

$$k_i = 1600 \pm 100\ (Br^-) + k_H\ (H_2O_2) \qquad (I)$$

Line 2 in Fig. 1 passes through the most accurate data and the slope of this line was taken as the numerical coefficient of the first term of rate law I.

In rate law I, k_H is not a true constant but varies with (H^+). A number of experiments were performed to study this variation; these results are presented in Fig. 3. At values of $(H^+) < 1.15 \times 10^{-3}$ M, (Br^-) was raised to 5×10^{-5} M to suppress reaction B. k_H, at any value of (H^+) within the range for which rate law I is valid, can readily be calculated by the use of this equation from the measured value of k_i. As will be shown later, at high (H^+), Br^- is present at the steady state largely as Br_2, and a new path for reaction A is available. Corrections, consistent with the later findings, are applied to the experimental values k_i to allow for these effects; these corrections are necessary only at the two highest values of (H^+). There is an uncertainty in applying the correction for the new path due to bromine in the present range of values for $(O_3)/(H_2O_2)$; the uncertainty is in such a direction that k_H is greater than the plotted value. For the point at highest (H^+), k_H may well be twice as great as the plotted value; for the next point, only slightly greater. In spite of this uncertainty, the results indicate that k_H approaches limiting values both at high and at low (H^+).

When (H^+) and the ratio $(O_3)/(H_2O_2)$ are increased, the kinetics of the reaction change radically. In Fig. 4, the results of a series of experiments for this concentration region are presented. To represent these results, it was found convenient to define a specific rate k_{ii} (not necessarily a constant) by the equation

$$-d(H_2O_2)/dt = k_{ii} \sqrt{(H_2O_2)(O_3)}$$

A single experiment is represented by a series of points starting at the right and usually covers a 6–12 fold change in the concentration of hydrogen oxide. The lines have been drawn in to conform to the rate law

$$k_{ii} = 1.26 \sqrt{(Br_2)/(H^+)} + 1.41 \times 10^2 \sqrt{(Br_2)(H_2O_2)} \qquad (II)$$

($(Br_2) = (Br^-)_0/2$ where $(Br^-)_0$ is the concentration of bromide ion added) and represent the data with satisfactory fidelity except at the lowest

value of (H^+) investigated in this series (upper part of the figure).

In preliminary work, the law of variation with the concentration of added Br^-, $(Br^-)_0$, was tested over a wider range than is done in Fig. 4. These data are presented in Table I. The results, though not strictly comparable with those of Fig. 4 (the ionic strength was less and (H^+) was not accurately known) are consistent with them. These results again show that k_{ii} varies directly with $\sqrt{(Br_2)}$.

TABLE I

VARIATION OF k_{ii} WITH ADDED Br^-

$HClO_4$ is *ca.* 0.15 *M* and μ is *ca.* 0.15. $(H_2O_2)_0 = 3.6 \times 10^{-4}$ *M*.

$(Br^-)_0 \times 10^6$	$(O_3) \times 10^4$	$k_{ii} \times 10^2$	$\frac{k_{ii}}{\sqrt{(Br_2)}}$
10	7.60	1.30	0.58
20	8.17	1.87	.59
40	7.17	2.64	.59
100	6.87	4.20	.59
300	6.90	7.80	.63

Discussion

The rate laws obtained show that at each of the extremes—low (H^+), low $(O_3)/(H_2O_2)$ and high (H^+), high $(O_3)/(H_2O_2)$—there are two paths for reaction A.

The first term of rate law I and the first term of rate law II both follow from the non-chain path represented by the following reactions (arrows designate rate determining steps).

PATH I

$$Br^- + O_3 \xrightarrow{k_1} BrO^- + O_2 \qquad (1)$$

$$H^+ + BrO^- = HBrO$$

$$Br_2 + H_2O \underset{}{\overset{K_{Br_2}}{\rightleftharpoons}} HBrO + H^+ + Br^-$$

$$H_2O_2 + HBrO \xrightarrow{k_2} H^+ + Br^- + H_2O + O_2 \qquad (2)$$

When reaction 1 is the sole rate determining step (*i. e.*, (Br_2) and $(HBrO) \ll (Br^-)$), the simple rate law corresponding to the first term of rate law I follows. It will be shown that this condition is realized in the experiments at low values of (H^+) and $(O_3)/(H_2O_2)$. The numerical coefficient of this term therefore gives the value of k_1; thus, the rate of interaction of O_3 and Br^- at 0° and $\mu = 0.2$ is 1600 ± 100 l. mole^{-1} min.$^{-1}$.

The following considerations show that at low (H^+) and low $(O_3)/(H_2O_2)$, $(Br^-) \gg (HBrO)$. At the steady state, $k_1(O_3)(Br^-) = k_2(H_2O_2)(HBrO)$ and $(Br^-)/(HBrO) = k_2(H_2O_2)/k_1(O_3)$.

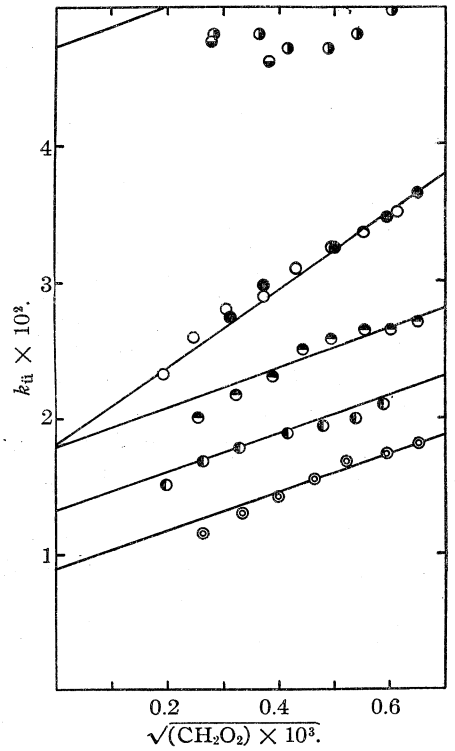


Fig. 4.—Variation of k_{ii} with (H_2O_2), (O_3), (H^+), $(Br^-)_0$ at high $(O_3)/(H_2O_2)$ and $\mu = 0.20$. All points obtained from a single experiment are distinguished with the same symbol.

Symbol	◎	◐	◓	●	○	◒	◑
$(O_3)_0 \times 10^4$	16.46	12.3	14.32	7.54	15.11	14.45	13.2
$(H^+) \times 10^2$	20.1	8.86	4.48	20.2	20.2	0.63	0.63
$(Br^-)_0 \times 10^5$	2	2	2	8	8	2	2

Bray and Livingston,[1] from an analysis of Balint's[3] measurements on the rate of reaction of bromine and peroxide at 0°, report for $k_2K_{Br_2}$ a value of $6.2 \times 10^{-4} \pm 9\%$. For the same ionic strength (zero) Liebhafsky[4] reports K_{Br_2} at 0° $= 6.9 \times 10^{-10}$. Thus $k_2 = 9 \pm 1 \times 10^5$.[5] When this value is substituted in the above expression together with $k_1 = 1600$, $(Br^-)/(HBrO) = 560$ when $(H_2O_2) = (O_3)$. For the experiments under consideration (H_2O_2) always exceeded (O_3) by more than a factor of 3 and $(HBrO)$ becomes correspondingly less compared to (Br^-).

To show that (Br_2) is small for the same conditions, the expression for the steady state concentration of Br^- when the hydrolysis is not complete and when $(HBrO) \ll (Br^-)$ (*i. e.*, $(O_3)/(H_2O_2)$ does not exceed *ca.* 25) is derived; the result is

(3) Balint, Thesis (in Hungarian), University of Budapest, 1910.

(4) Liebhafsky, THIS JOURNAL, **56**, 1500 (1934).

(5) This is the value calculated for $\mu = 0$; the value $\mu = 0.2$ should not differ widely since both molecules are neutral.

$$(Br^-) = \frac{\left(K^2_{Br_2} + 8(Br^-)_0 K_{Br_2} \frac{k_1}{k_2}(H^+)\frac{(O_3)}{(H_2O_2)}\right)^{1/2} - K}{4\frac{k_1}{k_2}(H^+)\frac{(O_3)}{(H_2O_2)}} \quad \text{(III)}$$

Using the values $k_1 = 1600$, $k_2 = 9 \times 10^5$ and K_{Br_2}[6] $= 1.1 \times 10^{-9}$, $(Br_2) = [(Br^-)_0 - (Br^-)]/2$ is calculated to be 5×10^{-7} for the most extreme case presented in Fig. 1 [lower right-hand point in Fig. 1; $(H^+) = 2.65 \times 10^{-3}$, $(Br^-)_0 = 3 \times 10^{-5}$, $(O_3)/(H_2O_2) = 0.148$]. The point under consideration is actually below the line through the other points; this effect may be attributed to the fact that some of the Br^- is in the form of Br_2 and the maximum rate is thus not observed.

A rate law of the form of the first term of rate law II follows from the mechanism above when (Br^-) and (HBrO) are small compared to (Br_2). It can readily be shown by using Equation III that this condition is realized for all the experiments in Fig. 4 except the two in the upper part of the diagram.

The rate law derived from the mechanism for this condition is

$$\frac{-d(H_2O_2)}{dt} = \sqrt{k_1 k_2 K_{Br_2}}\sqrt{\frac{(Br_2)}{(H^+)}}\sqrt{(O_3)(H_2O_2)}$$

where $(Br_2) = (Br^-)_0/2$. This has exactly the same form as the first term of rate law II. Comparing the coefficients of the theoretical and experimental laws we obtain the result: $k_1 k_2 K_{Br_2} = 1.60$. From the measured value of 1600 for k_1 and the estimated value of 1.1×10^{-9} for K_{Br_2} at $\mu = 0.20$ and 0°, we obtain for k_2 a value of 9.0×10^5. The agreement with the value of $9 \pm 1 \times 10^5$ calculated from Balint's results is good confirmation for the interpretation of the data. The limits of accuracy for the value of k_2 from the present work are about the same as for Balint's.

On the interpretation given, a discrepancy in the observed direction between the experimental points and those predicted by rate law II is expected at 6.3×10^{-3} M H^+ (experiments at the top of Fig. 4) since (Br^-) and (Br_2) have comparable values. However, a quantitative comparison of theoretical and experimental results is not possible since the contribution to the rate by the path corresponding to the second term of rate law II cannot be calculated accurately for this range of values for $(O_3)/(H_2O_2)$.

(6) Liebhafsky's value of $K_{Br_2} = 6.9 \times 10^{-10}$ for 0° and low ionic strength is corrected approximately for the change to $\mu = 0.2$ by dividing by γ^2_{HBr}. Livingston's value (THIS JOURNAL, **48**, 45 (1926)) of γ_{HBr} at $\mu = 0.2$ and 25° was used.

While the non-chain reactions of Path I give a consistent explanation for the first terms of both rate laws I and II, the last terms of these rate laws are best interpreted by chain reactions. Although the rate corresponding to the second term of rate law I is proportional to $(H_2O_2)(O_3)$, it cannot be explained by the direct interaction of ozone and hydrogen peroxide. The specific rate of interaction of these substances is 0.14 while k_H at 2.6×10^{-3} M is *ca.* 50. Experiments with inhibitors support the assumption of chain reactions. Table II presents data showing the effect of methanol in decreasing k_H.

TABLE II

EFFECT OF CH_3OH ON k_i AT 1.15×10^{-3} M $HClO_4$, 3×10^{-5} M Br^-, 4.18×10^{-4} M O_2

$(CH_3OH) \times 10^4$	$(H_2O_2) \times 10^4$	k_i	k_H
0	12.53	0.109	49
4	11.39	.076	25
10	11.18	.074	23
20	12.45	.074	21

Ethanol and phosphorous acid give similar results (the limiting value of k_H differing however for the different inhibitors) and a similar decrease in the rate under the conditions for which rate law II is valid is also observed. The fact that k_H (and the coefficient of the second term of rate law II) are not reduced to very low values is not inconsistent with the assumption of long chains. The radical which results from the reaction of the active intermediate with the "inhibitor" may itself catalyze the reaction[7a]; cases are known in which the resulting chains are longer than the original ones.[7b]

A rate expression of the form of rate law I follows (on the assumption of long chains) from the series of reactions (3)–(7).

PATH II

Chain initiating step

$$H_2O_2 + O_3 \xrightarrow{k_3} HO + HO_2 + O_2 \quad (3)$$

Chain continuing steps

$$HO_2 + O_3 \xrightarrow{k_4} HO + 2O_2 \quad (4)$$

$$HO + H^+ + Br^- = H_2O + Br \quad (5)$$

$$Br + H_2O_2 \xrightarrow{k_6} H^+ + Br^- + HO_2 \quad (6)$$

Chain breaking step

$$HO_2 + Br \xrightarrow{k_7} H^+ + Br^- + O_2 \quad (7)$$

Reactions 3 and 4 have been made plausible by other work[2]; 5, 6 (and 7 under limited conditions)

(7a) Taube and Bray, ref. 2, p. 3362.
(7b) Taube and Bray, ref. 2, p. 3363

find their exact analogy in experiments with $H_2O_2 + O_3 + Cl^-$.[2] Reaction 6 furthermore is a probable step in the photoreaction between peroxide and Br_2.[8] Br is presumably the intermediate which reacts with the inhibitors; the photochemical experiments of Dhar and Battacharya[9] indicate that Br and methanol do react.

If the reactions

PATH III

$$Br_2 + O_3 + H_2O \longrightarrow HO + Br + BrOH + O_2$$
$$\text{or } HO_2 + Br + Br^- + H^+ + O_2 \quad (8)$$
$$Br + Br \longrightarrow Br_2 \quad (9)$$

are substituted for the chain initiating and chain breaking steps, respectively, of Path II, the resulting mechanism (again assuming long chains) leads to a rate law of the form of the second term of rate law II. The following considerations show that these changes are not unreasonable. In going from the conditions for which rate law I is valid to those of II, (H^+), and (O_3) are increased, (H_2O_2) is decreased. (Br_2) increases markedly with respect to (H_2O_2), and reaction (8) becomes more probable than (3) on concentration considerations. Furthermore, increasing the ratio $(O_3)/(H_2O_2)$ increases $(Br)/(HO_2)$ and the chain breaking step (9) becomes more probable than (7).

It must be stressed that the second terms of rate laws I and II are limiting laws valid only for the extreme concentration ranges considered, where one or the other of the chain breaking steps (7) and (9) operate. Experiments which because of their complexity are not reported in detail suggest that in the intermediate range both chain breaking steps operate.

The variation of k_H with (H^+) observed in Fig. 3 can be explained if it is assumed the HO_2 is a fairly strong acid with $K_{diss.}$ *ca.* 10^{-2}. On this basis, at $(H^+) = 0.1\ M$, the free radical is present mainly as HO_2 and a limit for k_H at high (H^+) is expected; at $(H^+) = 10^{-3}\ M$, O_2^- will be the reactant, undergoing reactions similar to those of HO_2, and a limit for k_H at low acid will also result. Weiss,[10] Latimer[11] and Bray[12] suggest values of *ca.* 10^{-6}, *ca.* 10^{-6} and *ca.* 8×10^{-8}, respectively, but the evidence available for these low dissociation constants does not suffice to exclude the higher value indicated by the new kinetic data.[13] The experiments of Callow, Griffith and McKeown[8] and of Taube and Bray[2] on chain reactions of HO_2 do not give a clue to the value of K_{HO_2} since the substance was not involved in the chain breaking steps for the concentration range in which quantitative results were available.

In conclusion, a correlation of the present results with those obtained in the O_3, H_2O_2, H^+ and Cl^- system[2] may be interesting. In that case, the non-chain path corresponding to Path I contributed little to the reaction, due to the fact that the specific rate of interaction of O_3 and Cl^- is much less than that for O_3 and Br^- — 0.023 compared to 1600. For the same reason, (Cl_2) at the steady state was always very small, and the path corresponding to Path III was absent. The path analogous to Path II accounted for most of the reaction at high Cl^-; however, to eliminate HO, (Cl^-) had to be increased to such an extent that complications due to the formation of Cl_2^- appeared. Analogous to the behavior in the present system, there appeared to be a change (at low Cl^-) from $Cl + Cl \rightarrow$ as chain breaking step to $HO_2 + Cl \rightarrow$ when the ratio $(O_3)/(H_2O_2)$ was decreased. Finally, the system with Br^- present is less sensitive to stray impurities than with Cl^-, since Br is less reactive than Cl.

The author is grateful to Professor William C. Bray for helpful discussions of this work.

Summary

The rate of reaction A is studied over a wide range of the variables (O_3),(H_2O_2), (H^+) and (Br^-) at 0° and limiting rate laws, valid for extreme conditions, are obtained.

Three paths are necessary and sufficient to interpret the data. The results are consistent with the following conclusions:

Path I, a non-chain path, involves oxidation of Br^- by O_3 to BrO^-, and reduction of hypobromous acid by peroxide. The specific rate of the former reaction is found to be 1600 ± 100, and the value of 9×10^5 obtained for the latter reaction agrees with the value reported in the

(8) Callow, Griffith and McKeown, *Trans. Faraday Soc.*, **35**, 412–20 (1939).

(9) Dhar and Battacharya, *Z. anorg. allgem. Chem.*, **176**, 372 (1928).

(10) Weiss, *Trans. Faraday Soc.*, **31**, 968 (1935). Weiss promised publication of the experimental work on which his estimate is based. A search of the literature from 1935 to date failed to reveal this work.

(11) Latimer, "Oxidation Potentials," Prentice-Hall, Inc., New York, N. Y., 1938, p. 41.

(12) Bray, THIS JOURNAL, **60**, 86 (1938).

(13) An alternative explanation, suggested by the Referee, for the variation of k_H with (H^+) is that HO_2 forms a complex $HO_2 \cdot H^+$. Evidence for or against the existence of such a complex with a dissociation constant of 10^{-2} could not be found in the literature.

literature. No evidence is found for the oxidation by O_3 of Br^- by a free radical process.

Paths II and III are chain paths initiated by reaction of ozone with peroxide and bromine, respectively, to produce free radicals. The chain continuing steps are the same for both paths; the nature of the chain breaking step depends on the ratio $(O_3)/(H_2O_2)$. An explanation of the variation of the rate by Path II with (H^+) is afforded by the assumption that HO_2 is a fairly strong acid with $K_{diss.}$ *ca.* 10^{-2}.

ITHACA, NEW YORK RECEIVED MARCH 25, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY]

The System Sodium Nitrate–Dioxane–Water at 25°

BY B. SELIKSON AND J. E. RICCI

In connection with studies on the solubilities of salts in dioxane-water mixtures the formation of a two liquid system was observed in high dioxane solutions saturated with sodium nitrate. The experimental study of the phase relationships of such ternary systems involving a solid and two liquid components is in general rendered difficult by the problem of analysis for one of the liquid components in addition to the usually simple determination of the solid component. For solids forming no solid solvates with the liquid components the solubility curve is easily determined as a binary problem by using mixed solvents of known composition. Under favorable circumstances a binodal curve in such a system may be established by the synthetic method of titration with one of the liquid components, as in the system potassium carbonate–dioxane–water studied by Kobe and Stong.[1] Otherwise the analytical problem has usually been solved through the measurement of some physical property of the solution, or of the distillate from some ternary solution or phase, for the determination of the ratio of the two liquid components; examples of such properties are the refractive index (used for the study of the system lithium chloride–dioxane–water, by Lynch[2]), the density, or even the solubility of some reference salt in the unknown mixture of the two liquids. For more precise work it is desirable to attempt some direct determination of one of the liquid components. In the system silver nitrate–dioxane–water,[3] in which a solid dioxanate of silver nitrate appears at 25°, water was determined directly gravimetrically, with fairly accurate results, by volatilization of the solvents and absorption of water in barium monoxide. In the present system, a more rapid and possibly more exact method was attempted, by the application of the Karl Fischer reagent for the direct volumetric determination of water.[4]

Materials and Analysis.—The sodium nitrate was a C. P. sample used without further purification, after grinding and drying at 110°. The dioxane was treated and dried as described in previous similar investigations.[5] The Karl Fischer reagent (active ingredients: iodine, sulfur dioxide and pyridine, in methanol as solvent) prepared according to the directions of Smith, Bryant and Mitchell,[6] was used with synthetic "anhydrous" methanol as back-titrating solution, and was standardized against a standard solution containing a known weight of pure water in the same methanol. The water content of the methanol and the effective titer of the reagent itself were calculated from a set of titrations using 1, 2 and 5 ml. (all at least in duplicate) of the standard solution of water (1 ml. containing 0.01793 g. of H_2O by preparation). The titer of the Karl Fischer reagent was found to fall with time, as expected (from 0.002582 to 0.001986 g. of water per ml. in fifty-eight days); in the actual use of the reagent, however, standardization titrations against the standard water solution were always run just before and just after any set of analyses, all being done within a few hours at most, so that the error from such changing strength could be kept low. It was found, moreover, that the water content of the back-titrating methanol also changed (increased) with time, so that a curve of this effect was used to estimate the water content of the methanol for some of the standardizations for which there had not been a satisfactory simultaneous determination of the water equivalent of the methanol. These corrections were, of course, small, inasmuch as relatively only small volumes of the methanol were used in back-titration, and the change in its water titer was only from 0.00033 to 0.00056 g. of water per ml., in the same period of fifty-eight days.

Solubility Determinations.—The methods for the preparation of complexes, temperature control, attainment of equilibrium, sampling of liquids for analysis and approximate density determination, were as used in previous investigations.[3] The equilibrium solutions were analyzed

(1) Kobe and Stong, *J. Phys. Chem.*, **44**, 629 (1940).
(2) Lynch, *ibid.*, **46**, 366 (1942).
(3) Skarulis and Ricci, THIS JOURNAL, **63**, 3429 (1941).
(4) Fischer, *Angew. Chem.*, **48**, 394 (1935).
(5) Davis and Ricci with Sauter, THIS JOURNAL, **61**, 3274 (1939).
(6) Smith, Bryant and Mitchell, *ibid.*, **62**, 3504 (1940).

TABLE I

SYSTEM $NaNO_3$–DIOXANE–WATER AT 25°

No.	Original complex %$NaNO_3$	Original complex %H_2O	Lower liquid %$NaNO_3$	Lower liquid %H_2O	Lower liquid Density	Upper liquid %$NaNO_3$	Upper liquid %H_2O	Upper liquid Density	Solid phase	Extrapolation error, %H_2O
1	..	..	47.87	(52.13)	1.384				$NaNO_3$	
2	55.44	36.37	40.91	48.22	1.321				$NaNO_3$	+0.03
3	51.03	33.70	34.94	44.85	1.266				$NaNO_3$	− .23
4	49.28	32.41	32.35	43.27	1.252				$NaNO_3$	− .19
5	43.89	27.30	24.69	36.60	1.191				$NaNO_3$	+ .12
6	37.92	24.81	20.02	31.88	1.157				$NaNO_3$	+0.29
7	Excess $NaNO_3$		17.74	30.09	1.144	0.43	6.14	1.032	$NaNO_3$	
8	Excess $NaNO_3$		17.84	30.07	1.147	.46	6.22	1.030	$NaNO_3$	
9	Excess $NaNO_3$		18.02	29.92	1.146	.45	6.13	1.035	$NaNO_3$	
	Average		17.84	30.03[a]	1.146	.44	6.16[b]	1.032	$NaNO_3$	
10	By synthesis		15.36	29.20					None	
11	6.96	16.81	14.71	28.70	1.129	.57	7.08	1.035	None	
12	7.36	19.34	12.17	27.99	1.108	.74	7.88	1.033	None	
13	By synthesis					2.34	14.47		None	
14	14.90	4.13				.24	4.63	1.029	$NaNO_3$	+1.23
15	16.71	3.28				.12	3.86	1.028	$NaNO_3$	+0.37
16	18.54	1.62				.05	2.00	1.029	$NaNO_3$	− .05
a						.072	3.74		$NaNO_3$	
b						.032	2.86		$NaNO_3$	
c						.009	1.90		$NaNO_3$	
d						.005	0.96		$NaNO_3$	
e						.003	.00		$NaNO_3$	

[a] Point A of Fig. 1. [b] Point B of Fig. 1.

for sodium nitrate by evaporation to constant weight at 100–150°. For the determination of water weighed samples of the ternary solutions were diluted with dioxane in 25-ml. volumetric flasks, and suitable aliquots (usually 1 or 2 ml., requiring on the average about 15 ml. of titrating solution) were analyzed by means of the Karl Fischer reagent. Preliminary experiments had established that neither dioxane nor sodium nitrate interfered with the water determination. Addition of definite volumes of dioxane during standardizations showed the presence of only a very small amount of water in the dioxane, amounting to a practically negligible correction of only about 0.02 ml. of the reagent per ml. of dioxane.

Except for an occasional loss of sample, the solutions were all analyzed in duplicate for each of the two components determined. Five of the analyses (which were generally made after a day or two of rotation of the complexes) were repeated after a few more days or longer, to verify the attainment of equilibrium. The values listed in the table are the final average compositions thus determined for each point on the isotherm. The isothermally invariant solutions saturated with sodium nitrate were analyzed from three different complexes. The relative disagreement in the duplicate determinations of sodium nitrate were generally very small, as expected; for the water determination the disagreement of duplicates averaged 3–4 parts per 1000. The average absolute error in the water determination may be estimated from the algebraic extrapolations of the eight tie-lines for single liquids saturated with sodium nitrate as solid phase. These tie-lines extrapolate to 100% sodium nitrate with an average deviation of 0.31% calculated as water; conversely, assuming the solid phase to be pure sodium nitrate, as it evidently is, the average absolute error of the determination of the water content of these solutions is calculated to be 0.08%.

Results.—The results of the solubility determinations are listed in Table I and shown graphically in Fig. 1. The compositions are given in terms of weight per cent.

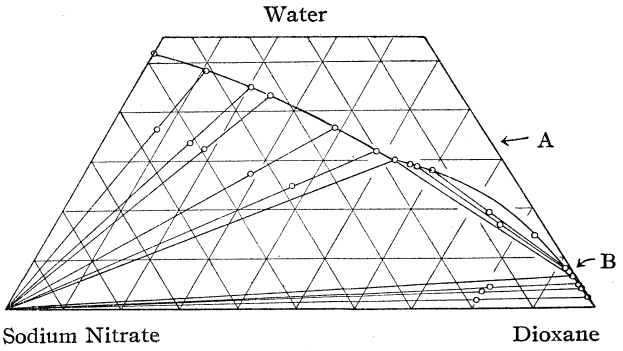


Fig. 1.—System sodium nitrate–dioxane–water at 25°.

Discussion.—On the basis of the diagram and of the algebraic extrapolation of tie-lines, the only solid phase is seen to be unsolvated sodium nitrate. The solubility curve of this solid, however, is seen to be broken by a rather flat binodal region in which immiscible liquids are formed. The isothermally invariant conjugate liquids in equilibrium with excess of solid sodium nitrate have the following compositions

	% $NaNO_3$	% H_2O	Density
Lower layer	17.84	30.03	1.146
Upper layer	0.443	6.16	1.072

Two pairs of conjugate solutions in the binodal area, not saturated with solid sodium nitrate, were determined by direct and complete analysis of the equilibrium phases formed from known mixtures of the three components (complexes 11 and 12 of Table I). The two tie-lines so obtained are sufficient to indicate that the plait point of the binodal curve must lie considerably over toward the dioxane-rich side. Two other points on the binodal curve (numbers 10 and 13 of Table I) were determined synthetically by a kind of titration: addition of solid sodium nitrate, in successive small portions, with shaking, to known weights of suitable mixtures of water and dioxane. The appearance of a turbidity indicating the formation of a second liquid marked a point on the binodal curve. In experiment no. 13 the liquids so formed were almost immediately approximately equal in volume, indicating proximity to the plait point, which, however, was not further investigated.

The last five values (a-e) listed in Table I were obtained in some earlier more precise work on the effect of water on the solubility of sodium nitrate in dioxane, using more highly purified dioxane and sodium nitrate. These mixtures were rotated for at least two weeks, and were analyzed in duplicate, and only for sodium nitrate, the percentage of water in the equilibrium solutions being calculated from the exact composition of the mixed solvent, prepared by weight. An enlarged plot of these special points for this region of the system is shown in Fig. 2, in which the shape of the curve is seen to be similar to the corresponding portion of the solubility curve of silver nitrate in dioxane containing small amounts of water.[3]

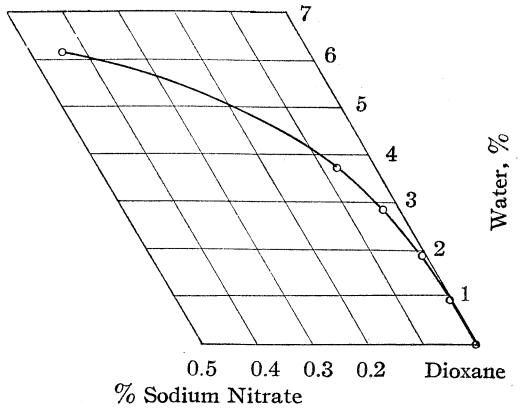


Fig. 2.—Effect of water on solubility of sodium nitrate in dioxane, at 25°.

Summary

The solubility relationships in the ternary system sodium nitrate–dioxane–water at 25° have been investigated, using a direct analytical determination of water in the equilibrium liquids by means of the Karl Fischer reagent. A small region of immiscible liquids appears, for solutions containing between 52.13 and 93.40% dioxane and between 17.84 and 0.44% sodium nitrate. Exact determinations are also given for the solubility of sodium nitrate in dioxane containing very small percentages of water.

NEW YORK, N. Y. RECEIVED JULY 13, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

The Relative Surface Tension of Potassium Chloride Solutions by a Differential Bubble Pressure Method[1]

BY F. A. LONG AND G. C. NUTTING

The surface tensions of dilute aqueous solutions of electrolytes have been investigated recently by a capillary height[2] and by a ring method.[3] Both show a minimum in the surface tension at about 0.001 normal although the depth of the minimum is considerably larger for the ring method. To explain the discrepancy of these results from the theoretical Onsager–Samaras[4] prediction, two different types of explanations have been advanced. Dole[5] and also Bikerman[6] have developed theories on the assumption that the results are true surface tensions. Langmuir[7] postulated that the true surface tension did not have a minimum and that the experimental results were due to the neglect of the zeta potential at the silica–solution interface. This theory has been discussed in more detail by Jones and Frizzell.[8]

(1) Presented at the Atlantic City meeting of the American Chemical Society, September, 1941.

(2) Jones and Ray, THIS JOURNAL, **59**, 187 (1937); **63**, 288, 3262 (1941).

(3) Dole and Swartout, *ibid.*, **62**, 3039 (1940).

(4) Onsager and Samaras, *J. Chem. Phys.*, **2**, 528 (1934).

(5) Dole, THIS JOURNAL, **60**, 904 (1938).

(6) Bikerman, *Trans. Faraday Soc.*, **34**, 1268 (1938).

(7) Langmuir, *Science*, **88**, 450 (1938).

(8) Jones and Frizzell, *J. Chem. Phys.*, **8**, 986 (1940).

The present paper reports an investigation of the surface tension of dilute potassium chloride solutions using another method of measurement. The procedure employed is a differential adaptation of the maximum bubble pressure method and is in essence a modification of the method devised by Warren.[9]

The Method.—For a capillary tube small enough so that the bubble formed is a true hemisphere the equation for the maximum bubble pressure method is

$$P_{max.} = gd\rho + (2\gamma/r) \qquad (1)$$

where d is the depth of immersion of the tube, ρ is the density difference between the liquid and the gas, γ is the surface tension and r is the radius of the tube. As this equation indicates the method is free from any assumption about the contact angle. Warren evolved a differential adaptation of this method by using two identical capillaries connected to a single source of gas under a slight pressure. These capillaries were immersed below the liquid surfaces of two different vessels, one containing pure solvent and the other the solution whose relative surface tension was to be measured. The heights of the vessels and thus the depths of immersion of the capillaries were varied with micrometer screws until bubbles came alternately from the two tubes. The maximum pressure in the bubbles is then the same and by measuring the depths to which the two tubes are immersed and the densities of the solutions, the ratio of the two surface tensions can be obtained.

The method used in the present work eliminates the difficult task of measuring the depths of immersion with precision and substitutes a measurement of surface areas and volumes. A sketch of the apparatus is given in Fig. 1. In this figure A and A′ are two similar circular glass vessels of about two-liter capacity and inner cross sections of about 250 sq. cm. The walls of these vessels are very nearly perpendicular. C is a bent T made of Pyrex glass through which gas flows. The two ends of this T that dip into the solutions have identical capillary exits from which the bubbles emerge. Saturated nitrogen gas under a pressure of a few cm. of water enters the other opening of the T and its rate of flow is regulated by a valve V which is an ordinary Hoke needle valve. The glass rod R which dips into the right vessel is attached to a screw of known pitch. Each vessel contains a stirrer, S and S′. In the actual setup the two vessels rest on a very rigid framework which allows them to be immersed in a constant temperature water-bath. The T apparatus is attached rigidly to the same framework. The stirrers and the rod R are attached to a separate rigid frame. L and L′ are close fitting glass lids with holes for the tubes and rods.

(9) Warren, *Phil. Mag.*, [7] **4**, 358 (1927).

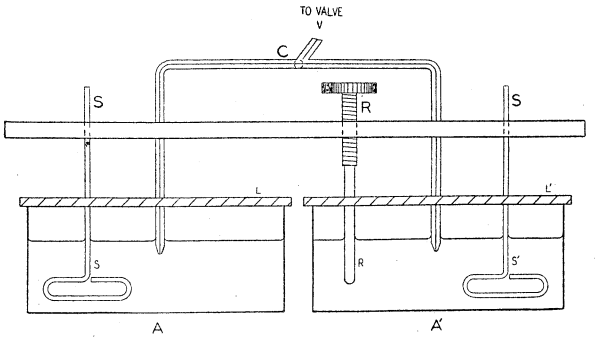


Fig. 1.—Differential bubble pressure apparatus.

The cross sectional areas of the two vessels were obtained by eight measurements of their diameters, taken at the height to which 1000 ml. of solution came. The net areas were obtained by subtracting the cross sectional areas of the rods and tubes that were present in the actual setup.

The tips of the T apparatus were obtained by breaking a selected piece of capillary tubing with a very nearly circular cross section. Tubes were used only if the breaks were smooth and perpendicular to the axis of the tube. By using two ends of a given break it was certain that the two orifices had the same diameter. The circularity and the diameter of the orifices were determined by six different measurements with a traveling microscope. Tubes were rejected if any diameter differed by more than 1% from the average. The diameter of the capillaries as measured by a traveling microscope is certainly not accurate to more than a few tenths of a per cent. but as will appear later, this is sufficient. Before use the area of the ends of the capillaries was reduced to approximately four sq. mm. by tapering the ends on a grinding wheel.

To make a surface tension determination the two vessels are filled with just less than 1000 ml. of water, placed in the water-bath and the stirrers, rod, lids and T apparatus are put in place. After an hour or so has elapsed, to ensure temperature equilibrium, a slow current of gas is allowed to pass into the T apparatus. This gas is at a constant pressure of 10 to 12 cm. of water and the valve V is adjusted so that bubbles form from one of the orifices at a constant rate of one bubble every twenty to forty seconds. Water is added to the vessels until a single drop will cause the bubbles to shift from one orifice to the other. The water in the two vessels is stirred, allowed two to four minutes to equilibrate and then the rod R is turned so that bubbles come with equal frequency from the two orifices. This indicates equal maximum bubble pressures and represents the zero point for the apparatus. The position of the rod R (which is equipped with a scale to measure the distance it is immersed) is a measure of this balance point. Three or four further determinations of this zero point are made. Usually the apparatus will show a constant balance for an hour or more. Since the two vessels contain only water, at the balance point the depths of immersion of the two tips are identical.

After the zero point is established, a few ml. of a potassium chloride solution of known concentration is added to one of the vessels from a weight pipet. This shifts the bubbling entirely over to the other orifice. Water is added to the other vessel, again from a weight pipet, until

the bubbles just shift back to the first orifice. The two vessels are then stirred and the final adjustment to a new balance, the condition where bubbles come from both orifices with equal frequency, is made by changing the position of the rod R. This new balance is checked as before to see whether it remains constant. If so the apparatus is disassembled, the depths to which the tips are immersed is determined to about 0.1 mm. and the final volume of the dilute potassium chloride solution in the one vessel is determined to about two ml.

The equation for the calculation of the relative surface tension follows directly from equation (1). At the initial balance since both vessels contain water and since the orifices are identical the equality of maximum pressures means that $d_0 = d_1 = d$. At the final balance point there is again a state of equal maximum bubble pressure. Hence

$$P_{\max.} = g\rho_0(d + \Delta d_0) + \frac{2\gamma_0}{r_0} = g\rho_1(d + \Delta d_1) + \frac{2\gamma_1}{r_1} \quad (2)$$

where the subscript zero refers to the water and the subscript one to the potassium chloride solution. Neglecting for the moment the zeta potential effect, $r_0 = r_1$. Δd_0 and Δd_1 are the increases in depth of immersion of the two tips. These can be calculated precisely from the surface areas of the two vessels and the volume increases caused by the additions of water and salt solution and by the change in position of rod R. A transformation gives

$$\frac{\gamma_1}{\gamma_0} = RST = 1 + \frac{gr}{2\gamma_0}[d(\rho_0 - \rho_1) + (\Delta d_0\rho_0 - \Delta d_1\rho_1)] \quad (3)$$

For dilute electrolyte solutions, when the capillaries are immersed only slightly, the last term involving the precisely known Δd's is considerably larger than the one involving d which is less precisely known.

For large capillaries the measured radius should not be used in the above equation; instead the problem should be solved by the use of the Bashforth and Adam tables.[10] For water solutions and for tubes of radius smaller than 0.07 cm., a corrected radius can be obtained from the Schrödinger[11] approximation

$$\frac{2\gamma}{g\rho} = rh\left(1 - \frac{2r}{3h} - \frac{r^2}{6h^2}\right)$$

For the capillaries used in the present work an effective radius was calculated for water by means of this equation and then used for the work with dilute solutions. This corrected radius differs so slightly from the measured value that the calculation is hardly necessary. More important is the fact that the difference in the correction for pure water and for dilute electrolyte solutions is quite negligible so that it is justifiable to use the same value of the radius for both.

Precision of the Method.—In order to illustrate the errors of the method, the data and calculations for a determination of the relative surface tension of a solution of 0.0048 molar potassium chloride are given in Tables I, II and III. The errors given for the original data are estimated but they are subsequently treated as probable errors.

TABLE I

PRELIMINARY MEASUREMENTS AND ESTIMATED ERRORS

Net surface area of left dish	= 247.74 ± 0.3 sq. cm.
Net surface area of right dish	= 247.06 ± 0.3 sq cm.
Capillary radius	= 0.0427 ± 0.0002 cm.
One turn of rod R	= 0.0407 ± 0.0004 cc.

TABLE II

Data for a determination of the relative surface tension of 0.0048 M potassium chloride. The initial potassium chloride solution was 1.086 ± 0.001 M and its density was 1.04667 ± 0.00005.

Data	
Initial balance of R	= 16.2 ± 0.1 turn
KCl solution added to left	= 4.6385 ± 0.0002 g. = 4.4316 ± 0.0002 cc.
Water added to right	= 4.4737 ± 0.0002 g. = 4.4869 ± 0.0002 cc.
New balance of R	= 18.4 ± 0.2 turns
Final volume of KCl solution	= 1000 ± 2 ml.
Final immersion of capillaries	= 0.67 ± 0.01 cm.
Derived data	
Volume on right due to rod R	= 0.0895 ± 0.0085 cc.
Net volume increase on right	= 4.5764 ± 0.0090 cc.
Δd_0, inc. of immersion on right	= 0.018481 ± 0.00005 cm.
Molar volume change on left (due to dilution of KCl)	= −0.0097 ± 0.0001 cc.
Net volume increase on left	= 4.4219 ± 0.0003 cc.
Δd_1, inc. of immersion on left	= 0.017849 ± 0.00002 cm.
Concentration of final KCl	= 0.00481 ± 0.00001 M
Density of final KCl	= 0.997304 ± 0.000005

TABLE III

CALCULATION OF RST BY EQUATION 4 FROM THE DATA OF TABLE II

$$RST = 1 + \frac{gr}{2\gamma_0}[d(\rho_0 - \rho_1) + (\Delta d_0\rho_0 - \Delta d_1\rho_1)]$$
$$= 1 + 0.289[0.65(-0.000230) + (0.018481\ \rho_0 - 0.017849\rho_1)]$$
$$= 1 + 0.289[-0.000149 + 0.000626]$$
$$= 1.000138 \pm 0.000016$$

An inspection of the data in Tables II and III shows that the largest errors arise from the determination of the position of the rod R and from the measurement of the surface areas. Errors in concentration, density and molar volume correction, which are unimportant in this example, become more important as the concentration increases

(10) Adam, "Physics and Chemistry of Surfaces," 2nd edition, p. 365.

(11) Schrödinger, *Ann. Physik*, **46**, 413 (1915).

but remain relatively small up to 0.05 molar potassium chloride.

The error in the surface areas can be examined by making a determination in the same way as for a salt solution but adding water to both vessels. For solutions of equal density equation 3 reduces to

$$RST = 1 + \frac{gr\rho_0}{2\gamma_0}(\Delta d_0 - \Delta d_1) \qquad (4)$$

Thus if the vessels both contain water ($\Delta d_0 - \Delta d_1$) should be zero. For one pair of vessels, a series of fourteen water determinations gave an average Δd difference of only 0.00002 cm. and it was concluded that the measured areas were mutually consistent. For a second pair of vessels, a series of twelve water determinations gave a Δd difference of 0.0015 cm. and this value was used to reduce the value of the area of one vessel by 0.38 sq. cm.

A more important function of these water determinations is to test the over-all behavior of the apparatus. For example, a series of fourteen water determinations gave a mean deviation of ($\Delta d_0 - \Delta d_1$), irrespective of sign, of 0.000032 cm. This figure agrees fairly well with the estimated error listed in Table III and clearly indicates that the apparatus shows a rather consistent behavior.

The inherent sensitivity of the apparatus can be tested by finding the least change in the immersion of the rod R, and thus the least height change, that will cause the bubble flow to shift from predominantly one capillary to predominantly the other. Lack of sensitivity is the cause of the error in the position of R which is shown in Table II to be the most important source of error in a determination. It has been found that various pairs of capillary tips show quite different sensitivities. For a good set of tips 0.1 turn of R will shift the bubble flow and the shift is reversible in the sense that a constant zero is maintained. For a poor set as much as 0.8 turn of R may be necessary. Tips that needed over 0.4 turn to cause a shift of bubble flow were not used in the surface tension determinations and one of the functions of the frequent water determinations was to test the sensitivity.

Errors from contamination are decreased in the present apparatus due to the fact that the bubbles are formed below the main surface of the liquids and are formed continuously. Even so, all parts of the apparatus were cleaned with hot chromic acid solution before every experiment. The only exception to this was that a surface tension determination was often preceded by a water run. No lubricated valves of any sort were used. The weight pipets used to introduce solutions were constructed on a siphon principle to eliminate stopcocks.

Temperature Control.—The temperature coefficients of the surface tension of water and of salt solutions are quite similar so that for this type of differential apparatus it is only important that the temperature of a given determination be constant. Actually the water-bath was maintained at 25 ± 0.01° and since any temperature fluctuations are damped by the lagging effect of the thick glass vessels errors due to temperature variation are well within the limit of other errors.

One factor which might affect the temperature equality is the heat of dilution of the added solution. The data[12] for potassium chloride and for sucrose indicate that for solutions below 0.01 molar this factor is negligible. However for more concentrated solutions or for solutions with large heats of dilution this effect can be of some importance.

Bubble Rate.—Since the present procedure involves a continuous flow of gas it is a dynamic method as contrasted with a truly static method like the capillary rise. Whether such a dynamic method will measure the true equilibrium surface tension of a solution depends upon the rate at which the bubbles flow and upon the speed with which the final surface tension is established. It seems reasonable that for solutions of materials like simple salts or sucrose where the adsorption is small and for which no barrier to diffusion seems probable the surface tension will be established in a very short time. Some experimental evidence is available which justifies this. Working with fairly concentrated sodium chloride solutions, Bond and Puls[13] concluded that the equilibrium surface tension is established in less than 0.003 second. From a fairly rough equation they calculated that the actual time is probably of the order of 10^{-10} seconds.

If the work of Bond and Puls gives the correct order of magnitude for the time required to reach equilibrium, then a bubble rate of the order of one every few seconds should allow ample time. To test this, experiments have been done with bubble rates ranging from one every five seconds to one

(12) Landolt–Börnstein, Erg. IIb, pp. 1538, 1545.
(13) Bond and Puls, *Phil. Mag.*, [7] **24**, 864 (1937).

every two minutes. Table IV gives the surface tension results for four potassium chloride solutions, all close to 0.0024 molar. As nearly as possible these four runs were carried out in an identical fashion. The same apparatus assembly and the same initial potassium chloride solution were used. The only difference was in the bubble rate. The constancy of the results for a ten-fold variation of bubble rate strongly suggests that both bubble rates are slow enough to allow the equilibrium surface tension value to be reached.

TABLE IV

COMPARISON DETERMINATIONS OF THE SURFACE TENSION OF 0.0024 *M* POTASSIUM CHLORIDE

Seconds per bubble	Molar concn.	*RST*
90	0.00229	1.000097
100	.00235	1.000099
9	.00249	1.000072
9	.00241	1.000106

Measurements of the surface tension of sugar solutions also afford evidence that the equilibrium surface tension is attained. The results obtained for sucrose with a rate of one bubble every twenty to forty seconds are in quite good agreement with Jones and Ray's truly static results. Since sucrose is a large molecule with a rather small diffusion coefficient it would be expected to afford a more severe test than electrolytes like potassium chloride. Consequently on the basis of these results and the previously mentioned work, it is concluded that for solutions of simple salts, sucrose and similar molecules a bubble rate of one every twenty seconds or slower will give equilibrium surface tension values.

Preparation of Materials.—The water used in all this work was conductivity water prepared in a Barnstead conductivity water still. No attempt was made to free the water from carbon dioxide. Occasional determinations of the conductivity of the water gave an average value of 0.8×10^{-6} mho. This water was stored in a settling tower similar to the type used by Jones and Ray.[2]

The nitrogen gas used for the bubbles was taken from a tank of water-pumped nitrogen and was passed through absorbent cotton and then through washing towers containing chromic acid and sodium hydroxide. It was finally passed through several washing towers containing water to saturate it with water vapor, into a twelve liter reservoir flask and so to the valve. The pressure of the gas was maintained at a constant value by maintaining a continuous flow of about 1 cc. per minute and letting the excess flow out of the system through a T tube immersed to a depth of 15 cm. in mineral oil.

Reagent grade potassium chloride was used without any preliminary recrystallization since the work of Jones and Ray indicated that small amounts of other salts would not affect the results. The salt was, however, fused in platinum dishes to remove any organic matter. Solutions were obtained by transferring weighed amounts of the fused potassium chloride to volumetric flasks and making the solutions up to the required volumes.

Sucrose Measurements.—Several measurements were made with sucrose in the range 0.001 to 0.01 molar. The capillary tips used in this work had radii of 0.0427 cm. The necessary density and molar volume data were obtained from Landolt–Börnstein.[14] The experimental results are shown graphically in Fig. 2 in which the data of Jones and Ray are plotted as solid circles for comparison. It is obvious that the values are a quite linear function of concentration and also that they agree rather well with the Jones and Ray data.

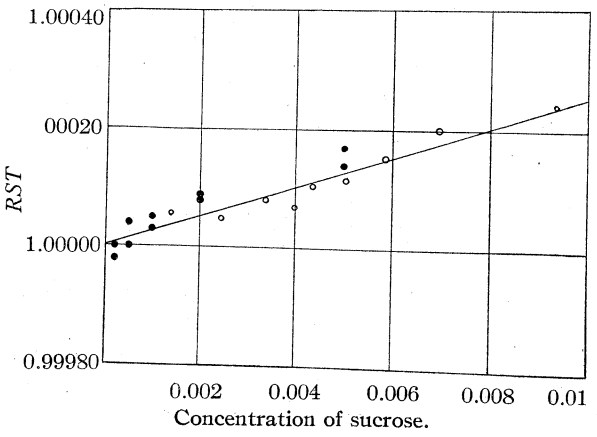


Fig. 2.—The relative surface tension of sucrose solutions. The open circles are from this investigation; the solid circles are taken from the results of Jones and Ray.

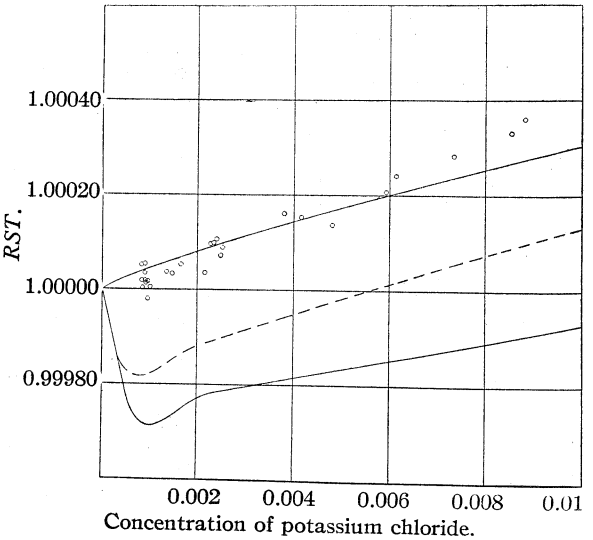


Fig. 3.—The relative surface tension of potassium chloride solutions. The points give the results of this research. The uppermost curve is the theoretical Onsager and Samaras prediction; the dotted curve is that given by Jones and Ray; the lowest curve is the one given by Dole and Swartout.

(14) Landolt–Börnstein, Vol. I, p. 428; p. 463.

Potassium Chloride Measurements.—A fairly large number of measurements on potassium chloride solutions were made. Several different starting solutions of the salt were used, ranging from 0.2 to 1 *M*. Four different sets of capillary tips were used but their size was close to $r = 0.042$ cm. Densities were calculated from the equation of Jones and Ray and the molar volume data were taken from the work of Geffcken.[15] The results are shown graphically in Fig. 3, where for comparison the curves of Jones and Ray and of Dole and Swartout as well as the theoretical Onsager–Samaras curve are also given.

The data in Fig. 3 show a wide deviation from the other two experimental curves. The minimum at 0.001 *M* is not present although there does seem to be a slight concavity in the curve near this concentration. For concentrations greater than 0.001 *M* the results roughly parallel those of Jones and Ray but they lie much higher. The deviation is, of course, well outside the experimental error and there seems to be no constant error which will explain the difference.

In order to see if the variation between the present results and those of the previous workers was maintained at higher concentrations, two determinations were made for approximately 0.05 molar solutions. The data are given in Table V where, for comparison, the figures of Jones and Ray and of Schwenker[16] (0°) are also given. The determinations at this concentration are less accurate than those for more dilute solutions primarily because the heat of dilution of the initial 3.86 molar potassium chloride solution is large enough to introduce an error due to temperature changes. Because of this error the first two surface tension values in Table V may be too large by as much as five in the last figure but even so the data show that the parallelism between the Jones and Ray data and the present work is approximately maintained.

TABLE V

POTASSIUM CHLORIDE RESULTS FOR MORE CONCENTRATED SOLUTIONS

Work	Concentration	*RST*	
Present	0.0437	1.00142	
Present	.0512	1.00179	
Jones and Ray	.0437	1.00123	(interpolated)
Jones and Ray	.0512	1.00146	(interpolated)
Schwenker at (0°)	.05	1.00141	

Discussion

The most obvious feature of the data for the relative surface tension of potassium chloride is the wide variation from the results of Jones and Ray and of Dole and Swartout. There is no minimum in the surface tension–concentration curve and in general the values agree fairly well with the Onsager and Samaras predictions.

There are several possible explanations for the disagreement. A conceivable one is that the data obtained with the bubble pressure apparatus are not true equilibrium values due to the speed with which bubbles are formed. If this were true the results could not be compared with the static values of Jones and Ray. However, for several reasons this explanation seems unlikely. The previously mentioned experiments with sucrose and with varying bubble rates both indicated equilibrium. The fact that the values parallel those of Jones and Ray at higher concentrations also indicates equilibrium since even if equilibrium were attained slowly in the region of the Jones and Ray minimum it should be attained much more rapidly in the region of negative adsorption where presumably the image forces predominate.

Another explanation for the discrepancy that suggests itself is that the contact angle does not stay at zero with salt solutions and that the minimum found by Jones and Ray and Dole and Swartout arises from failure to consider the variation of the contact angle. However, this explanation also seems rather unlikely. The contact angle of pure water against glass or fused silica is undoubtedly zero.[17] To account for the Jones and Ray minimum a change in contact angle to about 1° would be necessary. Although small, this is an angle which should be easily detected. More serious is the implication with respect to the spreading coefficient of water on silica or glass. A change of contact angle from 0 to 1° in going from water to a dilute salt solution would indicate either a large change in the spreading coefficient or an initial condition of W_{sl}, the work of adhesion, almost identical with 2 γ. Neither of these seems very probable.

A third explanation for the difference between the bubble pressure results and those obtained by Jones and Ray is that the reason for the minimum observed by the latter is the one proposed by Langmuir, a change in the effective radius of the capillary as the concentration of electrolyte changes. Since this change of effective radius is caused by the zeta potential at the glass-solution

(15) Geffcken, *Z. physik. Chem.*, **A155**, 1 (1931); Geffcken and Price, *ibid.*, **B26**, 81 (1934).

(16) Schwenker, *Ann. Physik*, [5] **11**, 525 (1931).

(17) Richards and Carver, THIS JOURNAL, **43**, 827 (1921); Bosanquet and Hartley, *Phil. Mag.*, [6] **42**, 456 (1921).

interface it should enter for the bubble pressure method also. But there are reasons why the effect should be smaller for the bubble pressure apparatus. The capillaries are of Pyrex instead of fused silica and it is probable that the Pyrex-solution zeta potential is smaller than for fused silica. In addition the capillary is larger by a factor of three than that of Jones and Ray and this will also decrease the importance of the zeta potential contribution. A third point is that the position of the meniscus is quite different for the bubble pressure method. In the capillary height apparatus the meniscus is formed completely within the capillary tube. In the bubble pressure apparatus the bubble extends down into the bulk of the solution and is in contact with glass only at the end of the tube. Although as formulated by Langmuir the effect of the zeta potential is treated in terms of a layer of solution along the capillary it can alternatively be discussed in terms of its effect on the radius at the lowest point of the meniscus. Because the region of close approach of the meniscus to the capillary wall is much less for the bubble pressure method it is very probable that the perturbation from the wall-solution zeta potential will be less. Thus the difference between the two methods of measurement seems likely to be due to a difference in the extent of the contribution of the zeta potential.

Summary

1. A differential maximum bubble pressure apparatus for the precise measurement of relative surface tensions is described. The relative surface tension values for dilute aqueous sucrose solutions, obtained with the apparatus, are similar to those obtained by the capillary height method.

2. The relative surface tension of potassium chloride solutions is considerably different from that obtained by previous workers. No minimum in the surface tension–concentration curve is observed and the results agree fairly well with the Onsager–Samaras predictions.

3. Explanations for the lack of agreement of the various results are considered and it is concluded that the most likely is the effect of the zeta potential as postulated by Langmuir.

ITHACA, N. Y. RECEIVED AUGUST 19, 1942

[CONTRIBUTION FROM THE CRYOGENIC LABORATORY, DEPARTMENT OF CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY]

The Heat Capacity of Benzene-d_6[1,2]

BY WALDEMAR T. ZIEGLER AND D. H. ANDREWS

Several years ago Lord, Ahlberg and Andrews made a semitheoretical calculation[3] of the heat capacities of crystalline benzene and benzene-d_6 based upon the spectroscopically determined frequencies[4] of the molecules in the gaseous state and certain assumptions concerning the contribution of lattice vibrations and the process of lattice expansion to the heat capacity. The agreement between the calculated and experimental values of C_p for crystalline benzene over the temperature range 4–270°K. may be described as very good, clearly indicating the general correctness of the frequency assignments for benzene. At that time certain of the fundamental frequencies of both benzene and benzene-d_6 were in doubt. Since then, the work of Langseth and Lord on the deuterated benzenes[5] has appeared which resulted in several changes in the frequency assignments previously made. These changes produce an almost insignificant change in the calculated values of C_p for crystalline benzene,[6] but decrease the calculated C_p values for benzene-d_6 by about 2% at 270°K.

It seemed to us of interest to determine the heat capacity of crystalline benzene-d_6 in order that the results might be compared with those predicted by a calculation of the type described above. Through the kindness of Dr. C. K. Ingold of University College, London, we obtained a loan of about 5 ml. of benzene-d_6 with which to carry out the measurements. The semi-micro heat conduction

(1) From a dissertation submitted to the Board of University Studies of the Johns Hopkins University in 1938 by W. T. Ziegler in conformity with the requirements for the degree of Doctor of Philosophy.

(2) Part of this research was presented in a paper with Dr. R. C. Lord, Jr., at the Boston meeting of the American Chemical Society, September, 1939.

(3) Lord, Ahlberg and Andrews, *J. Chem. Phys.*, **5**, 649 (1937). For a more complete exposition of the method used see Lord, *J. Chem. Phys.*, **9**, 693, 700 (1941).

(4) Lord and Andrews, *J. Phys. Chem.*, **41**, 149 (1937).

(5) Langseth and Lord, *Kgl. Danske Videnskab. Selskab. Math-fys. Medd.*, Vol. 16, No. 6 (1938).

(6) Brucksch and Ziegler, *J. Chem. Phys.*, to be published shortly.

calorimeter described by Stull[7] was used for the experimental determination of the heat capacity as it required only a 5-ml. sample, yet gave results accurate to 1–2%. Measurements were made throughout the temperature range 100–320°K.

Experimental

The experimental apparatus, operating procedure and method of calculation employed were identical with those described by Stull.[7]

Calibration of Calorimeter.—The temperature scale used by Stull was checked by determinations of the melting points of benzene, toluene, cyclohexane and aniline, and the transition in crystalline cyclohexane at 186°K. On the basis of these and other measurements described below we have estimated our temperature scale to be correct to ±0.3° below 180°K. and ±0.1° in the range 180–320°K. with respect to the International Temperature Scale (0°C. = 273.10°K.).

Benzene, 99.99 mole per cent. pure, was used as a primary standard for the calibration of the calorimeter. It was assumed to have the heat capacity values listed in Table II. The heat capacities of cyclohexane, aniline and toluene were measured to serve as a check on the operating procedure, since the heat capacities of these substances are known with good accuracy from absolute measurements.

Table I presents a summary of the melting points and heats of transition obtained for the various substances studied. The agreement with previously observed values is seen to be reasonably good, and served as another check on the accuracy of the calorimetric method.

On the basis of these comparisons it was concluded that the calorimeter would yield values of C_p benzene-d_6 probably accurate to about 2%.

Materials: Benzene.—A C. P. "thiophene-free" material was first distilled through a five-foot column made entirely of Pyrex glass and packed with small glass helices similar to those described by Young and Jasaitis.[8] The middle portion was then fractionally recrystallized six times, about one-fifth of the material being discarded each time. The resulting product was dried over phosphorus pentoxide for two weeks, refractionated and a fraction boiling over a range of about 0.03° collected. This material was used in all subsequent measurements. It melted very sharply, and from the observed premelting was judged to be 99.99 mole % pure.[8a]

Benzene-d_6.—This material was loaned to us by Professor C. K. Ingold of University College, London. As received, the sample (approximately 5 ml.) was labeled as being 99.8 mole per cent. pure benzene-d_6, but containing a trace of water. This was removed by distillation from phosphorus pentoxide in a vacuum. The sample was handled with all possible precautions to reduce exchange reactions to a minimum. From the observed premelting of the dry sample its purity was calculated to be 99.8 mole %. The benzene-d_6 melted at 6.7°.

Cyclohexane.—An Eastman Kodak Co. product was fractionally recrystallized eight times and then fractionally distilled through a small Vigreux column. The purity calculated from the observed premelting was 99.9%.

Toluene.—C. P. toluene was twice distilled from the five-foot packed column previously described, dried over phosphorus pentoxide for three days and finally redistilled. From the observed premelting its purity was estimated to be 99.7 mole %.

Aniline.—A C. P. product was fractionally distilled through a Vigreux column, recrystallized twice, and finally refractionated through the Vigreux column. The product was water white, and from its premelting was judged to be 99.85 mole % pure.

Experimental Results

Measurements of the heat capacity of benzene-d_6 were made throughout the temperature range 100–320°K. at approximately 6° intervals. 4.537 g. (0.05392 mole) of benzene-d_6 was used in each of the three series of measurements made. The experimental results obtained at each temperature (*i. e.*, mid-point of heating interval) in the three series of measurements were averaged[9] to obtain the values of C_p listed in Table II. The C_p values of crystalline benzene-d_6 listed in the last column of Table III were read from a smooth curve through the data of Table II.

The heats of fusion of benzene and benzene-d_6 were also measured, the results being 2370 and 2340 cal. mole^{-1}, respectively (see Table I). These values have been corrected for premelting and are probably accurate to 1–1.5%.

TABLE I

Substance	Melting point, °C. This research	Others	Heat of fusion (cal. mole^{-1}) This research	Others
Benzene	5.50	5.50[a]	2370	2349[a]
Benzene-d_6	6.70	6.8[b]	2340	
Cyclohexane[g]	−86.8	−87.2[c]	1630	1604[c]
	6.2	6.2[c]	652	623[c]
Toluene	−95.2	−95.15[d]	1565	1582[d]
Aniline	− 5.9	− 6.0[e]		
		− 6.3[f]	2610	2521[f]

[a] Huffman, Parks and Daniels, THIS JOURNAL, **52**, 1547 (1930). [b] Ingold, Raisin and Wilson, *J. Chem. Soc.*, 915 (1936), state that C_6D_6 melts 1.3° above benzene. [c] Parks, Huffman and Thomas, THIS JOURNAL, **52**, 1032 (1930). [d] Kelley, *ibid.*, **51**, 2738 (1929). [e] Lang, *Proc. Roy. Soc.* (London), **A118**, 138 (1928). [f] Parks, Huffman and Barmore, THIS JOURNAL, **55**, 2733 (1933). [g] The data in the first line for cyclohexane are for a crystalline transition.

(7) Stull, THIS JOURNAL, **59**, 2726 (1937).

(8) Young and Jasaitis, *ibid.*, **58**, 377 (1936).

(8a) The estimation of purity from the observed premelting was based upon the assumption that no solid solution was formed and that all of the impurity was present in (ideal) solution after a small fraction of the benzene had melted. The purity of the other substances studied was estimated in a similar manner.

(9) This averaging is possible when measurements are made with a heat conduction calorimeter due to the fact that the temperature intervals traversed are always the same.

TABLE II

EXPERIMENTAL VALUES OF C_p FOR BENZENE-d_6
(0°C. = 273.10°K.; 1 calorie = 4.1833 int. joules)

T, °K.	C_p (cal. mole^{-1} deg.$^{-1}$) Benzene[a]	Benzene-d_6	T, °K.	C_p (cal. mole^{-1} deg.$^{-1}$) Benzene	Benzene-d_6
101.9	12.10	12.4	234.6	24.10	28.0
112.0	12.76	13.7	240.4	24.85	28.7
121.6	13.42	14.4	246.0	25.59	29.4
130.6	14.06	15.2	251.6	26.37	30.3
139.2	14.68	16.1	257.1	27.25	31.0
147.4	15.28	17.3	262.5	28.15	32.0
155.3	15.94	18.3	267.8	29.10	33.1
162.9	16.53	18.3	273.1	30.15	34.3
170.3	17.13	19.3	M. p. 279.8°K.		
177.5	17.76	20.0	283.5	31.55	34.9
184.4	18.44	21.0	288.5	31.75	34.2
191.2	19.11	21.8	293.6	31.92	35.4
197.8	19.77	22.7	298.5	32.19	35.7
204.3	20.53	23.2	303.4	32.45	35.9
210.6	21.28	24.6	308.3	32.76	36.3
216.8	22.00	25.5	313.1	33.12	36.4
222.8	22.64	26.3	317.9	33.50	36.9
228.8	23.37	27.1	322.6	34.45	36.9

[a] These values were obtained by interpolation from a large-scale plot of the experimental data of (a) Ahlberg, Blanchard and Lundberg, *J. Chem. Phys.*, **5**, 539 (1937); (b) Nernst, *Ann. Physik*, **36**, 395 (1911); (c) Huffman, Parks and Daniels, THIS JOURNAL, **52**, 1547 (1930); (d) Daniels and Williams, *ibid.*, **46**, 903 (1924); (e) Richards and Wallace, *ibid.*, **54**, 2705 (1932).

Discussion of Results

The experimental values of C_p for crystalline benzene-d_6 have been compared with those calculated by means of the expression (see ref. 3)

$$C_p = C_v + [aC_{v(L)} + bC_{v(Vib.)}]^2 T \qquad (1)$$

In this expression $C_v = C_{v(L)} + C_{v(Vib.)}$ and T is the absolute temperature. $C_{v(L)}$ represents the contribution of torsional and translational motions of the molecules, considered as units of the molecular lattice, to the heat capacity at constant volume, and is assumed to be given by the expression $6D(\Theta/T)$, where $D(\Theta/T)$ is the Debye heat capacity function for one degree of freedom. Θ has been taken as 140°.[3]

$C_{v(Vib.)} = \sum_{i=30} E(\Theta_i/T)$, where $E(\Theta/T)$ is the Einstein heat capacity function, represents the contribution of the internal vibrational frequencies of the molecule to the heat capacity (at constant volume). The internal frequency assignments used were those of Langseth and Lord.[10]

The constants a and b (assumed temperature independent) were given the values 0.0090 cal.$^{-1/2}$ and 0.0057 cal.$^{-1/2}$, respectively, by analogy with crystalline benzene (see ref. 6).

The results of the calculation are presented in Table III together with the experimental values. The calculations also have been made for the range 10–100°K. in order to show the relative importance of the terms $C_{v(L)}$, $C_{v(Vib.)}$ and $C_p - C_v$.

TABLE III

HEAT CAPACITY OF BENZENE-d_6

T, °K.	C_v lattice	C_v vibration	$C_p - C_v$	C_p calcd.[a]	C_p obs.
10	0.34			0.34	
15	1.10			1.10	
20	2.28		0.01	2.29	
25	3.64		.02	3.66	
30	4.89		.03	4.92	
40	6.91		.15	7.06	
50	8.30	0.02	.28	8.60	
60	9.24	.07	.41	9.72	
70	9.84	.17	.56	10.57	
80	10.28	.34	.71	11.33	
90	10.60	.59	.88	12.07	
100	10.85	.91	1.06	12.82	12.8
110	11.01	1.31	1.25	13.57	13.6
120	11.14	1.78	1.46	14.38	14.4
130	11.24	2.33	1.70	15.27	15.2
140	11.32	2.95	1.97	16.24	16.1
150	11.38	3.64	2.27	17.29	17.1
160	11.44	4.36	2.62	18.42	18.1
170	11.50	5.15	3.00	19.65	19.2
180	11.55	5.98	3.43	20.96	20.3
190	11.60	6.38	3.90	22.33	21.6
200	11.64	7.71	4.42	23.77	23.0
210	11.67	8.61	4.99	25.27	24.4
220	11.69	9.52	5.60	26.81	25.8
230	11.71	10.43	6.25	28.39	27.2
240	11.73	11.32	6.94	29.99	28.5
250	11.74	12.30	7.73	31.77	30.0
260	11.75	13.15	8.49	33.39	31.6
270	11.76	14.05	9.33	35.14	33.6

[a] Calculated from Eq. (1).

Examination of Table III shows that there is good agreement (within experimental error) between the calculated and observed values of C_p in the range 100–170°K., but that there is a general trend for the calculated values of C_p to become greater than the observed for increasing temperatures, the calculated value of C_p being about 6% too large in the neighborhood of the melting point.

The reason for this discrepancy is not immediately apparent. Since the agreement is quite good in the range 100–170°K., it seems likely that both the contributions arising from lattice vibrations and from the *lowest* internal frequencies have been accurately evaluated. Above 170°K. the higher frequencies as well as the expansion term $(C_p - C_v)$ begin to play a more important role,

(10) See ref. 5, Table XVIII. Frequencies no. 14 and 15 were taken as 1550 and 850 cm^{-1}, respectively.

so that discrepancies at the higher temperatures presumably have their origin in one or both of these components of C_p. We conclude, then, that one or more of the medium-valued frequencies, possibly ν 17,[11] have been assigned values somewhat too low, and/or that the constant b in the expansion formula[12] has been set somewhat too high.

Acknowledgment.—The authors wish to thank Dr. R. C. Lord, Jr., of the Department of Chemistry for many helpful discussions.

(11) See ref. 5, p. 68.

(12) The constant a which gives the lattice portion of the expansion term, presumably is essentially correct because of the satisfactory agreement below 170°K.

Summary

1. The heat capacity of benzene-d_6 has been measured throughout the temperature range 100–320°K. with an accuracy of about 2%.

2. A comparison of the experimentally observed values of C_p with those calculated by a semi-theoretical method indicates that the low frequencies in the benzene-d_6 molecule have been correctly assigned.

3. The possibility that one or more of the medium-valued frequencies have been assigned values which are too low is presented.

BALTIMORE, MD. RECEIVED JUNE 27, 1942

[CONTRIBUTION FROM THE KNIGHT CHEMICAL LABORATORY, UNIVERSITY OF AKRON]

The Halogenation of *m*-Diphenylbenzene. II. The Monoiodo Derivative[1]

BY WALTER A. COOK AND KATHRYN HARTKOFF COOK

In a previous communication[2] the authors reported the preparation and proof of structure of the monochloro and monobromo derivatives of *m*-diphenylbenzene. The present communication describes the preparation of the analogous monoiodo derivative from the corresponding amine. The latter compound was prepared by ammonolysis of the monochloro and monobromo derivatives.

Experimental

Ammonolysis Experiment.—The ammonolysis studies were carried out in a steel bomb of 500-ml. capacity, electrically heated and equipped with a bimetallic thermoregulator, safety diaphragm valve, pressure gage and Hoke pressure regulator valve. The details of a typical run are given as follows: 12 g. of 4-chloro-*m*-diphenylbenzene, 340 ml. of 28% aqueous ammonia, 2 g. of cuprous chloride, 1.26 g. of calcium oxide and 2 g. of copper tinsel were heated with continuous agitation for thirty hours at 190° and 800–850 pounds pressure. After cooling the bomb contents were transferred to a 600-ml. beaker, the aqueous ammonia layer decanted and the reaction residue washed with water. The reaction product was dissolved in ether, filtered and saturated with dry hydrogen chloride gas. The precipitated and dried crude 4-amino-*m*-diphenylbenzene hydrochloride weighed 6 g. The ether layer, after subsequent washing with water and evaporation, yielded 2.5 g. of unreacted monochloro derivative. The combined yields of crude amine hydrochloride from several runs was purified by moistening with dil. hydrochloric acid and allowed to stand for several hours in contact with glacial acetic acid. After filtration it was washed with diluted hydrochloric acid and water. It was then converted into the free base with 6 *N* potassium hydroxide solution containing a trace of ammonium hydroxide and filtered. Recrystallization from 95% ethanol yielded pure 4-amino-*m*-diphenylbenzene, m. p. 74°. Similarly a specimen of the amine prepared by the Wardner and Lowy[3] method, and purified as described above, melted at 74°, although these authors reported a value of 64°. Mixed melting points of these products as well as a specimen of the amine prepared by Dr. Russell Jenkins[4] of Monsanto Chemical Co. agree with our value of 74°. The structure of the amine was recently reported by France, Heilbron and Hey,[5] although they were unable to solidify their specimen. A phenylthiourea derivative of 4-amino-*m*-diphenylbenzene was prepared in the usual way; m. p. 135°.

Anal. Calcd. for $C_{25}H_{20}N_2S$: N, 7.36; S, 8.43. Found: N, 7.51; S, 8.60.

4-Iodo-*m*-diphenylbenzene.—From 28 g. of the corresponding amine hydrochloride, 18.6 g. of a pale yellow oil b. p. (1 mm.) 235–240° (cor.) was obtained by diazotization and treatment with potassium iodide in the usual manner. The oil solidified after standing for several days and on crystallization from absolute ethanol melted at 67°.

Anal. Calcd. for $C_{18}H_{13}I$: I, 35.65. Found: I, 35.41.

Attempts to oxidize this compound to a substituted phenylbenzoic acid resulted in such small yield of product that it could not be isolated.

The authors acknowledge the helpful assistance of Professor D. E. Anderson in the design and construction of the bomb in which the ammonolysis studies were undertaken.

Summary

1. The preparation and properties of 4-iodo-*m*-diphenylbenzene are described.

(1) Presented before the Division of Organic Chemistry at the Memphis meeting of the American Chemical Society, in April, 1942.

(2) Cook and Cook, THIS JOURNAL, **55**, 1212 (1933).

(3) Wardner and Lowy, *ibid.*, **54**, 2510 (1932).

(4) Private communication to the authors.

(5) France, Heilbron and Hey, *J. Chem. Soc.*, 1283–1292 (1939).

2. Further proof of the structure of Wardner and Lowy's mononitro and monoamino derivatives is presented.

3. A corrected m. p. of 74° for 4-amino-*m*-diphenylbenzene is reported. For characterization purposes, the phenylthiourea derivative is also described.

AKRON, OHIO RECEIVED MAY 8, 1942

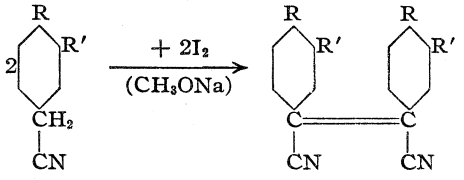
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

Symmetrical Cyanostilbenes

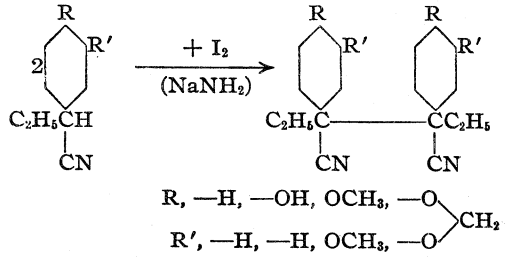
BY JOSEPH B. NIEDERL AND ALBERT ZIERING[1]

In a previous communication[2] the preparation of unsymmetrical cyanostilbenes was presented. The purpose of this communication is to give report on the preparation of symmetrical and variously ring and side-chain substituted cyanostilbenes and dihydrostilbenes related in structure to diethylstilbestrol. The ring substituents included the following: nitro, amino, hydroxy, acetoxy, methoxy, dimethoxy and methylenedioxy groups, while the side-chain substituents comprised either hydrogen or ethyl groups. The method of preparation of these compounds consisted in self-condensation of the respective benzyl nitriles by means of iodine in the presence of sodium methoxide or sodium amide as follows[3]

Dicyanostilbenes



Dicyanodihydrostilbenes:



Experimental

α,α'-Dicyanostilbenes.—One-tenth mole of the respective benzyl nitrile (*p*-methoxy-3,4-methylenedioxy-3,4-dimethoxy) was dissolved in 65 cc. of absolute methyl alcohol. To this solution 25.4 g. of iodine, dissolved in 130 cc. of absolute ether, was added, followed by the dropwise addition of a solution of 4.6 g. of sodium in 70 cc. of absolute methyl alcohol.[3] The precipitated solid was filtered and recrystallized from ethyl acetate. All dicyanostilbenes were colored and gave positive unsaturation tests with potassium permanganate dissolved in acetone; yields, 35% (approx.). The 4,4'-dihydroxy derivative was prepared by diazotizing the corresponding amine,[4] acetylating the resulting solid and then hydrolyzing the acetate with alkali to the phenolic derivative.

α,α'-Dicyanodihydrostilbenes.—One-tenth mole of phenylethylacetonitrile was added dropwise to a suspension of sodamide (0.1 mole) in 150 cc. of anhydrous ether. The mixture was refluxed until the evolution of ammonia had ceased. To this was then added slowly 0.05 mole of iodine in 100 cc. of absolute ether.[3] The precipitated solid was filtered, washed with water and recrystallized from ethanol. All dicyanodihydrostilbenes were colorless and the unsaturation tests with potassium permanganate in acetone were negative; yields, 25% (approx.).

Piperonylethylacetonitrile was treated in the same manner and the final reaction product was recrystallized from dioxane; yield, 25%.

The piperonylethylacetonitrile was prepared by first treating 3,4-methylenedioxybenzyl nitrile with diethyl carbonate in the presence of sodium at 60° in benzene to yield the ethyl piperonylcyanoacetate (b. p. 161° at 3 mm.). This ester was then ethylated in the usual manner with ethyl iodide and sodium ethoxide in absolute ethanol to give the ethyl piperonylethylcyanoacetate (m. p. 72°) which was then hydrolyzed with alkali in the cold to the piperonylethylcyanoacetic acid (m. p. 110°). The acid was decarboxylated by heating to 180°. The resulting piperonylethylacetonitrile boiled at 174° at 15 mm.

The corresponding phenolic derivative was prepared by nitrating phenylethylacetonitrile with fuming nitric acid at 0° to yield the *p*-nitrophenylethylacetonitrile (b. p. 165° at 3 mm.). The nitro compound was converted to the dihydrostilbene by means of iodine and sodium methoxide.[3] The resulting dihydrostilbene was then reduced to the amine, which was then diazotized and finally hydrolyzed to the phenolic derivative, which was recrystallized from benzene containing a little alcohol.

Physiological Tests.—All compounds were subjected to the Fluhmann[5,6] test for estrogenic activity. Most re-

(1) Abstracted from Part II of the thesis presented by A. Ziering to the Graduate School of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1942.

(2) J. B. Niederl and A. Ziering, THIS JOURNAL, **64**, 885 (1942).

(3) Knoevenagel and Chalanay, *Ber.*, **25**, 285 (1892).

(4) Heller, *Ann.*, **332**, 280 (1904).

(5) Fluhmann, *Endocrinology*, **18**, 705 (1934).

(6) Deckert, Mulhall and Swiney, *J. Lab. Clin. Med.*, **23**, 85 (1937).

active of all the substances was the α,α′-dicyanostilbestrol, which exhibited the following degrees of activity:

	Dose, microg.	Reaction
α,α′-Dicyanostilbestrol	6.25	5.0
α,α′-Dicyanostilbestrol	3.12	4.5
α,α′-Dicyanostilbestrol	1.56	4.3
α,α′-Dicyanostilbestrol	0.78	3.5
Stilbestrol	0.02	5.0
Estrone	0.08	5.0

TABLE I

α,α′-DICYANOSTILBENES

	Formula	M. p., °C. (uncor.)	Analyses, % N Calcd.	Found
4,4′-Dihydroxy	$C_{16}H_{10}N_2O_2$	287	10.7	10.5
4,4′-Diacetoxy	$C_{20}H_{14}N_2O_4$	217	8.09	8.17
4,4′-Dimethoxy	$C_{18}H_{14}N_2O_2$	187	9.65	9.50
3,4,3′,4′-Dimethylenedioxy	$C_{18}H_{10}N_2O_4$	235	8.81	8.90
3,4,3′,4′-Tetramethoxy	$C_{20}H_{18}N_2O_4$	205	8.00	8.20

α,α′-DIETHYL-α,α′-DICYANODIHYDROSTILBENES

Unsubstituted	$C_{20}H_{20}N_2$	175	9.72	9.51
3,4,3′,4′-Dimethylenedioxy	$C_{22}H_{20}N_2O_4$	213	7.45	7.26
4,4′-Dinitro	$C_{20}H_{18}N_4O_4$	225	14.8	14.6
4,4′-Diamino	$C_{20}H_{22}N_4$	205	17.6	17.4
4,4′-Dihydroxy	$C_{20}H_{20}N_2O_2$	218	7.95	7.80

Acknowledgment.—The authors wish to express their appreciation to Dr. F. R. Eldred of Reed and Carnrick, Jersey City, N. J., for the numerous physiological tests performed with these substances, as well as for repeated fellowship grants.

Summary

Various substituted symmetrical cyano- and dihydrocyanostilbenes have been prepared, characterized and tested for estrogenic activity.

WASHINGTON SQUARE COLLEGE
NEW YORK, N. Y. RECEIVED JULY 11, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY AND OF LAFAYETTE COLLEGE]

Phenylmercapto-thiazolines

BY JOSEPH B. NIEDERL AND WILLIAM F. HART

The condensation of allyl- and methallyl mustard oils with phenols yielded thiazolinephenols as shown in previous publications.[1,2] The same condensation procedure has now been applied to the reaction between allyl mustard oil and various thiophenols.

There were obtained excellent yields of hydrochlorides which analyzed correctly for the expected salts of thiazoline-thiophenols. From these, picrates were prepared which also analyzed as expected. However, when an attempt was made to prepare the free bases by neutralization of a solution of the hydrochlorides with sodium carbonate, hydrolysis occurred, one of the products being the thiophenol, and the other, 5-methyl-thiazolidone-2.

From these hydrolysis products it appears that the products of these condensations are the hydrochlorides of 5-methyl-2-phenylmercapto-thiazolines, instead of the expected thiazoline-thiophenols. The hydrochlorides of these thio-ethers are remarkably stable to acid treatment. The compounds, however, are completely hydrolyzed in dilute sodium bicarbonate solution.

(1) Niederl, Hart and Scudi, THIS JOURNAL, **58**, 707 (1936).
(2) Hart and Niederl, *ibid.*, **61**, 1145 (1939); **63**, 945 (1941).

Experimental

Condensation.—Allyl mustard oil was condensed with thiophenol, thio-*o*-cresol and thio-*m*-cresol in the manner previously described.[2] Condensation was usually complete within one week. The product was taken up in water, the acid solution extracted several times with ether, and the ether extracts discarded. The acid solution was then evaporated to dryness on a water-bath, yielding the hydrochloride in a quite pure form. The hydrochlorides were washed several times with dry acetone, and then recrystallized from 95% ethyl alcohol several times until the melting point was constant.

The picrates were made by adding a filtered, saturated picric acid solution to an equal volume of filtered aqueous solution of the hydrochloride. The resulting crystalline precipitate was washed several times with water, dried and recrystallized once from 95% ethyl alcohol.

Hydrolysis.—Twenty grams of the hydrochloride of the thio-*m*-cresol condensation product was dissolved in water, and the solution was made distinctly alkaline with sodium bicarbonate. A blue oil separated, which was removed by ether extraction and the ether extracts were in turn extracted with 10% hydrochloric acid, which removed the blue color. The ether solution was washed, dried, and the solvent removed by distillation. The residue was an almost quantitative yield of 10.5 g. of thio-*m*-cresol, which was identified by the boiling point, and by oxidation to di-*m*-cresyl di-sulfide with 3% hydrogen peroxide in acetone solution.

The hydrochloric acid extract was used to acidify the

original aqueous solution and this solution was evaporated to dryness on the steam-bath. The residue was exhaustively extracted with absolute alcohol, and the residual sodium chloride was discarded. Upon evaporation of the alcohol there was obtained an oil, which was soluble in dry acetone. This oil became crystalline on long standing in a desiccator, after which treatment with dry acetone yielded two fractions. The acetone insoluble fraction upon analysis proved to be the hydrochloride of 5-methyl-2-hydroxythiazoline. The acetone soluble fraction, which melted at 39°, proved to be its acid insoluble keto form. It was recrystallized from dry acetone and benzene.

TABLE I

Compound	M. p., °C. (uncor.)	Formula	N Analyses, % Calcd.	Found
5-Methyl-2-phenylmercapto-thiazoline				
Hydrochloride	171	$C_{10}H_{12}NS_2Cl$	5.69	5.57
Picrate	141	$C_{16}H_{14}O_7N_4S_2$	12.55	12.65
5-Methyl-2-(2′-methyl)-phenylmercapto-thiazoline				
Hydrochloride	164	$C_{11}H_{14}NS_2Cl$	5.39	5.75
Picrate	133	$C_{17}H_{16}O_7N_4S_2$	12.38	12.46
5-Methyl-2-(3′-methyl)-phenylmercapto-thiazoline				
Hydrochloride	139	$C_{11}H_{14}NS_2Cl$	5.39	5.32
Picrate	118	$C_{17}H_{16}O_7N_4S_2$	12.38	12.48
Sulfonic Acid		$C_{11}H_{13}O_3NS_3$	4.61	4.38
5-Methyl-thiazolidone-2				
Keto form[a]	39	C_4H_7ONS	11.96	12.12
Enol, hydrochloride	204	C_4H_8ONSCl	9.12	9.35

[a] Calcd.: C, 40.98; H, 6.02; S, 27.37. Found: C, 41.13; H, 6.08; S, 27.79.

Acknowledgment.—The authors desire to thank Merck and Company, Inc., Rahway, New Jersey, for a research fellowship.

Summary

Thiophenols on condensation with allyl mustard oil have been found to yield phenylmercaptothiazolines, in contrast with phenols, which yield thiazolinephenols. These heterocyclic thio-ethers do not rearrange in the presence of the usual acidic rearranging agents, but are readily hydrolyzed in alkaline solution.

WASHINGTON SQUARE COLLEGE, NEW YORK, N. Y.
LAFAYETTE COLLEGE, EASTON, PA.

RECEIVED JULY 13, 1942

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE OF AGRICULTURE AND APPLIED SCIENCE]

The Sterols of Alfalfa Seed Oil. II. Isolation of β-Spinasterol and δ-Spinasterol

BY L. CARROLL KING AND CHARLES D. BALL

In a previous communication[1] from this Laboratory the isolation of α-spinasterol from the unsaponifiable fraction of alfalfa seed oil was reported. In addition to α-spinasterol we have now obtained two other isomeric sterols, β-spinasterol[2] and a third substance whose properties indicate that it has not before been isolated. Since this new sterol is closely related to the known α- and β-spinasterols in structure and properties we have designated it as δ-spinasterol.

In order to separate these three isomeric substances, the crude alfalfa seed oil sterols were dissolved in a large excess of acetic anhydride. On cooling this mixture, the acetates of α-spinasterol and β-spinasterol separated as flaky crystals and were filtered off while the δ-spinasteryl acetate remained for the most part in the acetic anhydride mother liquors. α-Spinasterol and β-spinasterol were separated by taking advantage of the greater solubility of the latter in 85% ethanol.

Each of the three isomeric spinasterols was isolated from two different sources—first, from Hardigan alfalfa seed oil and second, from Grim alfalfa seed oil. The crude sterols from Hardigan alfalfa seed oil consisted of about 23% α-spinasterol, 39% β-spinasterol and 6% δ-spinasterol. The amounts of the corresponding substances isolated from the crude sterols of Grim alfalfa seed oil were 17, 28 and 4.5%, respectively.

The chemical reactions and relationships of α-, β- and δ-spinasterol are summarized in Fig. 1.

δ-Spinasterol was purified by fractional crystallization from 95% ethanol and from methanol. The purest product obtained had a melting point of 142–143° and $[\alpha]^{19}D$ 6.15°. It precipitated with digitonin and gave a positive Liebermann–Burchard test.

The analytical data for δ-spinasterol and its derivatives indicated the formula $C_{29}H_{47}OH \cdot {}^1/_2H_2O$ for the sterol. On catalytic reduction of the acetate in acetic acid solution, a compound identical with α-stigmastenyl acetate[3] (I) was obtained. δ-Spinasterol is, therefore, a doubly

(1) King and Ball, THIS JOURNAL, **61**, 2910 (1939).
(2) Heyl and Larsen, *J. Pharm. Assoc.*, **22**, 510 (1933).
(3) Fernholz and Ruigh, THIS JOURNAL, **62**, 2341 (1940).

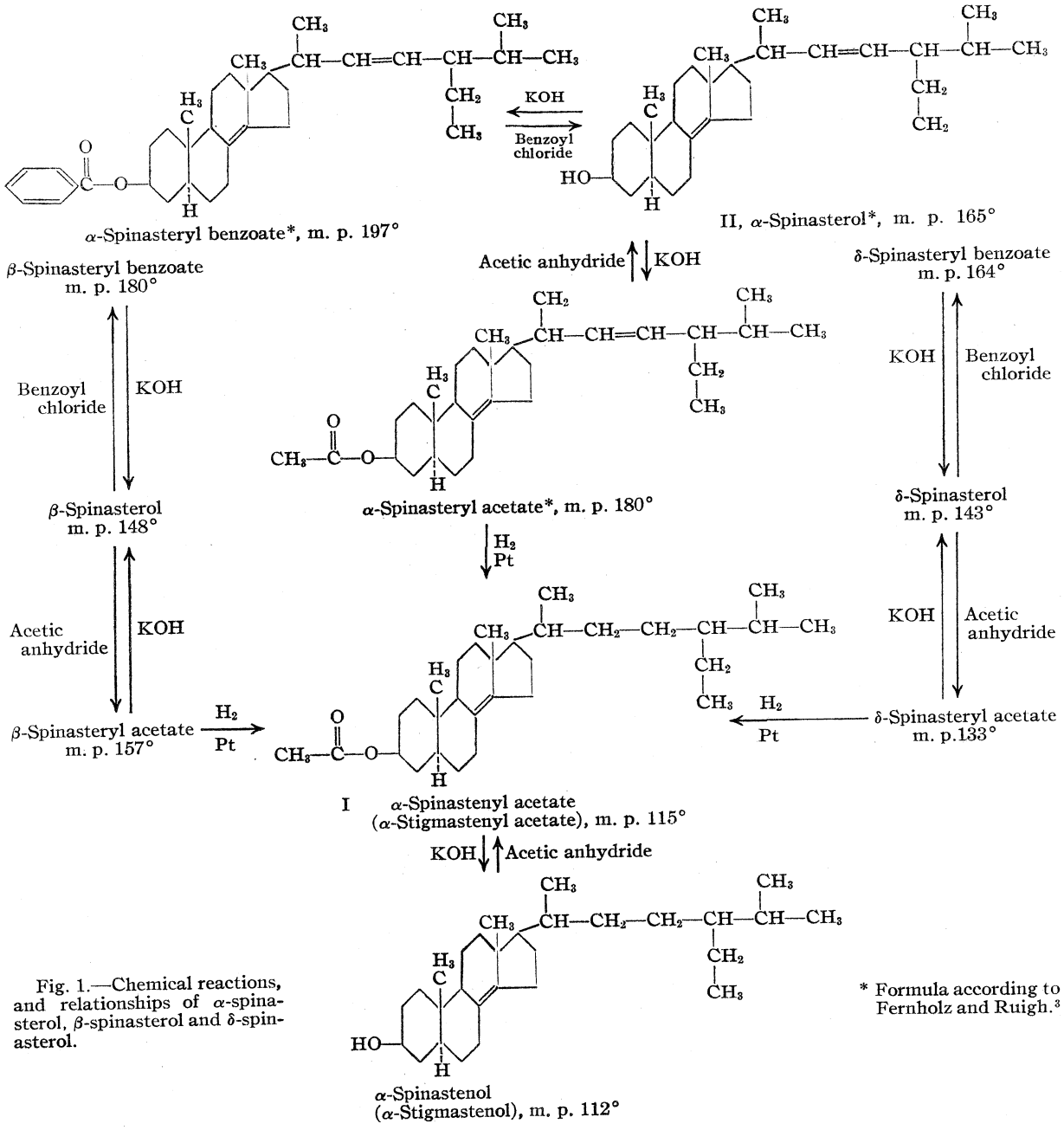


Fig. 1.—Chemical reactions, and relationships of α-spinasterol, β-spinasterol and δ-spinasterol.

* Formula according to Fernholz and Ruigh.[3]

unsaturated sterol having the same structural configuration as α-spinasterol except for the position of the double bonds. It has one double bond located at position Δ8:14 or in a position from which it can shift easily into the Δ8:14 configuration, when in the presence of hydrogenating catalysts.

The identity of the β-spinasterol isolated from alfalfa seed oil with that isolated from spinach fat is indicated by correspondence in physical properties, Table I, and also by similar behavior when subjected to catalytic reduction.

TABLE I

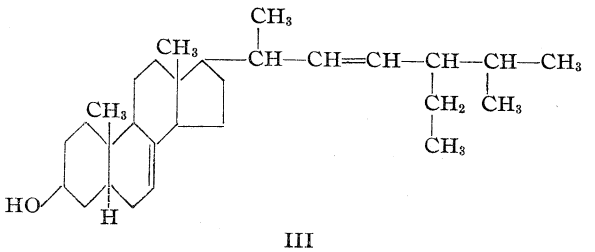
	M. p., °C.	$[\alpha]_D$ in $CHCl_3$, °C.	$[\alpha]_{5461}$, °C.
β-Spinasterol (isolated from alfalfa seed oil)	148–150	5.9	...
Acetate	153–155	5.1	...
Benzoate	181–183	7.5	...
β-Spinasterol (isolated from spinach fat)	145–148	...	7.65
Acetate	150–154	...	7.2

The β-spinasterol isolated from spinach fat gave analytical data for the formula $C_{29}H_{47}OH$·

$^1/_2H_2O$ or $C_{29}H_{47}OH$. On catalytic reduction of the acetate in acetic acid solution α-stigmastenyl acetate (I) was obtained. β-Spinasterol is, therefore, a doubly unsaturated sterol, related in structural configuration to α-spinasterol except for the position of the double bonds.

Recently Kuwada and Yosiki[4] reported that the bessisterol, isolated by them[5,6] from the rhizomes of *Mormordica cochinchenses* Spreng, was identical with α-spinasterol. The correspondence in chemical and physical properties of bessisterol and α-spinasterol is very good except that the specific rotation of bessisterol is $[\alpha]_D$ −13.5°, and that of bessisteryl acetate is $[\alpha]_D$ −13.47°, whereas the specific rotation of α-spinasterol is usually reported at $[\alpha]_D$ +1.7° to −3.5° and α-spinasteryl acetate at $[\alpha]_D$ −4.7°. In this Laboratory α-spinasterol was repeatedly recrystallized from methanol and from chloroform–methanol in an attempt to bring its rotation to a value similar to that reported for bessisterol. This attempt was unsuccessful; the best value obtained was $[\alpha]_D$ −2.7°. An attempt to obtain α-spinasteryl acetate with a specific rotation similar to the value reported for bessisteryl acetate also failed.

Fernholz and Ruigh[3] proposed for α-spinasterol the structures (II) and (III). It is of



III

interest to note that the specific rotation of structure II, calculated according to the method of Bernstein, Kauzmann and Wallis,[7] is $[\alpha]_D$ 8.2° while that of structure III is $[\alpha]_D$ −10.9. Neither of these values can be correlated with the observed value for α-spinasterol, but structure III is in fair agreement with the observed value for bessisterol.

Experimental

1. Separation of Crude Sterols from the Unsaponifiable Fraction.—One hundred and fifty grams of crude unsaponifiable material from Hardigan alfalfa seed oil, prepared as directed by King and Ball,[1] was dissolved in enough ethyl ether to make about 500 cc. A stream of water vapor[8] was passed through the solution until a slight turbidity occurred. After the mixture had stood overnight at 5°, the crystalline mass which separated was filtered off and recrystallized from ethyl ether. The original mother liquors and those from the subsequent recrystallizations were concentrated somewhat and the whole process repeated. In this way 26 fractions were obtained.

The 26 solid fractions weighing about 47 g. were nearly free of colored oily material. The first fraction isolated melted about 158°; subsequent fractions had lower and lower melting points, while the last fractions had very indefinite melting ranges in the vicinity of 60°. These crude solid fractions were combined and classified into two groups, those melting above 120° (Fraction A) and those melting below 120° (Fraction B). Fraction B appeared to consist of hydrocarbons, sterols and other alcohols. Further work on it is in progress in this Laboratory.

2. Fractionation of the Crude Steryl Acetates from Cold Acetic Anhydride.—The crude sterol fractions melting above 120° (Fraction A) were combined and dissolved in acetic anhydride (30 cc. per gram). This mixture was heated one hour, allowed to stand overnight, and then filtered. The solid steryl acetates (Fraction A_1) so obtained consisted mostly of α-spinasteryl and β-spinasteryl acetates; yield 24.5 g.; m. p. 152–157°.

The acetic anhydride mother liquors from the above were hydrolyzed by heating with water. The solid steryl acetates precipitated by this treatment (Fraction A_2) were filtered off and dried; yield 2.9 g.; m. p. 122–127°.

3. Separation and Identification of α-Spinasterol and β-Spinasterol. α-Spinasterol.—The crude acetates, m. p. 152–157° (Fraction A_1), were hydrolyzed by boiling one hour with 5% alcoholic potassium hydroxide. The reaction mixture was poured into water and extracted with ethyl ether. The ether solution was washed with water and evaporated to dryness on the steam-bath. The crude sterols obtained were dissolved in just sufficient boiling 85% ethanol to effect complete solution. After about twelve hours the crystalline material was separated, redissolved in a minimum amount of boiling 85% ethanol and let stand again. This procedure was repeated ten times. The resultant crystalline material was then recrystallized from methanol, and from chloroform–methanol; m. p. 168.5–169°; $[\alpha]^{27}D$ −2.7° (556 mg., 10 cc. chloroform, l = 2 dm., $\alpha^{27}D$ −0.30°, *average* reading).

α-Spinasteryl Acetate.—A quantity of α-spinasterol was dissolved in acetic anhydride and the mixture heated one hour. On standing the crystalline acetate separated. The product was filtered off and recrystallized from 95% ethanol; m. p. 180–182°; $[\alpha]^{21}D$ −6.4° (52.9 mg., 2 cc. chloroform, l = 2 dm., $\alpha^{21}D$ −0.34°, *average* reading).

α-Spinasteryl Benzoate.—Five hundred milligrams of α-spinasterol was dissolved in 1.5 cc. of pyridine and 0.5 cc. of benzoyl chloride added. The mixture was heated in a boiling water-bath two hours and allowed to stand twelve hours at room temperature. The product was recovered and recrystallized twice from 95% ethanol; yield 350

(4) Kuwada and Yosiki, *J. Pharm. Soc. Japan*, **60**, 161 (1940).
(5) Kuwada and Yosiki, *ibid.*, **57**, 155 (1937).
(6) Kuwada and Yosiki, *ibid.*, **59**, 282 (1939).
(7) Bernstein, Kauzmann and Wallis, *J. Org. Chem.*, **6**, 319 (1941).

(8) A small amount of water greatly facilitates the separation of the sterols from the oily mixture. These sterols tend to crystallize with one-half mole of water, if water is available.

mg.; m. p. 196–199°; $[\alpha]^{19}D$ 2.1° (51.6 mg., 2 cc. chloroform, l = 2 dm., $\alpha^{19}D$ 0.11°, *average* reading).

β-Spinasterol.—The combined mother liquors from the isolation of α-spinasterol were evaporated to a small volume and water added. The precipitate was filtered off and taken up in just enough boiling 85% ethanol to effect solution. After standing overnight at room temperature the solid material was filtered off. From the mother liquors a fraction, corresponding to the β-spinasterol of Heyl and Larsen,[2] was isolated. On recrystallization from 95% ethanol, flaky transparent crystals appeared; m. p. 148–150°. In melting they lost water of crystallization at 110–125°; $[\alpha]^{20}D$ 5.9° (52.7 mg., 2 cc. chloroform, l = 2 dm., $\alpha^{20}D$ 0.31°, *average* reading). The substance formed an insoluble precipitate with digitonin.

Anal. Calcd. for $C_{29}H_{47}OH \cdot {}^1/_2H_2O$: C, 82.58; H, 11.72. Found: C, 82.56; H, 11.98.

Anhydrous β-Spinasterol.—β-Spinasterol as isolated above was heated at 50° *in vacuo* for seven days. The product was free of water of crystallization; m. p. 148–150°.

Anal. Calcd. for $C_{29}H_{47}OH$: C, 84.38; H, 11.73. Found: C, 84.35; H, 12.12.

β-Spinasteryl Acetate.—One hundred milligrams of β-spinasterol was dissolved in acetic anhydride and the mixture heated one hour. On standing several hours at room temperature the crystalline acetate separated. The product was filtered off and recrystallized from 95% ethanol; m. p. 153–155°; $[\alpha]^{19}D$ 5.1° (44.7 mg., 2 cc. chloroform, l = 2 dm., $\alpha^{19}D$ 0.23°, *average* reading).

Anal. Calcd. for $C_{31}H_{50}O_2$: C, 81.88; H, 11.097. Found: C, 81.83, 81.54; H, 10.92, 11.38.

β-Spinasteryl Benzoate.—Five hundred milligrams of β-spinasterol in 1.5 cc. of pyridine was treated with 0.5 cc. of benzoyl chloride. The mixture was heated two hours on a boiling water-bath, allowed to stand overnight, and then handled as usual. The product was recrystallized from a mixture of ethyl ether and ethanol; yield 450 mg.; m. p. 181–183°; $[\alpha]^{19}D$ 7.5° (56.0 mg., 2 cc. chloroform, l = 2 dm., $\alpha^{19}D$ 0.42°, *average* reading).

Anal. Calcd. for $C_{36}H_{52}O_2$: C, 83.65; H, 10.15. Found: C, 83.81; H, 10.25.

Hydrogenation of β-Spinasteryl Acetate.—Nine hundred and fifty milligrams of β-spinasteryl acetate was dissolved in 25 cc. of glacial acetic acid and shaken for two hours in an atmosphere of hydrogen while in the presence of 100 mg. of Adams catalyst.[9] An additional portion of catalyst was added and the reaction continued about two hours more. The reaction mixture was filtered and the filtrate diluted with water. The product was then separated off and taken up in ethyl ether. The ether solution was washed with water, and the solvent removed by evaporation on the steam-bath. The product was recrystallized from 95% ethanol; yield 625 mg.; m. p. 115–116°; $[\alpha]^{17}D$ 9.6° (53.1 mg., 2 cc. chloroform, l = 2 dm., $\alpha^{17}D$ 0.51°, *average* reading).

Anal. Calcd. for $C_{31}H_{52}O_2$: C, 81.50; H, 11.48. Found: C, 81.90; H, 11.64.

This compound gave no depression in melting point when mixed with an authentic specimen of α-stigmastenyl acetate (prepared from authentic α-spinasterol).[10]

α-Spinastenol (α-Stigmastenol).[3]—The acetate mentioned above was hydrolyzed with 5% alcoholic potassium hydroxide. The product was recovered as usual and recrystallized from methanol; m. p. 111–112°; $[\alpha]^{15}D$ 21.2° (53.7 mg., 2 cc. chloroform, l = 2 dm., $\alpha^{15}D$ 1.14°, *average* reading).

Anal. Calcd. for $C_{29}H_{49}OH$: C, 83.97; H, 12.13. Found: C, 84.05; H, 12.28.

There was no depression in melting point when a specimen of this substance was mixed with authentic α-stigmastenol.

4. Fractionation of the Material Soluble in Cold Acetic Anhydride.—The crude acetates (Fraction A_2), m. p. 122–127°, were hydrolyzed with 5% alcoholic potassium hydroxide. The reaction mixture was poured into water and the product extracted with ethyl ether. The ether soluton was evaporated to dryness and the residue fractionally crystallized from ethanol. The more soluble fractions yielded a crystalline substance; m. p. 122–125°; $[\alpha]^{20.5}D$ −4.8° (48.7 mg., 2 cc. chloroform, l = 2 dcm., $\alpha^{20.5}D$ −0.23°, *average* reading). This material was not further studied.

δ-Spinasterol.—The less soluble top fractions from the above fractionation gave a product with a melting point of 142–143°. This substance, after repeated crystallization from methanol, gave a substance which appeared to be a chemical individual; m. p. 143–144°; $[\alpha]^{19}D$ 6.2° (49.6 mg., 2 cc. chloroform, l = 2 dm., $\alpha^{19}D$ 0.31°, *average* reading).

Anal. Calcd. for $C_{29}H_{47}OH \cdot {}^1/_2H_2O$: C, 82.58; H, 11.72. Found: C, 82.80, 82.33; H, 12.03, 11.94.

This substance formed an insoluble precipitate with digitonin and gave a positive Liebermann–Burchard test.

δ-Spinasteryl Acetate.—The sterol, m. p. 143–145°, was dissolved in a small amount of acetic anhydride and heated one hour. On standing at room temperature the acetate crystallized out. It was recrystallized from 95% ethanol; m. p. 132–133.5°; $[\alpha]^{16}D$ 0.8° (49.7 mg., 2 cc. chloroform, l = 2 dm., $\alpha^{16}D$ 0.04°, *average* reading).

Anal. Calcd. for $C_{31}H_{50}O_2$: C, 81.88; H, 11.097. Found: C, 81.42, 81.74; H, 11.30, 11.54.

This acetate on hydrolysis gave the sterol; m. p. 143–145°.

δ-Spinasteryl Benzoate.—Two hundred and ninety milligrams of the sterol was dissolved in 1 cc. of pyridine and treated with 0.5 cc. of benzoyl chloride. The mixture was heated two hours on a boiling water-bath and allowed to stand overnight at room temperature. The product was recovered as usual, and recrystallized four times from ethanol; m. p. 165–168° (softening gradually to a viscous liquid); $[\alpha]^{19}D$ 11.1° (50.4 mg., 2 cc. chloroform, l = 2 dm., $\alpha^{19}D$ 0.56°, *average* reading).

Anal. Calcd. for $C_{36}H_{52}O_2$: C, 83.65; H, 10.15. Found: C, 83.20; H, 10.37.

Hydrolysis with 5% alcoholic potassium hydroxide gave the original sterol, m. p. 143–145°, and the sterol recovered from the benzoate was converted to the acetate; m. p. 131–134°.

(9) Gilman and Blatt, "Organic Syntheses," Collective Volume I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., page 463.

(10) We are indebted to Dr. H. G. Kolloff of the Upjohn Research Laboratories who very kindly supplied us with a specimen of α-spinasterol.

Hydrogenation of δ-Spinasteryl Acetate.—One hundred milligrams of δ-spinasteryl acetate was dissolved in 10 cc. of glacial acetic acid and shaken for one hour in an atmosphere of hydrogen in the presence of 50 mg. of Adams catalyst. The product was recovered and recrystallized twice from 95% ethanol; yield 40 mg.; m. p. 111–112°; $[\alpha]^{24}D$ 8.6° (44.5 mg., 2 cc. chloroform, l = 2 dm., $\alpha^{24}D$ 0.38°, *average* reading). This product when mixed with an authentic specimen of α-stigmastenyl acetate showed no depression in melting point.

Summary

1. From the unsaponifiable portion of Hardigan alfalfa seed oil we have isolated three isomeric sterols of formula $C_{29}H_{48}O\cdot{}^1/_2H_2O$: namely, α-spinasterol, β-spinasterol and a new sterol which was designated as δ-spinasterol.

2. Several derivatives of each of the sterols have been prepared and the physical constants and analysis observed.

3. Each of the three isomeric sterols can be reduced to α-stigmastenol.

EAST LANSING, MICHIGAN RECEIVED JULY 2, 1942

[CONTRIBUTION FROM THE DEPARTMENT FOR INORGANIC AND ANALYTICAL CHEMISTRY OF THE HEBREW UNIVERSITY]

Catalysts for Peroxide Decomposition[1]

BY M. BOBTELSKY AND A. E. SIMCHEN

Introduction.—In a previous paper[2] some facts were given relating to the catalytic decomposition of hydrogen peroxide in the presence of complex cobalt citrates acting as catalysts. One of them, pink in color, is stable and without catalytic activity; in the presence of hydrogen peroxide it is transformed into a green complex and simultaneously oxygen is evolved by the decomposition of the hydrogen peroxide. Gasometric experiments showed that the velocity of this evolution depends on the velocity with which the green complex is produced.

Nature of the Cobalt Citrate Complexes.—Our first concern was to ascertain the nature of the cobalt citrate complexes. This was accomplished by means of conductometric titrations of solutions of mono-, di- and tri-sodium citrates containing cobaltous ions.

These titrations were carried out with a Lautenschläger "Lyograph," in a cell of constant 0.52 with platinized and calcined platinum electrodes at 15 and 30°. The solutions of mono- and di-sodium citrates were prepared by mixing solutions of tri-sodium citrate and citric acid.

Figures 1 and 2 give some of our results. The breaks in curves 3 and 4 (Fig. 1) at 0.5 cc. of 1 *M* solution prove the presence of a compound with $Co^{++}/Ci^{---} = 1$. The small slope before the break indicates formation of undissociated molecules. Qualitative tests show that sodium hydroxide has no effect on the cobalt in these solutions. Figure 2 shows breaks in curves 8 and 9 at 1.5 cc. of 1 *M* NaH_2Ci and 0.75 cc. of 1 *M* Na_2HCi. These results prove that *only tertiary* Ci^{---} *ions take part in the formation of the complexes.*

The Catalytic Decomposition of Hydrogen Peroxide in Presence of Cobalto-citrate Complexes.—There are two phenomena to be elucidated: the transformation of the pink into the green complex and the catalytic decomposition of the hydrogen peroxide.

There are several possibilities as to the mechanism of the transformation of the pink complex. Hydrogen peroxide may not take part in an oxidation–reduction reaction, since experiments prove that cobalt is divalent in the green complex too (see below). Another possibility is that a peroxidized compound may be temporarily produced and then transposed into the green form.

The catalytic decomposition to hydrogen peroxide may also take place in several ways: hydrogen peroxide may add to the green complex forming an unstable addition compound; or oxygen atoms may add to the green complex and the resultant compound decomposes later, or the divalent cobalt may be oxidized to a higher valence and then immediately be reduced to Co^{++} with evolution of oxygen.

To test the various possibilities the quantities of two of the reactants, Co^{++}, Ci^{---} and hydrogen peroxide were kept constant and that of the third reactant was varied and the resultant changes in the system were measured by different

(1) An extensive revision of the original manuscript, chiefly concerned, however, with the presentation, was required and this was carried out under the Editor's direction. Under the disturbed international conditions now prevailing, it appeared impractical to obtain the authors' approval of this revision, and, to avoid delay, this revised version is therefore published on the Editor's responsibility.—THE EDITOR.

(2) M. Bobtelsky and M. Rappoport, *Compt. rend.*, **205**, 234 (1937).

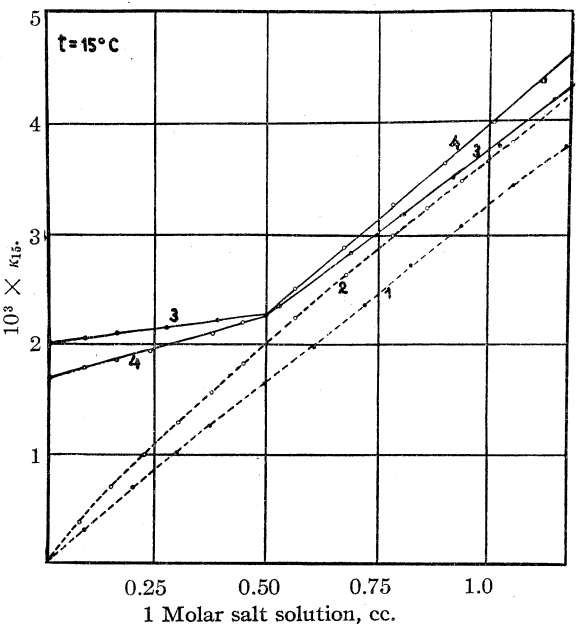


Fig. 1.—Conductometric titration curves, t = 15°: (1) 50 cc. of H_2O with $CoCl_2$ 1 m.; (2) 50 cc. of H_2O with Na_3Cl 1 m.; 50 cc. of Na_3Ci 0.01 m. with $CoCl_2$ 1 m.; (4) 50 cc. of $CoCl_2$ 0.01 m. with Na_3Ci 1 m.

methods. Optical measurements could not be made during an experiment because of the evolution of oxygen; they could, however, be carried out in solutions in which all of the hydrogen peroxide had decomposed.

(a) **Preliminary Experiments.**—The decomposition of hydrogen peroxide by the pink cobalto-citrate complex with simultaneous transformation of pink into green complex goes easily when the hydrogen peroxide is added to solutions containing more than 1 mole of tri-sodium citrate per mole of cobaltous chloride; in solutions with an excess of cobaltous ions the decomposition of hydrogen peroxide takes place very slowly.

Thus, *e. g.*, 20 cc. of a solution 0.1 *M* in cobaltous chloride and 0.05 *M* in tri-sodium citrate became green ninety minutes after addition of 1.5 cc. of hydrogen peroxide. At greater dilutions light-brown precipitates were formed.

(b) **Gasometric Experiments.**—Experiments with variable quantities of citrate. The results plotted in Fig. 3 show that the velocity of decomposition of hydrogen peroxide tends to zero for the ratio Na_3Ci/Co^{++} = 1. General composition of the solutions used in obtaining Fig. 3: x cc. of 1 *M* cobaltous chloride + y cc. of 1 *M* tri-sodium citrate + $(9 - x - y)$ cc. of water and 1 cc. of 2 *M* hydrogen peroxide (added last). The results for x = 0.50 cc. are plotted in Fig. 3 (those of x = 0.25 cc. are similar).

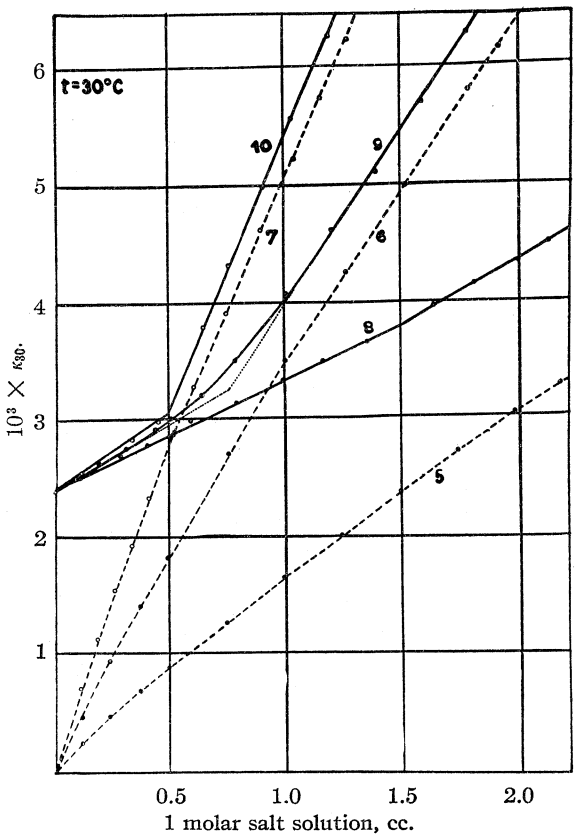


Fig. 2.—Conductometric titration curves, t = 30°: (5) 50 cc. of H_2O with NaH_2Ci 1 m.; (6) 50 cc. of H_2O with Na_2HCi 1 m.; (7) 50 cc. of H_2O with Na_3Ci 1 m.; (8) 50 cc. of $CoCl_2$ 0.01 m. with NaH_2Ci 1 m.; (9) 50 cc. of $CoCl_2$ 0.01 m. with Na_2HCi 1 m.; (10) 50 cc. of $CoCl_2$ 0.01 m. with Na_3Ci 1 m.

Experiments with Variable Quantities of Hydrogen Peroxide.—General composition of the solutions: 2 cc. of 0.2 *M* cobaltous chloride and 3 cc. of 0.2 *M* tri-sodium citrate + $(5 - x)$ cc. of water and x cc. of 1 *M* hydrogen peroxide (added last). The molar ratio $(H_2O_2)/(Co^{++})$ varied between 0.25 and 3.0. In every case 100% of the disposable oxygen of the hydrogen peroxide was evolved and the solution contained the green cobalto-citrate complex. Thus *no oxygen is used for the transformation of the pink into the green complex.* We may therefore conclude: (1) *in the final green solution the cobalt is only in the divalent state, and* (2) *citrate ion is not attacked during the reaction.*

The gasometric experiments were carried out with a specially constructed apparatus used in this Laboratory[3] permitting measurements up to 20 cc. with a precision of 0.02 cc. and enabling two experiments to be done simul-

(3) B. Kirson, Thesis, Jerusalem, 1938; M. Bobtelsky and L. Bobtelsky-Chaykin, *Compt. rend.*, **201**, 604 (1935).

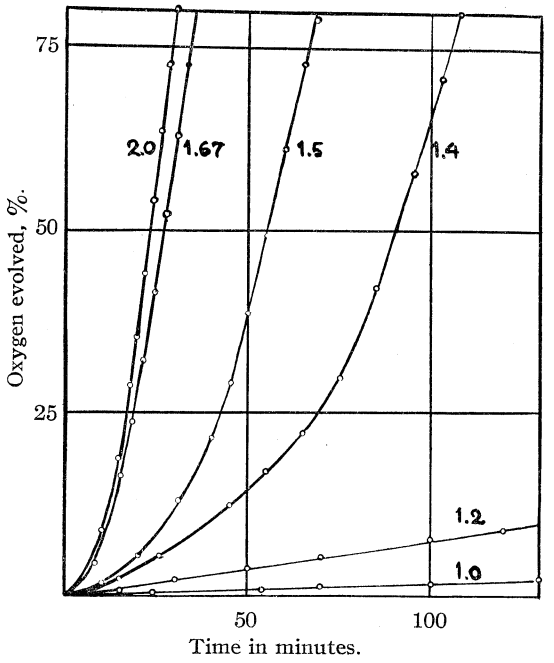


Fig. 3.—Oxygen evolved, % *vs.* time, at 15°, $[Co^{II}]$ = 0.05 m. The numbers on the curves indicate the ratio of ionic concns. $[Ci^{---}]/[Co^{++}]$.

taneously. The apparatus consists of two reaction vessels (glass flasks of 250-cc. volume) suspended on a rocking device seated in a water thermostat (±0.05°) and joined through rubber pressure tubes and three-way glass stopcocks to two micro-gas burets (seated in larger concentric glass tubes filled with water at room temperature). The reaction vessels are closed, after having introduced the reaction mixture, by means of rubber stoppers traversed by semi-capillary glass tubes (joined to the rubber tubes). In each rubber stopper a glass hook of about 5 cm. length is inserted on which a little glass bucket may be suspended containing the reactant to be added last. After having brought the reaction vessels to the thermostat temperature, the little glass bucket is thrown off the glass hook by sudden jarring; the mechanical rocking is then started and the evolution of gas recorded.

(c) **Conductometric Experiments.**—General composition of the solutions (30°): 1 cc. of 1 *M* cobaltous chloride + *x* cc. of 1 *M* tri-sodium citrate + *y* cc. of 1 *M* hydrogen peroxide (added last) + (49 − *x* − *y*) cc. of water. All initial conductivity values of the mixtures with hydrogen peroxide were lower than the corresponding values for solutions containing water in place of the peroxide. The latter has a depressing action on conductivities of electrolytes.[4] From the different results obtained we show in Fig. 4 only one series with *x* = 1.5 cc. in which the concentration of peroxide was varied. In all cases the conductivity

(4) M. Bobtelsky and A. E. Simchen, THIS JOURNAL, **64**, 454 (1942).

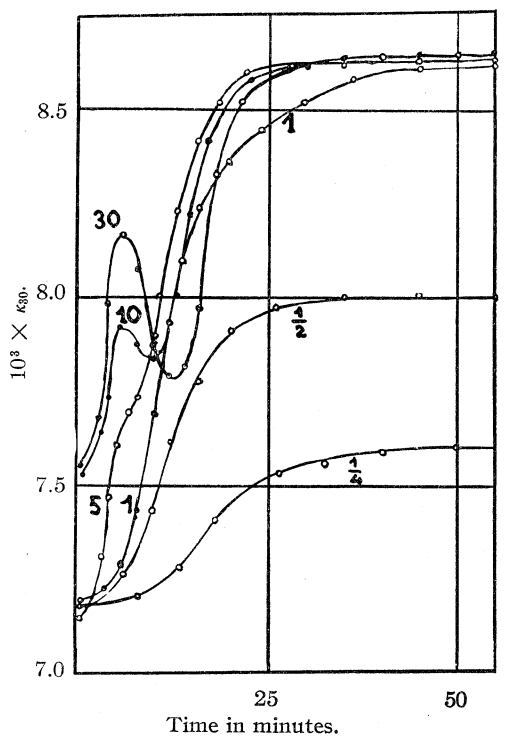


Fig. 4.—Conductivity × 10^3 *vs.* time, at 30°—composition: 1 cc. of $CoCl_2$ 1 m. + 1.5 cc. of Na_3Ci 1 m. + (47.5 − *x*) cc. of H_2O + *x* cc. of H_2O_2 1 m. Numbers on curves represent cc. of H_2O_2.

increases during the reaction until a constant maximum value is attained in about forty minutes. The numbers on the curves of Fig. 4 show the molar ratio $(H_2O_2)/(Co^{++})$ which varies from 0.25–30. It is of interest that only when the ratio is ≧ 1 do we get a constant maximum of conductivity; as we shall see later we have in all these last cases 100% of the green complex. *Thus the reaction is proven to be* $1Co^{++}/1Ci^{---}/1H_2O_2$.

The appearance of relative maxima and minima of conductivity in the experiments made with greater quantities of hydrogen peroxide is the result of a specific influence of hydrogen peroxide on the conductivity of electrolytes as shown in another paper.[4] These maxima and minima are fairly reproducible and reappear after addition of hydrogen peroxide to the green cobalto-citrate complex. The lower branch of the curve, before the relative maximum is attained, does not reappear upon fresh additions of hydrogen peroxide; it corresponds to the transformation of the pink into the green complex. When carrying out gasometric and conductometric experiments of the same composition and at the same temperature (Fig. 5), it is seen that the relative maxima and

minima of conductivity do not appear in the gasometric curve at all.

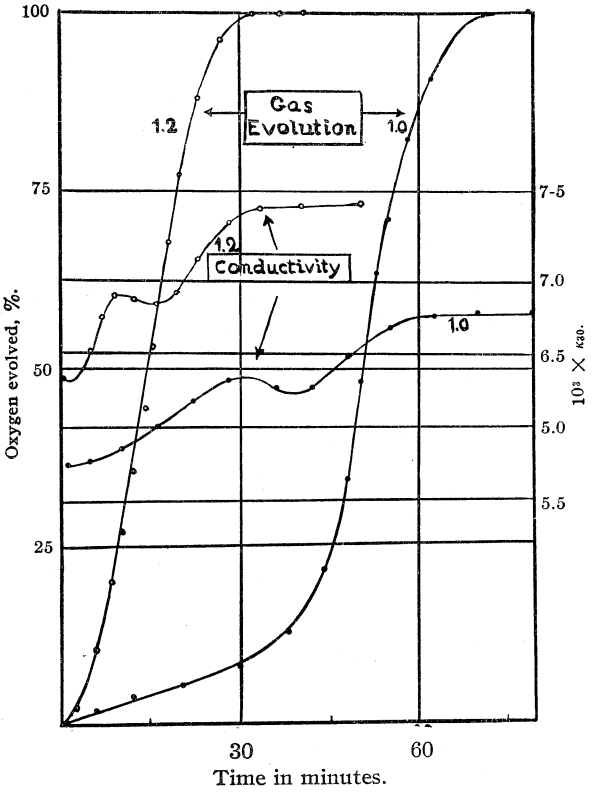


Fig. 5.—General composition: 1 cc. of $CoCl_2$ 1 m. + x cc. of Na_3Ci 1 m. + 10 cc. of H_2O_2 1 m. + (39 − x) cc. of H_2O. Numbers on curves represent cc. of Na_3Ci 1 m.

(d) **Optical Measurements.**—Composition of the five solutions: 1 cc. of 1 *M* cobaltous chloride + 1.5 cc. of 1 *M* tri-sodium citrate + (47.5 − x) cc. of water + x cc. of 1 *M* hydrogen peroxide (added last). x = 0.33, 0.67, 1.0, 2.0 and 3.0 cc. After complete decomposition of hydrogen peroxide the solutions are a mixture of the pink and the green complex. The measured percentages of green complex are plotted in Fig. 6. It is easily seen that here too the final value is obtained for H_2O_2/Co^{++} = 1.

The colorimetric measurements were made in a two-color colorimeter of the Duboscq type, of Hellige, using two solutions for comparison. Measurements were made at room temperature one hour after preparation in a layer 30 mm. thick. The solutions for comparison were (1) a green complex solution obtained in the above way with x = 6.0 cc. of 1 *M* peroxide (giving 100% green complex); (2) a pink complex solution without hydrogen peroxide (100% pink complex).

From the results of the conductometric as well as the colorimetric measurements the following conclusions may be drawn: the reaction between

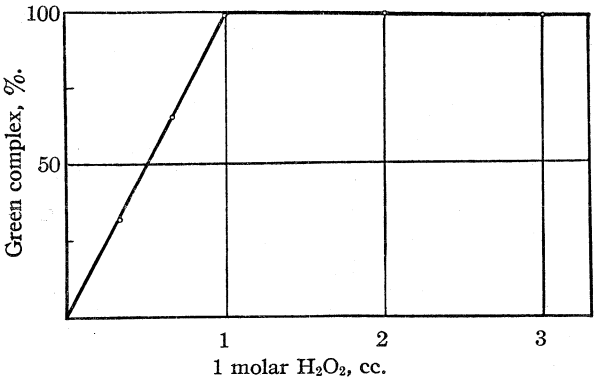


Fig. 6.—Green complex, %, *vs.* cc. of H_2O_2 1 m.—composition: 1 cc. of $CoCl_2$ 1 m. + 1.5 cc. of Na_3Ci 1 m. + (47.5 − x) cc. of H_2O + x cc. of H_2O_2 1 m.

hydrogen peroxide and the pink cobalto-citrate complex in the ratio $1Co^{++}/1Ci^{---}/1H_2O_2$ must go to completion almost immediately and there is no free hydrogen peroxide present during the slow transformation of the pink into the green complex.

(e) **Influence of Concentrated Neutral Salts.**—The influence of ammonium nitrate and chloride on the catalytic decomposition of hydrogen peroxide by cobalto-citrate complexes has been studied by Bobtelsky and Rappoport.[2] We give in Fig. 7 results of some gasometric experiments made with and without ammonium nitrate (the chloride gives analogous results). At a concentration of 3 *N* the rate of oxygen evolution has a maximum and then diminishes with increasing concentration. The influence of electrolyte at lower concentration may be in the stabilization of the cobalto-citrate complex (similar to citrate ion concentration in excess). In the presence of highly concentrated electrolyte (>3 *N*) the green

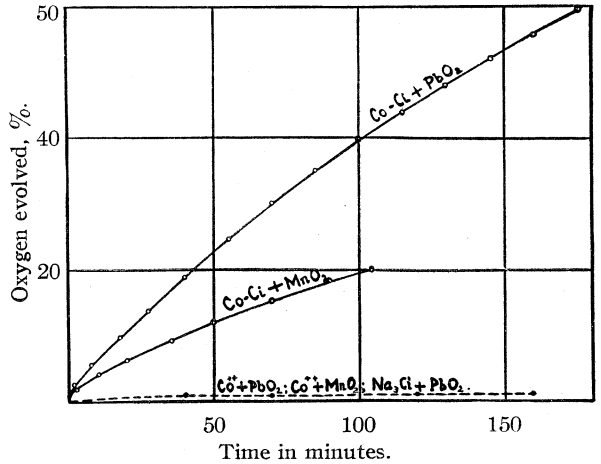


Fig. 7.

cobalto-citrate complex changes through a blue to a brick-red solution and this color remains stable for months.

Action of the Cobalto-citrate Complexes on the Solid Peroxides PbO_2 and MnO_2.—The catalytic decomposition of solid peroxides by the action of cobalto-citrate complexes was investigated by shaking the finely powdered peroxides at constant temperature (30°) with the pink and with the green complex and measuring the volume of oxygen evolved. A slow transformation of the pink complex into the green takes place with simultaneous evolution of oxygen. The last reactant added to the reaction mixture was either the cobaltous solution or the powdered lead dioxide. Composition of the reaction mixtures: with PbO_2: 4 cc. 1 *M* $CoSO_4$[5] + 12 cc. of 1 *M* Na_3Ci + 4 cc. H_2O + 0.5 g. PbO_2; with MnO_2: 4 cc. of 1 *M* $CoSO_4$ + 12 cc. of 1 *M* Na_3Ci + 4 cc. H_2O + 0.2 g. of MnO_2.

Figure 8 shows that more than half the peroxide oxygen is evolved from lead dioxide in two and one-half hours; lead dioxide is decomposed more quickly than manganese dioxide.

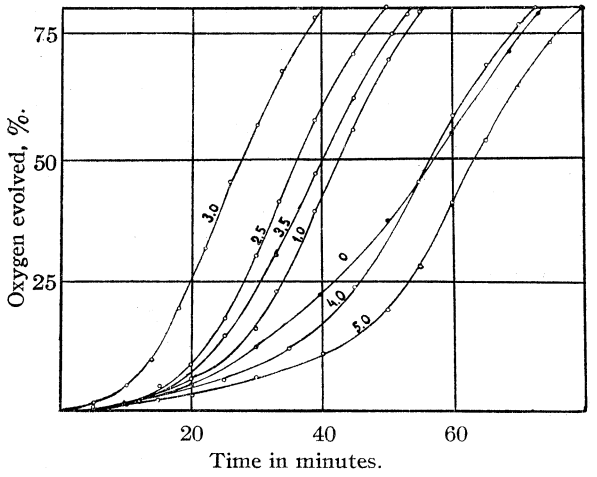


Fig. 8.—Influence of NH_4NO_3—composition: besides NH_4NO_3 the solutions contained per 20 cc.: 0.5 cc. of $CoCl_2$ 1 m. + 0.75 cc. of Na_3Ci 1 m. + 2 cc. of H_2O_2 1 m. Numbers on the curves represent the final concentration of NH_4NO_3; t = 15°.

In the decomposition of solid peroxides it is probably not possible to speak of an addition of these substances to the pink complex; therefore, we probably have, during the formation of the green complex, *a transitory oxidation of the pink complex* followed by decomposition with evolution of oxygen. It may well be that a similar path is followed during the reaction with hydrogen peroxide.

Shaking lead peroxide with a solution of the green complex formed by the action of excess hydrogen peroxide on a cobalto-citrate mixture showed that even after one and one-half hours no oxygen was evolved. *The green complex does not decompose these solid peroxides.*

The absorption spectrum of the green complex from the solid peroxides is identical with that of the green complex from hydrogen peroxide.

Comparison of Behavior of Cobalto-citrate and -tartrate Complexes.—(a) Qualitative experiments were made with Co^{++}- and di-sodium tartrate solutions. On mixing the two solutions a pink solution was obtained; its absorption spectrum was measured (Fig. 9) and compared to the absorption spectrum of the pink cobalto-citrate complex solution. Upon addition of hydrogen peroxide to the tartrate solution (*e. g.*, 0.5 cc. of 1 *M* cobaltous chloride + 1 cc. of 1 *M* di-sodium tartrate + 25 cc. of water to which was added 4.5 cc. of 1 *M* hydrogen peroxide) a pink precipitate is formed. In the presence of still greater quantities of hydrogen peroxide the solution becomes brownish-green with precipitate and oxygen is evolved.[6]

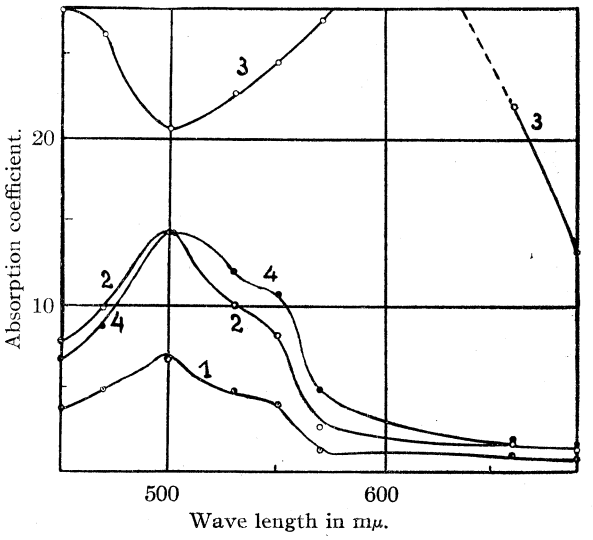


Fig. 9.—Light absorption curves: (1) $CoCl_2$; (2) pink cobalto-citric complex; (3) green cobalto-citric complex; (4) pink cobalto-tartaric complex.

(b) Conductometric titrations were carried out in solutions of 50 cc. of 0.01 *M* di-sodium tartrate

(5) Cobaltous chloride yields exactly the same values.

(6) Only a part of the disposable oxygen could be obtained, the tartrate having been attacked (unpublished results of M. Bobtelsky and L. Bobtelsky-Chaykin).

with 1 *M* cobaltous chloride and of 50 cc. of 0.01 *M* cobaltous chloride with 1 *M* di-sodium tartrate. In both cases breaks were obtained at exactly $Ta^{--}/Co^{++} = 1$ and $Ci^{---}/Co^{++} = 1$. At these points the Co^{++} ions as well as a part of the tartrate or citrate ions are bound with one another very strongly (sodium hydroxide gives no reaction with Co^{++}). From this fact the following computations can be carried out. The observed conductivities of 0.01 molar solutions were (30°): $CoCl_2$, $\kappa = 2.35 \times 10^{-3}$; Na_3Ci, $\kappa = 2.86 \times 10^{-3}$; Na_2Ta, $\kappa = 2.04 \times 10^{-3}$; and at 15°, $CoCl_2$ $\kappa = 1.70 \times 10^{-3}$; Na_3Ci, $\kappa = 2.0 \times 10^{-3}$. The ionic mobilities from a table are: $^1/_3\ Ci^{---}$, 60.3; $^1/_2\ Co^{++}$, 43; Cl^-, 65.4; Na^+, 43.5; $^1/_2\ Ta^{--}$, 55; acid Ta^-, 31. Table I is deduced from these values.

TABLE I

Ionic loss	$\kappa \times 10^3$ (15°) Calcd.	Found	$\kappa \times 10^3$ (30°) Calcd.	Found
$^1/_2Co^{++} + {}^1/_3Ci^{---}$	2.98	2.30	4.16	3.10
$1\ Co^{++} + {}^1/_3\ Ci^{---}$	2.64		3.70	
$1\ Co^{++} + {}^2/_3\ Ci^{---}$	2.25		3.15	
$^1/_2\ Co^{++} + {}^1/_2\ Ta^{--}$			3.36	3.02
$1\ Co^{++} + {}^1/_2\ Ta^{--}$			2.89	
$1\ Co^{++} + 1\ Ta^{--}$			2.32	
$^1/_2\ Co^{++} + HTa^-$			3.11	

It appears from the table that the last assumption is most probable in the case of citrate. There are several possibilities for the tartrate.

(c) Conductometric titrations of cobalto-tartrate complexes by sodium hydroxide and hydrochloric acid. The pink cobalto-citrate complex as well as the green complex was conductometrically titrated with 1 *N* sodium hydroxide and with 1 *N* hydrochloric acid (50 cc. complex solution contained 1 cc. of 1 *M* cobaltous chloride + 1.2 cc. of 1 *M* tri-sodium citrate). The titrations with hydrochloric acid did not give clear-cut phenomena; during this titration of the green complex solution, a slow transformation takes place of the green color into the color of cobaltous ions and the complex is destroyed (this is valid for the pink complex also).

The results of titrations with sodium hydroxide are plotted in Fig. 10. In the case of the pink complex there is a neat break at $NaOH/Co^{++} = 1$. In the case of the green complex there is probably a break at about $NaOH/Co^{++} = 2$.

The experiments described in this paper lead us to the conclusion that in the green complex, the cobalt is present in the *divalent* state. This green complex is an extremely active catalyst for the

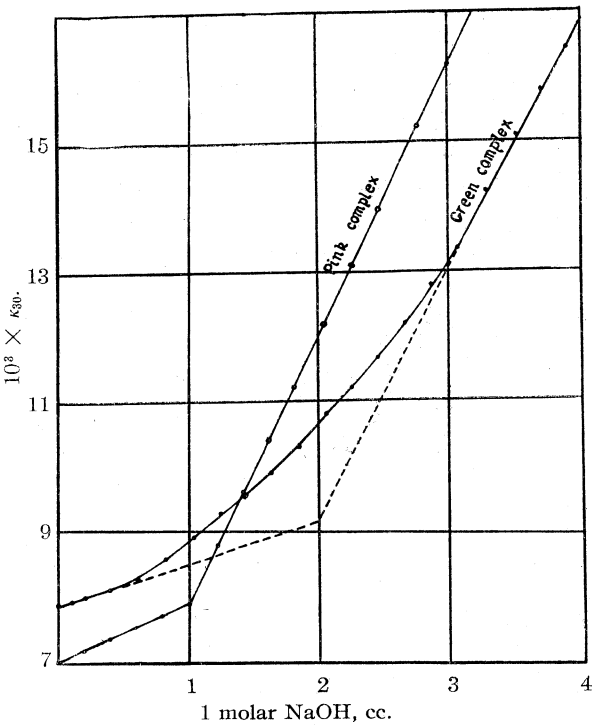


Fig. 10.—Conductometric titration curves with NaOH, at 30°: pink complex—1.0 cc. of $CoCl_2$ 1 m. + 1.2 cc. of Na_3Ci 1 m. + 47.8 cc. of H_2O titrated with NaOH 1 *n;* green complex: 1.0 cc. of $CoCl_2$ 1 m. + 1.2 cc. of Na_3Ci 1 m. + 42.8 cc. of H_2O + 5 cc. of H_2O_2 1 m., titrated one hour after preparation with NaOH 1 m.

decomposition of hydrogen peroxide. It is formed after a previous oxidation of the pink cobalto-citrate complex during which an intermediary peroxidized compound is produced and gradually transformed into the green complex, releasing the whole of the disposable oxygen at the same time. The green complex obtained in this complicated way is soluble in water and quickly catalyzes the decomposition of hydrogen peroxide (without itself being attacked) at concentrations as low as 10^{-6} mole g./l.

It is of interest to note that the ferric ion[7] shows in some respects a similar behavior, giving with tri-sodium citrate two[8] complexes, one of which is without catalytic activity while the second has a strong catalytic action.

The other citrate complexes of 2- or 3-valent cations (Cu^{++}, Mn^{++}, Ni^{++}, UO_2^{++}, Ce^{+++}, Pb^{++}, Al^{+++}, Mg^{++}, Ba^{++}, Cd^{++}, Zn^{++}) show scarcely any catalytic action upon the decomposition of hydrogen peroxide, they give generally one complex $Ci^{---}/Me^{++} = 1$; ferric ion on the

(7) M. Bobtelsky and B. Kirson, *Compt. rend.*, **208**, 1577 (1939).
(8) M. Bobtelsky and A. E. Simchen, *ibid.*, **208**, 1646 (1939).

other hand gives the complexes $(Fe_2Ci_3)^{---}$ (inactive) and $(Fe_3Ci_2)^{+++}$ (active). With cobalt, *both complexes, the green as well as the pink, contain divalent Co, in the ratio of* $Ci^{---}/Co^{++} = 1$, but they differ in their internal structure. The green cobalto-citrate complex proved to be the most sensitive catalyst of all the complex citrates studied by us for the decomposition of hydrogen peroxide.

The study of the structure of the citrate complexes compared with that of tartrate complexes will be the object of a special article. Di-sodium tartrate too yields with hydrogen peroxide a green complex which catalyzes the decomposition of the peroxide, but the tartrate is simultaneously attacked by the peroxide, gives a precipitate and is therefore unfit for study. The parallel study of Co^{++} and Fe^{+++}-citrate and -tartrate complexes gives a possibility for a deeper insight into the structure of these substances. It might be supposed that in the case of citrate (with only one oxy-group) complexes the hydrogen of the oxy-group is replaced by a metal valence and a stable compound is thus produced, while in the active form the metal may be found in another way through a secondary valence to the oxy-anion.

By comparison with cobalto-ammonia complexes which also catalyze the decomposition of hydrogen peroxide,[2] it seems probable that the structural difference between pink and green cobalto-citrate complexes is that in the case of the green complex the cobalt atom is linked to the citrate by a secondary valence, while the linking is much stronger in the case of the pink complex.

Summary

A mixture of Co^{++} and Ci^{---} ions (pink complex) with hydrogen peroxide in the ratio $1Co^{++}/1Ci^{---}/1H_2O_2$ immediately leads to a pink peroxidized compound (without change of color), which decomposes gradually with liberation of all the disposable oxygen into a green divalent cobalt citrate complex. This green complex can also be obtained by peroxidizing the pink cobalto-citrate complex with lead or manganese dioxide instead of hydrogen peroxide. The green cobalto-citrate complex thus obtained acts as an extremely active catalyst (the most active of all the complex citrates) for the decomposition of hydrogen peroxide, but it cannot decompose lead or manganese dioxides. During all these operations the citrates are not attacked at all while corresponding reactions with tartrates lead to attack of the tartrate ion.

The properties of the complexes were studied by gasometric, photometric and conductometric methods.

JERUSALEM, PALESTINE RECEIVED FEBRUARY 16, 1942[9]

(9) Reported to have been dispatched from Jerusalem on February 25, 1941, but suffered various vicissitudes.

NOTES

The Catalytic Effect of Electrolytes on Solvolytic Reactions

BY L. F. AUDRIETH, L. D. SCOTT AND O. F. HILL

In a series of publications from this Laboratory[1] it has been demonstrated experimentally that ammonolytic and aminolytic reactions, involving the action of ammonia and amines upon esters, are catalyzed, respectively, by ammonium and amine salts presumably acting as acids in these solvents. In order to characterize still further the catalytic effects of various classes of substances upon solvolytic reactions in general, the influence of electrolytes (salts) upon the reactions (a) between *n*-butylamine and ethyl phenylacetate and (b) between liquid ammonia and ethyl benzoate were subjected to study. The experimental results presented below show (a) that additions of relatively small quantities of various neutral salts speed up effectively the conversion of the esters into the corresponding solvolytic products; (b) that the catalytic effect of equimolar concentrations of these salts is not nearly as marked as for the corresponding "onium" salts; and (c) that the findings heretofore considered as evidences for acid catalysis in basic solvents by the solvated proton may be but special cases of what might more properly be regarded as examples of electrolyte catalysis.

(1) See Glasoe, Scott and Audrieth, THIS JOURNAL, **63**, 2965 (1941), for earlier articles.

Experimental

The experimental procedures employed in studying these reactions have already been described in previous publications.[2,3] The data presented in Table I constitute a summary of the results obtained using various electrolytes, and electrolytes plus definite additions of water, in *n*-butylamine. The essential data for the reaction between liquid ammonia and ethyl benzoate are given in Table II. For purposes of comparison some data are also included in both tables of results previously reported on the catalytic effect of the corresponding "onium" salts. In both cases the observed catalytic effects are emphasized in the last column in which are given the experimentally determined half time values (in hours) for each series of runs.

TABLE I

AMINOLYSIS OF ETHYL PHENYLACETATE IN *n*-BUTYLAMINE AT 25°

a = concn. of amine in moles per liter; *b* = concn. of ester in moles per liter.

Catalyst	Concn. of catalyst in moles per liter	*a*	*b*	$K \times 10^3$	$t^{1/2}$ (exp.)
None[a]	...	5.45	2.80	0.87	158
$NaClO_4$	0.1	5.38	2.80	1.55	92
$C_4H_9NH_2 \cdot HClO_4$[a]	.1	5.40	2.80	2.09	70
NaI	.1	5.37	2.81	2.06	73
NaI	.2	5.30	2.81	2.50	59
$C_4H_9NH_2 \cdot HI$[a]	.1	5.34	2.80	2.57	57
NaSCN	.1	5.37	2.81	2.07	73
NaSCN	.2	5.42	2.77	2.39	63
$C_4H_9NH_2 \cdot HSCN$[a]	.1	5.36	2.80	2.81	53
NaSCN + H_2O	.2 + 2.0	4.91	2.81	4.7	36
NaI + H_2O	0.2 + 2.0	5.11	2.81	5.7	26

[a] Taken from data summarized in ref. 3.

TABLE II

AMMONOLYSIS OF ETHYL BENZOATE IN LIQUID AMMONIA AT 0°

Moles $C_6H_5COOC_2H_5$ = 0.035; moles NH_3 = 0.082 ± 0.3; moles catalyst = 0.00935.

Catalyst	$K \times 10^4$	$t^{1/2}$ (exp.)
None	0.47	*ca.* 15000
NH_4Cl[a]	7.86	882
NaCl	2.52	2760
$NaNO_3$	1.28	5420

[a] Taken from data summarized in ref. 2.

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

RECEIVED MAY 22, 1942

(2) Fellinger and Audrieth, THIS JOURNAL, **60**, 579 (1938).
(3) Glasoe, Kleinberg and Audrieth, *ibid.*, **61**, 2387 (1939).

Attempt to Detect Free Hydroxyl as an Intermediate in Photochemical Reactions

BY W. J. BLAEDEL,[1] R. A. OGG, JR., AND P. A. LEIGHTON

Free hydroxyl has been proposed as an intermediate in several photochemical processes.[2,3] The mechanisms of all the following processes might involve this substance (at 2537 Å.)

(1) $CH_3I + O_2 + h\nu$
(2) $H_2O_2 + h\nu$
(3) $H_2O_2 + Hg + h\nu$
(4) $H_2O + Hg + h\nu$
(5) $H_2 + O_2 + Hg + h\nu$
(6) $CH_3OH + Hg + h\nu$

In any of these processes, if the reactions by which hydroxyl disappears have low rates compared to those by which it is formed, it is conceivable that steady-state concentrations might be attained which are sufficient to be detectable by the absorption spectrum. The purpose of the following work was to detect such absorption if possible.

Experimental.—The photochemical reaction vessel was a cylindrical quartz tube, 120 cm. long, and 3.5 cm. in diameter, with plane quartz end windows. Irradiation was effected by placing two low pressure mercury arcs, each 120 cm. long and 0.7 cm. in diameter, parallel to and on opposite sides of this tube. A cylindrical aluminum reflector, open at the ends, enclosed the arcs and quartz tube.

Light from a water discharge giving the 3064 Å. hydroxyl band in emission was passed lengthwise through the reaction cell and into the slit of a 21-ft. concave grating spectrograph. The intensity of the discharge in the region containing the Q_1 1 1/2 and Q_1 2 1/2 lines was measured in the focal plane of the spectrograph with a sensitive photocell-amplifier system. This region shows the highest absorption at room temperature. The absorption noted in this region when the low pressure arcs were turned on was taken as a measure of the steady-state hydroxyl concentration produced.

The limit of detection of hydroxyl was determined by a method similar to that of Oldenberg and Rieke,[4] by measuring the absorption of water vapor dissociated at a high temperature. Here, the quartz cell was replaced by a cylindrical furnace with quartz end windows. Oxygen and water vapor at known pressures were passed through this furnace at about 1400° Å. The temperature distribution was measured along the furnace axis with a Pt/Pt-Rh thermocouple. Zeise's data[5] on the dissociation constants of water at various temperatures enabled a calculation of the hydroxyl distribution along the furnace axis at the high temperature. From the rotational term levels of the hydroxyl molecule,[4] the absorption of this same distribution at room temperature was calculated. This, with the

(1) Present address, Northwestern University, Evanston, Illinois.
(2) Urey, Dawsey and Rice, THIS JOURNAL, **51**, 1371 (1929).
(3) Bates and Spence, *ibid.*, **53**, 1689 (1931).
(4) Oldenberg and Rieke, *J. Chem. Phys.*, **6**, 439 (1938).
(5) Zeise, *Z. Elektrochem.*, **43**, 704 (1937).

limit of absorption detectable by the photocell-amplifier system, allowed calculation of 5×10^{-5} mm. as the lowest hydroxyl pressure detectable at 25° in the 120-cm. path length of the quartz reaction vessel.

All the above reactions were studied at 25° by introducing the reactants into the quartz tube at the following pressures: reaction 1, CH_3I = 10 mm., O_2 = 1, 10, 100 mm.; reactions 2 and 3, H_2O_2 = 1.5 mm.; reaction 4, H_2O = 20 mm.; reaction 5, H_2 = 50, 140, 20 mm., and O_2 = 20, 140, 500 mm., respectively; reaction 6, CH_3OH = 10, 50, 100 mm. In the processes where mercury was required, a few drops were scattered along the bottom of the quartz cell before introducing the reactants.

Results.—No absorption due to hydroxyl was detectable in any of the reactions studied. Hence, the steady-state concentration of hydroxyl, if any, was less than 5×10^{-5} mm. in processes 2, 3, 4, 5 and 6. In processes 3, 4, 5 and 6, the mercury surface became coated with oxide. In process 1, there was a slow increase in absorption due to formaldehyde formation. Any absorption due to intermediate formation had to be sought superimposed upon this drift. This decreased the sensitivity so that for this reaction it may only be said that the steady-state pressure of hydroxyl was less than 0.0003 mm.

DEPARTMENT OF CHEMISTRY
STANFORD UNIVERSITY
STANFORD UNIV., CALIF. RECEIVED JULY 20, 1942

Photoöxidation of Methyl Iodide

BY W. J. BLAEDEL,[1] R. A. OGG, JR., AND P. A. LEIGHTON

Bates and Spence have postulated a mechanism[2] for the photoöxidation of methyl iodide which has a maximum quantum yield of two and involves the intermediate formation of free hydroxyl. This mechanism was based on a study of the products, which were iodine, paraformaldehyde, methylal and water, and on a measurement of the quantum yield as 2.3, using a chloroacetic acid actinometer, assuming its quantum yield to be unity. Since this work, experimental data from several sources indicate that this mechanism is not entirely correct.

Iredale found the photodecomposition of methyl iodide to be greatly accelerated in the presence of nitric oxide.[3] His kinetic studies on this process and a comparison of his data with those of Bates and Spence permitted the inference that the quantum yield of photoöxidation should lie below a maximum possible value of 1.6.

In the hydroxyl mechanism,[2] hydroxyl radicals disappear by the reaction $CH_3I + OH \longrightarrow CH_3OH + I$. This reaction probably has a high activation energy (15–20 kcal.) and, if the mechanism is correct, a high steady-state concentration of hydroxyl should be established. The failure to detect any hydroxyl[4] is an indication that this reaction is not an important one in the mechanism.

Lastly, the quantum yield of the chloroacetic acid actinometer has been shown to be greatly dependent on temperature,[5] being only 0.31 at 25°. Assuming that the photoöxidation quantum yield of 2.3 was measured at this temperature, the corrected value becomes only 0.71.

In the light of this evidence, suggestion of a new mechanism is possible, and the most likely is one involving the formation of a peroxide[2] as an intermediate.

$$CH_3I + h\nu \longrightarrow CH_3 + I \qquad I_a$$
$$CH_3 + I_2 \longrightarrow CH_3I + I \qquad k_2$$
$$CH_3 + O_2 \longrightarrow CH_3O_2 \qquad k_3'$$
$$CH_3O_2 + CH_3 \longrightarrow CH_3OH + CH_2O \qquad k_4'$$
$$2CH_3OH + CH_2O \longrightarrow H_2C(OCH_3)_2 + H_2O$$
$$nCH_2O \longrightarrow (CH_2O)_n$$
$$nCH_2O + h\nu \longrightarrow (CH_2O)_n$$
$$2I + M \longrightarrow I_2 + M'$$

This differs from the hydroxyl mechanism in reactions 3′ and 4′.

The rate of formation of methyl iodide, as deduced from the new mechanism is

$$-\frac{d(CH_3I)}{dt} = \frac{I_a(O_2)}{\frac{k_2}{2k_3'}(I_2) + (O_2)}$$

This is identical in form to the experimental rate equation of Bates and Spence. The maximum quantum yield of unity is in accord with the previously conflicting data of Iredale and of Bates and Spence.

A recalculation of the data of the latter authors gives $k_2/k_3' = 820$, meaning that the activation energy of process 3′ is 3.6 kcal. greater than that of process 2 at 0°.

Reaction 3′ is postulated to be a two rather than a three body process. The evidence for this lies in the data of Bates and Spence, which show that k_2/k_3' remains constant as the total pressure varies over an eight-fold range from 25 mm. to 400 mm. This would not be expected if 3′ were a three body process.

The agreement of this mechanism with the experimental data indicates that the recombination, $CH_3 + I \rightarrow CH_3I$, is negligible compared to reac-

(1) Present address, Northwestern University, Evanston, Illinois.
(2) Bates and Spence, THIS JOURNAL, **53**, 1689 (1931).
(3) Iredale, *Trans. Faraday Soc.*, **35**, 458 (1939).
(4) Blaedel, Ogg and Leighton, THIS JOURNAL, **64**, 2499 (1942).
(5) Smith, Leighton, Leighton, *ibid.*, **61**, 2299 (1939).

tion 2. This is contrary to the conclusions of Iredale,[3] who interpreted his data to mean that reaction 2 was negligible compared to the recombination. However, his data may be interpreted equally well in a second way; and in this case, the results are in accord with the findings on the photoöxidation. At present, work is in progress to determine which of the two processes is predominant in methyl iodide photolysis.

DEPARTMENT OF CHEMISTRY
STANFORD UNIVERSITY
STANFORD UNIV., CALIF. RECEIVED JULY 20, 1942

Vapor Pressures of Indene, Styrene and Dicyclopentadiene

BY P. E. BURCHFIELD

The vapor pressures of indene, styrene and dicyclopentadiene were determined over temperature ranges. The pressure–temperature data were desired for the development of distillation procedure for the separation of the components of light oil solutions.

Experimental.—The compounds used in this investigation were purified by recrystallization. The process of purification and the physical properties of the purified compounds are described elsewhere.[1] The vapor pressures were determined by the method developed by Booth, Elsey, and Burchfield.[2] The temperature was measured by means of a calibrated thermometer graduated to 0.1°. The necessary stem corrections were calculated and applied.

Due to the reactive nature of the compounds studied, a time factor was imposed upon the vapor pressure measurements with the exception of those of styrene. Two pressure readings, separated by a ten-minute time interval, were taken at equal temperatures for each determination. The vapor pressures of styrene at the three highest temperatures were determined by employing a new sample for each measurement, thus reducing the possibility of error through polymerization. Depolymerization was noticeable in the case of dicyclopentadiene at 100°.

The calculated constant, determined by methods of least squares, for the simplified, integrated Clausius–Clapeyron equation, and other pertinent data, are summarized in Table I.

TABLE I

VAPOR PRESSURE DATA OF INDENE, STYRENE AND DICYCLOPENTADIENE

Compound	Clausius–Clapeyron constants A	B	No. 4 measurements	Temp. range of measurements, °C.	Average % deviation from mean
Indene	7.919	−2291	13	56.2 to 181.8	1.4
Styrene	7.929	−2103	7	33.5 to 116.3	1.1
Dichloropentadiene	7.925	−2218	6	40.1 to 90.8	0.6

(1) Smoker and Burchfield, "Cryoscopic Analysis of Light Oil Hydrocarbons," unpublished.

(2) Booth, Elsey and Burchfield, THIS JOURNAL, **57**, 2066 (1935).

RESEARCH DEPARTMENT
UNITED GAS IMPROVEMENT CO.
PHILADELPHIA, PA. RECEIVED SEPTEMBER 4, 1942

A New Fructosan Isolated from *Yucca mohavensis*, Sarg.

BY KEENE P. DIMICK AND BERT E. CHRISTENSEN

Recently in connection with the chemical investigation of the *Yucca mohavensis*, Sarg. it was observed that its fructose content (3–5%) increased to as high as 60% on mild acid hydrolysis of the dried stem. This suggests the possibility of the presence of a considerable amount of fructosans which may be stored in the stem as a plant food. Further work on this material resulted in the isolation of a polyfructosan. This fructosan was first obtained from the 70% alcoholic extract of the stem of the *Yucca mohavensis* and comprised approximately 20% of the dry weight. It appeared to be similar to the compound Graminin, isolated from rye flour by Schlubach and Koenig,[1] in that it was a white hygroscopic powder, soluble in water and pyridine, and forms an addition product with ethyl alcohol.

Experimental

Isolation of the Fructosan.—The stem of the Yucca plant was stripped of its bark, cut into small pieces, dried at 60° and then ground in a small mill. The meal was then subjected to exhaustive and continuous extraction with petroleum ether, ether, absolute alcohol and 70% alcohol in the order given. The extract from the 70% alcohol, constituting 40% of the dry stem, was used in this study.

Twenty grams of the extract was dissolved in water and the solution made up to 100 ml. To this was added an equal volume of hot concentrated barium hydroxide suspension containing 20 g. of the hydrated base. When 200 ml. of 95% ethanol was added to this mixture, a heavy precipitate settled out. After cooling, the precipitate was removed and washed with 10% ethanol.

This material was suspended in 100 ml. of water, the barium removed with carbon dioxide, and the filtrate decolorized with 1 g. of charcoal. The compound was again precipitated with barium hydroxide and the treatment repeated.

To remove the last traces of barium the solution was treated with a small amount of dilute sulfuric acid until one drop would cause no further turbidity. By increasing the alcohol content of the aqueous solution the product was

(1) Schlubach and Koenig, *Ann.*, **514**, 182 (1934).

fractionally precipitated into three gummy fractions. It is important to precipitate the compound with alcohol in order to separate it from the small excess of sulfuric acid. If the solution is left even slightly acidic, the compound will completely hydrolyze to fructose.

The precipitate from each fraction was dissolved in a minimum of water and dried in a vacuum oven at 60°. These fractions appeared to be identical; yield 42%.

Anal. Calcd. for $(C_6H_{10}O_5)_x$: C, 44.4; H, 6.22. Found: C, 43.9; H, 6.27.

Preparation of the Acetate.—The acetylation was carried out by slightly modifying the directions of Haworth.[2] Three grams of the dried fructosan was added to 35 ml. of pyridine and shaken at 30° until dissolved. Thirty ml. of acetic anhydride was added slowly with stirring. The white precipitate which formed was easily redissolved. The mixture was allowed to stand at room temperature for eighteen hours and the straw colored mixture then poured into 500 ml. of ice water. The white precipitate was filtered, washed, dried over phosphorus pentoxide, and again acetylated. The acetyl content according to the method of Armstrong and Arup[3] was found to be 45.4%.

Anal. Calcd. for $(C_6H_7O_5 \cdot 3CH_3CO)_x$: C, 50.0; H, 5.5; acetyl, 44.8. Found: C, 49.8; H, 5.61; acetyl, 45.4.

Preparation of the Barium Salt.—The barium salt was prepared free from barium carbonate in the following manner. Pure fructosan was dissolved in a small amount of water and an excess of saturated barium hydroxide was added. The slightly turbid solution was filtered by suction, taking precaution against the passage of air through the filter. Alcohol was added to the now clear aqueous filtrate, and the snow-white granular precipitate was filtered immediately by suction. The precipitate was washed first with 50% ethanol, and finally with 95% ethanol. The barium salt was then allowed to air dry and was finally dried completely in a vacuum oven at 50°.

Two different samples prepared in a like manner contained 22.4 and 23.5% of barium. The barium salt of the fructosan is soluble in water.

Discussion

Although sufficient data are not on hand to suggest a possible structure for this compound, a few facts have been established.

The fructosan exists in considerable quantities in the stem of the *Yucca mohavensis*. It is very readily hydrolyzed, which suggests the possibility of a fructofuranose.

The compound appears to be similar to the graminin isolated from rye flour.

Although this fructosan was first obtained from the 70% alcohol extract, in later work it was isolated from the hot aqueous extraction of the ground and dried stem.

DEPARTMENT OF CHEMISTRY
OREGON STATE COLLEGE
CORVALLIS, OREGON

RECEIVED MAY 5, 1942

(2) Haworth and Percival, *J. Chem. Soc.*, 2277 (1932).

(3) Armstrong and Arup, *ibid.*, **85**, 1043 (1904).

Benzylidene Aminomorpholine Compounds

BY LEROY DUGAN, JR.,[1] AND HELMUT M. HAENDLER

The structure of 4-aminomorpholine suggested its possible use as a reagent for organic qualitative analysis. However, the only one of its reactions which appeared satisfactory was the condensation with aromatic aldehydes to form, in general, colorless, crystalline compounds, which may be of some value for the identification of certain specific aldehydes. 4-(*p*-Aminophenyl)-morpholine undergoes similar reactions, and also reacts with *o*-hydroxyacetophenone, but the resulting compounds will probably be useful only in isolated instances.

4-Aminomorpholine was prepared by the method of Knorr and Brownsdon[2] and was kept as the hydrochloride, m. p. 164–165°. Attempts to use reducing agents other than zinc and acetic acid resulted in the formation of morpholinium chloride and ammonium chloride.

The benzylidene compounds were prepared by reaction of ether or alcohol solutions of the free amine, formed from the hydrochloride by treatment with sodium hydroxide, with ether solutions of the aldehydes.

4-(*p*-Aminophenyl)-morpholine was prepared by the general methods of Kremer, Meltsner and Greenstein,[3] and Lubs,[4] m. p. 130–131°, from the nitro compound, prepared according to Harradence and Lions.[5] The condensation products were prepared by refluxing equivalent quantities of the reactants in alcohol, followed by crystallization.

The quantitative data for the compounds formed by both of these substances are listed in Table I.

TABLE I

4-AMINOMORPHOLINE AND 4-(*p*-AMINOPHENYL)-MORPHOLINE COMPOUNDS

Carbonyl compound	Color	M. p., °C.	Nitrogen analyses, % Calcd.	Found
With 4-aminomorpholine				
o-Hydroxybenzaldehyde	Colorless	75– 76.5	13.60	13.90
m-Hydroxybenzaldehyde	Colorless	145–147.5	13.60	13.85
p-Hydroxybenzaldehyde	Tan	167–168	13.60	13.85
o-Nitrobenzaldehyde	Orange	99–101	17.89	17.84
m-Nitrobenzaldehyde	Yellow	114–114.5	17.89	17.85
Vanillin	Colorless	153–154.5	11.86	11.68
Piperonal	Colorless	76– 77	11.91	12.19
With 4-(*p*-aminophenyl)-morpholine				
Salicylaldehyde	Orange	161–162	9.94	9.95
Piperonal	Tan	167.5–169	9.04	9.02
Vanillin	Yellow	205–207	8.98	9.03
Furfural	Brown	208–209	10.91	10.49
o-Hydroxyacetophenone	Yellow	206–207	9.43	9.52

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF WASHINGTON
SEATTLE, WASHINGTON

RECEIVED JULY 7, 1942

(1) Present address: Chemical Warfare Service.

(2) Knorr and Brownsdon, *Ber.*, **35**, 4474 (1902).

(3) Kremer, Meltsner and Greenstein, THIS JOURNAL, **61**, 2552 (1939).

(4) Lubs, U. S. Patent 2,004,763, June 11, 1935.

(5) Harradence and Lions, *J. Proc. Roy. Soc., N. S. Wales*, **70**, 406 (1937).

Hydrogen Exchange of Aromatic Amines with D_2O and T_2O

BY B. J. FONTANA

Ingold, Raisin and Wilson[1] first demonstrated the ready H-exchange of the *o*- and *p*- H-atoms of phenols and aromatic amines when catalyzed by dilute bases and acids, respectively. This reaction was studied extensively by Kharasch, Brown and co-workers[2] in the case of the aromatic amines. It has been concluded that the existence of the quinoidal resonance forms of the free amine or phenolate ion is the chief factor governing the labilization of the nuclear H-atoms.

The amino or phenolic character of dyes or dye intermediates should then lend these substances amenable to the above type of H-exchange. Herein are described some quantitative exchange data for both deuterium and tritium obtained concurrently with attempts to label some organic dyestuffs with tritium. Discontinuance of the latter project has prevented the accumulation of more complete data.

Experimental

Exchange.—In general, 1 g. of the compound was mixed with 1 cc. of water (containing the D or T) and, unless otherwise noted, 0.01 cc. of 36 *N* sulfuric acid. The sealed mixture was heated at 100°, usually for seven days. The water was then distilled off *in vacuo* and purified by distillation *in vacuo* from potassium permanganate and sodium carbonate.

Analysis.—In all cases the change in the D or T content of the water was determined before and after exchange. The initial mole fraction of D was either 0.99 or about 0.7; the change in density observed, in general, was from 0.01 to 0.02 g. per cc. The method of density measurement is described elsewhere.[3] Note that a 0.1% error in experiment results in a 10% error in the calculated exchange number in the case of deuterium.

The tritium[4] as recovered from the 60-inch cyclotron had an activity of approximately 600 microcuries per mole of water (about 10^{-10} *M* T_2O) and contained 0.7 mole fraction of D. The D and T exchange could thus be determined simultaneously. In some experiments this water was diluted 1000-fold with H_2O. The very weak beta-radiation from H^3, tritium,[5] requires that the activities be determined by direct introduction of the hydrogen as a gas (water vapor) inside the tube of a Geiger counter. A mixture of 1-cm. pressure of water vapor and 2 cm. of propane was very satisfactory as a counting gas. The change in activity observed, in general, amounted to 20–30%.

Results and Discussion

The experimental results are tabulated in Table I. The observed values of the exchange number are given in the columns headed nk_D and nk_T. The number of exchangeable hydrogens, *n*, is merely the number of unoccupied nuclear positions *o*- and *p*- to the activating amino groups. That only the *o*- and *p*-positions undergo exchange has been assumed in general in H-exchange of this type, and has been shown to occur conclusively in the cases of phenol and aniline by Best and Wilson.[6] The partition ratios follow, k_D for deuterium and hydrogen; and k_T for tritium and hydrogen, except in the cases of methylene blue and crystal violet where k_T is an over-all partition ratio for T, D and H. The values of *nk* given have been corrected, where necessary, for exchange with added catalyst, amino hydrogens (assuming k = 1.00 for D or T), for water of crystallization in the case of methylene blue and for hydrochloric acid in the experiments with benzidine.

TABLE I

EXCHANGE NUMBERS AND PARTITION RATIOS

Expt.	Compound	*n*	nk_D	k_D	k_D (cor.)	nk_T	k_T
1	Crystal violet	6	7.04	1.17	0.95	..	..
2			8.38	1.42	1.22	9.18	1.53[a]
3	Methylene blue	4	4.14	1.04	0.85	..	..
4			4.84	1.21[b]	0.98	..	..
5			5.65	1.41	1.22	5.21	1.30[a]
6	Methyl orange	4	4.96	1.23[c,d]	1.00	..	..
7	Congo red	8	3.78	0.47[d]	0.38	..	..
8	Benzidine	8	1.72	0.22	0.18	..	..
9			..	..	..	2.86	0.33
10			..	..	..	0.90	0.11[e,f]
11	Benzidine·1 HCl[g]		..	..	..	0.60	0.08[f,h]
12	Benzidine·2HCl		..	..	..	2.90	0.36[h]

[a] Usual heating period plus six weeks at room temperature. [b] 0.03 cc. of 12 *N* hydrochloric acid as acid catalyst. [c] Extensive decomposition; value fortuitous? [d] Eleven days at 100°. [e] 0.02 cc. of sulfuric acid catalyst. [f] Solvent 50% ethyl alcohol (95%) and 50% water; ten days at 100°, three months at room temperature. [g] Mixture 50% benzidine and 50% benzidine·2HCl. [h] No added acid catalyst.

The k_D values for methylene blue and crystal violet have been recalculated for zero D-content of water according to the theory of Brodskiĭ.[7] The average of the five corrected values gives k_D = 1.04, which then might be compared to the values 0.90 and 1.4 for the nuclear hydrogens in phenol, obtained, respectively, by Ingold, *et al.*, and Small and Wolfenden.[8] Partial exchange of

(1) C. K. Ingold, C. G. Raisin and C. L. Wilson, *J. Chem. Soc.*, 1637 (1936).

(2) M. S. Kharasch, W. G. Brown and J. McNab, *J. Org. Chem.*, **2**, 36 (1937); W. G. Brown, M. S. Kharasch and W. R. Sprowls, *ibid.*, **4**, 442 (1939).

(3) B. J. Fontana and M. Calvin, *Ind. Eng. Chem., Anal. Ed.*, **14**, 185 (1942).

(4) L. W. Alvarez and R. Cornog, *Phys. Rev.*, **56**, 613 (1939).

(5) S. C. Brown, *ibid.*, **59**, 954 (1941).

(6) A. P. Best and C. L. Wilson, *J. Chem. Soc.*, 28 (1938).

(7) A. I. Brodskiĭ, *Trans. Faraday Soc.*, **33**, 1180 (1937).

(8) P. A. Small and J. H. Wolfenden, *J. Chem. Soc.*, 1811 (1936).

the meta hydrogens might account for the latter high value. Using the average value of $k_D = 1.2$ (uncorrected) and the values for the over-all k_T's observed in experiments 2 and 5, the partition ratio for T and D is calculated to be approximately 1.2. The corresponding calculation for the k of T and H is very sensitive to experimental error; a value of approximately 2.0 is obtained, which seems very high. The apparent confirmation of this latter value by the results of experiments 8, 9 and 12 with benzidine is very probably fortuitous. The assumption that $k = 1.00$ for the exchange of T with amino H's is obviously questionable.

The triterated crystal violet lost only about 2% of its T-activity on standing in 2% aqueous solution for three months at room temperature. Heating this solution for seven days at 100°, with added sulfuric acid catalyst, caused a loss of 60% of the activity. The deuterated methylene blue (expt. 4) was heated with 1 cc. of water at 100° for two hours with no acid catalyst present. The calculated Δd for exchange of the $3H_2O$ of crystallization only was 0.0104, actually observed 0.0111. Such exchange was incomplete in only five minutes of heating or in twenty-four hours at room temperature.

As noted above, the values given for benzidine may not be valid. The calculated effect is a small one derived from the large observed effect due chiefly to exchange of the four amino H's. However, one interesting feature of the k values can be noted; that is, the very low values of the partition ratios in general. That these are real and not merely an indication of a slow rate of reaction is indicated first in experiment 10. Here, increased solubility was achieved by using a 50% aqueous ethyl alcohol mixture as the exchange medium. This is further substantiated by experiment 11. According to the theory and actual observations of Ingold, *et al.*,[1] on the exchange of phenol, and of Brown, *et al.*,[9] on dimethylaniline, the conditions in expt. 11 are such as to yield the maximum possible rate of exchange. The result of expt. 12 as compared to expt. 9 is also consistent with the latter theory. The lower partition ratio observed in the aqueous alcohol mixtures can be explained in part by the observation of Kharasch, Brown, *et al.*,[2,8] that k_D in pure ethyl alcohol as exchange medium is about 0.85 (as compared to approximately unity in water). The low value of k observed with benzidine seems to be in accordance with the theory of exchange activation by appearance of a negative charge on the ortho and para positions through the quinoidal resonance forms (of the free base in the case of aromatic amines). For in the case of benzidine there must be an interference between the resonances of the two groups with the aromatic nucleus, since the two resonance systems induce similar charges in the benzene rings. Such an effect does not seem to appear in the results obtained by Brown and Letang[10] with various dimethylamino-naphthalene derivatives.

A similar resonance interaction would account for the relatively small exchange observed with the symmetrical dyestuff congo red. Accordingly, it was also ascertained that under the conditions employed herein, little or no exchange occurred in the dyes trypan blue and trypan red. Other effects may also be operating here, including the steric hindrance of resonance ("peri-effect") observed in naphthalene derivatives.[9]

Acknowledgment.—The author gratefully acknowledges the interest and advice of numerous members of both the Radiation Laboratory and the Department of Chemistry. This work was supported by funds from the A. B. Miller Foundation.

(9) W. G. Brown, A. H. Widiger and N. J. Letang, THIS JOURNAL, **61**, 2597 (1939).

(10) W. G. Brown and N. J. Letang, *ibid.*, **63**, 358 (1941).

DEPARTMENT OF CHEMISTRY,
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIF.

RECEIVED JUNE 8, 1942

X-Ray and Optic Measurements on β-Lactoglobulin

BY I. FANKUCHEN

Through the courtesy of Dr. T. L. McMeekin, a large air-dried crystal of β-lactoglobulin was made available to the writer. In the only published work on this material,[1] no optic data (save the sign of the birefringence) and no correlation of the crystallographic axes with the physical directions of the crystal were given. It was thought desirable in view of McMeekin and Warner's[2] observations on shrinkage to make these measurements.

The crystals are of the orthorhombic variety designated by Crowfoot as tabular. The small-

(1) D. Crowfoot, *Chem. Rev.*, **28**, 215 (1941).

(2) T. L. McMeekin and R. C. Warner, THIS JOURNAL, **64**, 2393 (1942).

est refractive index, α, lies in the main prism face at right angles to the prism length. The other two vibration directions β and γ are parallel to the thickness and length of the crystal but could not be identified as the crystal is almost uniaxial. This agrees with Crowfoot's determination of the sign of the birefringence as negative.

The "*c*" axis was found to be 111 Å. and corresponds in direction to α, the crystal width. The crystal length, "*a*," is 60 Å. and the thickness "*b*" is 62 Å. These values agree very well with Crowfoot's cell values 110, 60 and 63 Å., respectively. This identifies the material as the lactoglobulin that Crowfoot studied, and, therefore, her unit cell measurements 154, 67.5 and 67.5 for the wet crystals can be used to determine cell shrinkage in the various crystal directions. The agreement between these shrinkages and those observed by McMeekin and Warner on the actual crystal is very good. It is also interesting to note that the approximate uniaxial optic character of the crystal agrees with the approximate tetragonal shape of the unit cell. This may, of course, be only a coincidence and have no bearing on any characteristics of the molecular arrangement.

ANDERSON INSTITUTE FOR BIOLOGICAL RESEARCH
RED WING, MINNESOTA, AND THE
DEPARTMENT OF PHYSIOLOGY
UNIVERSITY OF MINNESOTA
MINNEAPOLIS, MINN. RECEIVED JULY 9, 1942

The Hydrogenation of Disubstituted Acetylenes

BY KENNETH W. GREENLEE AND W. CONARD FERNELIUS

Campbell and Eby[1] have recently shown that the treatment of dialkylacetylenes with sodium in liquid ammonia produces the pure *trans* forms of the corresponding olefins. These investigators offer no explanation for this startling phenomenon. The following suggested mechanism seems to account satisfactorily for the observed results.

A solution of sodium in liquid ammonia contains electron ions[2]

$$Na \rightleftharpoons Na^+ + e^-$$
$$e^- + x\,NH_3 \longrightarrow e^-(NH_3)x$$

The reaction of sodium with double and triple bonds consists in the addition of electrons[3]

$$RC{\equiv}CR + e^- \longrightarrow R\bar{C}{=}\dot{C}R$$
$$R\bar{C}{=}\dot{C}R + e^- \longrightarrow R\bar{C}{=}\bar{C}R$$

followed by partial or complete ammonolysis

$$R\bar{C}{=}\bar{C}R + 2NH_3 \longrightarrow RHC{=}CHR + 2\,NH_2^-$$

In the ionic intermediate, the electrons would repel each other into positions as far apart as possible, *i. e.*, the *trans* form. The configuration once fixed in the ion (either before or after the addition of the second electron), persists in the ammonolysis (or hydrolysis) product. The pic-

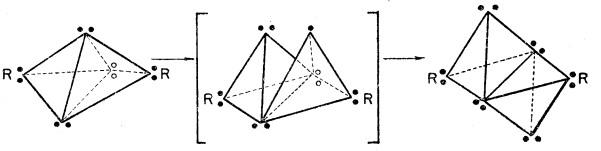


Fig. 1.

ture of one of the carbon tetrahedra turning inside out like the frame of an umbrella is the same mechanism as that frequently offered for the Walden inversion.[4]

(1) K. N. Campbell and L. T. Eby, THIS JOURNAL, **63**, 216-219 (1941).

(2) For references see W. C. Fernelius and G. W. Watt, *Chem. Reviews*, **20**, 195-258 (1937).

(3) For a review of reactions of solutions of metals see Fernelius and Watt, ref. 2.

(4) W. A. Waters, "Physical Aspects of Organic Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1936, pp. 331-336.

DEPARTMENT OF CHEMISTRY
THE OHIO STATE UNIVERSITY
COLUMBUS, OHIO RECEIVED JULY 13, 1942

The Nitration of 4-Phenylphenyl Benzoate

BY STEWART E. HAZLET AND HARRIS O. VAN ORDEN

Earlier studies on the bromination of esters containing diphenyl groups, including the bromination of 4-phenylphenyl benzoate,[1] have been reported from this Laboratory.[2] In the work here reported an attempt was made to compare the nitration of an ester with the bromination of the same compound. Methods of investigation were essentially the same as in previously reported work.[2] For reference compounds, the nitrophenylphenols were prepared by methods on record, and the corresponding benzoates were prepared by the action of benzoyl chloride on the nitrophenols.

Nitration of 4-phenylphenyl benzoate was effected under conditions somewhat similar to those employed in the bromination which was reported earlier,[1] and 4-(4-nitrophenyl)-phenyl benzoate resulted. The course of this nitration, then, is strictly parallel to the analogous bromination.

(1) Hazlet, Alliger and Tiede, THIS JOURNAL, **61**, 1447 (1939).

(2) *Cf.* Hazlet, Hensley and Jass, *ibid.*, **64**, 2449 (1942), for the last paper in this series.

TABLE I

BENZOATES OF THE NITROPHENYLPHENOLS

Nitrophenylphenol used	Yield, %	Solvent	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
2-Nitro-4-phenyl-[3]	82	Ethanol	111[6]				
4-(4-Nitrophenyl)-[4]	Quant.	Propanol	209–210	71.4	4.1	71.2	4.8
2,6-Dinitro-4-phenyl-[5]	91.5	Propanol	157–158	62.6	3.3	62.4	4.1
2-Nitro-4-(4-nitro-phenyl)-[4]	Quant.	Propanol	151–152	62.6	3.3	62.5	4.0
2,6-Dinitro-4-(4-nitrophenyl)-[5]	60	Propanol	168	55.8	2.7	55.4	3.3

Acknowledgment is gladly made to the Dow Chemical Company, Midland, Michigan, for the supply of 4-phenylphenol used in this work.

The Nitrophenylphenyl Benzoates.—These benzoates were prepared by treating the necessary phenols with benzoyl chloride in the presence of pyridine. The individual compounds are described in Table I.

Nitration of 4-Phenylphenyl Benzoate.—Ten grams of 4-phenylphenyl benzoate[1] dissolved in 80 ml. of glacial acetic acid was treated with a mixture of 5 ml. of fuming nitric acid and 2.5 ml. of concentrated nitric acid, which was added slowly at room temperature. The mixture was stirred and heated gently for a short time on an electric heater. After cooling, filtering and one recrystallization from glacial acetic acid, 4.8 g. of product was obtained. Several more recrystallizations from glacial acetic acid gave lustrous colorless plates which melted at 208–210°. A mixture of equal amounts of this product and 4-(4-nitrophenyl)-phenyl benzoate melted without depression at 209–211°.

(3) Raiford and Colbert, THIS JOURNAL, **47**, 1457 (1925).
(4) Bell and Kenyon, *J. Chem. Soc.*, **129**, 3048 (1926).
(5) Banús and Guiteras, *Anales soc. españ. fis. quim.*, **21**, 126 (1922).
(6) Colbert, Meigs and Stuerke, THIS JOURNAL, **56**, 2129 (1934).

DEPT. OF CHEMISTRY
STATE COLLEGE OF WASHINGTON
PULLMAN, WASHINGTON RECEIVED JULY 22, 1942

Some Reactions of Morpholine[1]

BY ALVIN R. INGRAM[2] AND W. F. LUDER

In the course of an investigation of the conductivity of morpholine solutions, the following reactions were observed.

Morpholine, a weak base, reacts with the acidic stannic chloride[3,4] to give the expected addition compound $SnCl_4 \cdot 2C_4H_9NO$. It is similar to the compounds of morpholine prepared by Haendler and Smith.[5] Dilute solutions of morpholine and stannic chloride in carbon tetrachloride were mixed in a ratio of two moles of morpholine to one of stannic chloride. A white precipitate formed immediately. This product was washed in carbon tetrachloride, absolute alcohol and petroleum ether. It was insoluble in the common organic solvents, water and dilute acids, but it dissolved with decomposition in hot concentrated acids. It melted with decomposition between 215° and 235°. *Anal.* Calcd. for $SnCl_4 \cdot 2C_4H_9NO$: Sn, 27.3; Cl, 32.7. Found: Sn, 27.3; Cl, 32.0.

Morpholine also reacts with carbon tetrachloride and chloroform to give morpholinium chloride. Similar reactions have been observed previously with piperidine to form piperidinium chloride.[6] Because these reactions of morpholine with carbon tetrachloride and chloroform were of no concern to the investigation under way, no attempt was made to isolate other products in addition to morpholinium chloride. However, from the work of Powell and Dehn,[6] the principal ones may be N-trichloromethyl and N-dichloromethyl morpholine.

A 4.5% by weight solution of morpholine in carbon tetrachloride, made up for another purpose, contained a large quantity of needle-like crystals when noticed about four months later. The crystals melted at 177° and when dissolved in water gave a white precipitate with silver nitrate. Mixed melting points, using morpholinium chloride prepared by the reaction of dry hydrogen chloride with morpholine, confirmed the conclusion that the crystals were morpholinium chloride. When approximately equal volumes of morpholine and carbon tetrachloride were warmed to temperatures from 50 to 100°, the morpholinium chloride was formed in a few hours, and the remaining liquid became yellow or brown depending on time and temperature. Distillation of the colored liquid gave a colorless distillate which deposited more morpholinium chloride immediately upon cooling. The residue was viscous and dark brown. When mixed in a ratio of two moles of morpholine to one mole of carbon tetrachloride (both being dried over calcium chloride or calcium sulfate)

(1) Abstracted from a portion of a thesis presented by Alvin R Ingram to the faculty of Northeastern University in partial fulfillment of the requirements for the M.S. degree, June, 1942.
(2) Present address: General Chemical Defense Corporation, Claymont, Delaware.
(3) G. N. Lewis, *J. Franklin Inst.*, **226**, 293 (1938).
(4) W. F. Luder, *Chem. Rev.*, **27**, 547 (1940).
(5) H. M. Haendler and G. McP. Smith, THIS JOURNAL, **63**, 1164 (1941).
(6) S. G. Powell and W. M. Dehn, *ibid.*, **39**, 1717 (1917).

crystals formed within one day at room temperature leaving a colorless solution. The reaction took place even with calcium oxide present.

The behavior of morpholine with chloroform is similar. Morpholinium chloride was identified as the product by its melting point, by its reaction with aqueous silver nitrate, and by taking a mixed melting point with morpholinium chloride prepared from hydrogen chloride and from carbon tetrachloride.

HAYDEN MEMORIAL LABORATORIES
NORTHEASTERN UNIVERSITY
BOSTON, MASSACHUSETTS RECEIVED JULY 11, 1942

Solubility of the Flavianates of Certain Organic Bases in Water, Ethanol, and *n*-Butanol at 3 and 30°

BY WILSON D. LANGLEY AND THOMAS R. NOONAN

The use of 2,4-dinitronaphthol-7-sulfonic acid (flavianic acid) for the purification and characterization of organic bases, first recommended by Kossel and Edlbacher, and Kossel and Gross,[1] has been extended by Sievers and Mueller[2] to include solubility data, and by Langley and Albrecht[3] to include crystallographic data. It has been our desire further to extend knowledge of the solubilities of the flavianates in certain solvents, so that flavianic acid may be more satisfactorily used for fractional precipitation of organic bases. Accordingly, we have determined the solubilities reported in the accompanying table. The solvents were selected as being suited for fractionation of extracts of tissues, and it was hoped that quantitative separations of bases could be accomplished readily once the components of mixtures were identified under the microscope. This work has been interrupted, and the prospects of it being resumed are remote.

The solvents used were purified by distillation just prior to use, and purity was established by constancy of boiling point, and by measurement of density (pycnometer). The flavianates used had been analyzed and reported upon previously.[3] Equilibrium was attained by frequent shaking of solvent in contact with solid for various lengths of time ranging from several days to several months. The saturated solutions were filtered, and were pipetted immediately by use of pipets which were calibrated at the temperatures used. Fifty-ml. portions (occasionally 20 ml.) of solutions were pipetted into weighed beakers, and the covered solutions were evaporated on a steam-bath. Final drying of the residue was done in an oven at 100°, constant weight being attained in each case.

SOLUBILITY OF FLAVIANATES IN G. PER LITER

Base	Water 3°	Water 30°	Ethanol (95%) 3°	Ethanol (95%) 30°	*n*-Butanol 3°	*n*-Butanol 30°
Acetylcholine	...	...	...	...	0.09	0.40
Ammonium	14.2	...	2.57	6.22	.29	.39
Choline	...	...	2.81	...	.17	.26
Creatinine	2.65	4.54	1.08	1.52	.09	.43
as-Dimethylguanidine	1.85	...	1.30	3.2	.21	.30
Ethanolamine	...	...	2.45	6.8	.14	.28
Guanidine	1.30	3.34	1.64	3.57	.19	.19
Hydroxylamine	16[a]	70[a]	...	26[a]	2.4[a]	5.2[a]
Hypoxanthine	1.3	3.6	0.95	3.36	0.34	0.4
Methylamine	7.6	...	1.95	4.10	.09	.17
Methylguanidine	2.53	5.7	2.6	4.7	.33	.35
Methylurea	...	...	...	36[a]	.66	1.4[a]
Piperidine	4.0	..	3.3[a]	1.3	.13	0.35
Potassium	3.7[a]	11.2[a]	0.12	0.16	.04[a]	.05
Putrescine	0.25	...	0.31	0.46	..	.06
Tetramethyl-ammonium	4.9[a]	12.8[a]	0.61	1.52	.04	.05
Trimethylamine	47[a]	...	4.4[a]	7.27	.12	.41
Tyramine	...	...	4.40	10.3[a]	.34	.8
Urea	15.7[a]	40[a]	12.4	17	.56	.81

[a] Single determinations.

The figures represent averages of values which were obtained after differences of several weeks in contact time, and which, except for the very small values, seldom disagreed by as much as 5%. Uncertain figures are depressed below the line. When the solubilities were great, duplicate determinations were not always made; these single values are marked.

DEPARTMENT OF BIOLOGICAL CHEMISTRY
UNIVERSITY OF BUFFALO MEDICAL SCHOOL
BUFFALO, N. Y. RECEIVED JUNE 27, 1942

1-Carbamyl-5-methylpyrazole-3-carboxylic Acid

BY ALBERT L. LEHNINGER

During the course of some work on the derivatives of acetopyruvic acid,[1] the reaction between semicarbazide and acetopyruvic acid became of interest as a means of identification of the latter compound. Von Auwers and Cauer[2] had reported that they were unable to obtain the expected product, 1-carbamyl-5-methylpyrazole-3-carboxylic acid (I), since the carbamyl group was apparently lost on ring closure, leading instead to 5-methylpyrazole-3-carboxylic acid (II).[3]

(1) A. Kossel and S. Edlbacher, *Z. physiol. Chem.*, **110**, 241 (1920); A. Kossel and R. E. Gross, *ibid.*, **135**, 167 (1924).

(2) H. Sievers and E. Mueller, *Z. Biol.*, **89**, 37 (1929); **92**, 513 (1932).

(3) W. D. Langley and A. J. Albrecht, *J. Biol. Chem.*, **108**, 729 (1935).

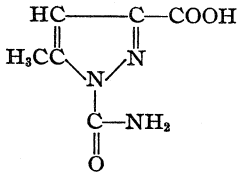
(1) Lehninger and Witzemann, THIS JOURNAL, **64**, 874 (1942).

(2) von Auwers and Cauer, *J. prakt. Chem.*, **126**, 146 (1930).

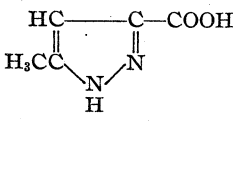
(3) Knorr and MacDonald, *Ann.*, **279**, 217 (1894).

By altering the conditions employed by von Auwers and Cauer, it was found that the expected carbamyl compound could be obtained easily and in large yields. Furthermore, the reason for their failure to obtain the compound became apparent on studying its properties.

This substance was found to hydrolyze readily to 5-methylpyrazole-3-carboxylic acid in water or in water–alcohol solutions on standing for several days at room temperature or on heating for short periods, with or without added acid. The long reaction periods employed by von Auwers and Cauer probably provided for the conversion of the primary product I into II.



I



II

The product of hydrolysis of the carbamyl compound was isolated and identified as 5-methylpyrazole-3-carboxylic acid.[3]

Experimental

1-Carbamyl-5-methylpyrazole-3-carboxylic Acid.—To a solution of 1.30 g. of acetopyruvic acid (prepared as previously described[1]) in 10 ml. of water was added 1.11 g. of semicarbazide hydrochloride dissolved in 10 ml. of water. The mixture was stirred and gently warmed. A white voluminous mass of microscopic needles immediately precipitated. The mixture was stirred for two minutes, filtered, washed copiously with cold water and dried over phosphorus pentoxide. The compound was thus obtained pure without recrystallization; yield, 80–85%; m. p. (dec. started at 155°, clear melt at 232–234° (cor.).

Anal. Calcd. for $C_6H_7O_3N_3$: C, 42.60; H, 4.17; N, 24.85. Found: C, 42.74; H, 4.13; N, 24.67. Amide N: Calcd. 8.28. Found (hydrolysis with H_2SO_4, followed by alkaline distillation of ammonia and titration), 8.12.

Hydrolysis to 5-Methylpyrazole-3-carboxylic Acid.—A suspension of 1.0 g. of the compound obtained above in 20 ml. of water was brought to the boiling point for one minute (evolution of carbon dioxide was apparent) and cooled. Crystals of 5-methylpyrazole-3-carboxylic acid separated. These were recrystallized from water; m. p. 236–236.5° (cor.); melting point of authentic sample (prepared according to Knorr and MacDonald[3]) 236–237°; a mixed melting point test showed no depression.

Anal. Calcd. for $C_5H_6O_2N_2$: C, 47.61; H, 4.80. Found: C, 47.42; H, 4.60. There was no detectable amide nitrogen.

DEPT. OF PHYSIOLOGICAL CHEMISTRY
UNIVERSITY OF WISCONSIN
MADISON, WISCONSIN

RECEIVED JULY 30, 1942

The Polymerization of Styrene Catalyzed by *p*-Bromobenzenediazonium Hydroxide

BY CHARLES C. PRICE AND DOROTHY ANN DURHAM

The presence of fragments from the catalyst in polystyrene and polymethyl methacrylate prepared in the presence of substituted peroxides[1] has been interpreted as evidence strongly supporting the suggestion that such catalysts first dissociate into free radicals[2] which then initiate the polymerization process.[3]

Since the reaction of alkaline diazotized *p*-bromoaniline with benzene and its derivatives to form *p*-bromobiphenyl and the corresponding derivatives[4] has been ascribed to the decomposition of the diazonium hydroxide to a *p*-bromophenyl free radical,[2] the action of the diazonium hydroxide as a catalyst for the polymerization of styrene has been tested.

p-Bromobenzenediazonium hydroxide has indeed been found to catalyze the polymerization of styrene. The directions followed for carrying out the polymerization were those described for the preparation of *p*-bromobiphenyl[4] with the single exception that styrene replaced benzene. Alkali was added slowly to a vigorously-stirred suspension of 30 cc. of styrene in an aqueous solution of 11 g. of diazotized *p*-bromoaniline at 0°. After the addition of alkali was complete, the reaction mixture was allowed to warm up to room temperature. The aqueous layer was decanted and alcohol was added to the viscous organic layer. The polystyrene which precipitated was purified further by several reprecipitations from ether solution by pouring into ice-cold alcohol. The viscosity of a sample of this polymer in tetralin was measured at 20°; $\eta_{sp.}/C_{gm.} = 1.16$. Using the revised[5] value for the constant of the Staudinger equation relating this expression to molecular weight, the polymer contained an average of about twenty-two styrene units.

Anal. Calcd. for $BrC_6H_4(C_8H_8)_{30}C_6H_4Br$: C, 88.07; H, 7.27; Br, 4.65. Calcd. for BrC_6H_4-

(1) Price, Kell and Krebs, THIS JOURNAL, **64**, 1103 (1942).

(2) Hey and Waters, *Chem. Rev.*, **21**, 169 (1937).

(3) Norrish and Brookman, *Proc. Roy. Soc.* (London), **A171**, 147 (1939); Norrish, *Trans. Faraday Soc.*, **35**, 1087 (1939); Kamenskaya and Medvedev, *Acta Physicochem., U. S. S. R.*, **13**, 565 (1940); Price and Kell, THIS JOURNAL, **63**, 2798 (1941).

(4) Gomberg and Bachmann, *ibid.*, **46**, 2339 (1924). See also Gilman and Blatt, "Organic Syntheses," Collected Volume I, 2nd Edition, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 113.

(5) Kemp and Peters, Division of Paint, Varnish and Plastics, 103rd meeting of the American Chemical Society, Memphis, Tenn., April, 1942.

$(C_8H_8)_{17}OH$: C, 87.75; H, 7.31; Br, 4.11. Found: C, 87.77; H, 7.24; Br, 4.2.[6]

Since no polystyrene was formed in a parallel experiment in which the diazonium salt was omitted, it appears that the *p*-bromophenyl radicals from the decomposition of *p*-bromobenzenediazonium hydroxide are capable of initiating the polymerization of styrene and are thereby incorporated in the polymer.

(6) This analysis was carried out by wet oxidation with silver and potassium dichromate in sulfuric acid. The halogen was absorbed in alkaline hydrogen peroxide according to Zacherl and Krainick (*Mikrochemie*, **11**, 61 (1932)) but analysis by titration of excess alkali was entirely unsatisfactory, evidently due to volatilization of organic acids. Volhard titration for bromide ion in the alkaline peroxide, however, proved very convenient and accurate.

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

RECEIVED AUGUST 10, 1942

The Composition of Alkylmagnesium Chloride Solutions in Ethyl Ether

BY C. R. NOLLER AND A. J. CASTRO

In previous work on the composition of *n*-butylmagnesium chloride solutions in ethyl ether,[1] it was thought that the values obtained were true equilibrium values expressing the relation between the amounts of *n*-butylmagnesium chloride, di-*n*-butylmagnesium and magnesium chloride as etherates in ether solution. On attempting to repeat, refine and extend this work, we have found that other factors seem to be involved. For example, in the original experiments it appeared that equilibrium was reached after fifty to one hundred and fifty hours. In the new series of experiments, at least in the higher concentrations, much less magnesium chloride had precipitated after seventy days than had been precipitated after 150 hours in the first series and did not reach the latter value until after 300 days. The only difference in procedure of which we are aware is that in the second series the solutions were kept in sealed glass tubes whereas in the first series the tubes were closed by stopcocks. It is possible, too, that in the second series somewhat more care may have been given to avoiding contact with air.

That exposure to air may be the cause of the discrepancy was indicated by a third series in which extreme care was taken to avoid contact with air by preparing the reagent and carrying out all transfers in an atmosphere of purified nitrogen. After 160 days practically no magnesium chloride had precipitated. In fact the chloride concentration of the solution was still greater than the alkylmagnesium concentration, a condition which had never been observed previously even in freshly prepared solutions of Grignard reagent. If no magnesium chloride precipitates, one should, of course, have an excess of chloride over alkylmagnesium because of side reactions which do not result in the formation of Grignard reagent. Similar but even more marked results were obtained with Grignard solutions from tertiary butyl chloride which after 150 days contained over 2.5 equivalents of chloride for each two equivalents of alkylmagnesium.

When increasing amounts of oxygen reacted with a 0.5 *N* solution of *n*-butylmagnesium chloride, the ratio of halogen to basic magnesium in the precipitate was about three to one for one-fourth oxidation, about one to one for the next fourth while complete oxidation caused removal of all of the halogen from the solution and all but a trace of basic magnesium. This indicates that if ROMgCl is the product of oxidation, it is capable of bringing down with it additional magnesium chloride, presumably by using the unshared electrons of the oxygen atom to form a complex with magnesium chloride much in the same way as dioxane forms an insoluble complex or as ether forms a soluble complex. If this is the case one might expect the precipitate to have ultimately the composition $ROMgCl \cdot 2MgCl_2$ in which the ratio of chloride to basic magnesium would be 5:1. To explain the behavior of the Grignard solutions on standing one might assume that, in the absence of oxygen, magnesium chloride is soluble in the Grignard solution either because the reagent is entirely in the form RMgCl or because the Grignard solution is a much better solvent for magnesium chloride than pure ether.[2] If oxygen is present, ROMgX, which itself is relatively insoluble, would be precipitated fairly rapidly, carrying down some magnesium chloride with it. This precipitate would then slowly go over to the still less soluble $ROMgCl \cdot 2MgCl_2$, causing slow precipitation of more magnesium chloride.

This picture, however, is incomplete because in the case of Grignard solutions from benzyl chloride, magnesium chloride precipitates fairly rapidly in spite of all precautions we have taken

(1) Noller and Raney, THIS JOURNAL, **62**, 1749 (1940).

(2) At present the latter seems to be the better explanation since we have obtained Grignard solutions from tertiary butyl chloride which contained as much as 0.3 mole of magnesium chloride per 1000 g. of solution above the 1:1 ratio while the solubility of magnesium chloride etherate in pure ether is of the order of 0.001 mole.

so far to exclude oxygen. Moreover, the precipitate contains as much as ten equivalents of chloride per equivalent of basic magnesium, which is much greater than the 5:1 ratio expected from the formula $ROMgCl \cdot 2MgCl_2$. Evidently, the effect of some Grignard solutions on the solubility of magnesium chloride is much less than others and magnesium chloride precipitates in addition to that brought down by the oxidized reagent.

Obviously this problem requires further study. It will be necessary to devise a technique for the preparation and sampling of the Grignard solutions entirely in the absence of oxygen. Moreover, the sampling will have to be done over a period of several years to ensure equilibrium conditions. We hope to initiate such experiments in the near future.

DEPARTMENT OF CHEMISTRY
STANFORD UNIVERSITY
STANFORD UNIV., CALIF. RECEIVED JULY 6, 1942

Preparation of Phenylpropiolic Acid

BY MARIE REIMER

Preparation of phenylpropiolic acid can be facilitated by a simple improvement in the preparation of cinnamic acid dibromide. The fact that the usual procedure for addition of bromine to the ethylenic linkage, using ice-cold solvents, is discouragingly slow in the case of cinnamic acid has led to the bromination of cinnamic ester.[1] The preparation of the ester can be eliminated, however, and a good grade of commercial cinnamic acid brominated quickly and in excellent yield by use of boiling carbon tetrachloride as solvent. A typical reaction is as follows: 74 g. (0.5 mole) of cinnamic acid and 500 ml. of carbon tetrachloride were placed in a three-necked flask fitted with an efficient stirrer, a reflux condenser and a separatory funnel. The mixture was heated to boiling, the stirrer started and the addition of 79.9 g. (0.5 mole) of bromine in 50 ml. of carbon tetrachloride begun. The color disappeared slowly at first, then so rapidly that all the bromine could be added in the course of forty-five minutes. Heating and stirring were carried on for an additional fifteen minutes and the stirring continued while the mixture cooled. The product, which began to separate from the solution when about two-thirds of the bromine had been added, consisted of fine colorless, shining needles, softening at 195° and melting with decomposition at 199–200°. This is sufficiently pure for subsequent use. The yield was 147 g. (95%) with an additional 2 g. of less pure material obtained by distilling the filtrate to 50-ml. volume. Repeated crystallization of the cinnamic acid dibromide from carbon tetrachloride did not improve the melting point appreciably, but after one crystallization from chloroform the compound separated in brilliantly shining needles, melting at 200–202°.

For obtaining phenylpropiolic acid in small amounts, a less elaborate procedure can be used than that recommended[2] for its preparation in larger quantity from the ester of cinnamic acid dibromide. Twenty-five grams of cinnamic acid dibromide was placed in an evaporating dish, 100 ml. of a 25% solution of potassium hydroxide in methanol added, and the mixture stirred over rapidly boiling water until nearly all the alcohol had evaporated. To the thick, pasty residue, 75 ml. of methanol was added and the procedure repeated to ensure complete reaction. The pale yellow granular product was cooled, subjected to strong suction to rid it of a small amount of residual liquid, washed with a few milliliters of chilled methanol and dissolved in 500 ml. of ice-water. To the solution, iced hydrochloric acid was added to faint acidity. As phenylpropiolic acid separates as an oil, the mixture was then seeded and the hydrochloric acid added slowly with vigorous stirring until the mixture was strongly acid. To make sure that all the oil had solidified, the mixture was left standing overnight in the ice-chest. The acid which had separated in 80% yield was pure white and melted at 128–136°. There was but slight loss on recrystallization from boiling carbon tetrachloride from which the acid separates in long, shining needles, melting at 136–138°.

(1) *Org. Syntheses*, **12**, 36 (1932).

(2) *Ibid.*, **12**, 60 (1932).

DEPARTMENT OF CHEMISTRY
BARNARD COLLEGE
NEW YORK, N. Y. RECEIVED JULY 29, 1942

Formation of Pro-carotenoids in "Monkey Flowers" under Some Conditions

BY W. A. SCHROEDER

An unpublished investigation, which has been carried out in these laboratories during the past year, has shown that the flowers of *Mimulus longiflorus* Grant (*Scrophulariaceae*), commonly termed "monkey flowers," contain no representative of the class of pro-carotenoids which possess

a partially *cis*-configuration.[1] This statement refers to flowers which have developed fully under natural conditions on the intact plant. In recent experiments it was found, however, that, if stems with buds were placed in water for several days and exposed only to diffuse light in the laboratory at room temperature, the flowers were noticeably different in tint and paler in color than flowers which developed on the intact plant in the open. Parallel chromatograms of extracts of the two materials established the fact that under these two sets of conditions, the polyene pigment mixtures differed both qualitatively and quantitatively with respect to the components found. The paler flowers contained a greater number of lycopene stereoisomers than the controls. The chromatogram of the paler flowers included considerable quantities of prolycopene, $C_{40}H_{56}$, and pro-γ-carotene, $C_{40}H_{56}$. The spectral maxima of these pigment fractions in petroleum ether (b. p. 60–70°) were 467, 440 mμ and 461, 431 mμ, respectively. Upon addition of iodine to the solutions, the bands showed the characteristic shift to 500.5, 469.5, 440 mμ and 494, 461 mμ. Both pro-carotenoids have been identified by mixed chromatograms with samples from other sources.

In the light of the above observation, it is possible that prolycopene and pro-γ-carotene are precursors of lycopene and γ-carotene in the biosynthesis of the *Mimulus* pigment.

(1) L. Zechmeister, A. L. LeRosen, F. W. Went and L. Pauling, *Proc. Nat. Acad. Sci.*, **27**, 468 (1941); A. L. LeRosen and L. Zechmeister, THIS JOURNAL, **64**, 1075 (1942); L. Zechmeister and W. A. Schroeder, *ibid.*, p. 1173.

GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIFORNIA RECEIVED JULY 1, 1942

Some Physical Constants of N-Octyl-, N-Dodecyl- and N-Cetyl-piperidine

BY F. H. STROSS AND R. J. EVANS

There exists little available information on the physical properties of the higher N-alkyl-piperidines. When, in the course of an investigation, it became necessary to prepare N-cetylpiperidine, only two references[1,2] were found which mentioned this compound. Its ionization constant was found to be surprisingly low in comparison with the known constants of the lower homologs, and, therefore, the N-dodecyl- and N-octyl-piperidines were also prepared and their characteristic properties measured. The results are given in Table I.

(1) P. Karrer, F. W. Kahnt, R. Epstein, W. Jaffe and T. Ishii, *Helv. Chim. Acta*, **21**, 233 (1938).

(2) H. W. Magnusson and E. R. Schierz, Univ. of Wyoming, Publications VII, 1–11 (1940).

TABLE I

PHYSICAL CONSTANTS OF N-OCTYL, N-DODECYL AND N-CETYL PIPERIDINES

Piperidines	N-Octyl			N-Dodecyl		N-Cetyl
M. p., °C.		..			..	21
B. p. °C.	89	112	122	141	161	176–177
B. p. Mm.	1	6	10	1	5	1
d^{20}_4		0.8324		0.8378		0.8468
$n^{20}D$		1.4544		1.4588		1.4620
N, % Calcd.		7.1		5.5		4.5
N, % Found	6.9	7.0		5.5		4.4
Mol. wt. Calcd.		197.4		253.5		309.6
Mol. wt. Found		197		253		304
pK_H at 27 °C.		8.28		5.92		5.8

While the N-cetyl and N-dodecyl compounds are weak bases of a strength close to that of pyridine, N-octylpiperidine occupies a position intermediate between the higher homologs and the N-methyl- to butylpiperidines. The latter are almost as strong bases as the unsubstituted piperidine, which has a pK_H of 11.1 at 25°.

The bases were prepared by the method described by Magnusson and Schierz.[2] Aqueous piperidine was refluxed with a slight excess of the alkyl iodide, while an excess of potassium hydroxide was gradually added. The upper of the two layers formed during refluxing was fractionally distilled over solid potassium hydroxide at 2 mm. pressure, yielding a clear distillate. The cetylpiperidine was yellow, the dodecyl compound had a slight yellow tinge, and the octylpiperidine was colorless. The analyses were made and the constants determined after redistilling these products.

SHELL DEVELOPMENT CO.
EMERYVILLE, CALIFORNIA RECEIVED AUGUST 11, 1942

Empirical Heat Capacity Equations of Gases

BY HUGH M. SPENCER AND GORDON N. FLANNAGAN

Since the publication of empirical heat capacity equations of simple gases,[1] values of thermodynamic functions for many gases have been derived from spectroscopic data.[2] In the case of

(1) Hugh M. Spencer and John L. Justice, THIS JOURNAL, **56**, 2311 (1934). The heat capacities of bromine and equilibrium chlorine are better represented by equations of form (2). The constants a, $b \times 10^3$, $c' \times 10^{-5}$, maximum and average percentage deviations are 8.911, 0.140, −0.0298, 0.09, 0.02 and 8.764, 0.271, −0.656, 0.24 and −0.11, respectively.

(2) E. B. Wilson, Jr., *Chem. Rev.*, **27**, 17 (1940).

TABLE I[a]

Compound	Source	Range, °K.	a	$b \times 10^3$	$c \times 10^7$	$c' \times 10^{-5}$	$d \times 10^9$	% Deviation Max.	% Deviation Average
Acetylene	3	273.1–1273.1	11.942	4.387		−2.322		1.28	0.48
Ammonia[b]	4	291.16–1000	6.189	7.887	− 7.28			0.65	.23
Bromoform	5	298.1–600	9.356	32.319	− 212.72			.17	.11
Bromomethane	5	298.1–1200	4.184	22.445	− 74.96			.66	.33
i-Butane[c,d]	6	298.1–1500	2.296	82.407	− 287.92			.54	.29
n-Butane[c,d]	6	298.1–1500	2.247	81.718	− 286.13			.29	.15
Carbon dioxide	7	300–1500	6.369	10.100	− 34.05			2.07	.62
Carbon dioxide	7	300–1500	5.166	15.177	− 95.78		2.260	0.35	.15
Carbon disulfide	8	298.1–1800	13.289	0.862		−2.502		1.86	.79
Carbon disulfide	8	298.1–1800	7.692	13.426	− 91.16		2.112	1.04	.41
Carbon oxysulfide	8	298.1–1800	12.288	1.321		−2.630		2.06	.94
Carbon oxysulfide	8	298.1–1800	6.554	13.880	− 88.18		1.964	1.19	.44
Carbon tetrabromide	5	298.1–600	15.238	28.987	− 225.76			0.21	.14
Carbon tetrachloride	9	273.1–773.1	22.675	3.274		−3.264		.57	.24
Chloroform	9	273.1–773.1	7.052	35.598	− 216.86			.69	.30
Chloromethane	9	273.1–773.1	3.563	22.998	− 75.71			.64	.24
Chlorotribromomethane[e]	10	250–600	12.917	36.565	− 294.64			.50	.23
Cyanogen[f]	4	291.16–1000	9.892	14.484	− 62.07			.74	.45
Deuteroformaldehyde[g]	11	291.16–1500	4.419	17.540	− 57.48			1.00	.42
Dichlorodibromomethane	10	250–600	12.902	34.713	− 265.10			1.01	.27
Dibromomethane	13	298.1–600	5.244	31.809	− 177.09			0.12	.06
Dichloromethane	10	250–600	4.309	31.673	− 163.51			.27	.08
Difluoromethane[h]	10	250–600	4.203	21.623	− 40.88			.95	.34
Diiodomethane	10	250–600	5.839	32.571	− 195.28			.13	.06
Ethyl alcohol[i]	12	300–1000	3.578	49.847	− 169.91			.28	.15
Ethane[j]	4	291.16–1000	1.375	41.852	− 138.27			.76	.26
Ethylene[k]	15, 4	291.16–1500	2.706	29.160	− 90.59			1.46	.92
Formaldehyde[l]	11	291.16–1500	4.498	13.953	− 37.30			1.90	.73
Fluorochloromethane	10	250–600	4.292	27.025	− 106.05			0.57	.21
Fluoromethane	13	298.1–600	3.616	18.239	− 20.35			.89	.32
n-Heptane[c,d]	6	298.1–1500	5.401	136.930	− 487.71			.23	.13
n-Hexane[c,d]	6	298.1–1500	4.296	118.661	− 421.30			.28	.12
Hydrogen cyanide[g]	14	300–1000	5.974	10.208	− 43.17			.23	.13
Hydrogen sulfide[m]	15, 16	298.1–1800	6.385	5.704	− 12.10			2.00	.50
Hydrogen sulfide[m]	15, 16	298.1–1800	6.955	3.675	+ 7.40		−0.585	1.02	.37
Iodomethane[n]	13	298.1–600	4.105	24.487	− 97.33			0.14	.07
Methane[o]	15, 4	291.16–1500	3.422	17.845	− 41.65			2.59	.97
2-Methylbutane[c,d]	6	298.1–1500	2.801	102.820	− 367.41			0.67	.35
Methyl cyanide	4	291.16–1200	5.018	27.935	− 93.02			.40	.21
Nitrous oxide	7	298.1–1500	6.529	10.515	− 35.71			1.26	.68
n-Octane[c,d]	6	298.1–1500	6.231	155.942	− 558.57			0.24	.14
n-Pentane[c,d]	6	298.1–1500	3.140	100.532	− 355.60			.32	.16
Phosgene	11	291.16–1000	16.051	2.894		−2.159		.59	.31
Phosphine[c]	17	298.1–1500	4.496	14.372	− 40.72			.29	.13
Phosphorus (diatomic)[c]	17	298.1–1500	8.643	0.202		−1.030		.13	.05
Phosphorus (tetratomic)[c]	17	298.1–1500	19.227	0.509		−2.975		.18	.08
Phosphorus oxychloride	17	298.1–1000	23.294	2.185		−3.534		.18	.07
Phosphorus pentachloride[p]	17	298.1–500	4.739	107.329	−1192.00				
Phosphorus tribromide[c,d]	17	298.1–800	18.154	2.045		−0.153		.05	.02
Phosphorus trichloride[c]	17	298.1–1000	20.068	−0.289		−2.706		.34	.11
Phosphorus trifluoride[c,q]	17	298.1–1000	17.559	1.972		−4.569		.17	.13
Propane[c,d]	6	298.1–1500	0.410	64.710	− 225.82			.73	.27
Sulfur dioxide	8	298.1–1800	11.895	1.089		−2.642		3.18	1.31

(3) E. Justi, "Spezifische Wärme, Enthalpie, Entropie und Dissoziation technischer Gase," J. Springer, Berlin, 1938, p. 150.
(4) H. W. Thompson, *Trans. Faraday Soc.*, **37**, 344 (1941).
(5) D. P. Stevenson and J. Y. Beach, *J. Chem. Phys.*, **6**, 25 (1938).
(6) K. S. Pitzer, *Chem. Rev.*, **27**, 39 (1940).
(7) L. S. Kassel, THIS JOURNAL, **56**, 1838 (1934).
(8) P. C. Cross, *J. Chem. Phys.*, **3**, 825 (1935).
(9) R. D. Vold, THIS JOURNAL, **57**, 1192 (1935).
(10) G. Glockler and W. F. Edgell, *Ind. Eng. Chem.*, **34**, 532 (1942).
(11) H. W. Thompson, *Trans. Faraday Soc.*, **37**, 251 (1941).
(12) J. G. Aston, *Ind. Eng. Chem.*, **34**, 514 (1942).
(13) W. F. Edgell and G. Glockler, *J. Chem. Phys.*, **9**, 484 (1941).
(14) A. R. Gordon, *ibid.*, **5**, 30 (1937).
(15) E. B. Wilson, Jr., *ibid.*, **4**, 526 (1936).
(16) P. C. Cross, *ibid.*, **3**, 168 (1935).
(17) D. P. Stevenson and D. M. Yost, *ibid.*, **9**, 403 (1941).

TABLE I (*Concluded*)

Compound	Source	Range, °K.	a	$b \times 10^3$	$c \times 10^7$	$c' \times 10^{-5}$	$d \times 10^9$	% Deviation Max.	% Deviation Average
Sulfur dioxide	8	298.1–1800	6.147	13.844	− 91.03		2.057	0.43	.23
Sulfuryl chloride[r]	18	291.16–450	8.557	43.918	− 353.57			.05	.03
Tetramethylmethane[c,d]	6	298.1–1500	1.340	109.879	− 411.71			.55	.28
Tetramethylmethane[c,s]	19	300–1500	6.076	98.954	− 353.69			.16	.06
Thiophosgene[t]	11	291.16–1000	17.773	1.750		−2.556		.62	.33
Thiophosphoryl chloride[c,d,u]	17	298.1–1000	23.923	1.968		−3.114		.48	.16
Trichlorobromomethane	10	250–600	11.462	39.983	− 318.76			.57	.24
Water[v]	15, 20, 21	298.1–1500	7.219	2.374	+ 2.67			.96	.40

[a] For a number of gases the heat capacities cited in the references are incorrect at one or more temperatures. New values for these, based on the same wave numbers, have been calculated, and are indicated as in Note *b*. [b] Rotational distortion correction amounting to $0.058 \times 10^{-3}T$ has not been included. At 500°K. for $C_p^0 = 10.14$, read 9.92. [c] Percentage deviation tested with respect to mean heat capacity. [d] Several heat capacity measurements by K. S. Pitzer (THIS JOURNAL, **63**, 2413 (1941)) have caused him to doubt the correctness of the frequencies used in ref. 6. [e] At 250°K. for $C_p^0 = 20.11$, read 20.12. [f] At 450°K. for $C_p = 15.23$, read 15.24. [g] At 650°K. for $C_p^0 = 13.53$, read 13.48. [h] At 350, 550 and 600°K. for $C_p^0 = 10.22$, 14.93 and 15.66, read 11.22, 14.88 and 15.65, respectively. [i] The values of the mean heat capacity to 400, 700 and 1000° were neglected in setting up and testing the equation. [j] At 700°K. for $C_p^0 = 24.33$, read 24.05. [k] At 700°K. for $C_p^0 = 18.3$, read 18.83. The rotational distortion correction ($0.031 \times 10^{-3}T$) has not been included. [l] At 650 and 1200°K. for $C_p^0 = 12.07$ and 15.92, read 12.00 and 15.88, respectively. [m] Rotational distortion correction amounting to $0.064 \times 10^{-3}T$ has been included. [n] At 350°K. for $C_p^0 = 11.48$, read 11.47. [o] The rotational distortion correction ($0.068 \times 10^{-3}T$) has not been included. [p] Only three values of the mean heat capacity were available; these were solved simultaneously. [q] The mean heat capacity (298.1–350) was excluded. [r] Simultaneous solution at $T = 300$, 380 and 450°K. [s] Graphically extrapolated values of mean heat capacity at 400, 500 and 600 were used in setting up and testing the equation. [t] At 400 and 650°K. for $C_p^0 = 16.68$ and 18.45, read 16.78 and 18.38, respectively. [u] The two largest deviations are for temperatures for which the theoretical values do not fall on the curve. [v] Rotational distortion correction based on ref. 21, amounting to $0.092 \times 10^{-3}T$, has been included. The correction based on Wilson's[15] theoretical value derived from the force constants of the molecule would have been $0.081 \times 10^{-3}T$.

several triatomic gases more complete spectroscopic data have been treated by more satisfactory statistical mechanical methods. Though it is still necessary to consider the polyatomic (including some triatomic) molecules as harmonic oscillators, thermodynamic data based on this conception have proved to be of satisfactory, though not absolute, accuracy. Use of the normal coördinate analysis of vibrations, the assignment of potential barriers due to hindered rotations by reference to thermochemical data at one or more temperatures, and the methods of extrapolation to closely related molecules have further increased the useful applications of this method.

The same remarks concerning the usefulness of empirical heat capacity equations for these gases might be made as were made in the earlier paper.[1]

Table I presents the equations and the percentage deviations of such equations representing the heat capacities of the various gases in the forms

$$C_p^0 = a + bT + cT^2 \quad (1)$$

$$C_p^0 = a + bT + c'/T^2 \quad (2)$$

$$C_p^0 = a + bT + cT^2 + dT^3 \quad (3)$$

Except as indicated in the notes to Table I, equations of the forms (1) and (2) have been obtained as least square solutions of all the data in appropriate forms of heat capacity or mean heat capacity. Depending on the relative contributions of the various wave numbers over the range of temperatures concerned, one or the other of forms (1) and (2) are to be preferred. If the change of curvature with respect to the horizontal (T) axis is greater at the higher temperatures of a given range form (1) is preferable, and *vice versa*. In some instances the range of temperatures is relatively so great that comparatively large deviations from the most appropriate three-constant equation occur.[22] Adjusted simultaneous solutions of form (3) are offered for these. It should be noted that empirical equations are unreliable for extrapolation.

The original articles must be consulted to ascertain the bases of the theoretical values which the equations represent. As in most of the original publications constants of the "International Critical Tables" have been used.

COBB CHEMICAL LABORATORY
UNIVERSITY OF VIRGINIA
CHARLOTTESVILLE, VA.

RECEIVED JULY 11, 1942

(18) H. W. Thompson, *Trans. Faraday Soc.*, **37**, 340 (1941).
(19) J. G. Aston, *Chem. Rev.*, **27**, 59 (1940).
(20) A. R. Gordon, *J. Chem. Phys.*, **1**, 308 (1933).
(21) C. C. Stephenson and H. O. McMahon, *ibid.*, **7**, 614 (1939).

(22) For one gas, carbon dioxide, a three-constant equation has been derived [R. L. Sweigert and M. W. Beardsley, Georgia School of Tech. State Eng. Expt. Sta. Bulletin No. 2 (1938)] involving T^0, T^{-1} and T^{-2} terms, which more accurately represents the values derived from spectroscopic data than do three-constant equations of forms (1) or (2).

Note on the Structures of the Gallium and Indium Trihalides

BY D. P. STEVENSON[1] AND VERNER SCHOMAKER

Brode[2] recently published the results of an electron-diffraction investigation of the structures of the so-called trihalides of aluminum, gallium and indium. We believe that the interatomic distances which he reported (given in row *a* of the table) have been falsified by his application of an unsuitable "correction,"[3] and that the values given below in rows *b* and *c* are significantly more reliable. Row *b* gives the values found by Brode with the use of the usual correlation method[4] (omitting the Wierl correction), while those of row *c* are the ones we have obtained by the application of the radial distribution method[5] to his data. These two sets of values agree reasonably well except in the case of Ga_2Br_6.

TABLE I

AVERAGE M–X BOND LENGTHS IN THE TRIHALIDES OF GALLIUM AND INDIUM

		Cl	Br	I
Ga	[a]	2.16	2.35	2.40[d]
	[b]	2.22	2.41	2.48
	[c]	2.22	2.34	2.50
In	[a]	2.39	2.49	2.67
	[b]	2.46	2.56	2.76
	[c]	2.46	2.58	2.76

[a] Brode's "corrected" value. [b] Brode's uncorrected value. [c] From the first peaks of the radial distribution functions. [d] GaI_3, coplanar equilateral triangle.

The bond angle values (∠ XMX) indicated by the relative positions of the first and second maxima of the radial distribution functions substantiate Brode's conclusion that under the conditions of his experiments gallium tri-iodide is monomeric and coplanar, whereas the five other trihalides are dimeric. Inasmuch as we could not take account of the minima, for which Brode reported no measurements, the radial distribution functions tend to show spurious features, in these cases beyond the first two peaks, and we can draw no conclusions with regard to the conformation of the dimers.

THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIFORNIA

RECEIVED JULY 13, 1942

(1) Present address, Shell Development Company, Emeryville, California.

(2) Brode, *Ann. Physik*, **37**, 344 (1940).

(3) The correction is one due to Wierl (*ibid.*, **8**, 521 (1931)), and implies a procedure of measurement different from that which has been found suitable by Pauling and his co-workers. Almost certainly this correction should not have been applied to Brode's measurements, for his measurements on aluminum chloride agree well with those reported by Palmer and Elliott (THIS JOURNAL, **60**, 1852 (1938)).

(4) L. Pauling and L. O. Brockway, *J. Chem. Phys.*, **2**, 867 (1934).

(5) L. Pauling and L. O. Brockway, THIS JOURNAL, **57**, 2684 (1935); V. Schomaker, A. C. S. meeting, Baltimore, Md., April, 1939.

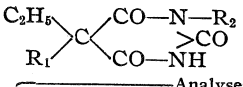
NEW COMPOUNDS

Some N-Aralkyl Barbituric Acids

The N-benzyl and N-phenethyl derivatives of amytal and neonal have been prepared by conventional methods from the corresponding malonic esters and benzyl and phenethyl ureas. They were crystallized from hexane. Data on these substances are presented in the table. The benzyl and phenethyl nembutals were also prepared, but, although general identity was shown by analysis, they were not obtained in a satisfactorily homogeneous condition.

TABLE I

1-ARALKYL-5-ETHYL-5-ALKYL BARBITURIC ACIDS



R_1	R_2	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
n-C_4H_9	$C_6H_5CH_2$	64	$C_{17}H_{22}O_3N_2$	67.50	7.34	67.79	7.59
n-C_4H_9	$C_6H_5CH_2CH_2$	74	$C_{18}H_{24}O_3N_2$	68.31	7.64	68.76	7.83
i-C_5H_{11}	$C_6H_5CH_2$	87–88	$C_{18}H_{24}O_3N_2$	68.31	7.64	68.38	7.56
i-C_5H_{11}	$C_6H_5CH_2CH_2$	106–107	$C_{19}H_{26}O_3N_2$	69.05	7.93	69.18	7.87

THE BURROUGHS WELLCOME & CO., U. S. A.
EXPERIMENTAL RESEARCH LABORATORIES
TUCKAHOE, NEW YORK

ALAN ARDIS
JOHANNES S. BUCK
RICHARD BALTZLY

RECEIVED AUGUST 5, 1942

Chaulmoogryl Quaternary Salts[1]

Since favorable bacteriological results have been obtained with methiodides and benzochlorides from mixtures of chaulmoogryl and hydnocarpyldimethylamines, it was decided to prepare some pure substances of this type.

Chaulmoogryl bromide[2] was heated in a bomb-tube at 105–110° with 33% methanolic dimethylamine in excess.

(1) Dittmar, *Z. Krebsforsch.*, **49**, 515 (1939), mentions a "Chaulmoogryl Zephirol." So far as the authors know these compounds have not been described.

(2) Sacks and Adams, THIS JOURNAL, **48**, 2397 (1926).

TABLE I

CHAULMOOGRYL AND OCTADECYLTRIALKYLAMMONIUM IODIDES, $R_1R_2Me_2NI$

R_1	R_2	Appearance	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
$C_5H_7(CH_2)_{13}$	CH_3	Irregular plates	> 170 (dec.)	$C_{21}H_{42}NI$	57.89	9.73	57.83	10.00
$C_{18}H_{37}$	CH_3	Platelets	227–230 (dec.)	$C_{21}H_{46}NI$	57.37	10.54	57.29	10.54
$C_5H_7(CH_2)_{13}$	$C_6H_5CH_2$	Yellow leaflets[a] Yellow needles[b]	99	$C_{27}H_{46}NI$	63.36	9.07	63.20	9.05
$C_{18}H_{37}$	$C_6H_5CH_2$	Elongated plates	93	$C_{27}H_{50}NI$	62.86	9.78	62.92	9.91

[a] From benzene. [b] From water.

The resulting tertiary amine boiled at 170° (0.5 mm.) and solidified in the refrigerator.

Chaulmoogryldimethylamine reacted with methyl iodide in absolute ether to form the methiodide, which is soluble in hot alcohol, sparingly soluble in cold alcohol, water, ethyl acetate and benzene, and insoluble in ether.

Attempts to prepare quaternary salts from the reaction of chaulmoogryldimethylamine with benzyl chloride, *p*-chlorobenzyl chloride and α-menaphthyl chloride resulted only in the formation of oils which presumably were in the main the desired quaternary salts but did not crystallize. Chaulmoogryldimethylbenzylammonium iodide, however, prepared from the chloride and sodium iodide, crystallized readily. It is soluble in alcohol, hot benzene, ethyl acetate and acetone, sparingly soluble in water and cold benzene, insoluble in ether and hexane.

For purposes of comparison octadecyltrimethylammonium iodide[3] and octadecyldimethylbenzylammonium iodide were prepared, the latter from the tertiary amine and benzyl iodide. Data on these and the preceding compounds are presented in Table I.

(3) Mentioned, but not described, by Shelton, Van Campen and Nisonger, at the Boston meeting of the Am. Chem. Soc., Sept., 1939.

THE BURROUGHS WELLCOME & CO., U. S. A.
EXPERIMENTAL RESEARCH LABORATORIES
TUCKAHOE, NEW YORK
RICHARD BALTZLY
WALTER S. IDE
JOHANNES S. BUCK

RECEIVED AUGUST 5, 1942

1,1,1-Trichloro-2-hydroxy-3-nitroalkanes and their Reduction Products

The halogenated nitroalcohols were made by a procedure essentially the same as that described by Nicodemus and Wulff.[1] Four-tenths of a mole (66.2 g.) of chloral hydrate was dissolved in a mixture of 200 cc. of water and 15 cc. of concentrated hydrochloric acid, in a 500-cc. round-bottomed, three-necked flask equipped with a mechanical stirrer and a thermometer dipping below the surface of the solution. A slight excess of nitroparaffin was added and the stirrer was started. A saturated aqueous solution of potassium carbonate was added until the mixture was just alkaline to litmus. The mixture was heated in a water-bath at a temperature of 50–52° for two hours (six hours when 1-nitropropane was used), with constant stirring. The dark yellow lower layer was removed and fractionally distilled under reduced pressure. The results are summarized in Table I.

(1) Nicodemus and Wulff, U. S. Patent 2,123,556 (1938).

The halogenated nitroalcohols were reduced at room temperature using 0.1 mole of the nitro compound dissolved in 150 cc. of absolute ethyl alcohol, 9 g. of freshly prepared Raney nickel catalyst[2] and starting with an initial hydrogen pressure of about 55 pounds per square inch. The catalyst was removed by suction filtration and the dark green filtrate was concentrated by distilling the alcohol under reduced pressure. Attempts to remove the color by treatment with decolorizing carbon were unsuccessful. Consequently, the dark brown or black solids were treated with benzoyl chloride in alkaline solution. The benzoyl derivatives were washed well with water and recrystallized by dissolving in hot ethyl acetate and then adding ligroin to the cooled solution. The time required for practically complete reduction, the melting points and analyses of the benzoyl derivatives are also given in Table I.

TABLE I

Nitroparaffin		Nitromethane		Nitroethane		1-Nitropropane	
Reduction time, hours		2		2		20	
Yield, %		63		53		36	
B. p.	°C.	138–146[a]		134–140[b]		136–142	
	Mm.	13		9		10	
Nitrogen, %	Calcd.	6.70		6.29		5.92	
	Found	6.75	6.68	6.21	6.19	5.86	5.82
Benzoyl deriv., m. p., °C., cor.		167.4		182.5		195.2	
Nitrogen, %	Calcd.	4.96		4.72		4.51	
	Found	5.01	4.98	4.77	4.79	4.59	4.53

[a] M. p., 44.7–45.7°, cor.; Henry,[3] 42–43°; Chattaway and Witherington,[4] b. p. 119° (3 mm.). [b] Chattaway, Drewitt and Parkes,[5] b. p. 115° (2 mm.).

In an attempt to obtain some pure 1,1,1-trichloro-2-hydroxy-3-aminopropane, it was found that the addition of acetone to a concentrated alcoholic solution of the amine resulted in the precipitation of an almost white solid. Repeated washing of the solid with acetone followed by recrystallization from a mixture of xylene and absolute alcohol and spontaneous evaporation of the solvent yielded white crystals which melted at 167.4–167.7° (cor.). The losses involved in this method of purification were enormous.

Anal. Calcd. for $C_3H_6Cl_3NO$: N, 7.84. Found: N, 7.69, 7.80.

DEPARTMENT OF CHEMISTRY
BOSTON UNIVERSITY
BOSTON, MASS.
SAUL MALKIEL
J. PHILIP MASON

RECEIVED JUNE 26, 1942

(2) Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).
(3) Henry, *Bull. soc. chim.*, **32**, 17 (1896).
(4) Chattaway and Witherington, *J. Chem. Soc.*, 1178 (1935).
(5) Chattaway, Drewitt and Parkes, *ibid.*, 1294 (1936).

Substituted Sulfonamides

N^1-Chloroacetyl-*p*-nitrobenzenesulfonamide.—To 10 g. of *p*-nitrobenzenesulfonamide dissolved in 100 cc. of 4.4% sodium hydroxide was added, dropwise with stirring at 5°, 7 g. of chloroacetyl chloride (Eastman Kodak Co.). After fifteen minutes, the solution was neutralized with acetic acid and unchanged *p*-nitrobenzenesulfonamide separated by filtration. The filtrate was acidified to congo red with hydrochloric acid to precipitate the product, which was collected and dried at 60°. It was then recrystallized once from toluene (1 g. per 50 cc.); yield 5 g.

N^1-Chloroacetylsulfanilamide was prepared from 5 g. of finely divided nitro compound which was added at 35° to 12.25 g. of $SnCl_2 \cdot 2H_2O$ dissolved in 15 cc. of concentrated hydrochloric acid. Some cooling was necessary at first. After standing for eighteen hours, the solution was cooled and made alkaline with 10% sodium carbonate solution. The precipitate was removed and the filtrate clarified with activated carbon. The product was precipitated, after removal of the carbon, by acidifying the filtrate to congo red. It was dried at 60°, and purified by one recrystallization from benzene–alcohol; yield 1.5 g.

Benzenesulfonamido heterocycles were obtained by the reaction of benzenesulfonyl chloride with the appropriate amino heterocycle in dry pyridine. The general method has been described previously[1]; yields ranged from 75–90%.

TABLE I

Compound	M. P., °C. (cor.)	Formula	Analyses, %[a] Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
N^1-Chloroacetyl-*p*-nitrobenzenesulfonamide[b]	172–173	$C_8H_7O_5N_2SCl$			10.1			10.4
N^1-Chloroacetylsulfanilamide[c]	157–158	$C_8H_9O_3N_2SCl$	38.6	3.6	11.3	38.7	3.9	10.9
2-Benzenesulfonamidopyridine	171–172	$C_{11}H_{10}O_2N_2S$			12.0			11.6
2-Benzenesulfonamidopyrimidine	229–230	$C_{10}H_9O_2N_3S$	51.1	3.8	17.9	51.0	4.1	17.9
2-Benzenesulfonamido-4-methylpyrimidine	193–194	$C_{11}H_{11}O_2N_3S$			16.9			16.7
2-Benzenesulfonamidothiazole	171–172	$C_9H_8O_2N_2S_2$	45.0	3.3	11.7	45.0	3.3	11.3
2-Benzenesulfonamido-1,3,4-thiadiazole	188–189	$C_8H_6O_2N_3S_2$			17.4			17.4

[a] Analyses were carried out in these laboratories under the direction of Mrs. Thelma Kirk. [b] Chlorine, calcd. 12.8%; found 12.6%. [c] Chlorine, calcd. 14.3%; found 14.6%.

(1) Roblin and Winnek, THIS JOURNAL, **62**, 1999 (1940).

STAMFORD RESEARCH LABORATORIES
AMERICAN CYANAMID COMPANY
STAMFORD, CONN.

JACKSON P. ENGLISH
DAVID CHAPPELL
PAUL H. BELL
RICHARD O. ROBLIN, JR.

RECEIVED JULY 31, 1942

COMMUNICATIONS TO THE EDITOR

BARBALOIN

Sir:

The recent note by Gardner and Campbell[1] on some reactions of the aloins emboldens us to place on record some experiments made in 1939. We can confirm Rosenthaler's statement[2] that barbaloin does not give methanol when hydrolyzed with borax and that Cahn and Simonsen's[3] observation is incorrect and we have observed also the formation of furfural under certain conditions. Our most fundamental result is however with reference to the empirical formula of barbaloin which was discussed at some length by Cahn and Simonsen.[3] Dr. E. G. Cox of the University of Birmingham has very kindly determined the molecular weight of barbaloin methyl ether by the X-ray crystal structure method and he finds it to be 521. There can therefore now no longer be any doubt that barbaloin methyl ether has the formula $C_{21}H_{17}O_2(OMe)_7$ from which it would apparently follow that barbaloin itself must be $C_{21}H_{17}O_2(OH)_7$. This formula for the methyl ether is in accord with the analytical data previously recorded (C, 64.5; H, 7.15; OMe, 40.7. Calcd. C, 64.8; H, 7.4; OMe, 41.9). We hope at some future date to be in a position to continue our experiments

(1) Gardner and Campbell, THIS JOURNAL, **64**, 1378 (1942).
(2) Rosenthaler, *Pharm. Acta Helv.*, **9**, 9 (1934).
(3) Cahn and Simonsen, *J. Chem. Soc.*, 2537 (1932).

and we shall then discuss in detail the important implications which follow from this result.

UNIVERSITY COLLEGE OF NORTH WALES, BANGOR
L. N. OWEN
J. L. SIMONSEN

RECEIVED AUGUST 15, 1942

THE TEMPERATURE COEFFICIENT OF THE CONDUCTANCE OF POTASSIUM CHLORIDE SOLUTIONS

Sir:

In THIS JOURNAL, **64,** 1544 (1942), Li and Fang give conductance data for aqueous solutions of potassium chloride at temperatures from 15 to 40°; they were apparently unaware, understandably enough, of our results both for potassium and sodium chloride solutions at temperatures from 15 to 45° (Gunning and Gordon, *J. Chem. Phys.* **10,** 126 (1942)). Their conductances at 25° are in moderate agreement with those of Shedlovsky, Brown and MacInnes [*Trans. Electrochem. Soc.*, **66,** 165 (1934)] and our own, and their 15° numbers are also in rough agreement with the measurements of Thompson and his associates [THIS JOURNAL, **59,** 2372 (1937); **61,** 1219 (1939)] and ourselves. For 15°, however, they employ a linear extrapolation of the Shedlovsky function Λ_0'; Shedlovsky, Brown and MacInnes showed that a c log c term was required for potassium chloride at 25°, and we showed that it was even more important for 15°. It is for this reason that the value Li and Fang give for Λ_0 at this temperature (120.88) is considerably less than the one we obtained by an extrapolation from much lower concentrations, *viz.*, 121.09.

The values of Λ_0 at 30° and 40° reported by Li and Fang are, however, about 0.25 and 1.1% less than those obtainable by interpolation in Gunning and Gordon's Table V. From LeRoy, Allgood and Gordon's transference data [*J. Chem. Phys.*, **8,** 418 (1940)] t^0_- is 0.5103 at 30° and 0.5120 at 40°; combining these with Li and Fang's values of Λ_0, one obtains 84.00 and 99.42 as the limiting mobility of chloride ion at these temperatures; Gunning and Gordon's Table VI, which resulted from a consideration of the transference and conductance measurements for *both* salts, gives 84.22 and 100.52. Interpolation of Owen and Sweeton's results for hydrochloric acid solutions [THIS JOURNAL, **63,** 2811 (1941)] gives 84.3 and 100.9; these are in agreement with Gunning and Gordon's values within the uncertainty of the transference numbers Owen and Sweeton were forced to employ.

If the discrepancy be ascribed to error in the temperature, this would correspond to a difference of 0.1° at 30° and to 0.6° at 40°; Li and Fang give no information about their temperature scale beyond stating that they used standard thermometers; our temperatures were determined by platinum resistance thermometer with N. B. S. certificate. It would therefore seem that Li and Fang's 30° and 40° data should be considered, for the moment at any rate, with reserve.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF TORONTO
TORONTO, ONTARIO, CANADA
A. R. GORDON

RECEIVED JULY 29, 1942

NEW BOOKS

Introduction to the Theory of Relativity. By PETER GABRIEL BERGMANN, Member, Institute for Advanced Study, 1936–1941; Assistant Professor of Physics, Black Mountain College. With a Foreword by Albert Einstein. Prentice-Hall, Inc., 70 Fifth Avenue, New York, N. Y., 1942. xvi + 287 pp. Illustrated. 15.5 × 23.5 cm. Price, $4.50.

This book not only appears with the *imprimatur* of Albert Einstein, but contains, p. 253, some hitherto unpublished work by Einstein and Bergmann. The proofreading has been astonishingly thorough: "mass" for "velocity" on p. 92, and superscript "s" for "5" in equation (18.24) on the very last page of the text, are the only errors the reviewer has found; he has, however, some differences of opinion with the author. The distinction between Riemannian and Lobachevskian spaces should be preserved, even if it is not of particular interest to the present discussion. The author recognizes, p. 60, that "only when n is 3 is the 'conjugate' tensor density to a tensor of rank 2 a vector density," but still adheres to Hamilton's definition of the vector product. (To one reader, at least, tensor densities seem "excess baggage.") The treatment of relativistic electrodynamics in Chapter VII is distinctly less elegant than that of E. B. Wilson and G. N. Lewis (1912), principally because the author has given the Cartesian interpretation of the derivation, step by step; to the reader who is not prepared to *think* in tensor terms this will not seem a defect.

The convention of calling tensors of negative rank "covariant" and those of positive rank "contravariant" is

not original with Dr. Bergmann, but that does not make it any less confusing.

In view of the use of subscript comma and semicolon to denote, respectively, ordinary and covariant differentiation, it is unfortunate that the equations have been punctuated. The hazards of combining punctuation with mathematical symbols are most amusingly illustrated by the caution on p. 239 "(do not sum over the index r)."

"*The Euclidean character of a space depends only on the metric,*" p. 162, seems a bit of an overstatement. An observer who found it possible, in a cylinder, to draw infinitely many geodesics between two given points, or who, in a cone of less than 60° vertex angle, found a geodesic intersecting itself, would have ground for questioning the Euclidean character of his space, in spite of the patently Cartesian metric tensor. Similarly on p. 74, "In . . . Riemannian spaces . . . there is, in general, a uniquely determined shortest connecting line between two points." This is certainly not the case for time-like intervals in *de Sitter* hyperspace.

In the matter of gravitational waves, p. 189, it might have been pointed out that in a gravitational collision, as in an electromagnetic collision between particles of like charge and equal mass, there is a first-order compensation of the components of the radiation field.

As for the "Schwarzschild singularity," p. 203, or the absence of plane-wave solutions of the *rigorous*, non-linear field equations, p. 189, what fails is, presumably, the fiction that either the field or the test particle can be unaffected by such extreme conditions.

It is refreshing that "from the point of view of . . . general formalism, there is no difference between the theories of Kaluza, Veblen and Hoffmann, and Pauli" (p. 268).

The book has both a synoptic table of contents and an index, and is so arranged as to suit readers of all grades of interest in the theory of relativity.

ELLIOT Q. ADAMS

Organic Analytical Reagents. By JOHN H. YOE, Ph.D., Professor of Chemistry, University of Virginia, and LANDON A. SARVER, Ph.D., Director of Research, Roanoke Plant Laboratory, American Viscose Corporation. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1941. ix + 339 pp. 2 figs. 15.5 × 23.5 cm. Price, $4.00.

Analytical Chemistry being a very old branch of the science, it would indeed be difficult to decide who first used an organic derivative or reagent to help identify or determine an element; the use of acetate, tartrate, citrate and other organic groups is far from new, as also are the ether extraction of iron and dimethylglyoxime for nickel. Modern pure analytical, industrial, biochemical and applied medical research, however, has vastly stimulated the application of organic compounds in analytical processes, and this book is an attempt to collect in one place the widely scattered literature dealing with this many-phased subject.

After an introductory Chapter (I), the authors proceed in Chapter II to group the compounds considered into a number of classes, according to their properties or functions: Solvents and Wash Liquids, Substances Used in Neutralizations, Organic Oxidizing Agents, Organic Reducing Agents, Indicators, Primary Standards (for volumetric analysis), Acidic Salinogenic Compounds, Basic Salinogenic Compounds, Photometric Acids and Substances for the Control of Adsorption, Diazotization and Coupling Agents (for nitrites), Alkaloids and Natural Products. In subsequent chapters are given more detailed theory and discussion of the major type groups of compounds, with many examples.

Organic solvents and wash liquids (Chapter III) may be used for washing and drying vessels and precipitates, lowering solubilities, extracting components of solid and liquid mixtures, displacing equilibria, aiding in distillation or other processes and serving as protective coatings. Most such compounds are hydrocarbons and their derivatives, such as thiols, halides, alcohols, glycols, ethers, aldehydes, ketones, esters, ester acids, amines (23 pp.). Chapter IV on organic acids and bases opens with a section on dissociation constants, lists typical acids and their properties, considers constants of bases and similarly lists a number of them. Organic oxidizing and reducing agents are taken up in six pages (V).

The subject of Indicators is discussed rather lengthily in Chapter VI, on the theory that these compounds are weak acids or bases and their salts, in colored or colorless form, containing chromophore groups which tautomerize or resonate. Many illustrative structural formulas are given, and tables of color changes and other properties, as well as numerous examples. Primary standards in volumetric analysis (Chapter VII) is an old field in which much profitable research has been done; the chapter is not long, since not many organic primary standards are in use. A number are described for alkaline and acid solutions, and a few for oxidimetry (for permanganate, iodine and thiosulfate).

Chapter VIII on valence and complex compounds seems to begin rather irrelevantly as one reads through a number of pages on the electronic theory of valence, types of linkage, Werner theory, complex compounds and their dissociation, and chelate groups, all this building up to a brief climax of compounds which form characteristic colored products with metals, such as various oximes, oxine, aurin, cupferron and nitrogen and sulfur compounds (with brief mention of isomerism of Werner complexes).

Salinogenic Reagents (Chapter IX) are defined as compounds capable of forming salts with metal or acid ions. The acidic ones are various types of ionizable —OH, —COOH, —NH and —SH compounds, while the basic ones are practically all trivalent nitrogen derivatives. Several pages are devoted to a discussion of ionization of the agents, the electronic and strain limitations on ring size and formation, covalent radii, planetary configuration of metal electrons and parachor; the remaining 40 pages list and describe the individual compounds in major and sub classes.

Chapter X (10 pp.) is entitled Photometric Aids: Colloids and Colorimetric Stabilizers, and deals briefly with protective colloids and their uses, the preparation, stabilization and precipitation of nephelometric suspensions. Miscellaneous Organic Reagents are grouped in Chapter XI (9 pp.), listing and describing compounds useful in electro-analysis, titration and a number of special analyses.

Part II consists of the Glossary and Bibliography. Chapter XII (22 pp.) is a listing of the reagents for various metals, ions and processes. Chapter XIII (53 pp.) is an alphabetical listing (with properties and uses) of the reagents considered. The book ends with a Bibliography of 2419 references, many of them as late as 1940, and a subject index. The descriptive theoretical parts of the book are neither extensive nor exhaustive; the rest of the work seems to succeed quite well in achieving its purpose. The typographical design and execution are good (except for a difficult block of matter in Chapter II), and obvious errors are scarce. The book should prove useful to a variety of readers and workers.

ALLEN D. BLISS

Chemical Dictionary. Compiled by F. H. CAMPBELL, D.Sc., F.A.C.I. Chemical Publishing Co., Inc., Brooklyn, N. Y., 1942. 85 pp. 15 × 22.5 cm. Price, $2.50.

In his introduction Dr. Campbell writes that terms which are known or can be found in textbooks are not included, while on the paper jacket the publishers state, "All chemical terms most commonly used are included." The compiler appears to have tried to effect a compromise between these two aims, for this list does indeed comprise many terms that perhaps should appear, but his obvious interest in physical chemistry has led to the retention of many also that should be replaced as being too rarely encountered to warrant inclusion in so small a volume. Thus enthalpy evacolation, Kurrol salts (but not Graham salt), liminal, and even some German terms are listed, while such new and important terms as co-polymer, chemurgy, precursor, molecular distillation and chemical warfare are omitted. The reference "Hydroxide, see Hydrate" does not conform with recommended practice. A valence table for pre-college students is included as a two-page appendix.

The definitions are often explanatory and informative. A student of chemistry in high school or college would be able to add considerably to his store of special knowledge by a careful study of this book page by page.

WILLIS A. BOUGHTON

War Gases. Their Identification and Decontamination. By MORRIS B. JACOBS, PH.D. Interscience Publishers, Inc., 215 Fourth Avenue, New York, N. Y., 1942. xiii + 180 pp. 8 illustrations. Cloth. 15.5 × 23.5 cm. Price, $3.00.

This book is a timely and concise compilation of the properties of chemical warfare agents and the methods for their analysis and destruction in areas and materials polluted by them. The subject matter is drawn from competent sources, including the most recent literature issued by American and British war and defense agencies. Many of the data are given in convenient tabular form.

Chapter I on Classification of the Chemical Agents gives a list of the war gases used or proposed in the last war and the recognized classifications of these gases based on their physiological action, their chemical composition, their physical properties or their tactical use.

Chapter II follows with a paragraph on the important physical and chemical properties and physiological action of each of the war gases arranged in order of their physiological classification. Further information on chemical properties is given in Chapter III which deals with their effect on water, food and other materials.

Chapter IV on Scheme of Analysis contains a useful table of data from several sources on the minimum detectable odor of war gases and the immediate physiological effect produced by them. The literature on field and laboratory tests appears to be well covered and procedures are concisely stated.

Chapter V (10 pages) is devoted to methods for the detection and estimation of arsenic, with special reference to foods suspected of contamination by Lewisite or other arsenical warfare agents.

Chapter VI gives the confirmatory tests for the identification of agents which have been chemically classified by the scheme of analysis given in Chapter IV. The qualitative procedures given are supplemented by reference to quantitative procedures in the literature.

Chapter VII is a well-arranged and concise description of methods for the decontamination of road surfaces, buildings, household articles, vehicles, clothing, water and food. Proper emphasis is given to the destruction of persistent gases such as mustard gas and the poisonous arsenicals. This chapter and the last one on the protection of foods are based on very recent publications issued by American and British defense agencies.

The book is well printed in legible type and should be very useful to anyone who has had some chemical education and has to deal with chemical warfare agents as an air warden, gas-identification officer or a decontamination officer. War gas chemists will find it a convenient manual for their work.

A. C. FIELDNER

The Physical Examination of Metals. Volume II. **Electrical Methods.** By BRUCE CHALMERS, D.Sc., Ph.D., F.Inst.P., Physicist, Tin Research Institute, and A. G. QUARRELL, A.R.C.S., Ph.D., F. Inst. O., Lecturer in Metallurgy, University of Sheffield. Longmans, Green and Co., Inc., 55 Fifth Avenue, New York, N. Y., 1941. viii + 280 pp. Illustrated. 14 × 22 cm. Price, $6.00.

The second volume of "The Physical Examination of Metals, Electrical Methods," carries forward the purpose set forth in "Volume I, Optical Methods." It presents a non-mathematical exposition and discussion of the techniques which have already proved of value to metallurgists or others to whom the examination of metals is important, as well as a discussion of new techniques which show promise. As a series, these volumes will form a convenient and valuable reference.

Under the general title of "Electrical Methods," the authors discuss magnetism, electrical measurements, X-ray diffraction, electron diffraction, the electron microscope and radiography. Each section presents a brief review of theory and general methods and then proceeds to discussion of the application of these methods to specific testing problems. Original references are given for the techniques discussed.

The section on magnetism and magnetic measurements is

introduced by a lucid and rapid review of magnetic theory followed by a description of precision apparatus for making magnetic measurements. Ballistic, oscillographic and general ferrometric methods are discussed. With respect to specific testing, the section on the Magnaflux method is particularly good, there being a detailed analysis of the applicability and limitations of Magnafluxing as well as of variations in technique. Of particular interest to metallurgists will be the sections on ferrographic metallography, the measurement of internal friction, the rapid determination of carbon content and the excellent section on thermomagnetic measurements which supplement routine metallography and are valuable in the identification of new phases. Measurement of the thickness of coatings and platings is also discussed.

In the section on electricity, the authors include a rather complete exposition of methods for making precision electrical measurements. These methods are applied to resistance thermometry, thermoelectricity, thermo-electric pyrometry, piezo-electricity, photo-electricity and electrical measurement of thickness from one side.

The longest and otherwise the most important section of the book is devoted to X-ray diffraction, but the treatment suffers from an attempt to present so much material in the space allotted. In the first place, the authors set up the diffraction problem with a non-vector formulation of the three Laue conditions—a procedure which is always somewhat involved and which, when treated in brief as it is here, adds nothing to the rigor or elegance of the presentation. The simpler Bragg formulation would perhaps have served the purpose better. On the other hand, many of the most important aspects of the diffraction technique are mentioned only in passing—particularly those aspects having to do with interpretation of diffraction patterns, the calculation of relative intensities of pattern lines, and other calculations of practical importance.

The experimental X-ray techniques are quite clearly presented, as are the various aspects of the particle size problem, and there is a very lucid treatment of the solid solution, superlattices and the order–disorder phenomena. Phase diagrams and intermetallic compounds are treated in a brief recapitulation of the work of Hume-Rothery and associates. There is also a short discussion of orientation effects and the effect of deformation upon diffraction patterns.

The section on electron diffraction is interesting and comprehensive. Principles, techniques, apparatus, particularly the Finch Diffraction Camera, are presented in detail. The application of electron diffraction to studies of basal-plane pseudomorphism, oxide layers, surface coatings, the Beilby layer and bearing surfaces is very enlightening. The discussion of the scope and limitations of the technique should be helpful.

Electron microscopy is a new technique which metallurgists are watching closely. Thus far it has proved difficult to adapt the microscope to metallographic use because reflection from a massive specimen has not been possible. The use of transparent surface replicas is at best a cumbersome and uncertain procedure. The authors present an account of the work that has been done in this field and give a detailed discussion of the construction of electron microscopes.

With respect to radiography the authors discuss the requirements for making satisfactory radiographs and the nature of flaws and defects which can be revealed.

The appendix contains data on electrolytic brightening, X-rays, crystal structure, spacing formulas, etc., and wave lengths associated with electrons. The index appears to be adequate.

J. N. HOBSTETTER

A Symposium on Respiratory Enzymes. Addresses given at an Institute held at the University of Wisconsin, September 11–17, 1941 (27 Contributors). The University of Wisconsin Press, Madison, Wisconsin, 1942. xii + 281 pp. Illustrated. 15.5 × 24 cm. Price, $3.00.

This book contains the following principal articles: Intermediate Carbohydrate Metabolism, O. Meyerhof; Oxidative Mechanisms in Animal Tissues, E. G. Ball; Pasteur Effect, F. Lipmann; Oxidases, Peroxidases and Catalase, K. G. Stern; Nicotinamide Nucleotide Enzymes, F. Schlenk; The Flavoproteins, T. R. Hogness; Cytochromes, E. Stotz; Phosphorylation of Carbohydrates, C. F. Cori; Metabolic Cycles and Decarboxylation, E. A. Evans, Jr.; and Transamination, P. P. Cohen. It also records discussions on hydrogen transport (Potter, Elliott, Ball and Lipmann, Stern and Haas, and Stotz), phosphorylation (Kalckar, Meyerhof, Johnson and Lipmann), tumor respiration (Baumann, Elliott, Potter, Burk and Kensler), bacterial respiration (Peterson, Wood and Burris, Werkman, Barron and Wilson, and Nord and Wilson), and animal tissue respiration (Elvehjem, Shorr, Elliott, Potter, Axelrod, Bernheim, Barron and Stare).

This symposium on respiratory enzymes fulfills the functions of a volume of this type. First, it reflects the best judgment of specialists in various branches of the subject in respect to the interpretation of data now available, and attempts to define the limits to which interpretations of physiological and pharmacological activities may safely be carried in terms of oxidative enzymes; secondly, it provides an up-to-date bibliography of the more important chemical, biochemical, and physiological literature in the field of biological oxidations and records, very satisfactorily in most instances, the advances which have been made in this field since the Cold Spring Harbor Symposium of 1939. During these three years there have been two major advances.

The first deals with the importance of phosphate transfer as a method of biological synthesis and has now reached the stage where phosphorylation can account for a number of chemical mechanisms underlying physiological activities. The paper by Cori and the discussion on phosphorylation supplement the earlier reviews of Kalckar and of Lipmann in bringing out the importance of phosphorylation in the control of carbohydrate metabolism.

The second major advance has been in the use of radioactive and other isotopes in tracing the chemical reactions concerned in the breakdown and utilization of carbohydrate, particularly the utilization of inorganic carbon dioxide by animal tissues to synthesize more complex carbon compounds. Various phases of this subject are here discussed by E. A. Evans, H. G. Wood and R. H. Burris.

The remarks of the latter two investigators should be particularly valuable to chemists and physicists desirous of applying such techniques to biological problems.

The article by F. Schlenk brings together a considerable amount of practical information regarding the properties of diphosphopyridine nucleotide and triphosphopyridine nucleotide which is not otherwise readily available in English.

The discussion on tumor metabolism will no doubt prove interesting to many, since it assembles for the first time much of the data currently available on the metabolism of butter yellow tumors and on the possible mechanism of formation of such tumors.

The book closes with a discussion of methods of handling tissue in metabolic experiments, including reference to certain techniques which have not been mentioned in earlier books on respiratory processes. The remarks of E. Shorr and K. A. C. Elliott on this subject should prove especially useful to chemists and physiologists who are anxious to study the relation of biological oxidations to their particular problems.

M. E. KRAHL

The Stone that Burns. By WILLIAMS HAYNES. D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N. Y., 1942. xii + 345 pp. 14.5 × 22 cm. Illustrated. Price, $3.75.

This timely and readable book is a history of the American sulfur industry. Mostly, it is the story of one man's flash of genius; of Herman Frasch's idea that sulfur deep down in the earth could be melted by steam and while still molten brought to the surface by an air lift. The book covers in detail Frasch's long and almost vain struggle to make this idea work, of his final success and of the great development which this process has experienced in later years.

In the current textbooks of chemistry Frasch's process is presented as something simple and easy. Nothing could be further from the truth. This book is illuminating in making clear the difficulties which even an apparently simple idea encounters in actual large-scale operation.

The latter part of the book, dealing with the period of the first world war and thereafter, is particularly valuable from an historical point of view. It traces in detail the development of the European sulfur cartel, one of the first representatives of this phenomenon destined to play so great and ominous a role in the subsequent economic life of the world. Moreover, it records in detail with abundant documentation the steps in the creation and growth of the great American sulfur companies of today.

This book, however, is more than a monograph on a special chapter of chemical engineering. The story it tells illustrates in a striking way the functioning of our economic system based on the profit motive. Naïve persons are often impressed with the philosophical weakness of this motive and it is true that as society develops this motive requires control. However, the particularized information and factual account of the development of the sulfur industry as given in this book cannot but impress the thoughtful reader with the ceaseless, multifarious, indomitable and ultimately successful operation of the profit motive. So long as individual initiative can function, so long as men are free, the lure of profit, of useful gain, operates. Driven by it men are unabashed by the most formidable obstacle; they attack first here, then there, again and again and again until it is at last overcome!

ARTHUR B. LAMB

Advances in Colloid Science. Edited by ELMER O. KRAEMER, Ph.D., Biochemical Research Foundation of the Franklin Institute, Newark, Delaware, in Collaboration with FLOYD E. BARTELL, Ph.D., Professor of Chemistry, University of Michigan, Ann Arbor, Michigan, and S. S. KISTLER, Ph.D., Associate Director of Research, Norton Company, Worcester, Mass. Volume I. Interscience Publishers, Inc., 215 Fourth Avenue, New York, N. Y., 1942. xii + 434 pp. 161 figs. 15.5 × 23.5 cm. Price, $5.50.

Colloid science is not an isolated subdivision of science; rather it cuts across many sciences. The breadth and diversity of its applications are perhaps responsible for the large number of devotees and their almost evangelistic enthusiasm.

The present volume, an outgrowth of this enthusiasm, is the first of a series intended to present new discoveries in colloid science, either experimental or theoretical, in a more comprehensive and unified fashion than is possible in the regular technical periodicals. As to the manner of presentation, the editors say in the Preface, "Since in each instance the author (or authors) will have been closely identified with the development under discussion, it is to be expected that the contributions should have an individualistic point of view, and should show a definite emphasis upon the author's own part in the development in question. The contributions are thus not intended to be reviews or compilations from the literature in the usual sense, and the editors are willing to share any censure that readers may be inclined sometimes to level at an author because he has apparently failed to do adequate justice to other investigators in the field."

This volume contains twelve chapters, as follows:

"The Measurement of the Surface Areas of Finely Divided or Porous Solids by Low Temperature Adsorption Isotherms," by P. H. Emmett.

"The Permeability Method for Determining Specific Surface of Fibers and Powders," by R. R. Sullivan and K. L. Hertel.

"A New Method of Adsorption Analysis and Some of its Applications," by Arne Tiselius.

"Solubilization and Other Factors in Detergent Action," by James W. McBain.

"Recent Developments in Starch Chemistry," by Kurt H. Meyer.

"Frictional and Thermodynamic Properties of Large Molecules," by R. E. Powell and Henry Eyring.

"The Constitution of Inorganic Gels," by Harry B. Weiser and W. O. Milligan.

"The Creaming of Rubber Latex," by G. E. van Gils and G. M. Kraay.

"Streaming Birefringence and its Relation to Particle Size and Shape," by John T. Edsall.

"Synthetic-Resin Ion Exchangers," by Robert J. Myers.

"The Study of Colloids with the Electron Microscope," by Thomas F. Anderson.

"Anomalies in Surface Tensions of Solutions," by Ernst A. Hauser.

These chapters are all excellently done and are of the greatest interest. Indeed, it is stimulating to see what great progress has been registered recently in every one of the fields covered. Moreover, the fields are so diverse that any reader can be sure to find much that is novel and illuminating.

The editors and contributors are to be complimented on the success of this volume, and the promise that it affords of similar volumes in the future.

ARTHUR B. LAMB

A Course of Instruction in the Qualitative Chemical Analysis of Inorganic Substances. By ARTHUR A. NOYES, Late Professor of Chemistry, and ERNEST H. SWIFT, Associate Professor of Analytical Chemistry, California Institute of Technology. Tenth edition, Revised and Rewritten. The Macmillan Company, 60 Fifth Avenue, New York, N. Y., 1942. xv + 418 pp. 13 figs. 14.5 × 22 cm. Price, $2.75.

Previous editions of this well known text by the late Professor Arthur A. Noyes have established a standard of excellence that has seldom been duplicated by other texts in the field of qualitative analysis, and in this new edition Professor Swift has wisely retained those features that have been responsible to such a great degree for the success of the previous editions. To quote from the Preface: "The division of the book into two main Parts, entitled The Course of Instruction and The System of Analysis has been retained, and as in the past the laboratory operations of the System of Analysis are described with as great definiteness as possible in short paragraphs entitled Procedures; and each of these is followed by Notes in which are given detailed facts regarding the operations, suggestions as to technique, the precautions necessary and the difficulties encountered in special cases, optional procedures for certain of these cases, and the indications frequently afforded of the presence of various constituents." "As a major change from previous editions, the treatment of the principles and more fundamental chemical facts connected with the procedure have been separated from the Notes and are given as Discussions immediately before the Procedure."

Although the revising author employs modern chemical principles liberally in the Discussions, and the method of treatment follows the best current usage, he has happily preserved a viewpoint that is realistic in its recognition of the complexity of many inorganic reactions and that thus avoids the pitfalls of too extensive and thoughtless application of hyper-simplified principles. For example, in his discussion of hydrogen sulfide separations the author quite correctly relegates to a minor role the dubious conclusions that so often result from the application of over-simplified solubility product reasoning, and stresses instead other important factors, such as complex ion formation, rate of precipitation, absorption and coprecipitation phenomena, which so frequently determine the success or failure of these separations.

Some noteworthy improvements in the Procedures include the use of potassium hydrogen sulfide for the separation of the Copper and Tin Groups, an improved scheme for the analysis of the Tin Group, the employment of isopropyl ether for the extraction of iron in the analysis of the Ammonium Sulfide Group, the complete precipitation of magnesium with the Alkaline Earth Group by means of solid ammonium carbonate, and the use of perchloric acid as a source of hydrogen ion in the Scheme of Analysis for Acidic Constituents, to mention only a very few. Considerable emphasis is placed on the analysis for acidic constituents, and provision is made for the detection of twenty-four anions (in addition to silicate, chromate, and permanganate) by a scheme whose degree of systematization approaches that of the scheme of analysis for the basic constituents, and which involves a minimal number of "side tests." An outstanding improvement in many of the Procedures has been attained by providing for the optional use of centrifugation to eliminate time-consuming filtrations.

During actual class use of this text for a semester the reviewer found only a surprisingly small number of errors, either typographical or otherwise, and only a few minor imperfections in procedural details. The book can be recommended to all those who believe that the primary purpose of a first course in qualitative analysis is to teach inorganic chemistry, rather than specialized techniques.

JAMES J. LINGANE

Annual Review of Biochemistry, Vol. XI. By JAMES MURRAY LUCK, Editor, and JAMES H. C. SMITH, Associate Editor. Annual Reviews, Inc., Stanford University P. O., California, 1942. ix + 736 pp. 16 × 23 cm. Price, $5.00.

With this volume, the Annual Reviews begins its second decade of a lifetime which has been of inestimable value to the biochemical research worker. The foresight of the original editorial committee is reflected in the unchanged editorial policy and subject matter of the series.

The present volume, in common with those earlier, deals with enzymes, vitamins, carbohydrates, proteins and various aspects of their metabolism. There are additional reviews of topics not so frequently considered. The following, which fall in this category, may be especially recommended: The Chemistry of Visual Substance, by S. Hecht; Avian Biochemistry, by T. H. Jukes and H. J. Almquist; Plant Tissue Cultures, by P. R. White; and Microbiology, by R. Dubos.

WILLIAM F. ROSS

Chemistry and Physiology of the Vitamins. By H. R. ROSENBERG, Sc.D. Interscience Publishers, Inc., 215 Fourth Avenue, New York, N. Y., 1942. xix + 674 pp. 25 figs. 15.5 × 23.5 cm. Price, $12.00.

This is the first attempt which has been made to cover the chemistry and physiology of all the vitamins in a single volume, and a very successful attempt it is, too. The book is beautifully arranged. There is first an introductory chapter on the vitamins in general, which contains precise

definitions of all of the terms to be used (although a definition of "enzyme" is, curiously enough, not given), a brief account of the history of the discovery of the vitamins, an explanation of nomenclature in this field, a list of the identified and unidentified vitamins and an outline of the methods of attack which various scientists, in their coöperative efforts, use to discover and elucidate the nature of a vitamin, together with the most important procedures that are employed. The specificity of the vitamins is here handled in a general way, along with the analytical methods which must be used, and then follows a brief discussion of the physiology and pathology which are connected with the vitamins. This first chapter is, in itself, an excellent general discussion of the whole subject of vitamins; with very minor changes it could be read with great profit by any individual who had no training in science but who wished to know something about what vitamins are, how they are discovered, how prepared, and how used, together with the "whys" of these questions.

Then follow separate chapters covering each of these vitamins: The A's, B_1, B_2, B_6, Nicotinic Acid, Pantothenic Acid, Inositol, *p*-Aminobenzoic Acid, C, the D's, the E's, H (Biotin), the K's, P, the non-identified Vitamins (the other B's, the L's, all the various factors such as T, U, Folic Acid, the Grass Juice Factor, etc.). Next come chapters on the Vitagens—Essential Fatty Acids, the Essential Amino-Acids, the Essential Carbohydrates and Choline, and the Essential, Transferable Methyl Group.

Within each major chapter, the material is systematically arranged into sub-topics, in general as follows: 1. Chronology, a brief table giving the "highlights" in connection with the development of the vitamin; 2. Occurrence; 3. Properties; 4. Isolation; 5. Chemical Structure; 6. Synthesis; 7. Industrial Methods of Preparation; 8. Biogenesis; 9. Determination; 10. Specificity; 11. Physiology; 12. Hypo- and Hyper-vitaminoses; and 13. Requirements. These topics are discussed in an authoritative and very entertaining manner. The citations are extremely numerous and are numbered by chapters, and there are over three thousand of them. The book closes with three very excellent indexes—patent, author, and subject—the preparation of which is a considerable achievement in itself.

It is possible that some specialists might consider their particular specialties to be treated in too elementary a manner, all the more so since books of approximately this same size could be written about almost any one vitamin, and have been written about some of them. But the reviewer found that those vitamins with which he is most familiar were treated comprehensively enough, and he thought these particular chapters were all the better for not having been written too exhaustively. It must be remembered that this is a book on "The Vitamins," and it is the first book of its kind to appear. Nowhere else is there, between the covers of one volume, so much information covering all the aspects of the whole field.

Dr. Rosenberg has worked in the laboratories of Ruzicka and of Reichstein; he was present in Zürich when Karrer announced the successful isolation of essentially pure vitamin A; and he has been, since 1936, engaged in researches on vitamins and hormones at the Jackson Laboratory of E. I. du Pont de Nemours and Company. Thus he has been active in this field for about fifteen years. It seems almost incredible, yet this short time has witnessed almost the whole of the development of the true chemistry of the vitamins. Although the pace is no longer quite as rapid as it was, yet it is still rapid enough, for almost literally while the ink was drying on the pages of this book, many important contributions in the field of the vitamins appeared. Thus, to mention only a few, it was shown that vitamin A_2 was definitely devoid of any activity and a new structure was proposed,[1] a new synthetic vitamin E factor was announced,[2] α-tocopheryl acetate was crystallized,[3] and new and accurate determinations of vitamin B_1[4] and of α-tocopherol[5] were published. One has to be daring, and to be possessed of a spirt of great eagerness, even to think of writing a book covering the whole of such an active field, and Dr. Rosenberg has done the job very well indeed. One could say, of course, that "this book fills a long-felt want," and he would be telling the truth—but it is even more than that. If the tired and busy chemist would like to have something he can read while relaxing and thoroughly enjoying himself; something authoritative and important, but which at the same time is easy to read and is exciting—this is it.

There are few errors in the book, and those few are, for the most part, rather obvious. Such things, for instance, as the use of "hydrocyanic" where "isocyanic" is meant on page 388; the use of "active" instead of "inactive" on page 409; and a few obvious mistakes in correcting the structural formulas. The printing and binding are excellent, and the only real criticism the reviewer has concerns the price of the book. Here is a book which merits a very wide circulation, but it is to be feared that the high price will effectively bar it from the libraries of the younger scientists and the general scientific reader, where it really belongs. This is a pity.

(1) Karrer, Geiger and Bretscher, *Helv. Chim. Acta*, **24**, 161E (1942).
(2) Smith, Renfrow and Opie, THIS JOURNAL, **64**, 1082 (1942).
(3) Robeson, *ibid.*, **64**, 1487 (1942).
(4) Kirch and Bergeim, *J. Biol. Chem.*, **143**, 575 (1942).
(5) Mayer and Sobotka, *ibid.*, **143**, 695 (1942).

LEE IRVIN SMITH

The Dynamic State of Body Constituents. By RUDOLF SCHOENHEIMER, M.D., Late Associate Professor of Biological Chemistry, Columbia University. Harvard University Monograph in Medicine and Public Health, Number 3. Harvard University Press, Cambridge, Mass., 1942. x + 78 pp. 6 figs. 15.5 × 23.5 cm. Price, $1.75.

The death of a scientist at the height of his intellectual powers and while engaged upon a problem of great importance is a tragic thing. In the case of Rudolf Schoenheimer, it is especially tragic since the problem had been brought so far toward solution that the results he had attained have already modified the current course of biochemical thinking.

The use of isotopes in the study of intermediary metabolism will, of course, continue, and probably at a rapidly accelerating pace. The application of these new techniques is a matter of such fundamental importance as far

to transcend the fate of the individual, whatever this may be. Accordingly it is fortunate that an opportunity was presented to Schoenheimer, by the invitation of Harvard University to deliver the Edward K. Dunham Lectures in the autumn of 1941, to bring together the whole of his labors with deuterium and the heavy isotope of nitrogen into a brief and simple account, unobscured by technical details.

These lectures have now appeared in the present slim volume. The first deals with the reactions of the body fats, the second with the state of the body proteins, and the third with the role of structural elements in the formation of excretory products. The thesis is developed that all components of the tissues are in a dynamic state and are constantly involved in rapid chemical reactions. If suitable starting materials are provided, all chemical reactions which the animal is capable of performing are carried out continually. No other conclusion is possible from the evidence afforded by the behavior of the isotopes used to trace the fate of various compounds administered to animals maintained in a state of nutritional equilibrium.

A brief preface explains that the printed lectures represent revisions by his colleagues from drafts prepared by the author, and there is, in addition, a biographical note and appreciation of Schoenheimer by Professor Hans T. Clarke who delivered the lectures and edited the manuscript.

H. B. VICKERY

The Nature of Thermodynamics. By P. W. BRIDGMAN, Hollis Professor of Mathematics and Natural Philosophy in Harvard University. Harvard University Press, Cambridge, Mass., 1941. xii + 229 pp. Illustrated. 21 × 14 cm. Price, $3.50.

Fifteen years ago in "Logic of Modern Physics" Bridgman made a notable contribution to epistemology by emphasizing that physicists, and similar scientists, actually acquired knowledge by operational procedures. Philosophers have been too much impressed with the finished products of the older and more theoretical sciences and have given too little attention to the ways in which scientists actually learn. Thus he joined the group containing C. S. Peirce, Wm. James, H. Poincaré, and L. J. Henderson, of scientists who philosophize, who for the most part do not labor their philosophies so much as the professional philosophers, but who bring to them the new ideas suggested from actual acquaintance with concrete phenomena.

In "The Nature of Thermodynamics" the author applies his operational analysis in detail to this difficult field. One can hardly fail to gain the impression that the sledding is a bit harder, but he is making a further and very useful effort to make clear whether the operations involved are instrumental or "paper and pencil" procedures. Especially to be noted is the discussion of the light thrown on methods of treating some irreversible phenomena by Bridgman's own researches. Those looking for "finality" and "finish" will be disappointed at such a frank assertion as: "I believe that no epistemology can be logically rigorous, but between rival epistemologies it can only be a question of which is logically the most tolerable in a particular setting." This is, however, true pragmatism, it is the method of getting ahead with the business of acquiring science; everything breaks down if pushed too far and practically no theory, surely no working hypothesis, subsumes all the known facts of its subject matter but shuts its eyes to some which are too stubborn.

Whether agreeing with him or not, every student of thermodynamics, that perplexing subject where things may not be too large without failing to satisfy equilibrium conditions nor yet too small without revealing fluctuations, will profit by the study of Bridgman's treatment of its nature.

EDWIN B. WILSON

BOOKS RECEIVED

August 10, 1942–September 10, 1942

ROGER ADAMS, Editor-in-Chief. "Organic Reactions." Volume I. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y. 391 pp. $4.00.

DONALD E. H. FREAR. "Chemistry of Insecticides and Fungicides." D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N. Y. 300 pp. $4.00.

REYNOLD C. FUSON and H. R. SNYDER. "Organic Chemistry." John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y. 506 pp. $3.50.

ANTONIO P. GUERRERO. "New Commercial and Technical Dictionary, Spanish-English, English-Spanish." Chemical Publishing Company, Inc., 234 King Street, Brooklyn, New York. 600 pp. $10.00.

HARRY N. HOLMES. "Strategic Materials and National Strength." The Macmillan Company, 60 Fifth Avenue, New York, N. Y. 106 pp. $1.75.

KURT H. MEYER. "Natural and Synthetic High Polymers." (High Polymers, Volume IV, edited by H. Mark, E. O. Kraemer and G. S. Whitby.) Translated by L. E. R. Picken. Interscience Publishers, Inc., 215 Fourth Avenue, New York, N. Y. 690 pp. $11.00.

WILLIAM RIEMANN, III, JACOB D. NEUSS and BARNET NAIMAN. "Quantitative Analysis. A Theoretical Approach." McGraw-Hill Book Company, Inc., 330 West 42nd Street, New York, N. Y. 496 pp. $3.50.

C. A. ROJAHN. "Preparación de Productos químicos y químico-farmacéuticos." ("Preparation of Chemical and Chemical-Pharmaceutical Products.") 2 Volumes. Translated and considerably amplified by Professor Francisco Giral. Editorial Atlante, S. A., Mexico, D. F. 1002 pp. $11.00.

LEE IRVIN SMITH, Editor-in-Chief. "Organic Syntheses." Volume 22. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y. 114 pp. $1.75.

"Studies of the Institutum Divi Thomae." Volume III, No. 1, November, 1941. Published by Institutum Divi Thomae of the Athenaeum of Ohio, Cincinnati, Ohio. 222 pp.

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

VOLUME 64 NOVEMBER 7, 1942 NUMBER 11

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

Ketene Acetals. XI. The Pyrolysis of Ketene Acetals and Orthoesters

BY S. M. MCELVAIN, HARRISON I. ANTHES AND SYDNEY H. SHAPIRO

The C-alkylation of α-methoxystyrene[1] and ketene acetal[1a] by means of certain reactive organic halides shows the similarity in behavior and the high reactivity of the heteroenoid systems that are present in these two structures. It seemed of interest, therefore, to undertake a study of the effect of heat on the ketene acetals to ascertain if they would undergo the same type of thermal rearrangement as the α-alkoxystyrenes which have long been known[2] to rearrange into phenyl alkyl ketones

$$C_6H_5C(OR)=CH_2 \longrightarrow C_6H_5COCH_2R$$

It previously has been reported[3] that ketene diethylacetal may be heated at 190–240° in *new* Pyrex tubes without any perceptible polymerization. In the work which is now reported, the effect of heat on ketene diethylacetal and its chloro and bromo derivatives has been studied. These ketene acetals have been heated under three different sets of conditions, *viz.*, (a) in glass tubes at 200° for six hours, (b) in a steel bomb at 150–200° for six to seventy-two hours, and (c) during rapid passage over a variety of surfaces in a furnace at 300–400°. Under all of these conditions the ketene acetals that were studied showed only one type of behavior, *viz.*, pyrolysis into ethylene and the acetic ester

$$XCH=C(OC_2H_5)_2 \longrightarrow XCH_2COOC_2H_5 + C_2H_4 \text{ (X is H, Cl or Br)}$$

There was no indication in any experiment that an ethyl group had rearranged from an oxygen to a carbon as it does in ethoxystyrene.[3]

Under the conditions (six hours at 200°) that caused complete pyrolysis of ketene diethylacetal in glass tubes, ketene dimethylacetal remained unaffected. Indeed, 95% of this dimethylacetal was recovered after twenty-four hours of heating at 200°.

The failure of ketene, chloroketene and bromoketene diethylacetals to undergo thermal rearrangement as do the alkoxystyrenes led to a study of the thermal behavior of ketene diallyl- and dibenzylacetals. These compounds contain the necessary structure, $>C=\overset{|}{C}-O-CH_2-\overset{|}{C}=C-$, for the well-known Claisen or allylic rearrangement and would be expected to rearrange quite readily. As a matter of fact, neither of these ketene acetals could be isolated from the products of the reaction of potassium *t*-butoxide in *t*-butyl alcohol with either diallylbromoacetal (I) or dibenzylbromoacetal (III); the only products that could be separated were allyl allylacetate (II) and benzyl *o*-tolylacetate (IV) which were obtained in yields of 43 and 46%, respectively.

$$BrCH_2CH(OCH_2CH=CH_2)_2 + KOBu(t) \longrightarrow$$

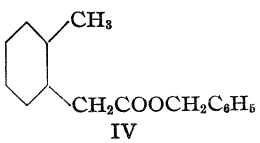
I

$$CH_2=CHCH_2CH_2COOCH_2CH=CH_2 + KBr + t\text{-BuOH}$$

II

$$BrCH_2CH(OCH_2C_6H_5)_2 + KOBu(t) \longrightarrow$$

III



$$+ KBr + t\text{-BuOH}$$

IV

(1) Mortenson and Spielman, THIS JOURNAL, **62**, 1609 (1940).
(1a) McElvain and Kundiger, *ibid.*, **64**, 254 (1942).
(2) Claisen, *Ber.*, **29**, 2931 (1896); Claisen and Haase, *ibid.*, **33**, 3778 (1900).
(3) Johnson, Barnes and McElvain, THIS JOURNAL, **62**, 964 (1940).

Undoubtedly the ketene acetal was the intermediate in each of these reactions, but it was so susceptible to rearrangement that it passed into the substituted acetic ester (II or IV) as rapidly as it was formed. It is interesting to note that these allylic rearrangements occur at or below the refluxing temperature (*ca.* 80°) of *t*-butyl alcohol which is an unusually low temperature for a rearrangement of this type. Also it should be noted that in the more widely studied rearrangements of the phenol ethers the allyl phenyl ethers generally rearrange with inversion of the allyl radical, while benzyl phenyl ether, in contrast to the allyl ethers and to the above benzyl-acetal, rearranges to the *o*- and *p*-benzyl phenols,[4] without any inversion of the benzyl radical.

Two reports of the pyrolysis of an orthoester into a ketene acetal and alcohol

$$RCH_2C(OEt)_3 \longrightarrow RCH{=}C(OEt)_2 + EtOH$$

have appeared in the literature. Reitter and Weindel[5] reported this pyrolysis for the compound in which R is carbethoxy and Staudinger and Rathsam[6] reported a similar behavior for the compound in which R is phenyl. These latter authors also reported that ethyl orthoacetate underwent a different type of pyrolysis, *viz.*, into ethyl acetate and ether, when passed over nickel on pumice at 250–260°.

Since, in some cases, orthoesters appear to pyrolyze into ketene acetals it seemed of interest to undertake a study of the pyrolysis of a variety of orthoesters and to determine, if possible, if there is any general tendency for them to pyrolyze into ketene acetals. In some preliminary experiments with ethyl orthoacetate it was found that this orthoester, when heated at 200° for twenty hours in a steel bomb with a glass liner, yielded alcohol, ethyl acetate and ethylene. These products could be the result of the pyrolysis of the orthoester into alcohol and ketene acetal followed by the pyrolysis of the acetal into ethylene and ethyl acetate. That this was actually the course which the pyrolysis took was shown by the products obtained when the orthoester was heated with an equivalent of phenol. It has been found in earlier work that the mixed orthoester obtained by the addition of phenol to ketene acetal decomposed on distillation into ethyl acetate and phenetole.[7] When ethyl orthoacetate was heated with phenol no ethylene was formed and practically quantitative yields of ethyl acetate and phenetole were obtained. The following sequence of reactions illustrates these transformations

$$CH_3C(OEt)_3 \xrightarrow{200^\circ} CH_2{=}C(OEt)_2 + EtOH$$

$$CH_2{=}C(OEt)_2 + C_6H_5OH \longrightarrow CH_3C(OEt)_2OC_6H_5 \longrightarrow CH_3COOEt + C_6H_5OEt$$

The ability of phenol to divert the ketene acetal into phenetole as rapidly as it is formed and before it is pyrolyzed into ethylene and ethyl acetate made possible the study of the decomposition of a mixed orthoester of the type $CH_3C(OR)_2OR'$. Such an ester, on pyrolysis, could follow two reaction courses, A and B, and the extent of each reaction would be measured by the amount of each of the alcohols, ROH and R'OH, among the reaction products. An additional measure of the extent of reaction B would be given by the sum of the products, C_6H_5OR' and CH_3COOR', which result from the decomposition of the mixed orthoester (V) by reactions M and N.

$$CH_3C(OR)_2OR' \begin{cases} \xrightarrow{A} R'OH + CH_2{=}C(OR)_2 \xrightarrow{C_6H_5OH} CH_3C(OR)_2OC_6H_5 \longrightarrow CH_2COOR + C_6H_5OR \\ \xrightarrow{B} ROH + CH_2{=}C(OR)OR' \xrightarrow{C_6H_5OH} \underset{V}{CH_3C(OR')(OC_6H_5)OR} \begin{cases} \xrightarrow{M} CH_3COOR' + C_6H_5OR \\ \xrightarrow{N} CH_3COOR + C_6H_5OR' \end{cases} \end{cases}$$

Table I is a summary of the results obtained from the pyrolysis of a number of orthoesters. In general, the esters of the unsubstituted acetic acid (runs 1–9) were heated at 200° for twenty hours in order to insure complete pyrolysis. The esters of the substituted acetic acids were heated at the same temperature and, in some cases, for shorter periods of time in order to show roughly their relative tendency to pyrolysis. In the cases of the mixed orthoesters (runs 3–9) the total percentage of reaction (100% in all runs) is subdivided into the per cent. of each of the reactions A, B, M and N and the ratios of the pyrolysis products ROH to R'OH and CH_3COOR' to C_6H_5OR', *i. e.*, B/A and M/N is indicated. The

(4) Behaghel and Freinensehner, *Ber.*, **67**, 1368 (1934); Short, *J. Chem. Soc.*, 528 (1928); Hickenbottom, *Nature*, **142**, 930 (1938); **143**, 520 (1939).

(5) Reitter and Weindel, *Ber.*, **40**, 3358 (1907).

(6) Staudinger and Rathsam, *Helv. Chim. Acta*, **5**, 646 (1922).

(7) Barnes, Kundiger and McElvain, This Journal, **62**, 1281 (1940).

TABLE I

PYROLYSIS OF ORTHOESTERS, $XCH_2C(OR)OR'$ AT 200°

Run	XCH_2 is	R is	R′ is	Reaction time, hr.	Total reaction, % React. A, %	React. B, %	B/A	React. M, %	React. N, %	M/N
1	CH_3	C_2H_5	C_2H_5	10	80					
2	CH_3	C_2H_5	C_2H_5	20	100					
3	CH_3	C_2H_5	n-C_4H_9	20	33	67	2.0	49	51	1.0
4	CH_3	C_2H_5	i-C_4H_9	20	33	67	2.0	60	40	.7
5	CH_3	C_2H_5	s-C_4H_9	20	22	78	3.5	14	86	6.1
6	CH_3	C_2H_5	i-C_5H_{11}	20	34	66	1.9	52	48	.92
7	CH_3	C_2H_5	$(CH_3)_3CCH_2$	20	44	56	1.3	100	0	0
8	CH_3	C_2H_5	$C_6H_5CH_2$	20	16	84	5.4	11	89	8.1
9	CH_3	n-C_4H_9	C_2H_5	20	39	61	1.6	51	49	.96
10	$EtOCH_2$	C_2H_5	C_2H_5	2.5	84					
11	$EtOCH_2$	C_2H_5	C_2H_5	5.0	100[a]					
12	$ClCH_2$	C_2H_5	C_2H_5	10	74					
13	$ClCH_2$	C_2H_5	C_2H_5	20	100					
14	$BrCH_2$	C_2H_5	C_2H_5	13	21[b]					
15	$BrCH_2$	C_2H_5	C_2H_5	32	37[c]					
16	Br_2CH	C_2H_5	C_2H_5	32	15[d]					

[a] In another run of this orthoester in which phenol was used, the total yield (97%) of the acetic ester in this run was composed of ethyl ethoxyacetate (47%) and phenyl ethoxyacetate (53%). [b] In this run 43% of the bromo-orthoester was recovered unchanged. [c] In this run no orthoester was recovered; in addition to the bromoacetic ester indicated above, 0.5 g. of acetaldehyde (identified as the 2,4-dinitrophenylhydrazone), 4 g. of ethyl bromide, 4.3 g. of ethyl acetate and a small amount of water (copper sulfate test) were obtained from a 30 g. run of the orthoester. [d] In this run 0.6 g. acetaldehyde, 11 g. of ethyl bromide, 2.9 g. of ethyl acetate, 10.8 g. of ethyl monobromoacetate and some water and alcohol were isolated from a 50 g. run of the orthoester.

simple orthoesters ($R = R' = C_2H_5$) in runs 10–16 were pyrolyzed without phenol and the total percentage of reaction is given in the sixth (reaction A) column of the table. These values were obtained from the amounts of acetic ester and unchanged orthoester that were present in the bomb after the heating period shown.

Runs 1 and 2 of Table I show that the time necessary for complete pyrolysis of ethyl orthoacetate at 200° is between ten to twenty hours. The behavior of the mixed orthoesters in runs, 3, 4, 6 and 9 show that the primary alkyl groups of either the normal or iso structure have practically the same tendency to be eliminated in the form of R′OH (reaction A). In each of these runs approximately one-third of the orthoester decomposes with the loss of the single alkyl group (R′) and two-thirds by the course in which one of the two like alkyl groups (R, reaction B) is lost. The neopentyl group (run 7) shows a noticeably greater tendency to be eliminated than do the other primary alkyl groups. The *s*-butyl group (run 5) and the benzyl group (run 8) are decidedly more resistant to elimination than are the ethyl and the other primary alkyl groups. Since the pyrolysis of an orthoester to a ketene acetal (reactions A and B) involves a rupture of the bond that holds the alkoxyl group in the orthoester, the behavior of the various alkyl groups in the mixed orthoesters is in line with the well-known fact that the oxygen–hydrogen bond is more reactive and the alkyl–oxygen bond less reactive in primary alcohols than in secondary (or benzyl) alcohols. In the decomposition of the mixed orthoester V it seems safe to assume that the phenyl ether is eliminated as C_6H_5O— and R (or R′) since in phenol the phenyl–oxygen bond is very stable as compared to the oxygen–hydrogen bond and also because of the high yields of the *s*-butylphenyl ether and benzylphenyl ether (reaction N, runs 5 and 8). It is interesting to note that reactions M and N take place to practically the same extent when R′ is *n*-butyl, isobutyl, isoamyl and ethyl (runs 3, 4, 6 and 9). This shows that these primary alkyl-oxygen bonds are, as are the bonds that hold the RO— and R′O groups in the orthoester, of the same order of strength. The failure of the mixed orthoester V, when R′ is neopentyl (run 7, Table I), to follow reaction N to any extent in its decomposition, together with the relatively high amount of reaction A in the run, shows the marked difference in the strength of a bond attached to a neopentyl group and one attached to a neopentoxy group.

In the group of ethyl esters of the substituted orthoacetic acids a number of interesting results

appear. Of all of the orthoesters that were studied the ethyl orthoethoxyacetate was pyrolyzed (runs 10 and 11) most readily. In one run (see footnote (a), Table I) in which the orthoester was pyrolyzed in the presence of phenol the resulting acetic ester was composed of about equal amounts of the phenyl and the ethyl esters. These products indicate that the mixed orthoester (VII), resulting from the addition of phenol to ethoxyketene acetal (VI), breaks down in two different ways, thus

$$EtOCH_2C(OEt)_3 \longrightarrow EtOH + \underset{\text{VI}}{EtOCH{=}C(OEt)_2} \xrightarrow{C_6H_5OH}$$

$$\underset{\text{VII}}{EtOCH_2C(OEt)(OC_6H_5)-OEt} \begin{cases} \longrightarrow EtOCH_2COOEt + C_6H_5OEt \\ \longrightarrow EtOCH_2COOC_6H_5 + EtOEt \end{cases}$$

The ethyl orthochloroacetate (runs 12 and 13) behaved as did the other orthoesters and, in contrast to the ethoxyacetate, is no more susceptible to pyrolysis than is ethyl orthoacetate. The bromo-substituted orthoesters, however, show a marked variation from the other orthoesters in the pyrolysis behavior. The yields of the corresponding bromo-acetic esters that were obtained from the pyrolyses that went to completion (runs 15 and 16) are quite low. Numerous other unexpected products (see footnotes *c* and *d*, Table I) were isolated from these pyrolyses. These products can best be explained upon the assumption that two competing modes of decomposition are followed by these esters. The one of these that occurs to the lesser extent, is the route (reactions A and B) that is followed by the other orthoesters.

The other, and main, reaction route appears to be connected with the positive character of the bromine of the mono and dibromo derivatives of ethyl orthoacetate[8] and to involve the loss of the elements of ethyl hypobromite from the orthoester. A ketene acetal with one less bromine than the original orthoester would be the result of this decomposition.[9] This ketene acetal would then pyrolyze into the corresponding acetic ester and ethylene or add hydrogen bromide (see below) to form the same acetic ester and ethyl bromide. Ethyl hypobromite does not appear to have been described in the literature, but if it were momentarily formed it would be expected to decompose into acetaldehyde and hydrogen bromide in a manner similar to that reported for ethyl hypochlorite.[10] The interaction of hydrogen bromide and alcohol to produce water explains the last of the various and unexpected products that were isolated from the pyrolyses of the orthobromoesters. The formation of these products from the pyrolysis of ethyl orthodibromoacetate is illustrated below.

The isolation of benzyl *o*-tolylacetate (IV) instead of the ketene acetal from the dehydrobromination of dibenzylbromoacetal (III) suggested the pyrolysis of benzyldiethyl orthoacetate (VIII) in the absence of phenol. This orthoester appears from run 8 of Table I to decompose to the extent of 84% into the mixed ketene acetal (IX) which,

$$CHBr_2C(OEt)_3 \begin{cases} \longrightarrow EtOH + Br_2C{=}C(OEt)_2 \longrightarrow Br_2CHCOOEt + C_2H_4 \\ \longrightarrow EtOBr + BrCH{=}C(OEt)_2 \longrightarrow BrCH_2COOEt + C_2H_4 \end{cases}$$

$$Br_2C{=}C(OEt)_2 \text{ (or } BrCH{=}C(OEt)_2) + HBr \longrightarrow EtBr + Br_2CHCOOEt \text{ (or } BrCH_2COOEt).$$

$$CH_3CH_2OBr \longrightarrow CH_3CHO + HBr \xrightarrow{EtOH} EtBr + H_2O$$

if not immediately diverted through reactions M and N by phenol, should rearrange into ethyl *o*-tolylacetate (X), thus

$$\underset{\text{VIII}}{CH_3C(OEt)_2-OEt} \longrightarrow \underset{\text{IX}}{CH_2{=}C(OEt)(OCH_2C_6H_5)} \longrightarrow \underset{\text{X}}{\text{(cyclohexyl)}(CH_3)(COOEt)}$$

When the orthoester VIII was heated alone at 200° for twenty-four hours there was considerable non-distillable tar produced, but from the volatile liquid portion of the pyrolysis mixture it was possible to isolate about 14% of the theoretical amount of X.

Finally an orthoester that has no α-hydrogen, and consequently cannot be converted into a ketene acetal, was pyrolyzed. Ethyl orthobenzoate, when refluxed gently under atmospheric pressure (b. p. 220–225°), slowly decomposed into the normal ester and diethyl ether.

$$C_6H_5C(OEt)_3 \longrightarrow C_6H_5COOEt + Et_2O$$

After six hours this decomposition amounted to 60%.

(8) McElvain and Walters, This Journal, **64**, 1963 (1942).

(9) The general method of preparation of ketene acetals involves the removal of the elements of ethyl hypohalite from α-halogenated orthoesters by means of sodium [Walters and McElvain, *ibid.*, **62**, 1482 (1940); McElvain, Clarke and Jones, *ibid.*, **64**, 1966 (1942)].

(10) Sandmeyer, *Ber.*, **18**, 1768 (1885).

Experimental

The ketene diethylacetals that were used in the pyrolysis experiments and for the preparation of mixed orthoesters were prepared by procedures previously described.[3,11] In the pyrolysis experiments ketene, chloroketene and bromoketene diethylacetals were used.

Methyl Orthobromoacetate and Ketene Dimethylacetal.—This acetal could not be prepared from the bromodimethylacetal by the action of potassium *t*-butoxide in *t*-butyl alcohol because the ketene acetal boiled (89–91°) too near to the alcohol to allow them to be separated. Consequently, it had to be prepared from methyl orthobromoacetate by the action of metallic sodium.[12] This bromoester was obtained by the bromination of methyl orthoacetate, prepared by the method of McElvain and Nelson[13] from acetonitrile, according to the procedure described for the preparation of ethyl ortho-α-bromoisovalerate.[14] **Methyl orthobromoacetate,** b. p. 74–75° (17 mm.); d^{25}_4 1.4771; $n^{25}D$ 1.4501, was obtained in yields of 70% of the theoretical.

Anal. Calcd. for $C_5H_{11}O_3Br$: Br, 40.15. Found: Br, 40.33.

Ketene dimethylacetal, b. p. 89–91° (740 mm.); d^{25}_4 0.9274; $n^{25}D$ 1.3962, was obtained from the bromoester[12] in 65% yields.

Anal. Calcd. for $C_4H_8O_2$: C, 54.53; H, 8.93. Found: C, 54.31; H, 9.15.

The Pyrolysis of Ketene Diethylacetals

(a) **In Glass Tubes.**—Pyrex bomb tubes of 80-ml. capacity were washed with alcohol and ether and then filled with concentrated aqueous sodium hydroxide and allowed to stand for four hours. Then they were washed with distilled water, alcohol and ether. When rigorous anhydrous conditions were used the tubes were heated in a bunsen flame, stoppered with a calcium chloride tube, and allowed to cool. Approximately 5 g. of the ketene acetal was placed in the tube; when extreme precautions against moisture were used the acetal was distilled directly into the dried bomb tube. After sealing, the tube was heated in a bomb furnace at 200° for six hours, after which time it was cooled in an acetone–dry-ice mixture and opened. All tubes contained a high pressure of an inflammable gas (ethylene). The acetic ester remaining in the tube was distilled and weighed. When new, rigorously dried tubes were used the pyrolysis never amounted to more than 20% of the ketene acetal; in used tubes, similarly dried, the amount of pyrolysis rose to 50%; in air-dried, used tubes the pyrolysis was complete in six hours at 200°.

(b) **In a Steel Bomb.**—A solution of 20–30 g. of the ketene acetal in 40–60 ml. of cyclohexane (if a solvent is not used the reaction product is invariably a tar) was placed in a 500-ml. steel hydrogenation bomb that was fitted with a valve for the release of gas pressure and heated at 200° for six hours. Under these conditions the pyrolysis of the ketene acetals was complete. However, when a temperature of 150° was used there was no appreciable decomposition of the ketene acetal even after twenty-four hours. After cooling the ethylene was slowly released from the valve in the bomb, through two dry-ice traps, into an aspirator from which the ethylene determination was made. The yields of ethylene in these runs generally were 5–10% lower than those of the esters. The amounts of esters were determined in the case of ethyl acetate from the refractive index of the cyclohexane solution and, in the cases of the ethyl halogenocetates, by fractional distillation.

(c) **In Furnace.**—A 50-cm. Pyrex tube, loosely packed for a length of 17 cm. with either glass chips, manganese dioxide, aluminum oxide, zinc oxide or chromic oxide was heated in a short (35 cm.) electric furnace. The temperature was read from a pyrometer placed in the interior of the tube. The ketene acetal in 10–20 g. samples, was added dropwise into one end of the furnace from a dropping funnel protected with a calcium chloride tube and the gases from the furnace were conducted into a 50-ml. receiving flask that carried an efficient reflux condenser. The vapors that passed from the top of the reflux condenser were led through a cold trap surrounded by a dry-ice–acetone mixture and into a pair of 25-cm. test-tubes in series, each containing 50 g. of bromine. The last bromine tube was connected to an aspirator of about 8-liters capacity.

The acetic ester formed in the pyrolyses was determined by distillation of the material in the first receiving flask and the cold trap. The only contaminant of this ester was a small amount of unchanged ketene acetal. The amount of ethylene bromide in the two bromine tubes gave a measure of the ethylene (generally 10–25% below the yields of the esters) that was formed in the reaction. The yields of ester from all of the ketene acetals used, either through an unpacked tube or one packed with glass chips, were 80% or more at 400° and practically zero at 300°. With manganous oxide and aluminum oxide, however, ester yields of 80% and 60%, respectively, were obtained at 300°. Zinc and chromium oxides gave very little improvement in ester yield at this lower temperature over that obtained from an unpacked tube.

A 20-g. sample of ketene dimethylacetal was heated in a sealed glass tube at 200° for twenty-four hours as in procedure (a). When the tube was cooled, opened and the contents distilled, 95% of unchanged ketene dimethylacetal was recovered.

Diallylbromoacetal.—To 86.1 g. (1 mol) of freshly distilled vinyl acetate was added with stirring 60 g. (1 mol) of bromine over a period of two hours. The temperature was not allowed to go above 5°. The resulting mixture was added with stirring to 290 g. (5 ml.) of anhydrous allyl alcohol over a period of three hours. The reaction mixture then was allowed to come to room temperature slowly and stirred overnight. After this time 100 ml. of water was added to the vigorously stirred mixture, followed by small portions of potassium carbonate, until the solution was no longer acidic. The aqueous layer was removed and the remaining product dried over anhydrous potassium carbonate. On distillation the fraction boiling at 101–102° (20 mm.); $n^{25}D$ 1.4712[15] was collected. The yield amounted to 100 g. (45%); % Br, 35.9 (calcd. 36.0).

Allyl Allylacetate from Diallylbromoacetal.—To a solution of 39 g. (1 atom) of potassium in 550 g. of *t*-butyl

(11) McElvain, *et al.*, THIS JOURNAL, **60**, 2210 (1938); **64**, 1059 (1942).

(12) Walters and McElvain, *ibid.*, **62**, 1482 (1940).

(13) McElvain and Nelson, *ibid.*, **64**, 1825 (1942).

(14) McElvain, Clarke and Jones, *ibid.*, **64**, 1966 (1942).

(15) *Cf.* Hurd and Pollack, THIS JOURNAL, **60**, 1905 (1938).

Table II

Properties and Analyses of Orthoesters, $CH_3C(OR)_2OR'$

R is	R' is	Formula	B. p., °C.	Mm.	$n^{25}D$	d^{25}_4	Analyses, % Calcd. C	Calcd. H	Found C	Found H
C_2H_5	n-C_4H_9	$C_{10}H_{22}O_3$	70–72	15	1.4057	0.8682	63.12	11.66	62.99	11.55
C_2H_5	i-C_4H_9	$C_{10}H_{22}O_3$	64–66	14	1.4017	.8616	63.12	11.66	63.09	11.70
C_2H_5	s-C_4H_9	$C_{10}H_{22}O_3$	63–65	15	1.4016	.8648	63.12	11.66	63.21	11.73
C_2H_5	i-C_5H_{11}	$C_{11}H_{24}O_3$	80–82	15	1.4077	.8626	64.66	11.84	64.56	11.83
C_2H_5	$(CH_3)_3CCH_2$	$C_{11}H_{24}O_3$	87–88	28	1.4037	.8481	64.66	11.84	64.88	11.77
C_2H_5	$C_6H_5CH_2$	$C_{13}H_{20}O_3$	121–122	8	1.4778	.9839	69.61	8.99	69.51	8.87
n-C_4H_9	C_2H_5	$C_{12}H_{16}O_3$	98–100	13	1.4119	.8623	66.01	12.01	65.92	12.00

alcohol was added 220 g. (1 mol) of diallylbromoacetal. After refluxing for five hours the mixture was cooled to room temperature and the precipitated potassium bromide removed by centrifuging. It weighed 108 g. (90%). After removal of the *t*-butyl alcohol the reaction product was fractionated carefully through a 15-cm. Widmer column. After 7 fractionations 60 g. (43%) of allyl allylacetate was obtained; b. p. 48–50° (8 mm.) or 160–162° (740 mm.); $n^{25}D$ 1.4198; d^{25}_4 0.8808; sap. equiv., 141 (calcd. 140).

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.71, 68.53; H, 8.97, 8.67.

Saponification of this ester yielded allyl alcohol, 3,5-dinitrobenzoate,[16] m. p., 47–48°, and allylacetic acid, the anilide of which melted at 92°.[17]

Dibenzylbromoacetal.—This compound was prepared in the same manner as the allyl acetal described above, except that benzyl alcohol instead of allyl alcohol was used. The yield of product when 1 mole each of vinyl acetate and bromine and 5 moles of benzyl alcohol were used amounted to 475 g. (75%); b. p. 190–195° (2 mm.); $n^{25}D$ 1.5620; d^{25}_4 1.2181.

Anal. Calcd. for $C_{16}H_{17}O_2Br$: Br, 28.8. Found: Br, 28.7.

Benzyl *o*-Tolylacetate from Dibenzylbromoacetal.—The dehydrobromination of this bromoacetal was carried out in the same manner as described above for the diallylbromoacetal. From 321 g. (1 mol) of the bromoacetal was obtained 146 g. of a distillate which after three fractionations gave 110 g. (46%) of benzyl *o*-tolylacetate; b. p. 158–162° (1.5 mm.); $n^{25}D$ 1.4575; d^{25}_4 1.0773.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.01, 79.90; H, 6.81, 6.90.

This ester showed a saponification equivalent of 242 (calcd., 240) and from its saponification was isolated benzyl alcohol, the α-naphthylurethan of which[18] melted at 133–134°, and *o*-tolylacetic acid,[19] m. p. 89–90°.

Preparation of Orthoesters.—The mixed orthoesters were prepared by the addition of the alcohol, R'OH, to the ketene acetal, $CH_2{=}C(OR)_2$. Triethyl orthoethoxyacetate and triethyl orthochloroacetate were prepared from the corresponding nitriles.[8,13] The mono- and dibromo-orthoacetates were prepared by the bromination of ethyl orthoacetate.[8,20] Ethyl orthobenzoate was prepared in the following manner. To a cold (5°) solution of 69 g. (3 atoms) of sodium in 1200 ml. of absolute alcohol in a 2-liter, 3-neck flask, fitted with a reflux condenser, a stirrer and a dropping funnel, was added dropwise 195 g. (1 mol) of benzotrichloride, b. p. 85–87° (10 mm.). After the chloride had been added the ice-bath was removed and the solution stirred for five hours while it came to room temperature. The reaction mixture then was refluxed for eleven hours, after which time it was cooled and the salt filtered off. This salt was washed with ether and the ether washings added to the alcoholic filtrate. The yield of salt was 100 g. (58%). After distillation of the ether and alcohol the remaining orthoester was fractionated through a modified Widmer column. The yield of ester, b. p. 108–112 (13 mm.)[21] amounted to 50 g. (22%).

The properties and analyses of those orthoesters that have not been described previously are listed in Table II.

Pyrolysis of the Orthoesters.—A 0.1-mole sample of the ester and one equivalent of phenol (in runs 3–9) were placed in the glass liner (40-ml. capacity) of a steel bomb and the bomb electrically heated for the time indicated in Table I. After this time the bomb was cooled and opened and its contents fractionated through a 15-cm. modified Widmer column. In the cases of the mixed orthoesters (runs 3–9, Table I) the ROH and CH_3COOR were taken off as one fraction and R'OH and CH_3COOR' as another fraction under atmospheric pressure. The ester was determined in each of these fractions by saponification values and the remainder of the fractions calculated as the alcohol. The ethers, C_6H_5OR and C_6H_5OR', were removed from the remainder of the reaction mixture by fractionation under diminished pressure.

The properties of *n*-butyl-, isobutyl-, isoamyl- and benzyl phenyl ethers correspond to those previously reported in the literature.[22,23,24,25]

s-Butylphenyl ether appears not to have been previously described in the literature. The product isolated from run 5, Table I boiled at 184–185°; d^{25}_4 0.9210; $n^{25}D$ 1.4828.

Anal. Calcd. for $C_{10}H_{14}O$: C, 80.0; H, 9.4. Found: C, 79.9; H, 9.3.

In runs 10–16, Table I, the substituted acetic esters, $XCH_2COOC_2H_5$ and other pyrolysis products were separated by fractional distillation. In these runs no phenol was used. However, one run with ethyl orthoethoxyacetate was carried out in the presence of one equivalent of phenol and both the ethyl ethoxyacetate and the

(16) Reichstein, *Helv. Chim. Acta*, **9**, 799 (1926).
(17) Wohlgemuth, *Ann. chim.*, **2**, 329 (1914).
(18) Bickel and French, This Journal, **48**, 747 (1926).
(19) Radiszewski, *Ber.*, **18**, 1281 (1885).
(20) Beyerstedt and McElvain, This Journal, **59**, 1274 (1937).
(21) Limpricht, *Ann.*, **135**, 87 (1865); Tschitschibabin, *Ber.*, **38**, 563 (1905).
(22) Pinette, *Ann.*, **243**, 32 (1887).
(23) Reiss, *Ber.*, **3**, 779 (1870).
(24) Orndorff and Hopkins, This Journal, **15**, 519 (1893).
(25) Stadel, *Ann.*, **217**, 40 (1883).

phenyl ethoxyacetate[26] along with diethyl ether and phenetole were isolated (*cf.* footnote *a* Table I).

The pyrolyses of the halogen containing orthoesters were carried out in sealed glass tubes as these esters at the temperature of the reaction attacked the inside of the iron bomb. When the glass tube was opened after the pyrolysis there was a considerable release of pressure (ethylene). The remaining liquid material was fractionated. From the ethyl orthobromoacetate pyrolysis (run 15, Table I) the following fractions were collected (a) 0.5 g., b. p. about 20°; (b) 10 g., b. p. 37–38°; (c) 6.6 g., b. p. 61–73°; (d) 11.2 g., b. p. 55–60° (11 mm.). Fraction (a) was acetaldehyde, m. p. of 2,4-dinitrophenylhydrazone, 146–147°; fraction (b) after washing with concentrated sulfuric acid weighed 4 g., and had the density and index of refraction of ethyl bromide; fraction (c) was composed of ethyl alcohol, ethyl acetate and water and saponification indicated the presence of 4.3 g. of the ester; fraction (d) possessed the lachrymatory characteristics of ethyl bromoacetate and its bromine content indicated that it contained 7.7 g. of this ester.

The fractionation of the liquid portion of run 16, Table I, yielded the products listed in footnote (d) of the table, together with 5.8 g. (15%) of ethyl dibromoacetate, b. p. 38–45° (2 mm.).

Pyrolysis of Benzyldiethyl Orthoacetate in the Absence of Phenol.—A 34-g. (0.15 mole) sample of this orthoester was heated at 200° for twenty-four hours, after which time the bomb was opened and the products fractionated. There was the usual pressure of ethylene produced by the pyrolysis. In the first fractionation the following fractions were collected (a) 6.7 g., b. p. 73–78° (740 mm.); (b) 4 g., b. p. 190–210° (740 mm.); (c) 5.6 g., b. p. 104–120° (10 mm.); (d) 1.5 g., b. p. 120–160° (10 mm.). A considerable amount of tar remained after this distillation. Fraction (c) was refractionated and collected as the following fractions (c-1) 0.3 g., b. p. 60–71° (3 mm.); (c-2) 0.4 g., b. p. 72–74° (3 mm.); (c-3) 0.6 g., b. p. 74–75° (3 mm.); (c-4) 0.8 g., b. p. 76–77° (3 mm.); (c-5) 2.3 g., b. p. 78–83° (3 mm.). A 1-g. residue remained after this second fractionation. Fraction c-4 showed the correct carbon and hydrogen content for ethyl *o*-tolylacetate[27] and had $n^{25}D$ 1.4990; d^{25}_4 0.9988.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.1; H, 7.9. Found: C, 74.1; H, 7.8.

Fraction c-5 was saponified and the *o*-tolylacetic acid obtained was identified as its amide.[19] If fractions c-3, c-4 and c-5 are considered to be ethyl *o*-tolylacetate, the yield of this rearrangement product amounts to approximately 14% of the theoretical.

Pyrolysis of Ethyl Orthobenzoate.—A 10-g. sample of this orthoester was gently refluxed (b. p. 220–225°) for six hours under a 40-cm. air condenser, the top of which was connected to a cold trap. After this time 1.6 g. of ether, b. p. 35°, had collected in the cold trap. The ester in the flask was fractionated and separated into 4 g. (60%) of ethyl benzoate and 4 g. of unchanged ethyl orthobenzoate.

(26) Sommelet, *Bull. soc. chim.*, [4] **1**, 368 (1907).

(27) The use of ethyl *o*-tolylacetate has been mentioned in two instances in the literature [Ruzicka and Hosking, *Helv. Chim. Acta*, **13**, 1411 (1930); V. Braun and Zobel, *Ber.*, **56**, 2147 (1923)] but no reference to a description of its properties or to its analysis could be found.

Summary

Ketene diethylacetal and its halogenated derivatives have been found to undergo pyrolysis at 200° with the formation of ethylene and the corresponding ethyl acetate. Ketene dimethylacetal, however, is quite stable at this temperature.

Attempts to prepare ketene diallyl- and dibenzylacetal have resulted in the isolation of the respective rearrangment products, allyl allylacetate and benzyl *o*-tolylacetate.

Ketene acetals have been shown to be the intermediates in the pyrolysis of a variety of orthoesters that have a structure that permits the decomposition to take the course

$$R_2CHC(OR')_3 \longrightarrow R'OH + R_2C{=}C(OR')_2$$

The pyrolysis of mixed orthoesters of the type $CH_3C(OR)_2OR'$ has been studied and the relative tendencies of these esters to eliminate the OR and OR′ groups determined. Diethylbenzyl orthoacetate on pyrolysis yields some ethyl *o*-tolylacetate as the result of the rearrangement of the intermediate ketene ethylbenzylacetal.

While ethyl orthochloroacetate follows the course of the other orthoesters on pyrolysis, the ethyl orthobromo- and orthodibromoacetates give only a small amount of this type of decomposition. The main products that result from the pyrolysis of these bromoesters appear to be the result of an initial loss of the elements of ethyl hypobromite (instead of ethyl alcohol) from the bromoester with the formation of a ketene acetal that contains one less bromine than the original orthoester.

Ethyl orthobenzoate, which has no α-hydrogen, yields the normal ester and diethyl ether on pyrolysis.

MADISON, WISCONSIN RECEIVED JULY 23, 1942

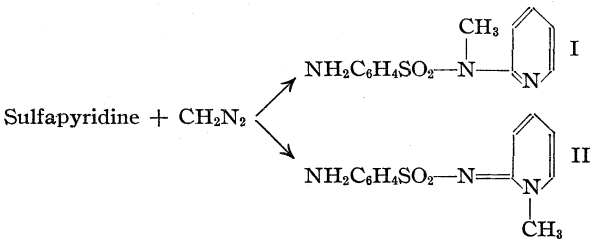
[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, THE JOHNS HOPKINS UNIVERSITY AND THE DEPARTMENT OF BIOLOGY, NEW YORK UNIVERSITY]

Properties of the Nitrogen–Carbon–Nitrogen System in N^1-Heterocyclic Sulfanilamides[1]

BY ROBERT G. SHEPHERD, A. CALVIN BRATTON[2] AND KENNETH C. BLANCHARD

Our chemotherapeutic studies led to the preparation of two types of isomeric derivatives of certain sulfanilamido heterocycles. The structures of these derivatives were determined[3] and direct evidence for the constitution of the parent sulfonamides was obtained by means of ultraviolet absorption measurements.

2-Sulfanilamidopyridine and 2-sulfanilamidothiazole[4] in absolute ether suspension both react rapidly with diazomethane at room temperature to give two methylated isomers. Although 2-(N^4-acetylsulfanilamido)-pyridine[5] under the same conditions reacts much more slowly, a mixture of two products likewise results. This reaction and others throughout this paper will be illustrated by sulfapyridine to represent the behavior of any of the three sulfonamides mentioned above. The



yield-ratio of I:II was 70:30 with the first two substances and 60:40 with the acetyl compound.

The structures of types I and II were determined by three methods. Hydrolysis of both types with 12 *N* hydrochloric acid gave sulfanilic acid and bases whose picrates or hydrochlorides were identified by mixed melting points with the same salts of bases of established structures. The preparation of the N^1-methyl[5] derivative (I) from N^1-methyl-N^4-acetylsulfanilamide and 2-bromopyridine[6] served as a check on the degradation procedure. Structures of type II were also obtained by synthesis from acetylsulfanilyl chloride and the corresponding base of known structure. The products of these two syntheses as well as the amines prepared by de-acetylation were compared by mixed melting points with the corresponding products from the diazomethane reaction.

Alkylation of the sodium salts of sulfapyridine, sulfathiazole and N^4-acetylsulfapyridine with dimethyl sulfate or various alkyl halides was found to produce compounds of type II. The structures of all the products were determined as described above in order to see if the product varied with the alkylating agent. Although our work does not eliminate the possibility of some N^1-alkylation, the main product in each case had structure II. Many of these substances have been erroneously assigned[7] structure I. Our structural conclusions are in direct opposition to the work of Ewins and Phillips, which presumably showed that alkylation of sodium 2-sulfanilamidopyridine produced N^1-alkyl derivatives. They reported the formation of N^1-methyl-2-(N^4-acetylsulfanilamido)-pyridine from condensation of N^1-methyl-N^4-acetylsulfanilamide and 2-bromopyridine by the Ullmann method and from coupling acetylsulfanilyl chloride with 2-methylaminopyridine. The products from both reactions melted at 231° and were de-acetylated to an amine melting at 225°. The corresponding substances from sodium salt methylation were found to have the same melting points and were therefore designated as N^1-methyl derivatives. The acetyl compound which we obtained from the Ullmann synthesis melted at 119.5–120.0° and gave on de-acetylation an amine melting at 86.5–87.0°. We were unable by exhaustive purification to raise these melting points to the values reported. Moreover, our results obtained from acid degradation and from unequivocal syntheses prove conclusively that these products are isomers of

(1) This investigation had been aided by a grant from the John and Mary R. Markle Foundation.

(2) Lalor Foundation Fellow.

(3) After completion of the present work, the proof of structure of certain of the 2-sulfanilamidothiazole derivatives described herein was reported by Druey, *Helv. Chim. Acta*, **24**, 226E (1941), and Jensen, *ibid.*, **24**, 1249 (1941).

(4) The usual names for these substances have been retained although our results indicate that 2-sulfanilimido-1,2-dihydropyridine and 2-sulfanilimido-2,3-dihydrothiazole are perhaps just as correct. They are hereafter referred to as sulfapyridine and sulfathiazole.

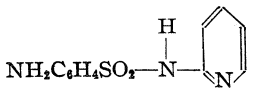
(5) Nomenclature of Crossley, *et al.*, THIS JOURNAL, **60**, 2217 (1938).

(6) Phillips, *J. Chem. Soc.*, 9 (1941).

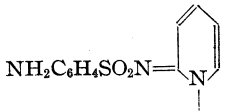
(7) Ewins and Phillips, British Patents 512,145 and 517,272; Phillips, *Nature*, **148**, 409 (1941); Marshall, Bratton, White and Litchfield, *Bull. Johns Hopkins Hosp.*, **47**, 163 (1940); Sprague and Kissinger, THIS JOURNAL, **63**, 578 (1941).

those resulting from sodium salt methylation. Contrary to the evidence of Phillips,[7] we have shown that reaction of sodium sulfapyridine with ethyl chloroacetate or chloroacetamide produces ring nitrogen substitution.

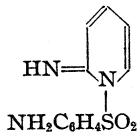
The sulfanilamido heterocycles prepared by coupling acetylsulfanilyl chloride with a heterocyclic amine may have the following three structures (illustrated by sulfapyridine)



III



IV



V

Structure V is eliminated by the preparation from sulfapyridine and sulfathiazole of *two* isomeric methyl derivatives as well as by their proof of structure. Likewise, Phillips' synthesis[6] of sulfapyridine from sulfanilamide and 2-bromopyridine excludes V. Structure IV cannot be eliminated on the basis of the evidence proposed by Crossley, *et al.*[8] The same sodium salt would be expected from III and IV since the negative ion of the salt is capable of resonance. Furthermore, the stability of these sulfonamides to alkaline cleavage is not valid evidence against IV since substituted compounds of that structure (such as II) are very stable compared to the 1-alkyl-2-pyridone imines. A more fundamental objection to the proposed analogy between IV and the 1-alkyl-2-pyridone imines is the fact that a compound having structure IV would first be changed in alkaline solution to a salt of unknown bond structure. The sodium salt alkylation cannot be used as suggested by Druey[3] as evidence of IV in the sulfanilamido heterocycles since this reaction involves a salt whose properties need have no simple relation to the parent.

The results of the diazomethane alkylation may indicate the presence of both III and IV. However, diazomethane cannot be considered a reliable diagnostic reagent for tautomeric equilibria if the reaction mechanism is ionic. In the case of compounds such as the sulfanilamido heterocycles which are capable of yielding a resonating negative ion, an ionic mechanism would invalidate its diagnostic use since the products would be determined by the electronic nature of this ion, obtainable by dissociation of H^+ from both tautomers. Moreover, even if the reaction is non-ionic, the rates of reaction of the tautomers with diazomethane must be approximately equal and be very great compared to the rate of tautomeric rearrangement in order to get a mixture of methyl derivatives comparable to the original tautomeric mixture.

These considerations necessitate a more direct approach to the constitution of such sulfonamides. A distinct difference was observed in the ultraviolet absorption spectra of the methyl derivatives represented by structures I and II, and comparison was made with the spectra of the parent compounds.

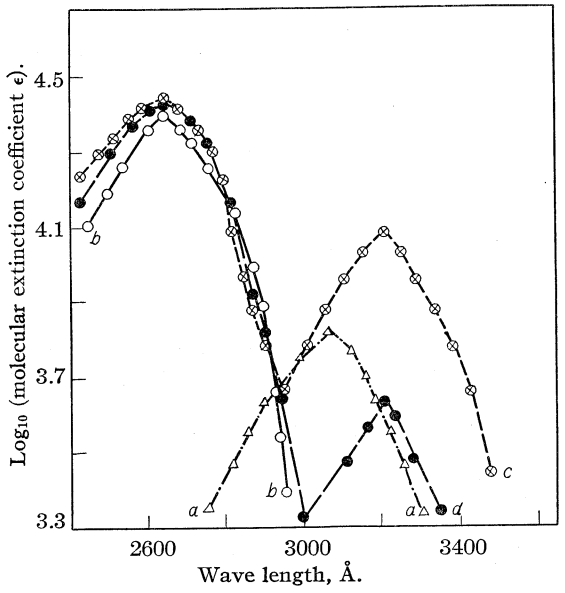


Fig. 1.—(a) Δ, 1-(β-Hydroxyethyl)-2-pyridone imine (Hilger-1 mg. %); (b) O, N^1-methyl-2-(N^4-acetylsulfanilamido)-pyridine (Hilger-0.5 mg. %); (c) ⊗, 1-methyl-2-(N^4-acetylsulfanilimido)-1,2-dihydropyridine (Hilger-0.5 mg. %); (d) ●, 2-(N^4-acetylsulfanilamido)-pyridine (Hilger-1 mg. %). The peaks at 3215 Å. in (c) and (d) had log ε = 3.98 (5.2 mg. %) and 3.7 (8.1 mg. %), respectively, when determined with the Beckman instrument.

The peak at 3215 Å. in Fig. 1 is assigned to the pyridone imine structure since it appears in (a) and (c) and not in (b). Likewise, the maximum at 2600 Å. in Fig. 2 is exhibited only by (a) and (d) which are known to contain the thiazolone imine structure and is not shown by the isomeric constitution (c). Qualitatively, the presence of structure IV in N^4-acetylsulfapyridine, sulfapyri-

(8) Crossley, *et al.*, THIS JOURNAL, **62**, 372 (1940).

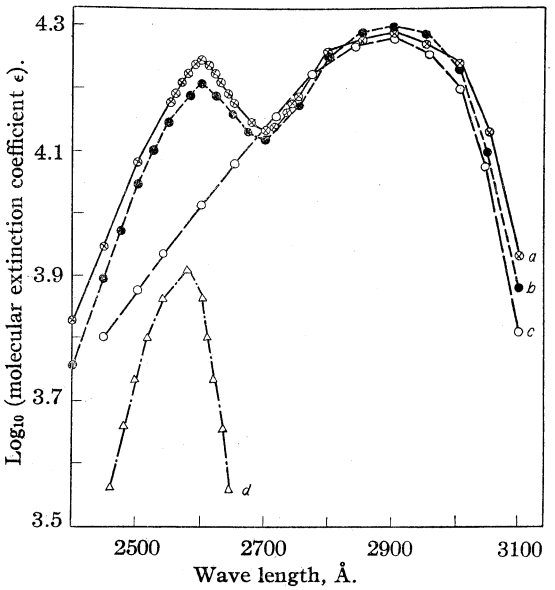


Fig. 2.—(a) ⊗, 3-Methyl-2-sulfanilimido-2,3-dihydrothiazole (Beckman-4.1 mg.%); (b) ●, 2-sulfanilamidothiazole (Beckman-2.6 mg. %); (c) O, N^1-methyl-2-sulfanilamidothiazole (Beckman-4.2 mg. %); (d) Δ, 3-methyl-2-thiazolone imine (Hilger-1 mg. %)—whole curve moved up 0.5 along ordinate axis.

dine and sulfathiazole is demonstrated by the observation of these maxima. The quantitative use of these results to determine the amount of this structure is based on the reasonable assumption that the extinction coefficients of the methyl derivatives are approximately the same as those of the corresponding hydrogen compounds. Therefore, the quantitative conclusions are not rigorous but are estimations subject to the limitations of this assumption.

On the basis of data obtained with the Beckman spectrophotometer, N^4-acetylsulfapyridine contains about 60% of structure IV. The spectra of sulfapyridine and its methyl derivatives show that this sulfonamide is similarly constituted. The maximum at 3215 Å. in 1-methyl-2-sulfanilimido-1,2-dihydropyridine has a slightly lower extinction coefficient ($\log_{10} \epsilon = 3.93$) than in its acetyl derivative. Although these measurements were made on absolute ethanol solutions, we observed the pyridone imine absorption in a few results on 95% ethanol or aqueous solutions. This is confirmed by Scudi's curve[9] for sulfapyridine in water which showed the characteristic pyridone imine maximum at about 3200 Å. The amount of this absorption indicates that a considerable proportion of tautomer IV is also present in aqueous solution. The absorption of sulfathiazole at 2600 Å. corresponds to the presence of about 90% of structure IV. The curve for this substance is the same as that found by Bergeim, *et al.*,[10] who also observed the 2600 Å. maximum in the 4-methyl and ethyl derivatives.

The region of absorption of the pyridine and thiazole rings has not been investigated at present. Observation of the absorptions of these rings in sulfapyridine and sulfathiazole would be necessary to prove the presence of structure III. The available data prove the presence of IV but do not permit one to decide whether these substances have that structure entirely or are tautomeric mixtures of both III and IV.

TABLE I

In Vitro ACTIVITY RATIOS, USING THE MACLEOD STRAIN OF *E. coli*

Compound		Activity ratio[a]
2-Sulfanilamidopyridine		1[b]
N^1-Methyl-2-sulfanilamidopyridine		1/128
( )-2-sulfanilimido-1,2-dihydropyridine	1-Methyl-	1/4
	1-(β-Hydroxyethyl)-	1/128
	1-Carboxymethyl-	1/256
2-Sulfanilamidothiazole		1[c]
N^1-Methyl-2-sulfanilamidothiazole		1/1024
( )-2-sulfanilimido-2,3-dihydrothiazole	3-Methyl-	1/16
	3-(β-Hydroxyethyl)-	1/128

[a] Based on the relative minimal inhibitory concentrations using an end-point reading after forty-eight hours incubation at 37°. [b] Taken as unity; actual min. inhib. concn. = 0.16 mg.%. [c] Taken as unity; actual min. inhib. concn. = 0.04 mg.%.

Chemotherapeutic Activity.—Table I shows the *in vitro* activity of these sulfonamides tested against *E. coli* in a synthetic medium by the method described in detail elsewhere.[11]

The *in vivo* activity of the ring N-methyl derivatives of sulfapyridine and sulfathiazole was determined in mice infected with β-hemolytic streptococcus (strain C 203) using the drug-diet method.[12] On the basis of blood concentrations, both were about equal to sulfanilamide in activity. Since it has been shown[13] that sulfapyridine and sulfathiazole are about equal to sulfanilamide in this infection, the two ring N-methyl compounds are as active as the parents. The ring N-(β-hydroxyethyl) derivatives appear to be as active as the

(9) Scudi, *Science*, **91**, 486 (1940).

(10) Bergeim, *et al.*, THIS JOURNAL, **62**, 1873 (1940).

(11) White, Litchfield and Marshall, *J. Pharmacol.*, **73**, 104 (1941).

(12) Litchfield, White and Marshall, *ibid.*, **67**, 437 (1939); **69**, 89 (1940).

(13) Marshall, Litchfield, White, Bratton and Shepherd, *ibid.*, in press.

TABLE II

Compound	M. p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Obs.	Hydrogen, % Calcd.	Hydrogen, % Obs.	Nitrogen, % Calcd.	Nitrogen, % Obs.	Colorimetric factor[a] Calcd.	Colorimetric factor[a] Obs.	Water soly. at 37° mg. %
N^1-Methyl-2-sulfanilamidopyridine	86.5–87.0[b]	$C_{12}H_{13}N_3O_2S$	54.74	54.76	4.98	4.82	15.96	15.94	0.654	0.658	136
( )-2-sulfanilimido-1,2-dihydropyridine											
1-Methyl-	232–3	$C_{12}H_{13}N_3O_2S$	54.74	54.68	4.98	4.85	15.96	15.90	.654	.670	112
1-Benzyl-	235[c]	$C_{18}H_{17}N_3O_2S$	63.70	64.00	5.05	5.04	12.38	12.18	.511	.511	
1-Carboxymethyl-	165 (dec.)	$C_{13}H_{13}N_3O_4S$	50.81	50.75	4.26	4.37	13.67	13.59	.560	.570	754
1-(β-Hydroxyethyl)-	184–5	$C_{13}H_{15}N_3O_3S$	53.23	53.41	5.15	5.18	14.33	14.35	.587	.630	440
N^1-Methyl-2-sulfanilamidothiazole	111–2	$C_{10}H_{11}N_3O_2S_2$	44.60	45.00	4.12	4.19	15.60	15.36	.639	.618	57
( )-2-sulfanilimido-2,3-dihydrothiazole											
3-Methyl-	250–1	$C_{10}H_{11}N_3O_2S_2$	44.60	44.49	4.12	4.13	15.60	15.54	.639	.656	22
3-(β-Hydroxyethyl)-	159–60	$C_{11}H_{13}N_3O_3S_2$	44.13	44.42	4.38	4.35	14.04	14.36	.575	.600	169

[a] Ratio of color produced by a compound to the color from an equal weight of sulfanilamide on diazotization and coupling according to Bratton and Marshall, *J. Biol. Chem.*, **128**, 537 (1939). [b] Ewins and Phillips (ref. 7) reported 225°. [c] Ewins and Phillips (ref. 7) found 179°.

unsubstituted sulfonamides against this streptococcus infection; the quantitative data have been reported elsewhere.[13]

When tested in a pneumococcus infection (Neufeld type I) of mice, both N^1-methyl derivatives (Table I) appeared to be practically inactive and quite toxic. On the other hand, the ring N-methyl isomers were active, less toxic than the N^1-methyl compounds and apparently less active than the parents. The inactivity of N^1-methyl-2-sulfanilamidothiazole with respect to its ring N isomer was also observed in duck malaria.[14]

Experimental Section[15]

Methylation of Sulfonamides with Diazomethane.—Sulfapyridine and sulfathiazole react rapidly enough with diazomethane to permit distillation of this reagent into a stirred mixture of the sulfonamide and ether. This continuous procedure avoids the danger of handling 10-g. quantities of diazomethane.

Diazomethane (7.5 g.) was distilled[16] into a stirred mixture of 0.25 mole of sulfonamide (200 mesh) and 75 cc. of absolute ether at 15–20°. The evolution of nitrogen proceeded during the addition of this reactant and the mixture was subsequently stirred until this evolution ceased. After warming to the boiling point, the reaction mixture was filtered and the insoluble material extracted twice with hot ether containing 3% ethanol. The residue from this extraction was shaken with 2 *N* sodium hydroxide to remove starting material, and the residual insoluble ring-nitrogen derivative was recrystallized from 6 *N* acetic acid. The original ether filtrate and the ether extracts were combined and evaporated to a sirup which crystallized after cooling and seeding. This was suction-filtered and carefully washed dropwise with methanol and absolute ether. Methanol was used for recrystallization of the N^1-methyl derivative thus obtained. The yield of methylated products was 50–80% of the sulfonamide, depending, primarily, on its state of subdivision. The yield-ratio of N^1-methyl to ring N-methyl derivative was about 70:30. This ratio was changed only slightly by methylation of 2-sulfanilamidopyridine immediately after liberation from its sodium salt at about −100°.

The lower order of reactivity of 2-(N^4-acetylsulfanilamido)-pyridine with diazomethane under these conditions necessitates using smaller quantities than above. Since the spontaneous inflammability of the vapors was regularly observed, the use of large quantities is somewhat dangerous. Isolation of the two products was carried out in essentially the same way as above. The yield-ratio of N^1-methyl to ring N-methyl derivative was about 60:40. N^1-methyl-2-(N^4-acetylsulfanilamido)-pyridine: m. p. 119.5–120.0°; *colorimetric factor*, calcd., 0.564, obs., 0.557. 1-Methyl-2-(N^4-acetylsulfanilimido)-1,2-dihydropyridine: m. p. 239–40°; *colorimetric factor*, calcd., 0.564, obs., 0.555.

The N^1-methyl derivatives of sulfapyridine, acetylsulfapyridine and sulfathiazole are all quite soluble in methanol, ethanol and ether containing 3% ethanol; their isomers are only slightly soluble.

Methylation of Sodium Sulfonamides with Dimethyl Sulfate.—Four-tenths of a mole of sulfonamide was alkylated in alkaline solution as described by Ewins and Phillips.[7] The product was recrystallized from 300–400 cc. of 6 *N* acetic acid with charcoal decolorization, washed with 20% ethanol and dried at 120°; yield 140–50%. Recrystallization from ethanol resulted in further purification.

Increasing the amount of dimethyl sulfate used in one step or re-treating the reaction filtrate did not increase the yield of desired product but increased the production of an alkali-insoluble gum. An important constituent of this gum was shown to be the result of methylation of the arylamine group as well as the heterocyclic nitrogen.

Preliminary tests demonstrated that these conditions do not give satisfactory methylation of certain sulfanilamido heterocycles derived from imidazole, pyrimidine and pyrazine.

Sodium Sulfonamide Benzylation.—The procedure of Ewins and Phillips[7] was modified slightly by the use of a 75% ethanol reaction mixture which resulted in an increased yield. 1-Benzyl-2-(N^4-acetylsulfanilimido)-1,2-dihydropyridine; m. p. 213–4°; *colorimetric factor*, calcd., 0.452, obs., 0.458.

Acetic Acid Derivatives of 2-Sulfanilamidopyridine.—To 48 g. of sodium 2-sulfanilamidopyridine in 55 cc. of 50% ethanol was added a solution of 40 cc. of ethyl chloroacetate in 95 cc. of 95% ethanol and the mixture refluxed for one hour, then cooled and precipitated with ice and water.

(14) Marshall, Litchfield and White, *J. Pharmacol.*, **75**, 89 (1942).
(15) All the melting points recorded are corrected.
(16) Hellerman and Newman, THIS JOURNAL, **54**, 2864 (1932).

After filtration the solid was shaken thoroughly with ether, then with 2 *N* sodium hydroxide and finally washed well with water. The yield of 1-carbethoxymethyl-2-sulfanilimido-1,2-dihydropyridine was 18 g; m. p. 200.5–201.0° after recrystallization from absolute ethanol or methanol. *Colorimetric factor:* calcd., 0.514; obs., 0.534. 1-Carbethoxymethyl - 2 - (N^4 - acetylsulfanilimido) - 1,2 - dihydropyridine obtained from a similar reaction melted at 212–3°; *colorimetric factor:* calcd., 0.457; obs., 0.463.

Five grams of the first ethyl ester and 8.9 cc. of 11% potassium hydroxide in 98% methanol were refluxed together for twenty minutes. After acidification with 1.1 cc. of 12 *N* hydrochloric acid, the potassium chloride was separated from the hot solution. The crystals of 1-carboxymethyl-2-sulfanilimido-1,2-dihydropyridine resulting from the cooled filtrate were suction-filtered and washed free of chloride ion with water. A monohydrate melting at 97–98° (sealed tube) was formed on recrystallization from water; *colorimetric factor:* calcd., 0.529; obs., 0.529.

1 - Carbamidomethyl - 2 - sulfanilimido - 1,2 - dihydropyridine was prepared by reaction of the sulfonamide in alkaline solution with chloroacetamide; m. p. 230° (dec.); *colorimetric factor:* calcd., 0.562; obs., 0.555. Alkaline hydrolysis of the amide group produced an acid identical to that obtained by the same treatment of the ester described above.

Reaction of Sodium Sulfonamides with Ethylene Chlorohydrin.—The anhydrous sodium salt of N^4-acetylsulfapyridine or N^4-acetylsulfathiazole was refluxed for thirty minutes in an oil-bath at 130° with five moles of ethylene chlorohydrin. The mass was then cooled, powdered, washed with ether, dried and washed with dilute sodium hydroxide, followed by water. The crude products were recrystallized from 6 *N* acetic acid with the addition of charcoal. 1-(β-Hydroxyethyl)-2-(N^4-acetylsulfanilimido)-1,2-dihydropyridine; m. p. 217–8°. *Anal.* Calcd. for $C_{15}H_{17}N_3O_4S$: C, 53.72; H, 5.11; N, 12.53. Obs.: C, 53.67; H, 5.26; N, 12.64. 3-(β-Hydroxyethyl)-2-(N^4-acetylsulfanilimido)-2,3-dihydrothiazole; m. p. 231–2° (dec).

The former substance was de-acetylated by refluxing for two hours with 2 moles of 1 *N* alcoholic sodium hydroxide. After concentrating on the steam-bath, the crystalline mass was washed with a little water and recrystallized from water. The latter compound was de-acetylated by boiling thirty minutes with 6 *N* hydrochloric acid (3 cc. per g.), precipitated by neutralization and recrystallized from alcohol with charcoal decolorization. The yield of both hydrolysis products was about 50%, based on the original sodium salts.

Structure Determination by Acid Degradation.—All of these sulfanilamide derivatives were hydrolyzed by heating one to two hours in a steam-bath with 10 moles of 12 *N* hydrochloric acid. After cooling, the precipitated sulfanilic acid was collected and recrystallized from dilute hydrochloric acid. It was identified by its decomposition point, strong acidity in the absence of chloride ion and quantitative diazotization. The acid filtrate from the hydrolysis was concentrated and the heterocyclic base was either allowed to crystallize as the hydrochloride or sodium acetate was added to *p*H 4 and the base precipitated as a picrate in 80–90% yield. The picrates were recrystallized from water or ethanol and then compared with the salts of bases whose structures had been established in the literature indicated. The melting points of the latter salts are recorded in Table III. These values are the same as those found for the picrates from hydrolysis and for the mixed melting points of the two groups.

TABLE III

DETERMINATION OF STRUCTURE

For	By degradation Picrate, m. p., °C.	By synthesis NH_2R,[a] m. p., °C.	By synthesis CH_3CONHR,[b] m. p., °C.
N^1 - Methyl - 2 - sulfanilamidopyridine	194–5[c]	86.5–87	119.5–120[d]
N^1 - Methyl - 2 - sulfanilamidothiazole	207–8[e]		
( )-2-Sulfanilimido-1,2-dihydropyridine			
1-Methyl-	205–6[f]	232–233	239–240[g]
1-Benzyl-	153–4[h,c]	235	213–214[g]
1-Carboxymethyl-	213[i]		
1-Carbamidomethyl-	213[i]		
1-(β-Hydroxyethyl)-	172–3[j]		
( )-2-Sulfanilimido-2,3-dihydrothiazole			
3-Methyl-	199–200[k]	250–251	272–273[g]
3-(β-Hydroxyethyl)-	160–162		

[a] NH_2R = the free amine of the sulfonamides. [b] CH_3CONHR = the N^4-acetyl derivatives of the sulfonamides. [c] Chichibabin, *Ber.*, **54,** 814 (1921). [d] Prepared according to Ewins and Phillips, British Patent 512,145. [e] Näf, *Ann.*, **265,** 113 (1891). [f] Chichibabin, *et al.*, *Ber.*, **54B,** 814–822 (1921). [g] Prepared by coupling acetylsulfanilyl chloride with the heterocyclic base. [h] The hydrochlorides were also compared: m. p. and mixed m. p. 207–208°. [i] Melts with decomposition; Chichibabin, *ibid.*, **57,** 2092 (1924); Reindel and Rauch, *ibid.*, **58,** 393 (1925); **59,** 2921 (1926). [j] Knunyantz, *ibid.*, **68B,** 397 (1935); Gautier, *Compt. rend.*, **196,** 1124 (1933). [k] This base is more conveniently prepared using dimethyl sulfate rather than methyl iodide; *cf.* Näf, ref. *e*.

The bases necessary for this comparison were synthesized by available methods, with the exception of 2-imino-3-(β-hydroxyethyl)-2,3-dihydrothiazole which was prepared as follows: In a large test-tube, a mixture of 4 g. of 2-aminothiazole and 8.6 g. of iodoethyl acetate was heated gradually in an oil-bath to about 130°, stirring the mixture constantly with a thermometer. Suddenly the temperature began to rise and the tube was placed in a cold oil-bath to prevent the temperature from exceeding 180°. After the reaction had subsided, the mixture was heated for thirty minutes at 150°, cooled and taken up in 15 cc. of hot absolute ethanol. The crystalline 2-imino-3-acetoxyethyl-2,3-dihydrothiazole hydroiodide, obtained on chilling, was recrystallized several times from glacial acetic acid; yield, 1.9 g.; m. p. 153.5–154.5°. *Anal.* Calcd. for $C_7H_{11}N_2O_2SI$: C, 26.76; H, 3.53. Found: C, 26.91, H, 3.41; m. p. of picrate 164–165° (recryst. from glacial acetic acid).

After hydrolyzing the ester by refluxing for thirty minutes with 1 *N* hydrochloric acid, the picrate was formed by adding picric acid to the concentrated and buffered hydrolyzate; m. p. 159.5–161.0° (recryst. from methanol). *Anal.* Calcd. for $C_{11}H_{11}N_5O_9S$: C, 35.39, H, 2.97. Found: C, 35.66, H, 3.04.

Structure Determination by Alkaline Degradation.—When 1 - (β - hydroxyethyl) - 2 - sulfanilimido - 1,2 - dihydropyridine was hydrolyzed by boiling for five hours with 6 *N* sodium hydroxide (10 cc. per g.), sulfanilamide and 1-(β-hydroxyethyl)-2-pyridone were obtained. It was found that the latter is dimorphic: m. p. 84–85° by rapid crystallization of the fused substance; m. p. 93.5–95° by slow crystallization from dilute solution. This accounts for the discrepancies in melting point which have been reported.[17]

It was impossible to decompose sulfapyridine under similar alkaline hydrolytic conditions. In this connection, it should be pointed out that in the short time required to completely decompose the alkyl pyridone imines with alkali, no appreciable cleavage of the ring N derivatives (II) of sulfapyridine was observed.

Structure Determination by Synthesis.—Coupling acetylsulfanilyl chloride with the 1-alkyl-2-pyridone imines[18] and 3-alkyl-2-thiazolone imines yields sulfonamides whose point of substitution is definitely established. This is also true for the product obtained by reacting N^1-methyl-N^4-acetylsulfanilamide with 2-bromopyridine according to the method of Ewins and Phillips.[7] The acetyl compounds prepared by these routes and the corresponding amines resulting from de-acetylation were proved to be identical with those prepared by alkylation of the acetylsulfanilamido and sulfanilamido heterocycles. The melting points are recorded in Table III; the mixed melting points were identical.

1-Carboxymethyl-2-sulfanilimido-1,2-dihydropyridine.—Having proved the position of substitution, there still remain two possible structures differing in the position of a hydrogen atom. One would be a carboxymethylpyridone imine derivative; the other, an aminopyridine betaine derivative. On methylation, the former would presumably give a methyl ester; the latter, an N-methyl derivative. On treating the compound in question with diazomethane, there was obtained a neutral substance which without purification contained 99.2% of an alkali-labile ester. Repeated treatment of the acid with dimethyl sulfate in alkaline solution gave no evidence of N^1-methylation. Although these results are not entirely conclusive, they indicate that the carboxymethyl-pyridone imine structure is probably correct.

Ultraviolet Absorption Measurements.—These data were obtained on absolute ethanol solutions with the aid of two instruments: a medium Hilger "Spekker" spectrograph employing a tungsten-steel arc as the light source and a 4-cm. cell; a Beckman quartz spectrophotometer with a hydrogen-discharge tube as the light source and a 1-cm. cell.

(17) Knunyantz, *Ber.*, **68B**, 397 (1935); *cf.* Gautier, *Compt. rend.*, **196**, 1124 (1933).

(18) Polyakova and Kirsanov, *cf. C. A.*, **35**, 2146 (1941).

Acknowledgment.—We are indebted to Drs. E. K. Marshall, Jr., J. T. Litchfield, Jr., and H. J. White for the determination of the chemotherapeutic activity of these substances. The ultraviolet absorption measurements with the Beckman spectrophotometer were obtained through the courtesy of the Department of Physiological Chemistry of the Johns Hopkins University. We are grateful to the American Cyanamid Company for the sulfapyridine and 2-aminopyridine, and to E. R. Squibb and Sons for the sulfathiazole used in this investigation.

Summary

1. 2-Sulfanilamidopyridine, 2-sulfanilamidothiazole and 2-(N^4-acetylsulfanilamido)-pyridine react with diazomethane to give both N^1-methyl and ring N-methyl derivatives, the ratio of products being 70:30 for the first two compounds and 60:40 for the last.

2. Alkylation of the sodium salts of these sulfonamides is shown to produce ring N-alkyl derivatives in all the cases examined.

3. The structures of the products from these two reactions have been conclusively determined by both degradative and synthetic methods.

4. The dimorphism of 1-(β-hydroxyethyl)-2-pyridone is demonstrated.

5. A method is proposed for determination of the constitution of the sulfanilamido heterocycles based on the comparison of the ultraviolet absorption spectra of the parent sulfonamide with the spectra of its two isomeric N-methyl derivatives. The available data indicate the presence of large amounts of the pyridone imine structure in sulfapyridine and N^4-acetylsulfapyridine solutions and of the thiazolone imine structure in sulfathiazole solution.

6. Chemotherapeutic results show that the ring nitrogen derivatives of sulfapyridine and sulfathiazole are approximately as active as the parent sulfonamides, while the isomeric N^1 compounds are practically inactive.

BALTIMORE, MD. RECEIVED JULY 21, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF EX-LAX, INC.]

Carvacrolphthalein

BY MAX H. HUBACHER

According to Curt Ehrlich,[1] carvacrolphthalein has a melting point of 246–247° and produces a prolonged purgative effect as compared with phenolphthalein. The compound obtained in this Laboratory was different in these properties. It melted at 294° and was devoid of laxative activity, showing a potency of under 0.05.[2]

It is believed that Ehrlich's compound of melting point 246–247° was thymolphthalein, the melting point of which is described as being 246–247°[3] and that he probably used impure carvacrol containing a substantial amount of thymol in the preparation of his compound. When a mixture of equal parts of carvacrol and thymol was condensed with phthalic anhydride and the crude product purified by crystallizations, then thymolphthalein was obtained.

Thymolphthalein was also prepared for comparison and likewise found to lack laxative activity,[2] though it is also stated to be a laxative compound.[1] It forms in much higher yields than carvacrolphthalein under the same experimental conditions. Thymolphthalein was found to have a melting point six degrees higher than the one given in the literature.[3]

The diacetate is described here because it has never been mentioned in the literature.

Experimental[4]

Carvacrolphthalein (I).—Zinc chloride as a condensing agent gave only traces of I. The yields on I when using stannic chloride were quite low and various changes such as quantities of condensing agent, temperature, etc., did not improve yields. Technical carvacrol of solidification point −11 to −10° gave the same yields as Eastman Kodak Co. carvacrol of crystallizing point −2°.

15.0 g. (0.1 mole) of carvacrol, 7.4 g. (0.05 mole) of phthalic anhydride and 15.0 g. of anhydrous stannic chloride were stirred for one hour at 100°. Unreacted carvacrol was steamed out and the residual phthalic acid was removed by extraction with hot water. The semi-solid brown crude I was crystallized directly from acetic acid (1 g. in 5 ml.) yielding 1.78 g. of m. p. 264–275° (8%). Further crystallizations from acetic acid (1 g. in 30 ml.) gave colorless crystals of m. p. 293.5–294.7°.

Anal. Calcd. for $C_{28}H_{30}O_4$: C, 78.11; H, 7.02; mol. wt., 430. Found: C, 78.30; H, 6.86; mol. wt., 415 ± 44 (Rast, in camphor).

Carvacrolphthalein turns from colorless to blue at a *p*H of 9.5 to 10.5. The solution of I in concd. sulfuric acid is purple-red. The crystals of I are not easily affected by 0.1 *N* sodium hydroxide, but after wetting them first with ethanol, they dissolve quite readily.

Diacetylcarvacrolphthalein (II).—This compound was prepared by refluxing for one hour 2.15 g. of I, 2.0 g. of acetic anhydride, 10 ml. of acetic acid and one drop of concd. sulfuric acid; 2.49 g. (96%) was obtained. The pure compound recrystallized from ethanol (1 g. in 33 ml.) formed cubes and melted at 217.8–219.7°.

Anal. Calcd. for $C_{32}H_{34}O_6$: C, 74.68; H, 6.66; mol. wt., 514. Found: C, 74.97; H, 6.82; mol. wt., 471 ± 13 (Rast, in camphor), 511 ± 40 (Signer method[5]).

Carvacrolphthalein Dimethyl Ether (III).—This compound was prepared by refluxing for ten hours 4.30 g. of I, 2.8 g. of potassium carbonate, 50 ml. of acetone and 3.7 ml. of methyl iodide. The crude was purified by crystallizations from ethanol as well as by sublimation at 180° and 50 microns. The pure III melts partially at 202°, then solidifies and melts again at 211.5–212.2°. III dissolves in concd. sulfuric acid with red color in transmitted light and violet in reflected light.

Anal. Calcd. for $C_{30}H_{34}O_4$: C, 78.57; H, 7.47; -OCH_3, 13.52. Found: C, 78.93; H, 7.77; -OCH_3, 13.29.

Thymolphthalein (IV).—30.0 grams (0.2 mole) of thymol and 14.8 g. (0.1 mole) of phthalic anhydride were heated to 95°. While stirring, 25 g. of anhydrous stannic chloride was then added over a period of thirty minutes. The reaction was continued for another thirty minutes at 96–103° (oil-bath temperature 99–104°). The reaction mass was taken up in hot 0.1 *N* hydrochloric acid, filtered and washed. The crude IV was finally dissolved in 700 ml. of acetic acid and 450 ml. distilled off from the filtrate: 26.6 to 30.1 g. (62–70% yield) of m. p. 247–252° was obtained. The pure IV obtained by recrystallization from acetic acid (1 g. in 9 ml.) melted at 252.4–253.1° (lit. 246–247°[3]).

When in place of pure thymol a mixture of 15.0 g. of technical carvacrol and 15.0 g. of pure thymol was used and the crude recrystallized twice from acetic acid, it melted at 243–245°. Further crystallization from the same solvent did not increase the melting point, but after two more crystallizations from ethanol, it melted at 251.8–252.4° (no depression when mixed with pure IV).

Thymolphthalein Diacetate (V).—A mixture of 2.15 g. of IV, 2.0 g. of acetic anhydride, 10 ml. of acetic acid and one drop of sulfuric acid was refluxed for one hour: 2.54 g. (99%) of m. p. 150–153° was obtained. Recrystallized twice from ethanol (1 g. in 8.5 ml.) it melted at 153.0–153.6°.

(1) Curt Ehrlich, German Patent 225,983 in *Friedlaender*, **10**, 1298 (1910).

(2) S. Loewe and M. H. Hubacher, *Arch. intern. pharmacodynamie*, **65**, 303 (1941). It was ineffective in the Rhesus monkey even in doses 20 times the Median Laxative Dose of U. S. P. phenolphthalein.

(3) R. Willstätter and E. Waldschmidt, *Ber.*, **56**, 488 (1923), footnote.

(4) All melting points are corrected.

(5) E. P. Clark, *Ind. Eng. Chem., Anal. Ed.*, **13**, 820 (1941). Acetone was used as a solvent and azobenzene as a standard.

Anal. Calcd. for $C_{32}H_{34}O_6$: C, 74.68; H, 6.66; -CO-CH_3, 16.71; mol. wt., 514. Found: C, 74.88; H, 6.71; -$COCH_3$, 16.43; mol. wt., 488 ± 7 (Rast, in camphor).

Thymolphthalein Dimethyl Ether (VI).—4.3 g. (0.01 mole) of IV, 3.73 ml. (0.06 mole) of methyl iodide, 50 ml. of acetone and 2.76 g. (0.02 mole) of potassium carbonate were refluxed for ten hours. The crude was recrystallized from ethanol (1 g. in 24 ml.) yielding 4.03 g. (88%) of m. p. 175–176°. After two more crystallizations, it melted at 175.9–176.7°.[6]

(6) Lin Che Kin, *Ann. chim.*, **13**, 344 (1940), reports m. p. 177°. He prepared VI by condensing the methyl ether of thymol with the methyl ether of the 2-thymoylbenzoic acid in the presence of aluminum chloride.

Summary

Carvacrolphthalein was shown to melt at 294° and to be devoid of laxative effect. The melting point of 247° given in the literature for this compound is wrong. Thymolphthalein was prepared with a melting point 6° higher than reported heretofore. The diacetyl derivative and the dimethyl ether of both compounds were prepared.

BROOKLYN, N. Y. RECEIVED JULY 6, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL CHEMISTRY, PURDUE UNIVERSITY AGRICULTURAL EXPERIMENT STATION]

Isolation of Lupeol from the Osage Orange (*Maclura pomifera* Raf.)[1]

BY LYLE JAMES SWIFT AND E. D. WALTER

In the isolation of osajin by Walter, Wolfrom and Hess[2] the dried osage oranges were first extracted with petroleum ether to remove latex and other interfering substances. In this paper the isolation of lupeol from this extract is described, and its crystallographic optical properties recorded. A wax-like material, to be described later, was also obtained.

Lupeol was discovered by Schulze[3] and described by Likiernik[4] and has since been isolated from several latex bearing plants. Ruzicka[5] recently proposed a structure for lupeol.

A characteristic reaction of lupeol is the red color it gives with concentrated sulfuric acid and acetic anhydride when in chloroform solution. This test also is given by the dried latex of the osage orange.

Acknowledgment.—We are indebted to Dr. M. L. Wolfrom, Department of Chemistry, Ohio State University for some of the extract used in this work.

Experimental

Isolation of Lupeol. The dried, ground osage oranges were completely extracted with low boiling petroleum ether. The extract was concentrated and passed through an aluminum silicate adsorbent described by Kraybill, *et al.*,[6] which removed the wax-like material. The concentrated petroleum ether extract was saponified with twice its volume of 95% ethanol saturated with potassium hydroxide. The mixture was diluted with water and extracted with ether. The ether was evaporated and the residue was mixed with about an equal weight of Nuchar W. The mixture was extracted in a Soxhlet apparatus with ether which was subsequently evaporated. Repeated crystallizations from acetone and then from 85% ethanol gave a product melting at 208–211°. Final purification was effected through formation of the acetate and saponification of this to get lupeol melting at 214–215°; yield, 5.1 g. of crude lupeol or 2.3 g. of pure lupeol from 1 kg. of dried osage oranges.

Anal. of lupeol. Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81; mol. wt., 426.7. Found: C, 84.45; H, 11.88; mol. wt. (freezing point depression using stearic acid), 448, 458; $[\alpha]^{22}D$ +27.63° ($CHCl_3$, c = 3.926). Ruzicka (7) obtained +27.2°.

Lupeol acetate was prepared by the method of Ruzicka[7]; yield, 1.88 g. (from 2.16 g. of lupeol) m. p. 216–216.5°. Ruzicka[7] reported a m. p. of 215–217°.

Anal. of lupeol acetate. Calcd. for $C_{30}H_{49}(OCOCH_3)$: C, 81.99; H, 11.18; mol. wt., 46.78. Found: C, 81.79; H, 11.29; mol. wt. (saponification equivalent), 469.5; $[\alpha]^{25}D$ +41.95° ($CHCl_3$, c = 1.652). Ruzicka obtained +40.7°.

Lupeol benzoate was prepared by the method of Ruzicka.[7] Lupeol (1.8 g.) yielded 1.57 g. of the benzoate m. p. 263–265°.

Anal. of lupeol benzoate. Calcd. for $C_{30}H_{49}(OCOC_6H_5)$: C, 83.72; H, 10.25; mol. wt., 530.8. Found: C, 83.59; H, 9.80; mol. wt. (saponification equivalent), 543; $[\alpha]^{25}D$ +61.36° ($CHCl_3$, c = 0.9908). Ruzicka obtained +60.9°.

(1) A portion of a thesis to be submitted by Lyle J. Swift to the Faculty of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Journal Paper No. 37, Purdue University Agricultural Experiment Station.

(2) E. D. Walter, M. L. Wolfrom and W. W. Hess, THIS JOURNAL, **60**, 574 (1938).

(3) E. Schulze and E. Steiger, *Landw. Vers.-Sta.*, **36**, 391 (1889).

(4) A. Likiernik, *Z. physiol. Chem.*, **15**, 415 (1891).

(5) L. Ruzicka and M. Brenner, *Helv. chim. acta.*, **23**, 1325 (1940).

(6) H. R. Kraybill, P. H. Brewer and M. H. Thornton, U. S. Patent No. 2,174,177, Sept. 26, 1939.

(7) L. Ruzicka and M. Brenner, *Helv. chim. acta*, **22**, 1523 (1939).

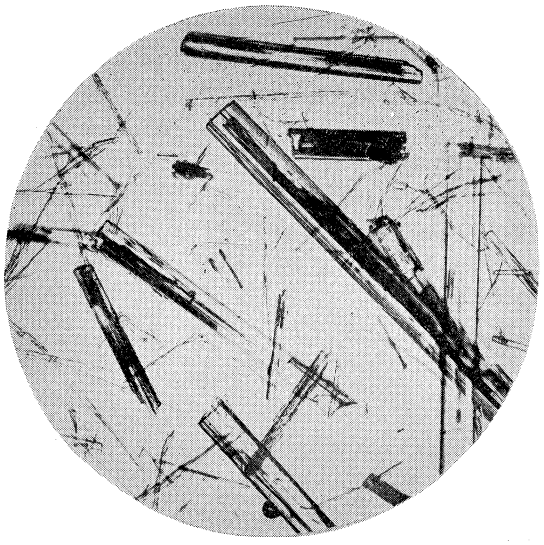


Fig. 1.—Lupeol (×60).

Crystallographic Optical Properties

Lupeol.—In parallel polarized light (crossed nicols), the extinction is parallel; the elongation is negative. In convergent polarized light (crossed nicols) an optic normal interference figure is found on faces showing brightest white color. Refractive indices: n_α = 1.551, found lengthwise; n_β = indet.; n_γ = 1.565, found crosswise (both values ±0.003) (see Fig. 1).

Lupeol Acetate.—In parallel polarized light (crossed nicols) many faces show practically no extinction, while a few show red and blue interference colors and parallel extinction. In convergent polarized light (crossed nicols) a biaxial, optic axis figure is common. The optic sign is negative. Refractive indices: n_α = 1.540; n_β = 1.567 (both ±0.003); n_γ = indet.

Lupeol Benzoate.—In parallel polarized light (crossed nicols) the extinction is parallel; the elongation is negative. Many of the rods show red, green and yellow interference colors. In convergent polarized light (crossed nicols) biaxial interference figures are common. The optic sign is positive. Refractive indices: n_α = 1.565 found lengthwise on rods with red and blue interference colors; n_β = 1.567 found on fragments showing an optic axis interference figure; n_γ = 1.634 found crosswise, all ±0.003.

Summary

1. Lupeol has been isolated from the osage orange. Apparently it is a constituent of the latex.

2. Some crystallographic optical properties are presented for lupeol, lupeol acetate and lupeol benzoate.

LAFAYETTE, INDIANA RECEIVED JULY 15, 1942

[CONTRIBUTION FROM KENT CHEMICAL LABORATORIES, UNIVERSITY OF CHICAGO]

Surface Tensions, Densities and Parachors of the Aliphatic Nitroparaffins

BY G. E. BOYD AND L. E. COPELAND

Introduction

The synthesis and chemical properties of the aliphatic nitroparaffins previously have attracted considerable attention.[1-4] In view of the unusually high dipole moments shown (CH_3NO_2 = 3.13) by the molecules of these substances, it is of interest to determine the effect of this property upon the surface tension and the parachor. Since these liquids are extremely polar the possibility of two or more molecular species arises. Questions of this type sometimes may be settled by surface tension investigations.[5]

In the study reported, the variation of the surface tensions in the interval 25.0 to 60.0° of the first four members of the aliphatic nitroparaffins and their secondary isomers have been measured. Additionally, the variation of density with temperature, the total surface energies at 25°, the parachors and the critical temperatures have been obtained.

Apparatus, Chemicals and Methods

Reports of measurements of the variation of the surface tension with temperature are far less numerous in the literature than is to be desired. The variety of methods suitable is limited by a number of practical considerations. In these researches the ring method[3] was employed, and a clean liquid surface was insured by repeatedly overflowing the cup in which it was contained.

Although the question of technique and errors in the ring method has been discussed,[3,6] our experience has convinced us of the necessity of stressing certain vital points again.

If accurate results are to be obtained, it is essential that the ring be entirely in one plane, and that the stirrup supporting the ring be such that this plane be horizontal to a high degree of trueness. The effect of ring tilt has

(1) C. L. Gabriel, *Ind. Eng. Chem.*, **32**, 887 (1940).

(2) W. D. Harkins, T. F. Young and L. A. Cheng, *Science*, **64**, 333 (1926).

(3) W. D. Harkins and H. F. Jordan, THIS JOURNAL, **52**, 1751 (1930).

(4) H. B. Hass, E. B. Hodge and B. M. Vanderbilt, *Ind. Eng. Chem.*, **28**, 339 (1936).

(5) E. L. Lind and T. F. Young, *J. Chem. Phys.*, **1**, 266 (1933).

(6) G. C. Nutting, F. A. Long and W. D. Harkins, THIS JOURNAL, **62**, 1496 (1940).

TABLE I

SURFACE TENSION, DENSITY, AND MOLECULAR SURFACE ENERGY OF THE ALIPHATIC NITROPARAFFINS FROM 25.0 TO 60.0°

Compound	*a*	*b*	*c*	*d*	*e*	
Nitromethane	39.25	0.1387	1.16576	0.001383	992.7	1.610
Nitroethane	34.03	.1090	1.06823	.001202	996.6	1.520
1-Nitropropane	31.74	.0985	1.02300	.001093	1056.2	1.578
2-Nitropropane	30.78	.1084	1.01208	.001119	1104.2	1.805
1-Nitrobutane	31.65	.0979	0.99170	.000960	1193.2	1.801
2-Nitrobutane	31.32	.1067	.98455	.000963	1251.2	2.026

been studied.[3] However, warping of the plane of the ring is probably an error of a greater degree of seriousness. Although it is difficult to estimate quantitatively the error from this source, invariably low surface tension values are obtained unless precaution is taken.

It is desirable to carry out an analysis of errors in order that a precision measure of our results may be stated. The surface tension, γ, is given by the formula

$$\gamma = [Mg/4\pi R]F(R/r, R^3/V)$$

where M = maximum mass of the liquid column supported by the ring, g = gravitational constant, R = radius of ring (center of ring to center of wire), r = radius of wire. The maximum volume, V, of the liquid column elevated above the free surface of the liquid is given by

$$V = M/(D_L - D_v)$$

where D_L and D_v are, respectively, the densities of the liquid and of air saturated with the vapor of the liquid at the prevailing temperature and pressure. Evidently, the precision measure of the derived result (*i. e.*, the surface tension) is governed by the precision measure of components involving mass and length only.

Repeated experiments have shown that M can be determined to within ± 0.1 mg., and R to within ± 0.0005 cm. Harkins and Jordan[3] state that the values of F are accurate to 0.3%, with a probable error of less than 0.2% for rings whose R/r ratios lie between 30 and 80. Using these data, a numerical computation of the actual error in the derived surface tension due to the actual error in each component in the case of nitromethane at 25° gave 35.78 ± 0.12 dyne cm.$^{-1}$, or an accuracy of 0.33%.

The ring employed was made of platinum–iridium, and its mean radius was 0.6378 cm.; the value of R/r was 39.87. As a result of many observations, it was found that the precision of measurement was appreciably better than the 0.33% accuracy claimed. In the series of results being reported a reproducibility in a given surface tension value was observed to better than 0.20%.

Density determinations, performed simultaneously at the same temperatures as surface tension measurements, were carried out in conventional Ostwald pycnometers of approximately 18-ml. volume equipped with ground glass caps to check evaporation losses.

Temperatures were read to 0.05° on a totally immersed 0–50° thermometer graduated in tenths of a degree which had been compared with a calibrated Bureau of Standards thermometer.

Refractive indices were obtained with a Zeiss dipping refractometer maintained at 25.0° within 0.1°.

The compounds used throughout our researches were supplied through the generosity of the Commercial Solvents Corp. by Messrs. F. K. Hoover and E. B. Hodge, and were of a high degree of purity. Their physical constants are given in Table III. The liquids were stored in the dark away from air, and, with the exception of nitromethane, no decomposition occurred over a period of three months.

Results

The results of the measurements of density and surface tension when plotted in a large graph against the temperature indicated that within the range 25 to 60° these quantities may be represented by linear equations. Thus the surface tension equation is

$$\gamma = a - bt \qquad (1)$$

where a and b are constants independent of the temperature of the surface, t, in °C. Similar type equations for the density and molecular surface energy, $\gamma(Mv)^{2/3}$, can be written

$$\rho_4^t = c - dt \qquad (2)$$

and

$$\gamma(Mv)^{2/3} = e - fT \qquad (3)$$

where M is the molecular weight, v, specific volume and T the absolute temperature. The values for the constants in the least squares equations summarize the experimental results (Table I).

The least squares equations fit the experimental surface tension data with a precision of better than 0.13%, and the densities better than 0.018%, with the exception of nitromethane where the precision is 0.06%.

An attempt to evaluate our surface tension and density data in terms of individual values existing in the literature met with small success. With the exception of the first two members of the series, no values were found. In the example of nitromethane a satisfactory comparison can be made. Table II lists values for the densities and surface tensions chronologically.

From the results of Table II, it would appear that the density of nitromethane at 25° must lie within the range: 1.1307 to 1.1313. The agreement between our value for the surface tension

TABLE II

A COMPARISON OF DENSITIES AND SURFACE TENSION VALUES FOR THE ALIPHATIC NITROPARAFFINS AT 25°: NITROMETHANE

ρ^{25}_4	Year	Author[7]
1.1297	1917	Jaeger
1.1325	1925	Williams
1.1319	1926	Mathews
1.1304	1929	I. C. T.
1.1312	1931	Wright, Murray-Rust and Hartley
1.1313	1932	Timmermans and Hennaut-Roland
1.1307	1933	Walden and Birr
1.1312	1940	Present work
γ_{25}		
34.99	1913	Morgan and Stone
34.9	1917	Jaeger
36.13	1929	I. C. T.
36.25	1932	Timmermans and Hennaut-Roland
35.78	1940	Present work

and that of the "International Critical Tables" (I. C. T.) is within 0.3 dyne cm.$^{-1}$.

No comparison of the densities for the other members of the homologous series can be made owing to the complete absence of reports of such measurements on pure compounds in the literature. In the case of nitroethane a comparison of the surface tension values can be made. The value of 31.6 dyne cm.$^{-1}$ at 25° interpolated from the "I. C. T." values is comparable with our value of 31.30 at the same temperature. It is believed that the general self-consistency of the parachor values (see Table III) and their increments offer additional evidence of the accuracy of the surface tension and density values found in this study.

Discussion

The data of Table I permit the calculation of three additional quantities of importance. The total surface energy, E_l, at any one temperature may be obtained from the equation

$$E_l = \gamma_l - T\left(\frac{d\gamma_l}{dT}\right) \qquad (4)$$

and some values are given in Table III.

(7) Jaeger, *Z. anorg. Chem.*, **101**, 1 (1917); Williams, THIS JOURNAL, **47**, 2648 (1925); Mathews, *ibid.*, **48**, 562 (1926); Wright, Murray-Rust and Hartley, *J. Chem. Soc.*, 199 (1931); Timmermans and Hennaut-Roland, *J. Chim. Phys.*, **29**, 529 (1932); Walden and Birr, *Z. physik. Chem.*, **163A**, 263 (1933); Morgan and Stone, THIS JOURNAL, **35**, 1505 (1913).

Parachors were computed from Sugden's[8] formula

$$[P] = M\gamma^{1/4}/(D_l - D_v) \qquad (5)$$

where M is the molecular weight; γ the surface tension; D_l the density of the liquid; and D_v the density of the saturated vapor at the desired temperature. This latter quantity was computed by means of the equation

$$\log (D_v/D_b) = 5(T/T_b - 1) \qquad (6)$$

where D_b is the density of the vapor at the boiling point T_b, and was estimated, following Sugden, by the relation

$$D_b = 0.0122\, M/T_b \qquad (7)$$

The magnitude of the correction of the density of the saturated vapor to the liquid density, D_l, was less than 0.02%, and might have been neglected.

Molecular surface energies calculated in Table I are of use in the estimation of the critical temperatures, T_c, of these compounds. The equation of Ramsey and Shields

$$\gamma(Mv)^{2/3} = k(T_c - T - 6) \qquad (8)$$

was used in conjunction with equation (3) in the calculations summarized in the eighth column of Table III.

TABLE III

Compound	ρ^{25}_4	η^{25}_D	T_b	γ_{25}	E_{25}	$[P]$	T_c	T_b/T_c
Nitromethane	1.13118	1.37872	375.0	35.78	77.11	132.7	622.7	0.60
Nitroethane	1.03819	1.39015	387.9	31.31	63.78	171.0	661.8	.59
1-Nitropropane	0.99569	1.39901	404.6	29.28	58.44	208.1	675.2	.60
2-Nitropropane	.98410	1.39206	393.1	28.07	60.38	208.3	617.9	.64
1-Nitrobutane	.96770	1.40851	426.7	29.20	58.39	247.6	668.5	.64
2-Nitrobutane	.96047	1.40222	413.1	28.65	60.46	248.3	623.7	.66

It is apparent that the well-known rule that secondary compounds show a lower surface tension than corresponding primary members of a series is obeyed by the nitroparaffins.

The value listed by Sugden[9] for the parachor of nitromethane is 132.0, in excellent agreement with Table III. The increment in the parachor per CH_2 group is 39 which compares favorably with the average of 38.3 from Table III. It is apparent also that the parachors of isomers are identical as is required by the principle of the additivity of atomic parachors.

The unusually high values for the critical temperatures of the nitroparaffins suggest that there may be considerable association in the liquid state. Thus, the compounds 1-nitrobutane, butyric acid, 1-amyl nitrile and butyl alcohol show values

(8) S. Sugden, *J. Chem. Soc.*, **127**, 1540 (1925).

(9) S. Sugden, "Parachor and Valency," p. 119.

of T_c equal to 669, 628, 602 and 560°K., respectively. However, allotropy of the liquid nitroparaffins, whether due to changes in molecular aggregation or to other causes, would probably affect surface tension. Within the temperature range here reported, such effects seem to be absent.

Summary

1. The surface tensions of the aliphatic nitroparaffins at 25.0° vary from 35.78 for nitromethane to 29.20 dyne cm.$^{-1}$ for 1-nitrobutane. The secondary isomers show characteristically lower free surface energies, with 2-nitrobutane giving 28.65 ergs cm.$^{-2}$.

2. The total surface energies of the nitroparaffins at 25.0° vary from 77.11 ergs cm.$^{-2}$ for nitromethane to 58.39 ergs cm.$^{-2}$ for 1-nitrobutane. The secondary isomers, however, exhibit a higher surface energy, with 2-nitrobutane giving 60.46 ergs cm.$^{-2}$.

3. The parachor values calculated from the measured surface tension and density are in good agreement with the predictions of Sugden.

4. Values of the critical temperatures calculated from the Ramsey–Shields equations are: nitromethane, 623°K.; nitroethane, 662°K.; 1-nitropropane, 675°K.; 2-nitropropane, 618°K.; 1-nitrobutane, 669°K.; and 2-nitrobutane, 624°K.

CHICAGO, ILLINOIS RECEIVED JUNE 3, 1942

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

The Composition and Structure of Molybdenum Blue

BY F. B. SCHIRMER, JR., L. F. AUDRIETH, S. T. GROSS, D. S. MCCLELLAN AND L. J. SEPPI

The composition of molybdenum blue has been the subject of controversy ever since it was first discovered by Berzelius[1] in 1826. Even modern investigators are not yet in agreement as to its formula, the most recently reported values varying from Mo_5O_{14} to Mo_8O_{23}.[2,3,4] There is little doubt but that products of different composition are obtained when heteropoly acid formers such as phosphoric and arsenic acids are present, or when oxidizing agents such as nitric acid are used in acidifying solutions of molybdate. There is also the very good possibility that the common practice of "purifying" molybdenum blue by extraction from aqueous solution by means of organic solvents gives products which are different. For these reasons the authors undertook to develop methods of synthesis which would avoid these complicating factors.

Molybdenum blue has been prepared by a number of methods, carefully purified and analyzed. Samples were subjected to an X-ray examination and found to yield identical diffraction patterns. The colloidal nature of molybdenum blue was verified subsequently by a study of these products under the electron microscope.

(1) Berzelius, *Pogg. Ann.*, **6**, 380 (1926).
(2) Auger and Ivanoff, *Compt. rend.*, **204**, 1815 (1937).
(3) Auger, *ibid.*, **205**, 1070 (1937).
(4) Lautié, *Bull. soc. chim.*, [5] **1**, 105 (1934).

Experimental

Preparation

(a) **Reduction of Molybdate with Trivalent Molybdenum.**—The recommended procedure, by which the majority of the samples were prepared, involves interaction of a solution of trivalent molybdenum, obtained by reduction of molybdate in a Jones reductor, with an acidified molybdate solution (*p*H 0.4). Specific directions follow: a receiver containing 500 ml. of 0.4 *M* sodium molybdate, $Na_2MoO_4 \cdot 2H_2O$, and 200 ml. of 6 *N* hydrochloric acid is attached to the reductor. A solution containing 40 ml. of 0.4 *M* sodium molybdate, 60 ml. of 6 *N* hydrochloric acid and 100 ml. of water is passed slowly through the column and the resulting olive-green solution of trivalent molybdenum is allowed to drop directly into the solution of hexavalent molybdenum. The last of the solution in the reductor is washed into the receiver with dilute hydrochloric acid. The precipitate of molybdenum blue forms in the flask.

The precipitate and the solution are separated by centrifugation and the slightly colored supernatant liquid, containing an excess of trivalent molybdenum, is either discarded or treated as in method (c). The precipitate is washed by centrifuging three to five times with a solution of 5 ml. of 6 *N* hydrochloric acid in 100 ml. of distilled water. This is followed by similar treatment of the precipitate with successive portions of distilled water until both the supernatant liquid and the precipitate are chloride free. After each washing the suspension is centrifuged and the supernatant liquid decanted.

During the washing with dilute hydrochloric acid very little of the product is lost. As the electrolyte is subsequently removed by washing with distilled water considerable peptization takes place with the result that the

supernatant solutions assume a deep blue color. While the yield of molybdenum blue is decreased by this final treatment, a purer product is obtained which more than compensates for this loss. The molybdenum blue is then dried and stored in a vacuum desiccator. Using the quantities specified above yields of 16 to 18 g. of purified molybdenum blue may be obtained. These yields correspond to about 45–55% calculated on the assumption that the hydrate obtained has the average composition $Mo_8O_{23}\cdot 10H_2O$.

(b) **Oxidation of Trivalent Molybdenum with Molybdate.**—This method is essentially similar to (a), but involves addition of acidified molybdate to an excess of a solution containing trivalent molybdenum prepared by reduction with zinc in a Jones reductor.

(c) **Oxidation of Lower Valent Molybdenum.**—The supernatant liquid which remains upon centrifugation of the reaction mixture in (a) above contains an excess of lower valent molybdenum. An additional yield of the blue can be obtained by passing oxygen through the solution for several days. The precipitated molybdenum blue is centrifuged, washed and dried as described under (a).

Analysis.—The water content was determined by heating gradually a weighed sample of the blue to a temperature of 500° in a stream of oxygen and absorbing the moisture in tared bulbs containing magnesium perchlorate. The residual molybdenum trioxide was either weighed directly or dissolved in dilute ammonium hydroxide and its molybdenum content determined volumetrically as outlined by Scott.[5] Samples of molybdenum blue were also analyzed directly for their molybdenum content. The oxygen content was calculated by difference.

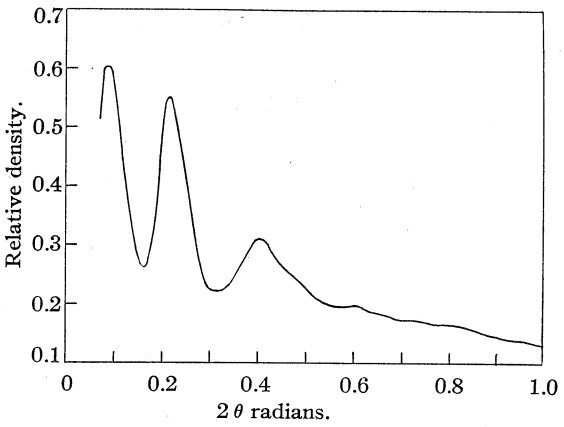


Fig. 1.—Relative density curve made from X-ray diagram of molybdenum blue using Leeds and Northrup microphotometer; filtered molybdenum radiation, circular camera (radius 6.4 cm.), wedge sample.

The analytical results presented in Table I indicate that the composition of molybdenum blue, prepared by four different methods and purified carefully, may be represented approximately by the empirical formula $Mo_8O_{23}\cdot xH_2O$, where x varies from six to fourteen depending upon how long the product has been dried.

TABLE I

COMPOSITION OF MOLYBDENUM BLUE

Method of prepn.	Samples analyzed	Value of x in Mo_8O_x
a	14	23.04 ± 0.12 (extremes, 22.85–23.31)
b	2	23.31 ± 0.10
c	2	22.97 ± .06
d[6]	2	23.41 ± .06

X-Ray and Electron Microscope Study.—Molybdenum blue preparations were examined by the X-ray diffraction method using both filtered molybdenum and filtered copper radiation with the wedge technique. Three intense and four faint halos or diffuse bands were observed. The intense interferences correspond to the following "*d*" values.

Cu K-alpha, Å.	Mo K-alpha, Å.
8.43	8.57
3.28	3.25
1.79	1.76

Measurements of the remaining halos are uncertain, two of them partly overlapping more intense interferences, and the remaining two corresponding to very faint diffuse bands. A tracing of the microphotometer curve obtained for molybdenum blue from an X-ray pattern with molybdenum radiation is shown in Fig. 1. This pattern is apparently perfectly characteristic of the purified material regardless of the method of preparation.[7] It seems significant that this halo pattern shows little resemblance to the diffraction pattern of molybdenum trioxide, a fact which suggests the presence of a definite structure other than any known form of molybdenum trioxide.

In view of a question raised by one of the referees relative to the interpretation of the broad X-ray diffraction interferences obtained with molybdenum blue, it was suggested by Professor G. L. Clark that electron photomicrographs be made of these preparations.[8] The sample was

(5) "Standard Methods of Chemical Analysis," Vol. I, D. Van Nostrand Co., Inc., New York, N. Y., 1939, p. 594.

(6) Prepared by reduction of acidified molybdate with stannous chloride.

(7) Burgers and van Liempt, *Z. anorg. Chem.*, **202**, 325 (1931), examined qualitatively molybdenum bronzes by the X-ray method, but give no experimental details, measurements, calculations or interpretation. They reproduce photographs of patterns obtained (a) from a so-called molybdenum blue, (b) from an ignited product and (c) from a sample of sublimed molybdenum trioxide. They describe the first of these as different from the other two which are identical. All of their samples are crystalline materials. The patterns obtained consistently by the authors bear no resemblance to those published by Burgers and van Liempt.

(8) The R. C. A. instrument was employed by Dr. Martha Barnes Baylor at a magnification of 15,500 X and the photographs were then enlarged fourfold for a final magnification of 62,000 X.

shaken up with water, allowed to settle and a drop of the top of the aqueous suspension applied to the collodion film and dried. The remarkable dispersion of particles is shown in Fig. 2 (magnification 62,000 X). A fairly uniform distribution of single primary particles some of which are only 100 Å. in diameter, appears in the background. These particles are narrower in one dimension than the other and probably lie flat as still thinner flakes. As might be expected otherwise, these are too small to show definite crystalline faces. Some small flocs representing the first stages of agglomeration of the individual particles appear in the center of the photograph. Finally, there is a distribution of larger, darker and more nearly spherical particles which must represent larger primary particles of the order of several hundred Ångström units in size.

This proof of a typical colloidal structure, therefore, confirms the interpretation of the broad X-ray interferences by means of which calculations can be made of a particle size of the order of 100 Å., or somewhat less. It is not necessary to claim absolute crystalline perfections of these extremely small particles. That some lattice organization is present is indicated by the number of diffraction halos on the patterns—several more than for carbon black which is known to be built up into particles from crystalline layers which are stacked at random like a twisted deck of cards.



Fig. 2.—Electron photomicrograph of molybdenum blue (62,000 ×).

Summary

Molybdenum blue has been prepared by a number of new methods and purified carefully. Its composition may be represented by the empirical formula, $Mo_8O_{23}\cdot xH_2O$. Samples prepared under the prescribed conditions yield identical and characteristic diffraction patterns. Electron photomicrographs confirm the colloidal nature of molybdenum blue.

URBANA, ILLINOIS RECEIVED MAY 4, 194

[CONTRIBUTION FROM THE RESEARCH LABORATORY, UNITED STATES STEEL CORPORATION]

The Adsorption of Gases at Low Temperature and Pressure on Smooth Silver

BY MARION H. ARMBRUSTER

This paper reports the results of measurements of the adsorption of hydrogen, nitrogen, argon, carbon monoxide, carbon dioxide and oxygen at pressures up to 0.1 cm. on a substantially plane, reduced surface of silver over the temperature range −195 to 20°. The investigation was undertaken to determine the nature and properties of the smooth surface of a typical, pure, homogeneous metal as a first step toward a better understanding of the characteristics of the surface of a less pure or less homogeneous metal, such as steel. Silver was selected chiefly because it is readily obtainable in a high degree of purity in the form of foil, a form which provides a large, smooth and reproducible surface; it is also relatively inert so that, aside from the sorption of oxygen, there should, in the range of experimental conditions covered, be no complex chemisorption which might confuse interpretation of the results.

Materials and Apparatus.—The quality of the several gases used, the apparatus, and the experimental procedure already have been described.[1]

Silver Surface.—The silver used (99.98+ % Ag) was foil 0.021 cm. thick, cut into strips, 1.8 × 11.0 cm. to form a bundle weighing 846.5 g. and having a total geometric area of 8002 sq. cm. X-Ray diffraction patterns of the foil, obtained by D. S. Miller, indicated a fairly high degree of preferred orientation of the grains on the surface of the foil. The crystallographic plane in the surface was not one of simple indices, but appeared to be one which made an angle of 15° with the (110) plane. The strips were degreased with absolute alcohol and anhydrous ether, suitable precautions being taken to guard against subsequent contamination. Since oxygen sorbed on silver is not readily removed by baking in vacuum even at a temperature as high as 300°,[2,3] the surface was, before each run, freshly reduced for four to eight hours at 400° in a stream of purified hydrogen. The adsorption bulb was then sealed off in an atmosphere of hydrogen after which the sample was outgassed at 450° under a pressure of 10^{-6} mm. This pretreatment sufficed to give a surface on which the adsorption was reproducible within the precision of measurement, which is about 0.001 cc. As direct test showed that hydrogen is not measurably sorbed on smooth silver in the range of temperature and pressure covered, the sample was cooled in hydrogen to hasten equalization of temperature. At least two, and usually four, check runs were made with each gas at each temperature. After several measurements the surface of the silver developed an etched appearance, probably as a result of evaporation but this was not accompanied by any appreciable increase of surface area since the sorption was not measurably altered. The Pyrex bulb containing the silver also developed a slight brown discoloration, indicating probable contamination by silver.

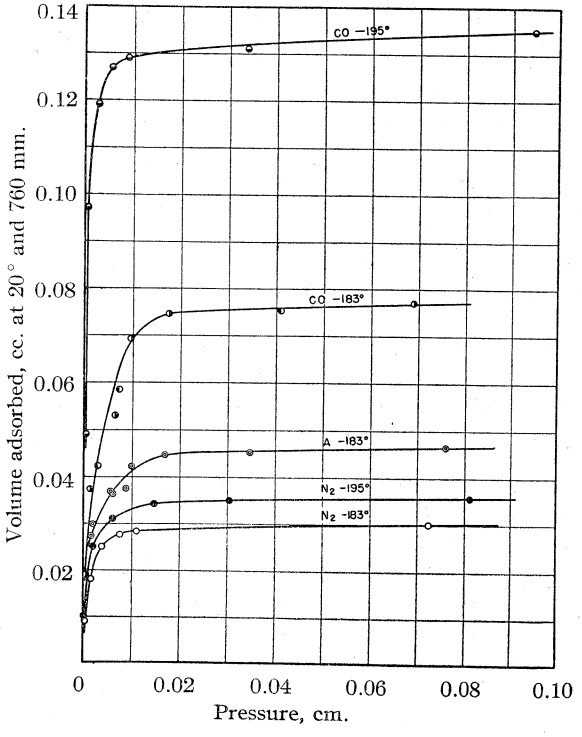


Fig. 1.—Isotherms for CO, A and N_2 at −183 and −195°.

Results.—Hydrogen was not measurably sorbed at any temperature investigated; argon, nitrogen and carbon monoxide were sorbed at −195° and −183° but not at −78° or 20°. Carbon dioxide was not sorbed at 20°, but at −78° was sorbed to the slight extent of 6 cu. mm. at a pressure of 0.02 cm. Typical isotherms for nitrogen, argon and carbon monoxide at −195° and −183°, selected as representative from among the several concordant runs made with each gas, are given in Fig. 1. For each gas, adsorption was instantaneous and completely reversible in the sense that measurements on desorption agreed with those for adsorption, and a surface pumped out at temperature gave results identical with those obtained on a baked out surface.

The sorption of oxygen is illustrated by the typical isotherms presented in Fig. 2. At −195° and −183° the adsorption was fairly rapid, being substantially complete within a few minutes.

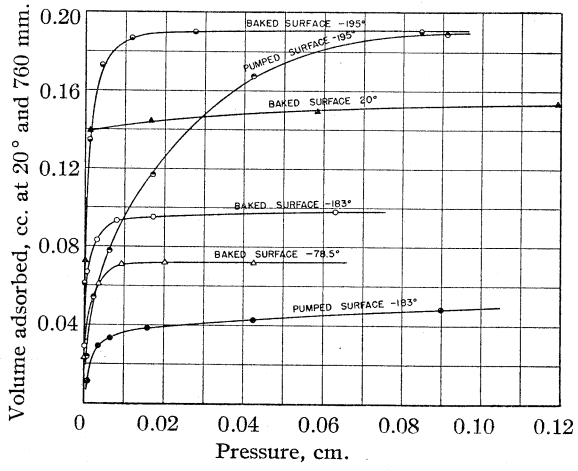


Fig. 2.—Isotherms for oxygen at −195, −183, −78.5 and 20°.

The adsorption was not, however, entirely reversible since the amount of gas sorbed was not the same on a surface which had been pumped out at temperature as on one which had been freshly reduced and baked out. Thus, at −183°, the sorption on the pumped out surface was markedly less than on the surface which had been reduced and baked, whereas at −195° it was less in the lower range of pressure but probably was greater

(1) Armbruster and Austin, THIS JOURNAL, **60**, 467 (1938); **61**, 1117 (1939).
(2) Benton and Elgin, *ibid.*, **48**, 3027 (1926).
(3) Benton and Drake, *ibid.*, **56**, 255 (1934).

at higher pressures. At −78° and 20°, on the other hand, the rate of adsorption was relatively slow; the first portion of oxygen admitted came to equilibrium only after an hour or more, as is illustrated by the typical rate curves shown in Fig. 3; subsequent additions attained equilibrium more rapidly. At these higher temperatures, the volume of oxygen sorbed was, over most of the range investigated, virtually independent of pressure. Moreover, at −78° and above, the sorbed oxygen could not be removed by pumping at temperature but was taken off by reduction and baking in vacuum at 400° or higher.

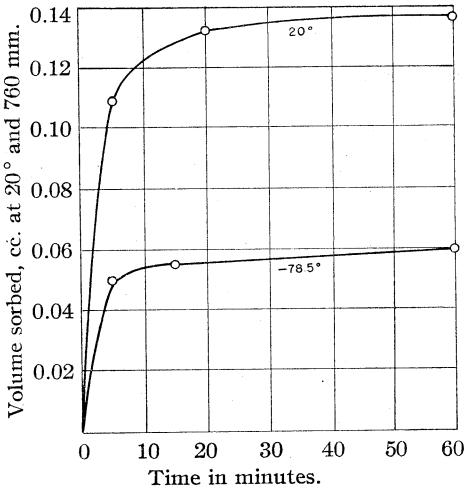


Fig. 3.—Rate of initial adsorption of oxygen at −78.5 and 20°.

Discussion of Results

Nature of the Adsorption.—The fact that nitrogen, argon, and carbon monoxide are adsorbed instantaneously and reversibly, together with the fact that the volume sorbed at a given pressure increases with decreasing temperature, indicates that the adsorption is of the van der Waals type. The sorption of oxygen at −195° and −183° is, in part, likewise of the van der Waals type but at least some portion of the sorbed film appears to be held to the surface more tightly than would be expected from the action of purely physical forces. Thus, at −183°, the sorption on the pumped out surface is less than on the freshly reduced and baked surface, which suggests that all the sorbed oxygen was not removed by evacuation. At −78° and 20°, the rate of adsorption of oxygen is slow and the sorbed gas is not removed from the surface by evacuation of the system, indicating that the sorption is of the activated type, a conclusion which is confirmed by the fact that the volume of gas sorbed at a given pressure increases with increasing temperature, as is illustrated by the typical isobar shown in Fig. 4.

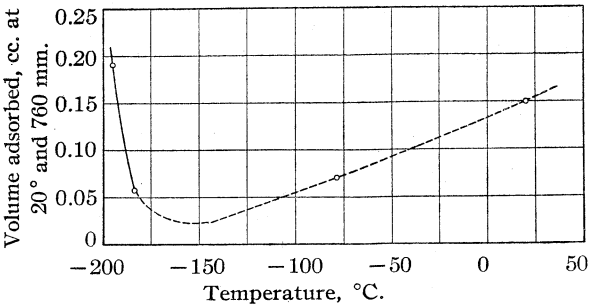


Fig. 4.—Isobar for oxygen at $P = 0.05$ cm.

Form of the Isotherms.—Since the curves in Figs. 1 and 2 appear to be of the Langmuir type, representative isotherms for the several gases have been replotted in Fig. 5 as p/v against p, a method which yields a straight line if the observations conform to either the Langmuir equation[4] or to the formally identical equation for monomolecular adsorption developed by Bru-

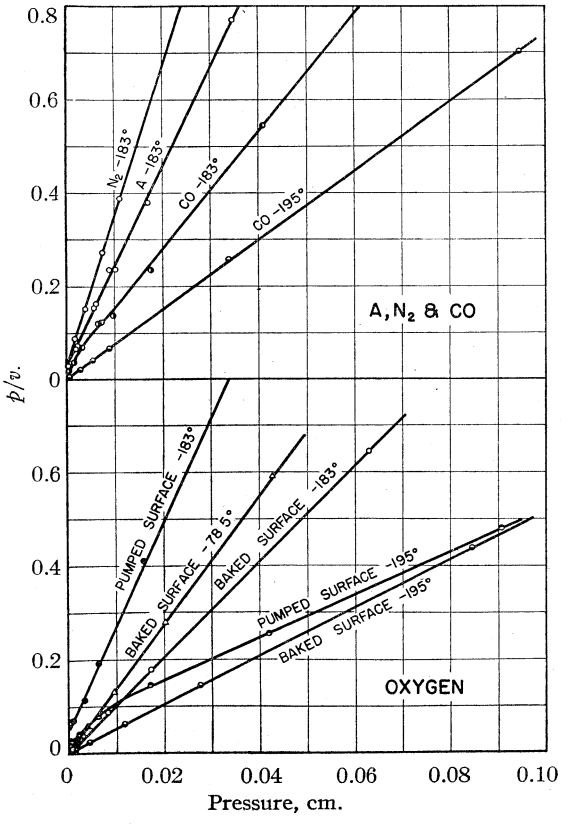


Fig. 5.—Isotherms plotted as p/v against p. Upper section shows data for N_2, A and CO; lower section shows data for O_2.

(4) Langmuir, THIS JOURNAL, **40**, 1361 (1918).

nauer, Emmett and Teller.[5] It is evident from this diagram that a linear relation is obtained except at the lowest pressures, hence, over virtually the entire range of pressure covered, the data are represented with satisfactory accuracy by either of these relations.[6] The greatest deviation from a straight line is in the isotherm for oxygen at −195° at pressures up to 0.010 cm.; another, less marked, departure occurs in the same range of pressure in the isotherm for carbon monoxide at −183°.

In Fig. 6 the isotherms for −183° are plotted in the form of v, the volume (reduced to 1 atm. and 20°) sorbed at pressure p, against the logarithm of the adsorption potential ϕ,[7] as suggested by Palmer and Clark.[8] This method of plotting is of interest in connection with the calculation of the force-area curve, since, if a straight line is obtained, as it frequently is,[8,9] the spreading force can be calculated by means of an equation derived by Palmer.[10]

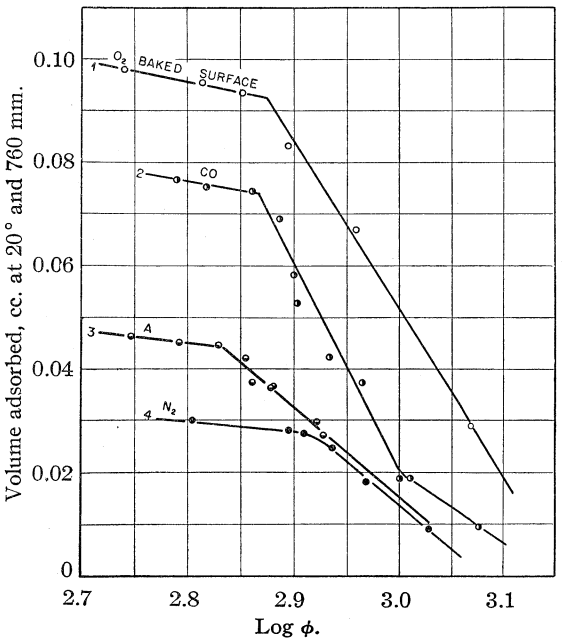


Fig. 6.—Isotherms at −183° plotted as volume sorbed against log ϕ.

All the isotherms in Fig. 6, except that for carbon monoxide, consist of two straight lines which intersect at a value of v approximately equal to that at which the corresponding curve in Figure 1 flattens off. The isotherm for carbon monoxide consists of three sections, two of which intersect at a value of v which, just as with the other gases, corresponds approximately to the value at which the isotherm in Fig. 1 flattens off; the other intersection occurs in the range of higher adsorption potentials, that is, at lower pressure, at a value of v which corresponds fairly well with the pressure at which deviation from linearity becomes evident in the isotherm shown in Fig. 5. The isotherms for the several gases at −195° fall so close to the corresponding curves for −183° that they have not been included in Fig. 6.

Fraction of Surface Covered.—The limiting volume, V_s,[11] for each gas at each temperature, as derived from the slope of the p/v–p isotherm, is given in Table I. On the assumptions that the geometric area of the foil represents the true area of the surface, and that the mean cross-section of a sorbed molecule is the same as that of a molecule in the liquid, the fraction of the surface covered, in the pressure range in which the isotherm is virtually horizontal, can be estimated from the value of V_s. The coverage derived on this basis is shown in the last column of Table I. In only one instance, the sorption of oxygen on a pumped out surface at −195°, is the coverage substantially complete; in every other, only from

TABLE I

V_s, VOLUME OF GAS SORBED AND FRACTION OF SURFACE COVERED AT SATURATION AS CALCULATED BY MEANS OF THE LANGMUIR EQUATION

Gas (surface)	Temp., °C.	V_s, cc. at 20° and 760 mm.	Molecules sorbed per sq. cm. as derived from V_s	Fraction of surface covered
A	−183	0.0486	0.153×10^{15}	0.20
N_2	−183	.0305	.096	.15
N_2	−195	.0355	.112	.17
CO	−183	.0769	.242	.37
CO	−195	.1360	.428	.65
O_2	−78.5	.0729	.230	.29
O_2 (Baked)	−183	.0980	.309	.40
O_2 (Pumped)	−183	.0450	.142	.18
O_2 (Baked)	−195	.1904	.560	.78
O_2 (Pumped)	−195	.2295	.722	.94

(5) Brunauer, Emmett and Teller, THIS JOURNAL, **60**, 309 (1938).

(6) This does not preclude the possibility that at higher pressures the isotherms might curve upwards to become convex to the pressure axis.

(7) The adsorption potential ϕ is equal to $RT \log p_0/p$, where p_0 is the vapor pressure of the adsorbate in the liquid phase at temperature T.

(8) Palmer and Clark, *Proc. Roy. Soc.* (London), **A149**, 360 (1935).

(9) Armbruster and Austin, THIS JOURNAL, **60**, 474 (1938).

(10) Palmer, *Proc. Roy. Soc.* (London), **A160**, 254 (1937).

(11) This is the volume which investigators of adsorption at low pressure on plane surfaces have commonly called the maximum volume sorbed, or the saturation maximum, and have designated b, c_1, x_s or v_m, (*cf.* Langmuir, ref. 4; Bawn, THIS JOURNAL, **54**, 81 (1932); Wilkins, *Proc. Roy. Soc.* (London), **A164**, 510 (1938)). It is to be distinguished from the volume v_m defined by Brunauer, Emmett and Teller (ref. 5) as the volume required to form a close-packed monolayer.

one-third to two-thirds of the surface is covered. Although it is customary to calculate coverage of the surface in this manner, it is entirely permissible, and in some ways preferable, to interpret the apparent saturation of the surface in terms of effective cross-section of the sorbed molecules, that is, in terms of the density of packing in the sorbed film. On this basis, the effective cross-section derived from V_s (Table I) is considerably greater than that of a molecule in a three-dimensional condensed phase.

Apparent saturation of the surface, as indicated by the flattening of the isotherm, at such a relatively low pressure is in marked contrast to the behavior of metal powders for which there is no comparable flattening even at a much higher pressure. Moreover, the relatively small estimated coverage of the smooth surface in the range of apparent saturation appears to be characteristic of a number of metals. For example, Langmuir[4] reports saturation of a surface of platinum foil with hydrogen, carbon monoxide and oxygen at a coverage not exceeding a few per cent. More recently, Wilkins[12] in more extensive measurements on platinum foil, observed saturation at $-183°$ by argon, nitrogen and oxygen with a coverage of 34, 30 and 42%, respectively. With argon at $-195°$ the surface appeared to be completely covered at saturation by a monomolecular layer. Wilkins found further that when his data were plotted as p/v against p, there were marked deviations from linearity at low pressures, the departures becoming more marked the lower the temperature. Finally, Smittenberg[13] reports that on a smooth surface of nickel at $-183°$ the greatest adsorption of hydrogen or argon corresponded to a coverage which does not exceed 2 and 8%, respectively. It is evident, therefore, that the observed adsorption on the silver surface is typical of that on a smooth metallic surface.

The sorption of oxygen at $-195°$ has another feature worthy of special mention in that V_s is greater for the pumped out surface than for a surface which has been freshly reduced and baked. This difference is reflected in a difference in the form of the isotherms (Figs. 2 and 5) which was confirmed by repeated measurements. The cause of the difference is not apparent for it is difficult to visualize a mechanism by which merely pumping the gas from the system should so condition the surface that it can subsequently adsorb a significantly greater volume of oxygen. The observations suggest, however, that at $-195°$, as at $-183°$, all the sorbed oxygen is not removed by pumping, and that the molecules remaining so alter the surface that it becomes virtually an oxide surface capable of forming a complete monolayer of the van der Waals type of adsorption. In line with this difference it should be noted that the calculated heat of sorption, as derived in a later section, is 2800 cal. for the pumped out surface, which is significantly less than the value 3400 cal. for the surface which has been reduced and baked.

Variation of V_s with Temperature.—As indicated in Table I, V_s increases markedly with decreasing temperature, a variation seemingly characteristic of adsorption in which there is an apparent saturation of the surface. Wilkins and Ward[14] have suggested that this temperature coefficient is due to some factor which alters the number of molecules which can be packed into the adsorbed phase, the volume of which is independent of temperature; that is, the temperature coefficient of V_s corresponds to the expansion coefficient of a gas at constant pressure. On this basis, $dV_s/V_s dT$ should have about the same value as dV/VdT for an ideal gas, which is equal to $1/T$. The value of $dV_s/V_s dT$ derived from the present measurements (Table II) is, for nitrogen, approximately that of an ideal gas but for carbon monoxide and oxygen it is very much greater, which suggests that the molecular interactions in the sorbed film are much greater for carbon monoxide and oxygen than for nitrogen. The value derived for nitrogen also agrees fairly well with that derived from Langmuir's measurements on mica. Thus, if the value of $dV_s/V_s dT$ is taken as 0.0145 at $-150°$ and varies about 2% per degree, as given by Langmuir, the difference in V_s for nitrogen at $-183°$ and $-195°$ should be 7 cu. mm., which is in excellent agreement with the observed value of 6 cu. mm.

TABLE II

VALUES OF $-dV_s/V_s dT$

Gas	$-dV_s/V_s dT$
N_2	0.0130
CO	.034
O_2 (total)	.040
Ideal gas ($1/T$)	.012

Heat of Sorption.—Of the several methods for calculating heat of sorption, that described by

(12) Wilkins, *Proc. Roy. Soc.* (London), **A164,** 510 (1938).
(13) Smittenberg, *Rec. trav. chim.*, **53,** 1065 (1934).
(14) Wilkins and Ward, *Z. physik. Chem.*, **144,** 259 (1929).

Brunauer, Emmett and Teller[5] appears to be the most reliable. This method, which yields the average heat of sorption, when applied to the present data for −195° and −183°, yields the heat effects shown in Table III, which includes, for comparison, the heat of liquefaction of each gas. In every case, the heat of adsorption lies in the range 2800 to 3600 calories and is about twice the heat of liquefaction, again indicating that the sorption is chiefly of the van der Waals type. The heats of sorption on silver are also virtually identical with those for adsorption of the same gases on platinum foil at −183° (last column Table III) as calculated by the same method from Wilkins' measurements.[12]

TABLE III

COMPARISON OF THE CALCULATED HEAT OF SORPTION ON SILVER FOIL WITH THE HEAT OF LIQUEFACTION AND WITH THE CALCULATED HEAT OF SORPTION ON PLATINUM FOIL

Gas (surface)	Temp., °C.	Heat of adsorption, (cal./mole) Silver	Platinum[b]	Heat of liquefaction at nominal boiling point, cal./mole
A	−183	3500	3280	1505
N_2	−183	3600	3385	1330
N_2	−195	3050	3244[a]	1330
CO	−183	3600		1410
CO	−195	3270		1410
O_2 (Baked)	−183	3700	4302	1630
O_2 (Pumped)	−183	3530		1630
O_2 (Baked)	−195	3400		1630
O_2 (Pumped)	−195	2800		1630

[a] Temperature −189.5°. [b] Calculated from data of Wilkins.

Force–Area Curves.—Two methods, both based upon the Gibbs adsorption equation, are available for deriving the force–area curve of a sorbed film. The first was devised by Palmer,[15] who suggests that if the observations yield a straight line when log ϕ is plotted against v (Fig. 6), that is, if the potential can be represented as a function of v by the relation $\phi = \phi_0 e^{-sv}$, then the spreading force, F, of the film when volume v is adsorbed is given by

$$F = f\phi_0 e^{-sv}(v + 1/s) + I$$

where f is a constant for adjusting units, ϕ_0 is the extrapolated value of the adsorption potential at zero volume adsorbed, s is the slope of the log $\phi - v$ line, (d log ϕ/dv), and I is an integration constant which is evaluated on the assumption that F is zero when v is zero. In applying this equation to adsorption data which yield a plot with two linear portions (Fig. 6), the value of the integration constant of the section covering the range of higher volume sorbed has been adjusted so that the value of F agrees with that of the other linear section at the intersection. The value of A, the area occupied per molecule, corresponding to a given value of F is calculated by dividing the geometric area of the surface by the number of molecules contained in the volume of gas sorbed.

The force–area cuvres for the several gases at −183°, derived on this basis, are shown in Figs. 7 and 8, which also include the force–area curve for an ideal two-dimensional gas at the same temperature, calculated by means of the relation $FA = 1.372T$. In every case the spreading force calculated by Palmer's method is less than that for an ideal gas in the range of relatively large values of A but is greater in the range of small values of A. The curves for argon and nitrogen are, as might be expected, very similar (Fig. 7). The curve for carbon monoxide falls very close to the ideal curve over the major part of the range covered. In the case of oxygen the deviation from ideality in the region of the larger values of A is more marked than in the case of any other gas at −183°. The curve for oxygen on a pumped out surface has not been given since it lies very close to that for total oxygen.

The corresponding force–area curves for the several gases at −195° have not been included. However, it may be said that these bear similar relation to the ideal curve at −195° with two exceptions. The curve for carbon monoxide at −195° falls more markedly below the ideal curve in the region of the larger values of A; the curves for oxygen lie closer to the ideal curve, that for oxygen on a pumped out surface practically coinciding with it.

The resemblance of these curves to the corresponding P–V curve of a three-dimensional gas is striking, yet the data are not adequately represented by a two dimensional analog of van der Waals' equation of the form $(F + C/A^2)(A - A_0) = kT$, where C and A_0 are constants. The deviations from this relation are, however, of the same kind as are obtained when the van der Waals' equation is applied to a three dimensional gas.

The force–area curves bear an even stronger resemblance to those for certain insoluble films on water. Thus, in a number of them there is a rather sudden break in the curve in the range of lower values of A, indicating a much more marked

(15) Palmer, *Proc. Roy. Soc.* (London), **A160**, 254 (1937).

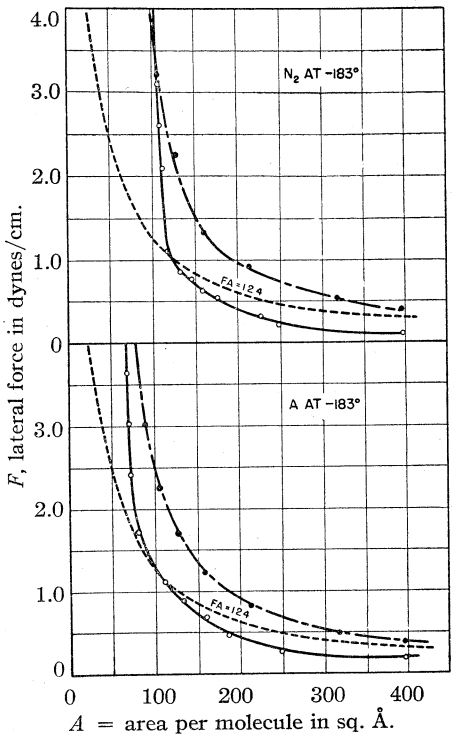


Fig. 7.—Variation of lateral force with surface area per molecule for N_2 and A sorbed at −183°. Full lines calculated by Palmer's method, dot-dash lines by method of Innes and Rowley. Dotted curve for an ideal two dimensional gas ($FA = 1.372T$).

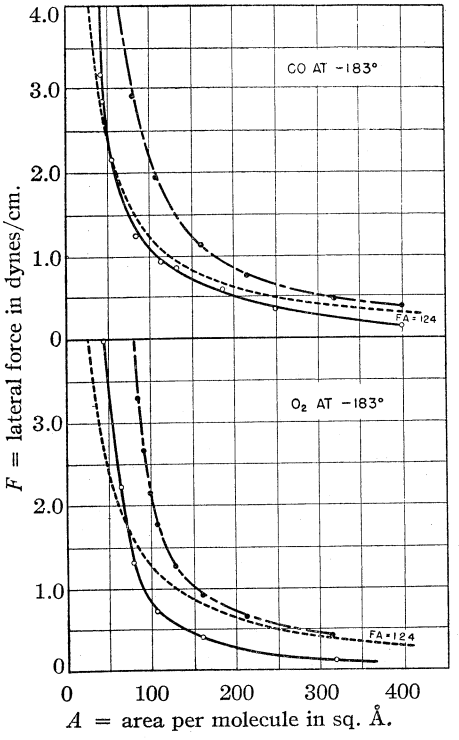


Fig. 8.—Variation of lateral force with surface area per molecule for CO and O_2 (baked surface) at −183°. (Curve for O_2 on pumped out surface lies close to that for the baked surface.) Full lines calculated by Palmer's method, dot-dash curves by method of Innes and Rowley. Dotted curve is for an ideal two dimensional gas ($FA = 1.372T$).

increase in spreading force with decrease in area. Too much emphasis should not be placed upon the significance of this break, however, since the occurrence of the break is in part probably a consequence of the assumption that the Palmer isotherm consists of two linear branches, that is, that there is, in effect a discontinuity on the isotherm. It is, nevertheless, interesting to compare the value of A obtained by extrapolating the steep part of the curve to $F = 0$ with the area per molecule as calculated from v_s. This comparison is made in Table IV. For argon and nitrogen at −183° and for carbon monoxide at −183 and −195°, the agreement is fairly good, but in the other cases the value of A obtained from the force–area curve is of the order of twice that calculated from v_s. This is the deviation which is to be expected, however, since the force–area curve indicates the area at which the virtual compressibility of the film becomes markedly less, whereas the other method gives the value in a much more highly compressed film. It should be noted that in every case the area per molecule is many times greater than the mean cross section of the molecule in liquid phase at this temperature; moreover, the area per molecule at saturation is less at −195° than at −183°.

TABLE IV

COMPARISON OF CROSS-SECTIONAL AREA/MOLECULE FROM FORCE–AREA CURVE AND LANGMUIR'S ISOTHERM

Gas (surface)	Temp., °C.	Area/molecule in sq. Å. at break in force–area curve	Area/molecule in sq. Å. at Langmuir saturation
A	−183	70	65.3
N_2	−183	128	104.1
N_2	−195	120	89.2
CO (Baked and	−183	44	41.3
pumped)	−195	27	23.4
O_2 (Baked)	−183	52	33.0
O_2 (Pumped)	−183	113	70.4
O_2 (Baked)	−195	37	17.9
O_2 (Pumped)	−195	25	13.9

The second method of calculating the force–area curve is a graphical one based on the following equation reported by Innes and Rowley[16]

$$FA = v_1 RT + RT \int_{p/v \text{ as } v \longrightarrow 0}^{p_1/v_1} v \, \mathrm{d} \ln \left(\frac{p}{v}\right)$$

(16) Innes and Rowley, *J. Phys. Chem.*, **45**, 158 (1941).

in which F is the spreading force in dynes/cm., and v and v_1 are the volumes of gas adsorbed at pressures p and p_1, respectively.[17] Hence, by plotting v against ln (p/v) and measuring the area under the curve between the desired limits, the value of FA may be readily computed. The extrapolation involved in this method introduces some uncertainty since reliable values of v and of p/v are difficult to obtain experimentally as v approaches zero. The several force–area curves derived by this method are shown by the dash-dot lines in Figs. 7 and 8. Without exception they lie above the curve for an ideal two-dimensional gas and they do not show the sharp break evident in the curves derived by Palmer's method.

The curves derived by the Innes–Rowley method indicate the existence of large repulsive forces acting between the sorbed molecules over the entire range of sorption covered, whereas, the curves derived by the Palmer method indicate that attractive forces predominate in the range of small volume sorbed but that repulsive forces predominate when the volume sorbed approaches saturation. This difference in the two methods is not easy to explain but is probably due in part to the extrapolations necessary in each case.

Comparison of Sorption of Oxygen on Foil and on Powder.—The sorption of oxygen on two samples of finely-divided silver at −183° and −78.5°, and at pressures up to one atmosphere, has been measured by Benton and Drake[18] with results which, though in many respects similar to those obtained with silver foil, are in others significantly different. Thus, on the powder, as on the foil, the sorption at −183° is chiefly of the van der Waals type with, however, an indication of a small amount of a somewhat stronger sorption characterized by a relatively slow rate of sorption for the initial additions of oxygen. At −78.5°, the sorption is in each case chiefly of the activated type; moreover, at this temperature the isotherm is in each case of the saturation type in which the amount of oxygen adsorbed is substantially independent of pressure over virtually the entire range of pressure studied, that is, up to 0.1 cm. on the foil and on the powder up to the dissociation pressure of silver oxide.

The chief point of difference is in the isotherms at −183°. On the foil there is a flattening of the curve at a pressure of less than 0.01 cm. and at a volume of gas sorbed corresponding to only a fraction of a close-packed monolayer, with no appreciable further sorption up to a pressure of about 0.15 cm. In contrast, the isotherm for the powder gives no indication of flattening of the curve at low pressures, although the data for this range are not very satisfactory, but has the S-shape characteristic of adsorption which is multimolecular at the higher pressures. On the basis that the beginning of the linear portion of the isotherm for the powder corresponds to the first appearance of a second layer, an assumption used to estimate the surface area of powders,[19] the first layer on the powder is complete at a pressure of approximately 10 cm. which is 1000 times greater than the pressure at which the surface of the foil appears to be saturated. It should also be noted that on the pumped out foil at −195° the sorbed oxygen forms a substantially complete monolayer, and that this apparent saturation is very nearly achieved at a pressure of the order of 0.1 cm. These facts indicate that although the forces involved may be basically the same they differ in degree between the surface of a powder and that of foil. This difference is further illustrated by a comparison of the heat of adsorption on the different surfaces. Thus the heat derived by means of the Brunauer–Emmett–Teller equation for powder II, used by Benton and Drake, is 2390 cal. which is significantly lower than the heat of 3560 cal. calculated for the foil by the same method. A difference such as this between the surfaces, also the fact that the range of pressure studied is considerably lower than is used for powders, may account for the apparent flattening of the curve at relatively lower pressures in the case of the foil.

Another interesting comparison is that the surface concentration of oxygen in the activated adsorption at −78.5° is the same on the foil as it is on the powder. Thus, on the foil, the concentration is 0.22×10^{15} molecules per sq. cm., as calculated from the value of V_s and the geometric surface area. The surface area of the powders used by Benton and Drake, as estimated by means of the Brunauer–Emmett–Teller equation, is 13 and

(17) The relation given by Innes and Rowley is

$$FA = RT \int_{v=0}^{v=v_1} \ln \frac{p_1}{p}\, dv$$

but in a personal communication they have suggested the alternative form above because it requires a less difficult extrapolation.

(18) Benton and Drake, THIS JOURNAL, **56**, 255 (1934).

(19) Emmett and Brunauer, *ibid.*, **59**, 1558 (1937).

26 sq. m., respectively,[20] for powders I and II. On the basis of these areas, the surface concentration of oxygen at $-78.5°$ is 0.21×10^{15} and 0.16×10^{15} molecules per sq. cm. which is virtually identical with that on the foil. The fact that the oxygen held on the foil so strongly at $-183°$ that it could not be pumped off at temperature was also present on the surface at a concentration of 0.16×10^{15} molecules per sq. cm. suggests, though it does not prove, that the sites which hold oxygen so strongly at $-183°$ are the same upon which activated adsorption occurs at $-78.5°$.

It is interesting to note that if one assumes that the activated adsorption at $-78°$ represents the formation of a silver oxide complex on the surface, the number of sites is about equal to the observed number of molecules sorbed. Thus, on this basis, each oxygen molecule would be associated with 4 atoms of the silver on the surface. The X-ray diffraction patterns indicate that as a first approximation the silver grains are so arranged that the (110) planes lie on the surface, and since, on this plane, four silver atoms occupy an area of about 46 sq. Å., the concentration of groups of sites of four silver atoms is about 0.22×10^{15} per sq. cm., which corresponds very well with the observed concentration of oxygen sorbed at $-78°$, and to the concentration of oxygen held so tightly at $-183°$ that it cannot be removed by pumping at temperature.

(20) Assuming that the cross section of an oxygen molecule in a complete monolayer is 12 sq. Å.

Summary

The adsorption of hydrogen, nitrogen, argon, carbon monoxide, carbon dioxide and oxygen at pressures up to 0.1 cm. on a substantially plane, reduced surface of silver has been measured over the temperature range -195 to $20°$. Hydrogen is not measurably sorbed at any temperature; argon, nitrogen and carbon monoxide are sorbed at -195 and $-183°$ but not at -78 or $20°$. Carbon dioxide is not sorbed at $20°$ but at $-78°$ is sorbed to the slight extent of 6 cu. mm. at a pressure of 0.02 cm. The adsorption is in each case instantaneous and reversible. Oxygen is sorbed at -195 and $-183°$ and although most of the gas appears to be held by van der Waals forces some part of it cannot be removed by pumping at temperature. At -78 and $20°$ there is activated adsorption of oxygen. All the isotherms are of the type observed in a plane surface of other metals, and are satisfactorily represented by the Langmuir equation. The values of V_s as derived from the slope of the $p/v - p$ isotherm, correspond to a surface only partially covered, the coverage varying from about 20 to 90% of a close-packed monolayer.

Force–area curves are derived by two different methods, with results which differ significantly. The adsorption of oxygen on smooth silver is compared with the adsorption of oxygen on finely-divided silver as reported by Benton and Drake.

KEARNY, NEW JERSEY RECEIVED MAY 14, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Attachment and Detachment of Dropping Mercury under Various Conditions

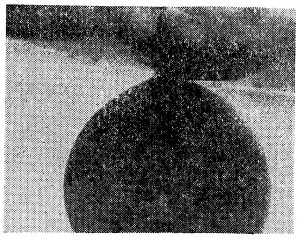
BY I. M. KOLTHOFF AND G. J. KAHAN

Although the mercury–water interfacial tension is little affected by dissolved non-capillary active electrolytes in the aqueous phase, it has been found by several workers that the drop time of mercury from a glass capillary into air-saturated water can be quite different from that into electrolyte solutions. For example, J. Heyrovský reports[1] that his capillary had a drop time of six to eight seconds in distilled water and of three seconds in electrolyte solutions. On the other hand, Kolthoff and Lingane[2] mention that with their capillary the drop times in water and in 0.1 *M* potassium chloride were hardly different. It is not stated whether the water used was air-free.

In our experiments we found that the drop time of an electrically disconnected capillary in air-containing water was badly reproducible and, as a rule, much larger than in 0.1 *M* salt solutions. Slight deviations from the vertical in the position of the capillary resulted in large variations of the drop time, whereas no such effect was found in not

(1) J. Heyrovský, in W. Böttger, "Physikalische Methoden der analytischen Chemie," Vol. II, Akadem. Verlagsges, Leipzig, 1936, p. 276.

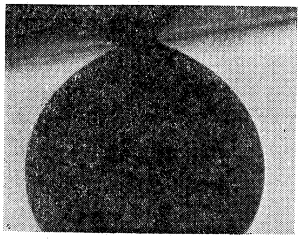
(2) I. M. Kolthoff and J. J. Lingane, *Chem. Rev.*, **24**, 26 (1939).



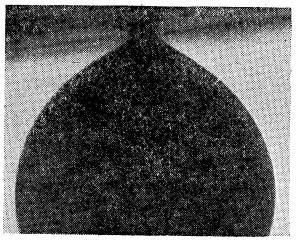
Capillary 1.—Drop in distilled water; picture 1.



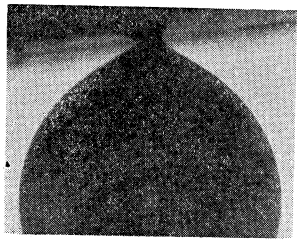
Capillary 1.—Drop in 0.1 *M* KCl; picture 2.



Capillary 2.—Drop in distilled water at intermediate stage of its life; picture 3.



Capillary 2.—Drop in distilled water at last stage of its life; picture 4.



Capillary 2.—Drop in 0.1 *M* KCl; picture 5.

Fig. 1.

too dilute electrolyte solutions. By slightly changing the angle of inclination it was sometimes possible to obtain the same drop time in air-containing water as in electrolyte solutions, the agreement being merely accidental and not readily reproducible. Moreover, it was found that the ratio $t_{H_2O}/t_{0.1\ M\ KCl}$ of an electrically disconnected capillary in air-saturated solutions depended greatly upon the properties of the capillary. A ratio of the order to 2 to 3 was found with capillaries of small diameter and small length, while wider capillaries with greater length gave ratios close to 1.

The present study attempted to find the reason for the large erratic drop time found in air-containing water when narrow, short capillaries were used. Microscopic observation of the drops revealed that in case of an abnormally large drop time the drop of mercury remained attached to the glass during its life-time (Fig. 1). Pictures 1 and 2 were obtained with capillary no. 1 which was short and had a small diameter. Picture 1 shows the drop of mercury in air-saturated water just before it fell. Picture 2 was made with the same capillary but in 0.1 *M* potassium chloride solution. In distilled water the drop touched the glass and it was larger than in 0.1 *M* potassium chloride solutions. In the electrolyte solution the drop did not touch the glass, but was suspended symmetrically from the bore of the capillary. In air-containing distilled water it hung sideways from the glass. The area of glass touched by the mercury depended upon the inclination of the capillary, and upon small irregularities of the glass surface. The short capillary (no. 1) delivered 1.62 mg. of mercury per second in 0.1 *M* potassium chloride solution without electrical connection. The drop time of this capillary was 2.5 seconds in 0.1 *M* potassium chloride solution and was of the order of three and one-half to four seconds in air-saturated distilled water.

In 0.1 *M* potassium chloride solution the drop time is approximately given by the equation

$$mgt = 2\pi r\sigma \qquad (1)$$

in which m is the mass of mercury that flows from the capillary per second, g is the acceleration due to gravity, t is the drop time, r is the radius of the bore of the capillary and σ is the interfacial tension between mercury and the solution. Experimental data which demonstrate the validity of the expression[1] are found in Kolthoff and Lingane.[3] When the drop is attached to the glass, this equation does not hold. Here not only the mercury-solution interfacial tension but also the mercury-

(3) I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1941, p. 68.

glass interfacial tension contribute to the support of the drop. The drop weight is greater under these conditions than when the drop is not attached to the glass.

Pictures 3, 4 and 5 were obtained with capillary no. 2, which had a wide bore, a length of 20 cm. and a drop time of three seconds in 0.1 *M* potassium chloride. The dropping mercury was always electrically disconnected unless otherwise stated. Picture 3 in Fig. 1 was taken when the mercury was dropping into air-saturated water. At the moment when the picture was taken the mercury was attached to the glass. At a later stage during the life of the drop the weight became large enough to detach it from the glass, but the force resulting from the interfacial tension between the mercury and the solution kept the drop suspended. Equation (1) was found to hold approximately, even though the drop was attached to the glass during part of the time. After the drop became detached from the glass its appearance and characteristics became closely similar to that of the drop formed in 0.1 *M* potassium chloride (pictures 4 and 5, Fig. 1). The ratio of the drop time in water and 0.1 *M* potassium chloride solution was close to unity.

In order to find the factors which are responsible for the attachment or detachment of the mercury to the glass experiments were carried out with water or aqueous solutions from which the air had been displaced by hydrogen. The capillary used (no. 3) had approximately the same characteristics as capillary no. 1. It was found that in the absence of oxygen the drop time of the electrically disconnected capillary in water was normal and close to the drop time in 0.1 *M* potassium chloride solutions. However, when connection was made with a pool of mercury in the bottom of the cell, the drop time in water became abnormally large and the drop became attached to the glass during its lifetime. When a positive potential was applied to the dropping mercury electrode, the drop time increased, whereas it decreased upon application of a negative potential. When the current became zero or cathodic, the drop time became normal. A normal drop time was accompanied by detachment of the drop from the glass. Some typical data are found in Table I.

In air-free 0.001 *M* potassium chloride solution, the results were qualitatively the same as in distilled water, but the drop times were smaller (see Fig. 2).

TABLE I

MERCURY DROPPING INTO AIR-FREE DISTILLED WATER SATURATED WITH HYDROGEN (CAPILLARY NO. 3)

E, applied volts	*i*, microamp.	*t*, seconds	Microscopic observation
Not connected	..	5.5	Detached
+0.8	−1.5	13.2	Attached
+ .5	−0.5	13.5	Attached
+ .1	− .1	13.5	Attached
.0	− .03	11.9	Attached
− .1	− .02	8.5	Attached
− .2	− .005	7.4	Attached
− .3	.000	5.5	Detaching
− .4	+ .01	5.5	Detached
− .5	+ .02	5.5	Detached
− .7	+ .04	5.5	Detached
−1.0	+ .06	5.2	Detached
−1.5	+ .16	4.6	Detached

When the experiments were carried out in air-free 0.001 *M* potassium iodide solution no abnormalities were observed. The drop remained detached at all applied voltages as it did in 0.1 *M* potassium chloride solution.

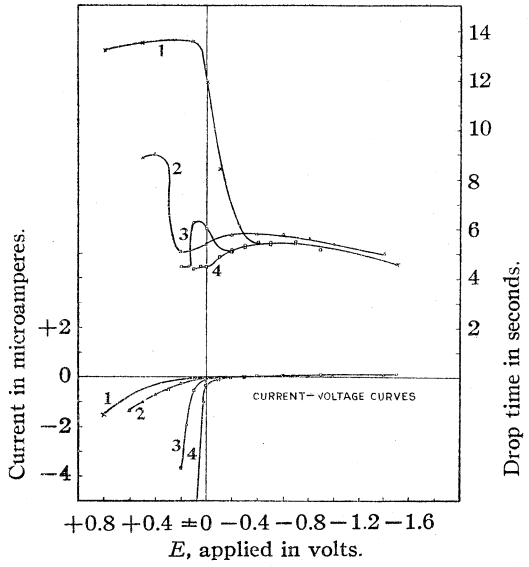


Fig. 2.—Drop times (upper part) and currents (lower parts) at various applied voltages in different solutions—Capillary 3, mercury pool in cell as reference electrode: Curve 1 in distilled water; 2, in 10^{-5} *M* lanthanum chloride; 3, in 10^{-3} *M* postassium chloride; 4, in 0.1 *M* potassium chloride.

A normal behavior, the same as in 0.1 *M* potassium chloride was observed in 5×10^{-5} *M* thorium nitrate solutions at all applied voltages.

In 10^{-5} *M* thorium nitrate and in 10^{-5} *M* lanthanum chloride a normal behavior was found at an applied voltage of zero or upon cathodic polarization. When the dropping mercury electrode was anodically polarized, the drop time be-

came abnormally large in these solutions and the drop remained attached to the glass. The data for 10^{-5} M lanthanum chloride are given in Table II.

TABLE II

MERCURY DROPPING INTO AIR-FREE 10^{-5} M LANTHANUM CHLORIDE SATURATED WITH HYDROGEN (CAPILLARY NO. 3)

E, applied volts	i, microamp.	t, seconds	Microscopic observation
Disconnected	..	5.8	Detached
+0.5	−0.95	8.9	Attached
+ .4	− .68	9.0	Attached
+ .3	− .50	8.5	Attached
+ .2	− .26	5.1	Detached
.0	− .13	5.4	Detached
− .2	− .08	5.8	Detached
− .4	− .04	5.8	Detached
− .6	− .02	5.8	Detached
− .8	+ .03	5.6	Detached
−1.0	+ .06	5.4	Detached
−1.4	+ .10	5.0	Detached

Discussion

From the fact that the drop time of the electrically disconnected mercury in air-free water was normal but became abnormal upon connection with the mercury pool, it was concluded that normal or abnormal drop time, accompanied by detachment or attachment of the drop of mercury to the glass depended upon the interaction of the double layers at the glass and mercury interfaces. Glass in contact with distilled water acquires a negative charge and the sign of its electrokinetic potential is negative. In distilled water the electric field of the electrokinetic potential extends relatively far beyond the layer of liquid firmly attached to the glass. Electrically disconnected mercury dropping into pure air-free water is uncharged and there is no electrokinetic potential at the mercury–water interface. However, when the dropping mercury is electrically connected with the mercury pool at the bottom of the cell, it acquires a positive charge and the electrokinetic potential is positive. Again the electrokinetic field at the mercury–water interface extends far beyond the liquid layer firmly attached to the mercury surface. Thus when the glass with its firmly adhering water layer and the mercury with its adhering water layer come together, the negative field around the glass attracts the positive field around the mercury, and the drop remains attached to the glass.

This explanation is substantiated by several of the experiments described. In 0.1 M or more concentrated electrolyte solutions the double layers are compressed and do not extend beyond the firmly adhering liquid films. Detachment results.

In 0.001 M potassium iodide solutions there is a strong adsorption of iodide ions on the mercury and a negative instead of a positive electrokinetic potential at the mercury results.[4] In this case the two double layers have the same sign; they repel one another and detachment results.

In 5×10^{-5} M thorium nitrate the electrokinetic potential of the glass is positive. At the positive side of the isoelectric point of the mercury the sign of the double layer is also positive. The double layers at the glass and mercury surfaces repel each other and the drop remains detached.

At first glance one might expect that on the negative side of its isoelectric point the mercury in the thorium nitrate solution would become attached to the glass. However, the tetravalent thorium ions compress the negative double layer around the mercury so much that the electric intensity outside the attached liquid film is zero.

Not explained are the facts that the drops of anodically polarized mercury become attached to the glass in 10^{-5} M lanthanum chloride and 10^{-5} M thorium nitrate.

In the experimental part it was shown that the electrically disconnected mercury becomes attached to the glass when it is dropping into air-saturated water. Under these conditions the mercury is no longer electrically neutral. By the adsorption of oxygen it acquires a positive charge. Hence, there again results interaction between the negative field close to the glass and the positive field close to the mercury, leading to attachment.

In the above we have considered the interaction between the two liquid films as the primary cause of the attachment. Whether there is an aqueous film between the attached mercury and the glass or whether the liquid is squeezed out cannot be answered on the basis of our experiments. In view of the experiments of Frumkin, *et al.*,[5] one could expect that such a film between the attached drop and the glass should exist.

In order to avoid the abnormal effects described in this paper it is recommended that the characteristics of a capillary—drop time and mass of mercury per second—always be determined in

(4) For a detailed picture of the potential curves in iodide see I. M. Kolthoff and J. J. Lingane, "Polarography," p. 99.

(5) A. Frumkin, A. Gorodetzkaja, B. Kabanow and N. Nekrassow, *Physik. Z. Sowjetunion*, **1**, 255 (1932); B. Derjaguin and M. Kussakow, *Acta Physicochim.*, **10**, 25 (1939).

0.1 *M* electrolyte solutions and not in distilled water.

Acknowledgment is made to the Graduate School of the University of Minnesota for a grant which enabled us to carry out this investigation.

Summary

1. When electrically disconnected mercury drops into air-saturated water or when mercury connected with a pool of mercury drops into air-free water an abnormally large drop time is found. The drop of mercury remains attached to the glass. The abnormal behavior becomes more pronounced the smaller is the bore of the capillary.

The results obtained with an abnormally dropping capillary are badly reproducible and depend greatly on the degree of inclination of the capillary.

2. The abnormal behavior has been interpreted on the basis of interaction between the electric double layers at the glass and at the mercury–aqueous phase interfaces.

MINNEAPOLIS, MINNESOTA RECEIVED JULY 18, 1942

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

Studies in Stereochemistry. II. Steric Strains as a Factor in the Relative Stability of Some Etherates of Boron Fluoride

BY HERBERT C. BROWN AND RICHARD M. ADAMS[1]

Modern physical techniques for studying gaseous molecules have contributed much information regarding molecular configurations.[2,3] In the main, these later results have confirmed those of the early workers in stereochemistry who drew their conclusions from isomer number and chemical reactions. In many instances, however, detailed data on atomic dimensions and valence angles and the careful study of small irregularities in the physical and chemical properties of substances has made possible some interesting extensions of the classical principles of stereochemistry.

One recent extension of this kind is based on evidence that steric interference between two groups may weaken considerably the bond joining the groups. To illustrate, the per cent. dissociation of the tetraaryldialkylethanes and the dixanthyldialkylethanes increases with increasing size of the alkyl group[4]; and the ortho methyl groups of sym-tetraphenyldi-*o*-tolylethane increase the dissociation into free radicals more than do the methyl groups of the corresponding meta or para derivatives (25% *vs.* 5%).[5]

Unfortunately, these examples are not entirely satisfactory. The molecules are large and complicated; moreover, interpretation of the results is made particularly hazardous by the fact that resonance plays an important part in the dissociation of such ethane derivatives. It would be highly desirable to have more substantial evidence of this same effect in simpler molecules in which resonance is not important. Recently, such examples of unmistakable weakening of bonds by steric strains have been found.[6] A study of the relative stability of some coördination compounds of borine, boron fluoride and trimethylboron with amines revealed that trimethylamine is a stronger base (in the generalized Lewis sense[7]) than pyridine toward the acids hydrogen chloride, borine and boron fluoride, but that the reverse is true when trimethylboron is used as the reference acid.

This "anomalous" result is apparently due to steric strains, for molecular models reveal that in the compounds studied considerable steric interference is to be expected only in trimethylamine-trimethylboron.[8,9]

There are reasons to believe that such steric strains are more common than has been supposed

(1) This paper is taken from a dissertation submitted by Richard M. Adams to the Faculty of the Division of the Physical Sciences of the University of Chicago, in partial fulfillment of the requirements for the degree of Master of Science.

(2) Stuart, "Molekülstruktur," Julius Springer, Berlin, 1934.

(3) Pauling, "The Nature of the Chemical Bond," 2nd ed., Cornell University Press, Ithaca, N. Y., 1940.

(4) Conant and Bigelow, THIS JOURNAL, **50**, 2041 (1928); Conant, Small and Sloan, *ibid.*, **48**, 1743 (1926).

(5) Marvel, Mueller, Himel and Kaplan, *ibid.*, **61**, 2777 (1939).

(6) Brown, Schlesinger and Cardon, *ibid.*, **64**, 325 (1942).

(7) Lewis, *J. Franklin Inst.*, **226**, 293 (1938).

(8) For a discussion of the nomenclature used for these coördination compounds, see Davidson and Brown, THIS JOURNAL, **64**, 316 (1942), footnote 11.

(9) It was pointed out that steric strains present in trimethylamine-trimethylboron must be duplicated in its isostere, hexamethylethane, since the dimensions and configurations of the two molecules are almost identical.[6] It is of considerable interest that in a recent electron-diffraction study of this hydrocarbon, Bauer and Beach [*ibid.*, **64**, 1142 (1942)] find evidence that the central C–C bond is stretched (1.58 *vs.* 1.54 Å.).

and that they play a far more important role in determining the physical and chemical properties of substances than has hitherto been realized. It appears highly desirable to obtain more information concerning the existence and magnitude of these effects. Accordingly, a study was made of the addition compounds between boron fluoride and some representative aliphatic ethers (methyl ether, ethyl ether, isopropyl ether and tetrahydrofuran). Particular attention was given to the effect of steric strains on the relative ease with which the addition compounds dissociate.

Experimental Part

Apparatus and Methods.—The high vacuum apparatus shown in Fig. 1 was constructed and used in the preparation and study of the etherates of boron fluoride. The materials were introduced into the apparatus through the tube opener, TO, and condensed in the desired section of the apparatus (*e. g.*, in the storage bulbs, SB) with aid of liquid nitrogen. The starting materials were purified by fractional distillation and fractional condensation in the fractionation system, FS. The homogeneity of the substances used in this investigation was usually established by vapor pressure measurements. (In some cases purification by distillation outside the vacuum system was relied upon.) The vapor pressure of the more volatile substances could be measured satisfactorily on the manometers, M_1 and M_2, in the fractionation system, FS. The vapor pressures of the less volatile substances were studied in the apparatus HTB (high temperature bulb).[10]

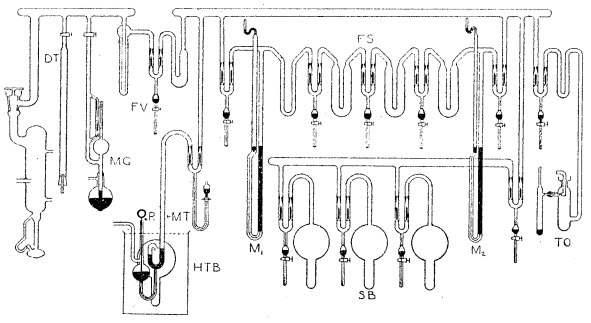


Fig. 1.—Diagram of apparatus.

This apparatus (HTB) was used as follows. The material was condensed in the apparatus with liquid nitrogen, the mercury was allowed to rise in the tube, MT, by raising the rod, R, thus shutting the flask off from the rest of the vacuum line. The entire apparatus was immersed in a heated bath and the pressures read with a cathetometer. The bath was constructed from a 3-liter beaker carefully selected for freedom from striations. The sides of this beaker were insulated with several layers of asbestos paper, but a narrow section opposite the manometer was left uncovered to serve as a window for observing the pressure. A close-fitting asbestos lid covered the beaker, which rested on a heavy copper plate heated with a gas flame. An air-driven stirrer kept the bath liquid (either water or paraffin oil) well stirred. With this bath the temperature could be maintained constant for periods of time more than sufficient for the purposes of the investigation.

Preparation and Study of the Etherates of Boron Fluoride.—The usual procedure for the preparation of the etherates of boron fluoride was to condense equal volumes (measured as gases under standard conditions)[11] of the ether and boron fluoride in the high temperature bulb, HTB. Very shortly after the liquid nitrogen was removed, the components reacted to form the addition compound.

The flask was heated by means of the bath previously described and the saturation pressures of the complex noted. After a series of measurements had been completed, a portion of the compound was removed to another part of the apparatus, and the observations were repeated on the portion remaining. The reproducibility of the values observed was taken as satisfactory evidence of the homogeneity of the products.

The degree of dissociation of the addition compounds ($R_2O:BF_3 \rightleftarrows R_2O + BF_3$) over a range of temperatures was studied in the same apparatus, HTB. Equal volumes of ether and boron fluoride were introduced into the flask and the pressures observed over a range of temperatures. Since the size of the samples introduced was selected so that the total pressure would be considerably below the saturation pressure of the complex, the degree of dissociation, α, could be calculated from the ratio of the observed pressure to the pressure calculated assuming no dissociation. The equilibrium constant at each temperature was then calculated from the value of α by the use of the equation

$$K_p = \alpha^2 P/(1 - \alpha^2)$$

The free energy change, ΔF, was calculated from the equilibrium constant

$$\Delta F = -RT \ln K$$

Finally, from the variation in K with temperature, ΔH could be calculated by the well-known thermodynamic equation

$$\Delta H = RT^2 \frac{\mathrm{d} \ln K}{\mathrm{d}T}$$

Since the etherates of boron fluoride dissociate almost completely at temperatures where the saturation pressures of the complexes are high, it was necessary to work at comparatively low pressures (10–30 mm.). Preliminary experiments indicated that it was possible to measure pressures over a considerable range of temperature to better than 0.1 mm. This accuracy was considered satisfactory. The observed readings were, of course, corrected for the density of mercury and its vapor pressure (the latter correction was necessary because one limb of the manometer was open to a high vacuum).

Results

Methyl Ether–Boron Fluoride, $(CH_3)_2O:BF_3$.—The addition compound, methyl ether–boron fluoride, was prepared by the reaction of 12.5 cc. of

(10) Burg and Schlesinger, THIS JOURNAL, **59**, 785 (1937).

(11) All volumes given in this paper refer to gases at standard conditions.

boron fluoride (p = 309 mm. at −111.6°)[12] and 12.4 cc. of methyl ether (p = 119.6 mm. at −60°)[13] at a low temperature. The product was a white solid which melted to a colorless liquid at −14 to −12°. The saturation pressure data of the complex are given in Table I and represented graphically in Fig. 2-A. It has been previously reported

Table I

Saturation Pressures of Methyl Ether–Boron Fluoride

Temp., °C.	0	10	15	20	30	40
Press., mm.	0.9	1.6	2.3	3.0	6.1	9.5
Temp., °C.	50	60	70	80[a]	90[a]	98.5[a]
Press., mm.	17.2	31.2	52.7	90.3	144.3	179.0

[a] The measurements from 80° on were made on a larger sample, prepared from 38.0 cc. each of methyl ether and boron fluoride.

that the "boiling point" of the complex is 126–8°.[14] Extrapolation of the saturation pressure curve to 760 mm. yields a value of 127° for the "boiling point." This is not a true "boiling point," since at this temperature the complex is practically completely dissociated into its components, methyl ether and boron fluoride.

The dissociation of the complex was studied over a range of temperatures in the manner previously described. Methyl ether, 5.83 cc., and 5.83 cc. of boron fluoride were condensed in the high temperature bulb (volume, 247.6 cc.) and permitted to react. The apparatus was then heated to a temperature at which the total pressure was below the saturation pressure of the complex and observations made over a range of temperatures. The results are summarized in

Table II

Dissociation Pressures of Methyl Ether–Boron Fluoride

Temp., °C.	Pressure observed, mm.	Pressure calculated, mm.	Degree of dissociation, α	Dissociation constant, K (atm.)
66	36.2	22.4	0.631	0.032
70	37.4	22.5	.662	.038
73	38.2	22.7	.682	.044
75.5	39.1	22.9	.707	.051
78.5	40.2	23.0	.748	.067
81	40.7	23.2	.754	.071
83.5	41.4	23.4	.769	.079
86	42.1	23.5	.791	.091
89	43.0	23.7	.814	.111
93	44.0	24.0	.833	.131
99	45.4	24.4	.861	.171

(12) Ruff, *Z. anorg. allgem. Chem.*, **206**, 60 (1932).
(13) Maass and Boomer, This Journal, **44**, 1713 (1922).
(14) Gasselin, *Ann. chim. phys.*, [7] **3**, 5 (1894).

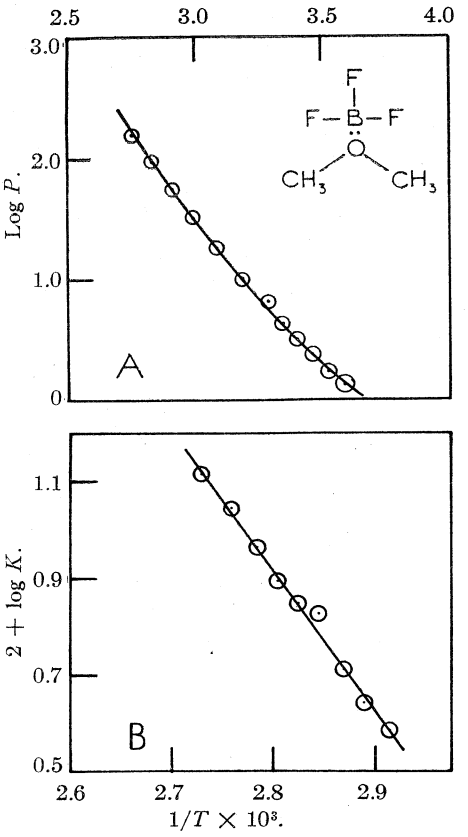


Fig. 2.—Methyl ether–boron fluoride: A, saturation pressure data; B, dissociation data.

Table II and Fig. 2-B. The data may be represented by the equation

$$\text{Log } K_p = -(2904/T) + 7.049$$

Ethyl Ether–Boron Fluoride, $(C_2H_5)_2O:BF_3$.—The addition compound, ethyl ether–boron fluoride, was prepared by the reaction of 28.0 cc. of boron fluoride and 28.3 cc. of ethyl ether (p = 186.1 mm. at 0°)[15] at low temperatures. The slight excess of ethyl ether was pumped out of the flask after the compound had warmed up to room temperature. The product was a white solid which melted to a colorless liquid at −50 to −52°. The saturation pressure data of the complex are given in Table III and represented graphically in Fig. 3-A.

Table III

Saturation Pressures of Ethyl Ether–Boron Fluoride

Temp., °C.	0	5	10	20	30	40
Pressure, mm.	0.4	0.7	1.0	1.9	3.8	7.8
Temp., °C.	50	60	70	79	91	98.5
Pressure, mm.	15.2	28.2	50.1	83.3	148.8	187.1

(15) Taylor and Smith, This Journal, **44**, 2457 (1922).

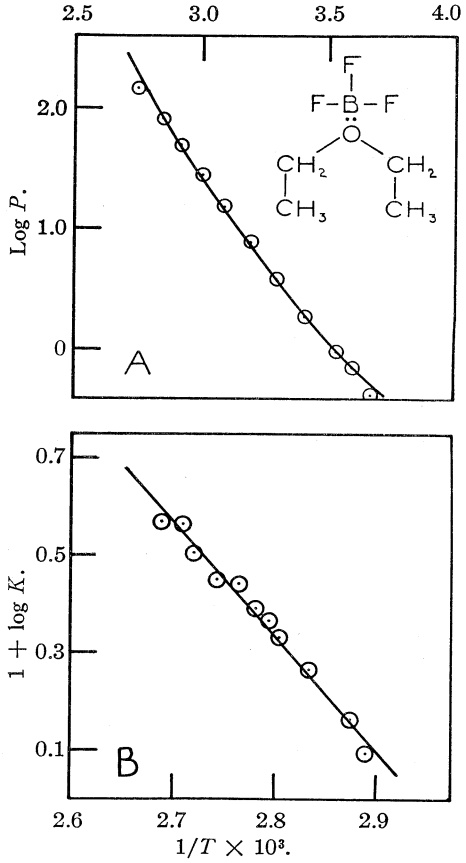


Fig. 3.—Ethyl ether–boron fluoride: A, saturation pressure data; B, dissociation data.

The "boiling point" of the complex has been previously reported as 123–125°,[14] and as 125–126°.[16] Extrapolation of the saturation pressure curve to 760 mm. gives 124° for the "boiling point."

The dissociation of the complex was studied over a range of temperatures in the manner previously described; the sample used was prepared from 5.80 cc. of ethyl ether and 5.83 cc. of boron fluoride. The results of this study are summarized in Table IV and Fig. 3-B. The data may be expressed by the equation

$$\text{Log } K_P = -(2384/T) + 6.013$$

TABLE IV

DISSOCIATION PRESSURES OF DIETHYL ETHER–BORON FLUORIDE

Temp., °C.	Pressure observed, mm.	Pressure calculated, mm.	Degree of dissociation, α	Dissociation constant K(atm.)
73	41.6	22.7	0.833	0.124
75	42.2	22.8	.851	.146
80	43.3	23.1	.874	.184
83.5	44.1	23.4	.885	.215
85	44.5	23.5	.894	.233
86.5	44.8	23.6	.898	.246
88.5	45.2	23.7	.907	.276
91.5	45.6	23.9	.908	.282
94.5	46.2	24.1	.917	.321
96	46.6	24.2	.926	.369
99	47.0	24.4	.926	.372

(16) Hennion, Hinton and Nieuwland, THIS JOURNAL, **55**, 2858 (1933).

Isopropyl Ether–Boron Fluoride, $(i\text{-}C_3H_7)_2O$: BF_3.—A commercial sample of isopropyl ether was purified by distillation through a 16-plate column. The fraction boiling at 68° under 751 mm. with $n^{20}D$ 1.3682 was used. The addition compound, isopropyl ether–boron fluoride, was prepared by condensing together (in the high temperature bulb) 31.0 cc. of boron fluoride and 31.0 cc. of isopropyl ether at the temperature of liquid nitrogen. The addition compound is a white solid at room temperature; its melting point is above 68°, but quite indefinite, apparently because of rapid decomposition of the complex at these temperatures.[17] This instability was also evidenced by its behavior during preliminary studies of its saturation pressures. At temperatures up to 45–50°, the complex did not undergo any apparent change. Above 50°, however, a slow, irreversible change of some sort occurred, for the pressure began to increase slowly, although the temperature was maintained constant. At about 68°, decomposition was so rapid that within a few minutes, the pressure rose to 180 mm.—about twice 97.8 mm., the value at 61°. After reaching this maximum value, the pressure dropped, rapidly at first, then more slowly. By working fast, and using freshly prepared samples of the complex, it was found possible to obtain reproducible values of the saturation pressures at temperatures up to 61°. The data are listed in Table V and are represented graphically in Fig. 4-A.

TABLE V

SATURATION PRESSURES OF ISOPROPYL ETHER–BORON FLUORIDE

Temp., ° C.	23	30	40	50	61
Pressure, mm.	6.4	10.1	20.6	42.5	97.8

Because of this instability of the complex its dissociation could be studied only over a relatively

(17) This decomposition was studied, but no definite conclusion was reached as to the reactions involved. It is probable that the first step is the splitting of the ether with the formation of isopropyl fluoride and isopropoxy boron fluoride, a reaction similar to the well-known reactions of boron chloride and boron bromide with ethers [Wiberg and Sütterlin, *Z. anorg. allgem. Chem.*, **202**, 22 (1931); Benton and Dillon, THIS JOURNAL, **64**, 1128 (1942)]. The isopropyl fluoride then probably reacts with the boron fluoride present [Burwell and Archer, *ibid.*, **64**, 1033 (1942)], forming polymeric materials of low volatility.

short temperature range. Boron fluoride, 3.10 cc., was condensed with 3.10 cc. of isopropyl ether in the high temperature bulb in the usual manner. (It was necessary to work with a small sample in order to volatilize completely the material at a temperature where the rate of decomposition was comparatively slow.) The small size of the sample and the necessity for making rapid measurements reduce the accuracy of the data. However, they clearly indicate that the complex is highly dissociated. The results of the dissociation studies are listed in Table VI and shown graphically in Fig. 4-B. Because of the low accuracy and short temperature range, no attempt has been made to draw a line through the points on the graph (4-B).

TABLE VI

DISSOCIATION PRESSURES OF ISOPROPYL ETHER–BORON FLUORIDE

Temp., °C.	Pressure observed, mm.	Pressure calculated, mm.	Degree of dissociation, α	Dissociation constant, K(atm.)
42	20.1	11.0	0.827	0.057
44	20.5	11.0	.864	.079
46.2	20.8	11.1	.874	.089
46.5	20.9	11.1	.883	.097
51.5	21.4	11.3	.894	.112

Tetrahydrofuran–Boron Fluoride, $C_4H_8O:BF_3$. —Tetrahydrofuran was prepared by the decarboxylation of 2-furancarboxylic acid[18] followed by reduction of the resulting furan.[19] The product was distilled through a fractionating column with a rated efficiency of 16 theoretical plates, and a middle fraction (b. p. 65° at 747 mm.; $n^{20}D$ 1.4049) was taken for use in this investigation. The addition compound, tetrahydrofuran–boron fluoride, was prepared by the reaction of 35.0 cc. of tetrahydrofuran with 35.0 cc. of boron fluoride at the temperature of liquid nitrogen. The product was a white solid which melted to a colorless liquid at 8–10°. The saturation pressure data of the complex are given in Table VII and Fig. 5-A.

TABLE VII

SATURATION PRESSURES OF TETRAHYDROFURAN–BORON FLUORIDE

Temp., ° C.	39.5	58	68	79	88	98.5
Pressure, mm.	1.0	2.3	4.0	7.3	12.0	20.7

The dissociation of the complex was studied over a range of temperatures in the manner previously described, using a sample prepared from 2.46 cc. of tetrahydrofuran and 2.49 cc. of boron fluoride. The results are summarized in Table VIII and in Fig. 5-B. The data are expressed by the equation

$$\text{Log } K_P = (-2918/T) + 5.882$$

(18) "Organic Syntheses," Coll. Vol. I, 269 (1929).

(19) "Organic Syntheses," **16**, 77 (1936).

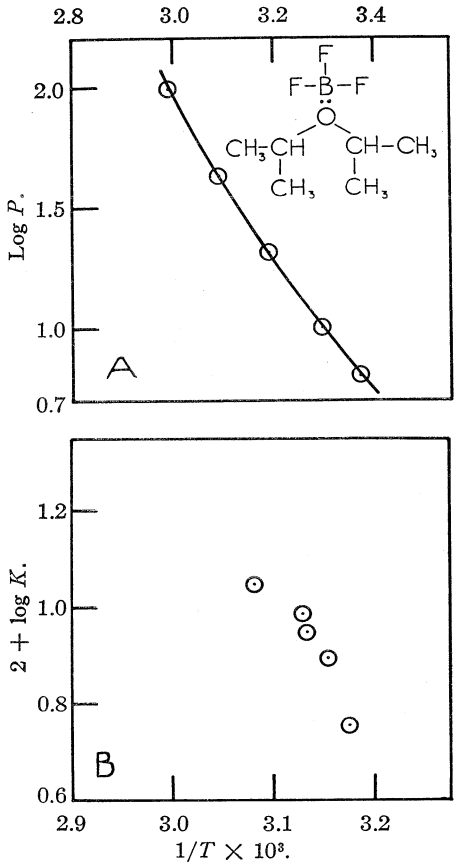


Fig. 4.—Isopropyl ether–boron fluoride: A, saturation pressure data; B, dissociation data.

TABLE VIII

DISSOCIATION PRESSURES OF TETRAHYDROFURAN–BORON FLUORIDE

Temp., °C.	Pressure observed, mm.	Pressure calculated, mm.	Degree of dissociation, α	Dissociation constant, K(atm.)
94.5	15.7	10.2	0.539	0.0079
97	16.1	10.2	.578	.0106
99	16.3	10.3	.583	.0110
104	17.1	10.4	.644	.0159
108	17.4	10.5	.657	.0174
110	17.6	10.6	.660	.0178
113	18.0	10.7	.682	.0206
117	18.5	10.8	.713	.0252
123	19.1	11.0	.736	.0297

Discussion

It is a generally accepted postulate of modern electronic theories of organic chemistry that the substitution of an alkyl group for hydrogen in a molecule produces an electronic displacement away from the substituent.[20] The increase in

(20) Ingold, *Chem. Revs.*, **15**, 225 (1934).

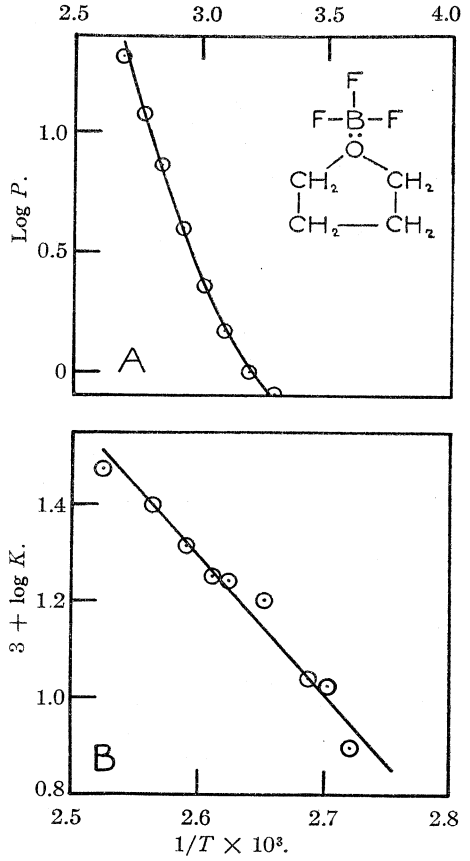


Fig. 5.—Tetrahydrofuran–boron fluoride: A, saturation pressure data; B, dissociation data.

basicity noted in the series[21] ammonia, methylamine and ethylamine is thus explained.

NH_3	$CH_3 \rightarrow NH_2$	$CH_3 \rightarrow CH_2 \rightarrow NH_2$
$K = 1.8 \times 10^{-5}$	5.0×10^{-4}	5.6×10^{-4}

The decrease in acidity in the series water,[21] methyl alcohol[22] and ethyl alcohol[23] is similarly interpreted.

HOH	$CH_3 \rightarrow OH$	$CH_3 \rightarrow CH_2 \rightarrow OH$
$K = 1 \times 10^{-16}$	7×10^{-18}	7×10^{-20}

It would, therefore, be predicted that ethyl ether should be a somewhat stronger base than methyl ether. However, if boron fluoride is used as the reference acid, the opposite is true. Under comparable conditions ethyl ether–boron fluoride is more highly dissociated than the corresponding methyl ether complex (Table IX).

It is suggested that this inversion is due to steric strains which are more important in the ethyl ether complex than in the corresponding methyl ether derivative. This conclusion is based on the following considerations. Three possible configurations of the ethyl ether molecule are shown in Fig. 6-B, D, F. The last of these may be immediately discarded because of the tremendous strains involved—the distance between the two methyl groups is only 1.7 Å. whereas the van der Waals radius of each methyl group is approximately 2.0 Å. It is more difficult to decide be-

(21) "Handbook of Chemistry and Physics," 25th ed., Chemical Rubber Company, Cleveland, Ohio, 1941, p. 1341.
(22) Faurholt, *Z. physik. Chem.*, **126**, 103 (1927).
(23) Danner, THIS JOURNAL, **44**, 2841 (1922).

TABLE IX

SUMMARY OF DISSOCIATION DATA FOR ETHERATES OF BORON FLUORIDE

Compound	K_{100}	K_{50}	ΔF_{100}	ΔF_{50}	ΔH	ΔS
Methyl ether–boron fluoride	0.184	0.011	1250	2900	13,300	32.3
Ethyl ether–boron fluoride	.420	.043	640	2020	10,900	27.5
Isopropyl ether–boron fluoride	..	.0115	..	1340	..	..
Tetrahydrofuran–boron fluoride	.0011	.0007	3310	4660	13,400	27.1

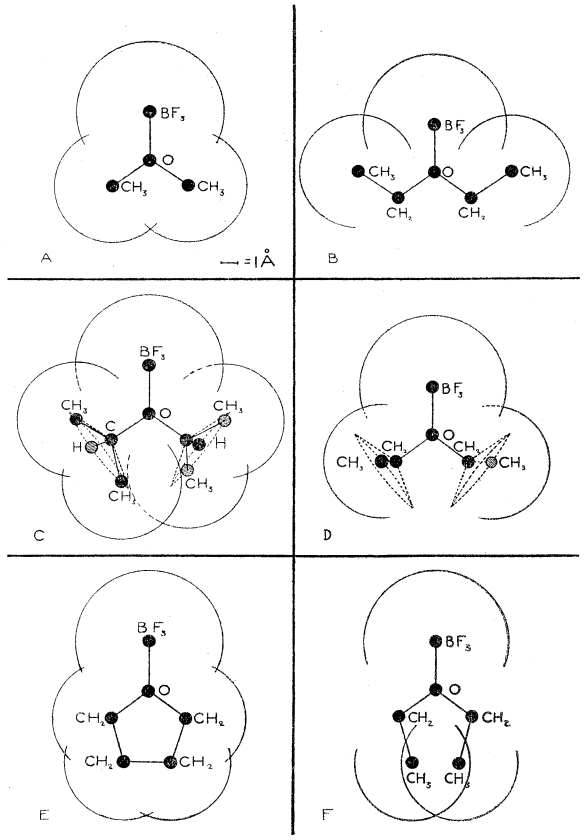


Fig. 6.—Molecular models: A, methyl ether–boron fluoride; B, D, F, ethyl ether–boron fluoride; C, isopropyl ether–boron fluoride; E, tetrahydrofuran–boron fluoride. These models are constructed using the bond distances and van der Waals radii given by Pauling.[3] The van der Waals radii are reduced somewhat (25%) to permit clearer visualization of the relative steric strains.

tween the other two possibilities (Fig. 6-B, D), but there are good reasons to believe that the arrangement shown in Fig. 6-B is the normal configuration of the ethyl ether molecule.[24]

The addition of boron fluoride to an ethyl ether molecule with this configuration must be markedly hindered as a result of the position of the end methyl groups and the size of the boron fluoride molecule (Fig. 6-B). In all probability, the addition of the boron fluoride group to the oxygen atom is accompanied by a rearrangement of the ethyl ether molecule into a configuration of somewhat higher energy, such as is shown in Fig. 6-D. As a result, the stability of the ethyl ether complex with respect to dissociation into its components is lowered relative to the corresponding methyl ether complex (Fig. 6-A).

The argument may be extended to the isopropyl ether–boron fluoride complex (a possible configuration for which is shown in Fig. 6-C), leading to the conclusion that the dissociation of this complex is also favored by the steric effects. Of the three ethers, isopropyl ether is the weakest base (Table IX), although from the inductive effect of the alkyl groups, it would have been predicted to be the strongest.

In order to test the hypothesis, the study of the dissociation of tetrahydrofuran–boron fluoride was undertaken. On the basis of the factors commonly believed to control base strength, it would be predicted that this cyclic ether would be approximately equal in strength to ethyl ether. If steric strains play the important role ascribed to them in this publication in altering the stability of addition compounds, it follows that the base strength of this cyclic ether should be markedly greater than that of ethyl ether, since the rigidity of the five-membered ring greatly reduces the possibility of steric strains (Fig. 6-E). The fact that tetrahydrofuran–boron fluoride is by far the most stable of the etherates studied (Table IX) lends considerable support to the hypothesis of steric strain.

(24) Stuart, *op. cit.*, pp. 101–102, 236; *Phys. Rev.*, **38**, 1372 (1931); *Z. Physik*, **63**, 533 (1930). Stuart bases his conclusion upon evidence from dipole moment studies, upon his investigations of the Kerr constant, and upon considerations of atomic dimensions and bond angles.

Summary

1. The boron fluoride addition compounds with methyl ether, ethyl ether, isopropyl ether and tetrahydrofuran have been prepared and characterized.

2. The dissociation of these compounds (R_2O: $BF_3 \rightleftarrows R_2O + BF_3$) was studied over a range of temperatures; and ΔH, ΔF and ΔS for the reaction were obtained.

3. The basic strength of the ethers decreases in the order: tetrahydrofuran, methyl ether, ethyl ether, isopropyl ether. This order is inexplicable on the basis of the factors generally believed to control base strength. The anomalies may be accounted for by taking into consideration the probable steric strains resulting from spatial limitations within the respective molecules.

CHICAGO, ILLINOIS RECEIVED JUNE 4, 1942

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

Studies in Stereochemistry. III. The Preparation of *d*-1-Deutero-2-methylbutane and the Study of Its Optical Rotation

BY HERBERT C. BROWN AND CORNELIUS GROOT[1]

The discovery of isotopes has brought about far-reaching changes in the prevalent concepts and has opened up a wide variety of problems for investigation. One of these which is of considerable importance to stereochemistry has not yet been conclusively solved, in spite of numerous attempts. The point at issue is whether a substance such as $R'—\overset{R_1}{\underset{R_2}{C}}—R''$, in which the two atoms or groups R′ and R″ differ only in their isotopic composition, exhibits optical activity. At the present time, all attacks upon the problem have been restricted to the use of hydrogen and deuterium as the isotopic substituents. These two isotopes differ much more than others in their chemical and physical properties; moreover, until

(1) This paper is taken from a dissertation submitted by Cornelius Groot to the Faculty of the Division of the Physical Sciences of the University of Chicago, in partial fulfillment of the requirements for the degree of Master of Science.

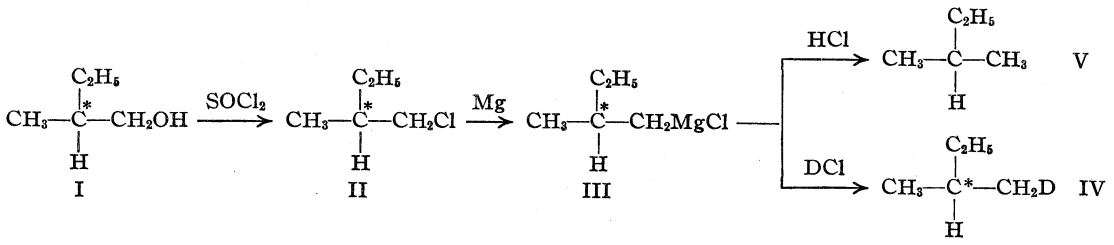
recently they have been the only isotopes available in large quantities.

The question whether the difference between hydrogen and deuterium may give rise to optical activity has been investigated mainly by three general methods: (1) resolution of a suitable hydrogen–deuterium compound by classical means; (2) introduction of deuterium into a compound containing one asymmetric center so as to induce a new asymmetric center (partial asymmetric synthesis); and (3) introduction of deuterium into a suitable active compound in such a way that two groups attached to the asymmetric center become structurally identical but isotopically distinct.

In spite of repeated investigations[2] involving each of the three general procedures, no definite decision to the question of isotopes as a source of optical activity can yet be made. It is evident that the first two methods (resolution and partial asymmetric synthesis) are less satisfactory than the third method mentioned. Failure to resolve a compound or failure to induce a new asymmetric center does not permit valid conclusions to be drawn with regard to the cause of the failure. This failure may be due to the experimental techniques, or to the insensitivity of the instruments used, or perhaps to the inherent nature of the substance. On the other hand, more definite information should be obtainable by suitable application of the third method. The compound formed will either be observed to be optically active or an upper limit will be put on the optical activity resulting in this instance from the hydrogen–deuterium asymmetry. To obtain such definite results, it is however essential that the starting material be optically active, easily obtained in moderately large quantities and easily purified; that it be readily transformed into the desired product by reactions which are very unlikely to affect the active center; and that the reaction product be one which can be rigorously purified.

(2) Previous work on the subject is reviewed by Buchanan, *J. Soc. Chem. Ind.*, **57**, 748 (1938).

These stringent conditions for the starting product are satisfactorily filled by *d*-2-methylbutanol-1 (I). Large quantities of this material can be isolated readily in a high state of purity from fusel oil[3]; moreover, the substance can be transformed by simple reactions (II, III) into the desired product, *d*-1-deutero-2-methylbutane (IV), which may be rigorously purified by distillation through an efficient column. The boiling point of isopentane (27.7°) or of its deuterium derivative is much lower than that of any probable optically active impurity.[4]



Accordingly, the preparation of *d*-1-deutero-2-methylbutane by these reactions was undertaken. A total of five preparations were carried out. In three of the preparations the Grignard reagent (III) was treated with deuterium chloride; in the other two, with hydrogen chloride. The product (IV or V) of each run was carefully fractionated in a column (rated efficiency: 100 theoretical plates) and 10 approximately equal fractions (10–12 cc.) collected. This material was then examined for possible activity in a sensitive polarimeter at the University of Illinois.[5]

The instrument, a Schmidt and Haensch (Berlin) product, was constructed to read rotations to a thousandth of a degree. Since for a colorless substance the magnitude of the rotation of plane polarized light is approximately inversely proportional to the square of the wave length, the mercury green line at 5461 Å. was utilized for the observations. After a number of preliminary experiments, the zero reading (the average of five consecutive determinations) could be reproduced with an average deviation of 0.001°.

(3) Brauns, *J. Research Natl. Bur. Stand.*, **18**, 315 (1937); Whitmore and Olewine, THIS JOURNAL, **60**, 2569 (1938).

(4) To illustrate this point, calculation reveals that the distillation of a 50:50 mixture of *d*-1-deutero-2-methylbutane and *d*-1-chloro-2-methylbutane through a column operating at an efficiency of 50 theoretical plates yields a product which, per mole, *contains less than* 10^{-30} *mole of the active chloride.*

(5) The authors wish to express their appreciation of the kindness of Professors Roger Adams and Duane T. Englis in placing this instrument at their disposal. They also wish to acknowledge the assistance given them by Professor Englis and numerous students in the Department of Chemistry of the University of Illinois during this phase of the investigation.

In each run, fractions 2 through 9 were examined in the polarimeter in a tube of 1 dm. in length (the end fractions 1 and 10 were not studied, since such impurities as may have been present in the crude product would have concentrated in these fractions). Five consecutive readings of each fraction were taken. The results for all eight fractions in a run were then averaged to obtain the value for the run. These values, with the average deviations, are listed in Table I.

TABLE I

SUMMARY OF OPTICAL ROTATION DATA (1-DM. TUBE) FOR *d*-1-DEUTERO-2-METHYLBUTANE AND ISOPENTANE

Run	Substituent	Rotation	Average deviation
A	Deuterium	0.002	0.003
B	Hydrogen	.003	.005
C	Deuterium	.000	.003
D	Hydrogen	− .001	.002
E	Deuterium	.001	.001
Average for deuterium runs		.001	.001
Average for hydrogen runs		.001	.002

In Table II the data for run E are expanded to illustrate the accuracy which was attained. It is concluded that the optical rotation (1-dm. tube) of *d*-1-deutero-2-methylbutane is definitely less than 0.005° and is probably less than 0.002°.[6]

butanol-1 from fusel oil was packed with single-turn metal helices.[7] The dimensions of the packed section were 108 inches by 7/8 inch. For convenience in assembling and handling, the column was constructed in three sections of equal lengths which fitted together by means of standard ground glass joints. Each section was vacuum-jacketed and equipped with an individual heating jacket. Since these heating jackets offer some advantages over the more conventional designs, they will be described in some detail. Each jacket consists of a 36-inch length of 2-inch glass tubing, the ends of which fit into grooves cut into Transite plates. These plates are held against the glass tube by four 0.25 inch steel rods, threaded at the ends and fitted with nuts. (In later designs of this heating jacket used for other fractionating columns, the end plates are constructed of Bakelite and the supporting rods are included within the glass tube, making a very compact unit.) The heating element consists of 12 lengths of 24 gage (B. and S.) nichrome wire. These wires, encased in lengths of 4-mm. glass tubing, extend longitudinally through the jacket, and are joined in series by means of connections on the Transite ends. A thermometer is suspended in each jacket. Since the heat loss from the column is greatly reduced by the vacuum jacket, it is unnecessary to control the temperature of the heating jackets very closely. Usually the temperature was maintained at 2–5° below the boiling point of the material being distilled, but considerably greater variations (such as sometime occurred at night during continuous operation) did not noticeably affect the efficiency of the column.

The construction of the column in three individual sec-

TABLE II

EXPANDED DATA OF DISTILLATION AND OPTICAL ROTATION (1-DM. TUBE) OF *d*-1-DEUTERO-2-METHYLBUTANE (RUN E)

Fraction	Volume, cc.	Boiling point, °C.	Barometric pressure, mm.	Polarimeter readings	Average	Rotation[a]
1	11	19.2–26.8	746	.....	...	...
2	10	26.8–27.0	746	2.323, 2.324, 2.322, 2.325, 2.327	2.324	0.001
		Zero readings		2.331, 2.325, 2.326, 2.324, 2.327	2.327	
3	10	27.0	746	2.325, 2.325, 2.324, 2.324, 2.323	2.324	.001
4	10	27.0	746	2.327, 2.327, 2.329, 2.325, 2.321	2.326	.003
		Zero readings		2.316, 2.326, 2.319, 2.323, 2.313	2.320	
5	10	27.0	746	2.328, 2.329, 2.351, 2.354, 2.334	2.339	.016[b]
6	12	26.9	744	2.326, 2.321, 2.321, 2.323, 2.322	2.323	.000
7	10	26.9	744	2.330, 2.329, 2.329, 2.330, 2.329	2.329	.006
		Zero readings		2.326, 2.328, 2.317, 2.322, 2.314	2.321	
8	10	26.9	744	2.327, 2.325, 2.326, 2.326, 2.326	2.326	.003
9	10	27.0	744	2.312, 2.322, 2.323, 2.311, 2.325	2.318	− .005
10	9	Holdup	...	.....	...	...

[a] Calculated using the zero value 2.323 (average of 2.327, 2.320, 2.321). [b] Large part of fraction lost by evaporation in course of making measurements—unable to repeat observations to check result. Value is not included in average.

Experimental Part

Fractionation Column. Isolation of *d*-2-Methylbutanol-1.—The column used for the isolation of *d*-2-methyl-

tions permits compensation for the difference between floor and ceiling temperatures (often as high as 20°). The glass construction of the column and the jackets permits instantaneous observation of flooding and constant examination of the condition of the packing. The efficiency of a single section of the column was examined in considerable detail with a *n*-heptane-methylcyclohexane test mixture, using the convenient graph of Lecky and

(6) It had been hoped that a more definite answer to the problem under discussion could be obtained by the use of a meter-long tube for the measurements. However, a number of circumstances made this impossible. The present activities of the authors make it highly improbable that they will be able to carry this project out within the next few years. The preparations have been carefully preserved, and will be available to anyone with the time and means for making the measurements.

(7) Fenske, Tongberg and Quiggle, *Ind. Eng. Chem.*, **26**, 1169 1934); Fenske, Tongberg, Quiggle and Cryden, *ibid.*, **28**, 644 (1936).

Ewell.[8] This section reached equilibrium conditions in less than forty-five minutes. At this time the composition of the test mixture in the head indicated an efficiency of 17 theoretical plates; at the end of four hours, the indicated efficiency was but slightly higher, 18 theoretical plates. The efficiency is thus one theoretical plate for every two inches of column length—a result which corresponds fairly well with the value obtained by Fenske and his co-workers.[7]

The fusel oil, a product of the United States Industrial Alcohol Company, contained 15.6% of the active material. Roughly 17% of the material distilled below 126°; this portion consisted chiefly of isobutyl alcohol (*ca.* 60%) and *n*-butyl alcohol (*ca.* 20%). Two distillations of the 2-methylbutanol-1-isoamyl alcohol fraction raised the concentration of the active alcohol to 85–90%. This material was considered satisfactory for the purposes of the investigation.

Preparation of *d*-1-Chloro-2-methylbutane.—The active alcohol was transformed into the corresponding active chloride by treatment with thionyl chloride and pyridine, according to Darzens' procedure.[9]

Four moles each of the active amyl alcohol and pyridine were placed in a 2-liter flask cooled by an ice–salt mixture. An efficient reflux condenser was attached to the flask by a ground glass joint; to the top of the condenser was fixed a dropping funnel and a tube to carry away the evolved gases. Through the dropping funnel 6 moles of thionyl chloride was added, the first two moles slowly over a period of sixty minutes, the remainder rapidly. The mixture was allowed to stand overnight at room temperature, then heated on the steam-bath for twenty-four hours, and finally poured into a 2-liter separatory funnel. The lower layer was drained off. The upper layer was treated with ice (to decompose excess thionyl chloride) and then washed first with small portions of water, next with saturated sodium carbonate solution, and finally again with water. The crude product was dried with calcium chloride and distilled. The fraction taken boiled from 98–102°. The yield of this crude product was 87%. This product was carefully fractionated and the fraction boiling at 99.5° at 750 mm., with $n^{20}D$ 1.4126 and $\alpha^{25}D$ +1.33°, was used in the subsequent experiments.

Preparation of *d*-1-Deutero-2-methylbutane.—The Grignard reagent was prepared from the active chloride in *n*-butyl ether and treated with deuterium chloride, conveniently generated by the action of benzoyl chloride on "heavy water."[10]

A 2-liter 3-necked flask was fitted with a 500-cc. dropping funnel, a mercury-sealed stirrer, and a reflux condenser protected by a calcium chloride tube. In this flask were placed 36 g. (1.5 moles) of magnesium, 100 cc. of *n*-butyl ether, and a few drops of methyl iodide to catalyze the formation of the reagent. Active 1-chloro-2-methylbutane, 143 g. (1.33 moles), was placed in the dropping funnel, and a few cc. were run into the reaction flask. The flask was heated on the steam-bath until cloudiness of the liquid indicated that reaction had begun. The dropping funnel was then nearly filled with *n*-butyl ether (approximately 350 cc.), its contents stirred, and the mixture run into the flask, drop by drop. The reaction was kept under control by cooling the flask with a water-bath (20–25°). (A colder bath stopped the reaction completely, thus causing a dangerous accumulation of the active 1-chloro-2-methylbutane.) The mixture of *n*-butyl ether and 1-chloro-2-methylbutane was added over a period of two hours, after which the water-bath was removed and the reaction mixture allowed to stand. After another hour, heat was no longer evolved, and the reaction was assumed to be complete. The mixture was then diluted to a total volume of 1000 cc. with more *n*-butyl ether.

A 2-ml. sample was pipetted out, added to about 40 ml. of 0.1 *N* standard acid, heated to boiling, and back-titrated with standard base, using phenolphthalein as indicator. The yield of Grignard reagent was 1.16 moles, or 87% of the amount calculated.

The apparatus for generating deuterium chloride[10] was connected to the reaction flask in place of the dropping funnel and deuterium oxide, 11.7 g. (1.17 equiv.), was converted to deuterium chloride, which was passed into the solution, cooled by means of an ice-bath, over a period of two to three hours. The solution was agitated vigorously in order to prevent caking of the magnesium salt. When the reaction appeared complete, the contents of the dry-ice trap were returned to the reaction flask, the deuterium chloride apparatus was replaced by a Vigreux stillhead and condenser, and the reflux condenser was replaced by a cork holding a thermometer. The receiving flask, immersed in an ice-bath, was connected to the condenser by an adapter. The only air outlet was through a side-arm on the adapter; this outlet led through a dry-ice trap. The reaction flask was heated in an oil-bath (at *ca.* 150°) until the inside temperature was 142°, the boiling point of pure *n*-butyl ether. The receiving flask was removed and weighed: the yield of crude product was 79 g. (1.08 moles), 92% of the calculated quantity based on either the Grignard reagent or the deuterium oxide. The material was then carefully fractionated in a Podbielniak "Heli-Grid" column.[11]

Summary

The object of the investigation was to determine whether a compound of the type $R_H—\overset{R_1}{\underset{R_2}{C}}—R_D$ (where the groups R_H and R_D differ only in their hydrogen and deuterium composition), exhibits a measurable optical activity. *d*-1-Deutero-2-methylbutane was prepared from *d*-2-methylbutanol-1 and examined in a sensitive polarimeter. It is concluded that the optical activity of the pure hydrocarbon in a 1-dm. tube is definitely less than 0.005° and probably less than 0.002°.

CHICAGO, ILL. RECEIVED JUNE 12, 1942

(8) Lecky and Ewell, *Ind. Eng. Chem., Anal. Ed.*, **12**, 544 (1940).

(9) Darzens, *Compt. rend.*, **152**, 1314 (1911); Gerrard, *J. Chem. Soc.*, 99 (1939).

(10) Brown and Groot, THIS JOURNAL, **64**, 2223 (1942).

(11) The column, somewhat modified from the standard design of the Podbielniak Centrifugal Super-Contactor Company, was constructed for use with a total reflux-partial takeoff head. Solid carbon dioxide was used as the refrigerant in the head to minimize losses of the volatile product. The rated efficiency of the column is 100 theoretical plates. Its holdup, approximately 15 cc., is remarkably small for a column of such high efficiency, and made the column particularly useful for the purpose.

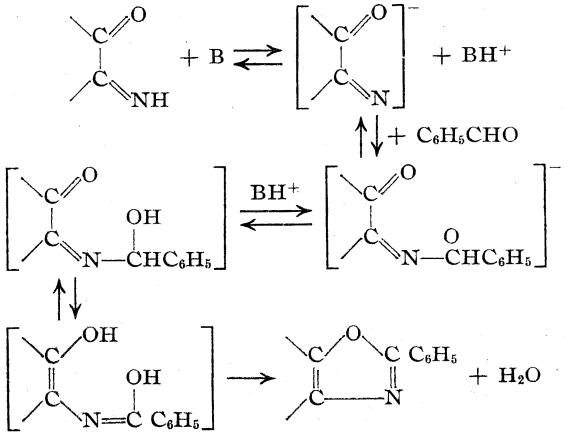
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

The Reactions of Retenequinonimine and Phenanthraquinonimine with Aldehydes. A New Example of an Aldol-Type of Condensation[1]

BY CHARLES W. C. STEIN[2] AND ALLAN R. DAY

In the course of the preliminary work leading to the present investigation, it was noted that the interaction of retenequinonimine, benzaldehyde, and *n*-butylamine gave excellent yields of 2-phenylretenoxazole. When aniline was substituted for the *n*-butylamine, a much lower yield of 2-phenylretenoxazole was obtained. The use of retenequinonimine, *n*-butyraldehyde, and *n*-butylamine produced 2-propylretenoxazole in excellent yields. Careful consideration of the components involved suggested two possible courses of reaction: (1) the aldehyde may undergo an aldol-type of condensation with retenequinonimine under the influence of the basic catalyst *n*-butylamine; and (2) the aldehyde and amine may react to form the Schiff base, benzal-*n*-butylamine, which then might condense with the quinonimine. It is possible that both courses of reaction could proceed simultaneously in the reactions noted above. Since the reactions of aldehydes with the quinonimine proved to be less complicated, they are presented first.

Several types of aldol condensations have been reported for compounds which contain the carbonyl group but apparently none have been reported where a quinonimine furnishes the labile hydrogen. To test the possibility of basic catalysis, amines were chosen which could not react with aldehydes to form Schiff bases. It was found that retenequinonimine and benzaldehyde reacted in the presence of triethylamine or piperidine to give excellent yields of 2-phenylretenoxazole. When the weaker base pyridine was used, however, no oxazole was formed. The above evidence indicates an aldol-type of condensation as the first step in the reaction. This is followed by an allylic-type shift of hydrogen and subsequently by the splitting out of water to form the oxazole. The course of the reaction may be represented as shown in the accompanying formulas. The last step, being irreversible, is an important determining factor in the reaction. In all of the reactions in which oxazole was formed, the solutions became dark red within a few minutes and then changed to yellow. Alcoholic potassium hydroxide can also be used to catalyze the reaction but the yields of oxazole (about 25%) were greatly reduced, due to side reactions between the quinonimine and potassium hydroxide. When sodium ethylate was employed, no oxazole was formed.



This reaction appears to be a general method for the preparation of 2-substituted retenoxazoles. For example, when *n*-butyraldehyde was used with triethylamine as the catalyst, a 92% yield of 2-propylretenoxazole was isolated. Even salicylaldehyde, which is known to produce a mixture of 2-(2′-hydroxyphenyl)-retenoxazole and 2-(2′-hydroxyphenyl)-retenimidazole when treated with retenequinone in the presence of ammonia, yields only the oxazole when treated with retenequinonimine and an amine.

The reactions of phenanthraquinonimine with aromatic aldehydes yielded similar results. The direct action of phenanthraquinonimine and benzaldehyde in the absence of basic reagents failed to produce 2-phenylphenanthroxazole. In the presence of piperidine and triethylamine good yields of the oxazole were obtained, but with the weaker base, aniline, lower yields were obtained. The reactions of *n*-butyraldehyde and phenanthraquinonimine gave similar results.

Experimental

All of the melting points given below are corrected values, and, unless otherwise stated, check the literature values.

(1) Presented at the Memphis Meeting of the American Chemical Society in April, 1942.

(2) Present Address, General Aniline Works, Grasselli, N. J.

Preparation of Retenequinone.—This compound was prepared by the method of Kreps and Day[3] from retene (Eastman Kodak Co. practical grade). It was recrystallized from chloroform; yield 50%; m. p. 197–199°.

Preparation of Retenequinonimine.—The quinonimine was prepared by the method of Bamberger and Hooker.[4] This preparation must be carried out in the absence of moist air. The crude product was recrystallized from absolute alcohol saturated with dry ammonia (below 55°), yield 60%, m. p. 107–108°.

Preparation of Phenanthraquinone.—In this preparation the directions of Graebe[5] for the oxidation of phenanthrene were modified, in that the purification was carried out according to Courtot[6]; m. p. 208–209.5°.

Phenanthraquinonimine.—The method of Pschorr[7] was used for preparing phenanthraquinonimine. The crude product was recrystallized from absolute alcohol saturated with ammonia. As in the case of retenequinonimine, the temperature should be kept below 55° and the time of heating should not exceed fifteen to twenty minutes; yield 75%; m. p. 156–157.5°.

Reactions of Retenequinonimine with Aldehydes and Amines.—In general the reactions were carried out by dissolving 2 g. (0.0076 mole) of retenequinonimine, 0.0076 mole of the aldehyde, and 0.0076 mole of the amine in 50 cc. of absolute alcohol and refluxing the solution on the water-bath.

(1) **With Benzaldehyde and *n*-Butylamine.**—The solution was refluxed for one hour. After cooling, the 2-phenylretenoxazole was removed by filtration and recrystallized from absolute alcohol; yield 68%; m. p. 174.5–175°.[8]

Anal. Calcd. for $C_{25}H_{21}NO$: N, 3.99. Found: N, 4.02.

(2) **With Benzaldehyde and Aniline.**—In this case the refluxing was continued for four hours. On cooling and diluting with water, a mixture of retenequinonimine and 2-phenylretenoxazole separated. Pure 2-phenylretenoxazole was obtained by recrystallization from 80% dioxane–water solution and subsequently from absolute alcohol; yield 9.7%; m. p. 174.5–176°.

(3) **With *n*-Butyraldehyde and *n*-Butylamine.**—After refluxing for four hours, the 2-*n*-propylretenoxazole was precipitated by the addition of water to the hot solution. The crude product was recrystallized from 60% dioxane–water and finally from dilute alcohol and obtained as colorless needles; yield 85%; m. p. 100.5–101.3°. This compound has not been reported previously.

Anal. Calcd. for $C_{22}H_{23}NO$: C, 83.17; H, 7.31; N, 4.42. Found: C, 82.99; H, 7.12; N, 4.26.

(4) **With Benzaldehyde and Triethylamine.**—The solution was refluxed for four hours. On cooling, an 84% yield of crude 2-phenylretenoxazole was obtained. It was recrystallized from absolute alcohol; yield 74%; m. p. 178.5–180°.

Anal. Calcd. for $C_{25}H_{21}NO$: N, 3.99. Found: N, 3.93.

(5) **With Benzaldehyde and One-half an Equivalent of Triethylamine.**—After refluxing for four hours, a 78% yield of 2-phenylretenoxazole was obtained. Recrystallization from absolute alcohol gave the characteristic white, fibrous needles, m. p. 177–178.5°.

(6) **With Benzaldehyde and Piperidine.**—After refluxing for four hours and cooling, a 92% yield of 2-phenylretenoxazole was obtained. It was recrystallized from absolute alcohol, m. p. 174.5–176°.

Anal. Calcd. for $C_{25}H_{21}NO$: N, 3.99. Found: N, 3.89.

(7) **With Benzaldehyde and Small Amounts of Alcoholic Potassium Hydroxide.**—One and one-half grams (0.0057 mole) of retenequinonimine, 0.59 g. (0.0056 mole) of benzaldehyde, and 10 drops of 10% alcoholic potassium hydroxide were mixed with 50 cc. of absolute alcohol and refluxed for four hours. On cooling, a mixture of orange and yellow solids separated. Recrystallization from 80% dioxane–water and finally from absolute alcohol gave a 25% yield of 2-phenylretenoxazole, m. p. 174–175.5°. Evaporation of the original filtrate produced a reddish-brown intractable gum. The substitution of one equivalent of sodium ethylate for the potassium hydroxide in the above reaction gave no observable yield of oxazole.

(8) **With *n*-Butyraldehyde and Triethylamine.**—After refluxing for sixteen hours, the solution was diluted with water and cooled. The 2-propylretenoxazole so obtained was washed with 50% alcohol and then recrystallized from 80% alcohol; yield 92%; m. p. 100–101°.

Anal. Calcd. for $C_{22}H_{23}NO$: N, 4.42. Found: N, 4.40.

(9) **With Salicylaldehyde and *n*-Butylamine.**—The solution was refluxed for thirty-five minutes. After cooling, the crude 2-(2′-hydroxyphenyl)-retenoxazole was removed by filtration. The filtrate was evaporated to dryness and the residue treated with hot 95% alcohol. The yellow solid remaining after this treatment was added to the first precipitate and recrystallized from a dioxane–water solution with the use of decolorizing carbon; yield 51%; m. p. 245.5–247°.

Anal. Calcd. for $C_{25}H_{21}NO_2$: N, 3.81. Found: N, 3.71.

Reactions of Phenanthraquinonimine.—In these reactions the same molar equivalents of reactants were used as in the reactions with retenequinonimine.

(1) **With Benzaldehyde.**—When an absolute alcohol solution of phenanthraquinonimine and benzaldehyde was refluxed, no reaction occurred and only unchanged quinonimine could be isolated.

(2) **With Benzaldehyde and Aniline.**—The solution was refluxed for four hours. After cooling for several hours, the crude product was removed and recrystallized from 80% dioxane–water until colorless needles of 2-phenylphenanthroxazole were obtained; yield 17.5%, m. p. 205–206°.

Anal. Calcd. for $C_{21}H_{13}NO$: N, 4.74. Found: N, 4.62.

(3) Kreps and Day, *J. Org. Chem.*, **6**, 140 (1941).
(4) Bamberger and Hooker, *Ann.*, **229**, 102 (1885).
(5) Graebe, *ibid.*, **167**, 140 (1873).
(6) Courtot, *Ann. chim.*, (10) **14**, 69 (1920).
(7) Pschorr, *Ber.*, **35**, 2739 (1902).
(8) The pure samples of 2-phenylretenoxazole obtained during the course of the work usually melted at 174–176°, but occasionally a higher melting sample (178–180°) was obtained. However, careful examination disclosed the fact that all the samples had the same crystal structure and mixed melting point determinations showed no appreciable depression.

(3) With Benzaldehyde and Piperidine.—The solution was refluxed for two hours. The 2-phenylphenanthroxazole, obtained after cooling the solution, was recrystallized from absolute alcohol; yield 97%; m. p. 204.5–205.5°.

Anal. Calcd. for $C_{21}H_{13}NO$: N, 4.74. Found: N, 4.58.

(4) With Benzaldehyde and Triethylamine.—In this reaction the solution was refluxed for only thirty minutes. The 2-phenylphenanthroxazole, obtained after cooling the solution, was recrystallized from absolute alcohol; yield 77%; m. p. 204–205.5°.

Anal. Calcd. for $C_{21}H_{13}NO$: N, 4.74. Found: N, 4.69.

(5) With *n*-Butyraldehyde and Aniline.—No oxazole was formed in this reaction even after long refluxing.

(6) With *n*-Butyraldehyde and Two Equivalents of Triethylamine.—After refluxing the solution for sixteen hours, it was evaporated and the gummy residue taken up in 10 cc. of methyl alcohol. On the addition of 2 cc. of water, a dark, viscous oil slowly separated. After four hours the supernatant liquid was decanted and let stand in the ice-box overnight. On standing, a small amount of 2-propylphenanthroxazole separated. The dark, viscous oil was stirred with 50% methyl alcohol and a few pellets of sodium hydroxide until it had entirely solidified. The combined solids were recrystallized from 80% alcohol, with the aid of decolorizing carbon, until colorless crystals were obtained; yield 50%; m. p. 84–86°. This compound has not been reported previously.

Anal. Calcd. for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.67; H, 5.74; N, 5.38.

Summary

1. Retenequinonimine and phenanthraquinonimine have been shown to react with aldehydes, in the presence of amines, to form 2-substituted retenoxazoles or phenanthroxazoles.

2. The first step in the reaction has been shown to consist of an aldol-type of condensation, with the quinonimine supplying the labile hydrogen.

3. The base-catalyzed reaction is a new and useful method of synthesis for 2-substituted retenoxazoles and phenanthroxazoles, giving high yields and products of excellent purity.

PHILADELPHIA, PA. RECEIVED JULY 14, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

The Reactions of Retenequinonimine and Phenanthraquinonimine with Schiff Bases. A New Example of an Aldol-Type of Condensation[1]

BY CHARLES W. C. STEIN[2] AND ALLAN R. DAY

It was noted in the previous paper in this series[3] that the interaction of retenequinonimine or phenanthraquinonimine with aldehydes, in the presence of amines, gave excellent yields of 2-substituted retenoxazoles or phenanthroxazoles. It was shown that where secondary or tertiary amines were used, the first step in the reaction consisted of a basically catalyzed aldol-type of condensation between the aldehyde and the quinonimine. However, where a primary amine such as *n*-butylamine was employed, it was realized that another possible course of reaction existed. The amine and aldehyde may react to form a Schiff base and the latter then might undergo an aldol-type of condensation with the quinonimine. Schiff bases are known to behave like aldehydes in many respects (the =NR acting as the carbonyl oxygen) and so it appeared to be quite reasonable to expect them to undergo a similar condensation with the quinonimine.

To test this possibility, benzal-*n*-butylamine was prepared and treated with retenequinonimine. A rapid reaction took place, with the formation of good yields of 2-phenylretenoxazole. Since these reactions were carried out under anhydrous conditions, the possibility that the benzal-*n*-butylamine underwent hydrolysis before reaction was practically excluded. Definite proof was obtained, however, by testing the benzal-*n*-butylamine for free aldehyde in dry toluene solution. Addition of phenylhydrazine to the solution of the Schiff base produced no precipitate of benzaldehyde phenylhydrazone, even when heated on the water-bath for thirty minutes, the approximate time of many of the reactions. A similar test carried out with a sample of freshly distilled benzaldehyde gave an immediate precipitate of phenylhydrazone. It was further noted that *n*-butylamine was evolved in nearly quantitative amounts when retenequinonimine and benzal-*n*-butylamine in equivalent quantities were heated at 100° in dry solvents.

A consideration of all the evidence available at

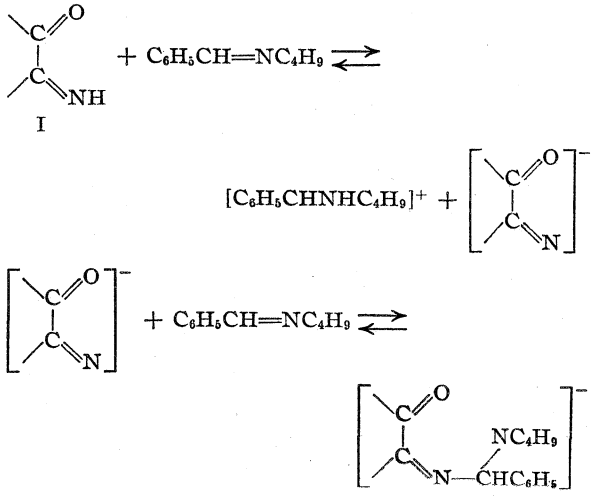
(1) Presented at the Memphis Meeting of the American Chemical Society in April, 1942.

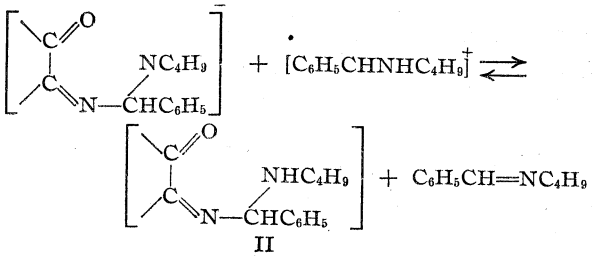
(2) Present address, General Aniline Works, Grasselli, N. J.

(3) Stein and Day, THIS JOURNAL, **64**, 2567 (1942).

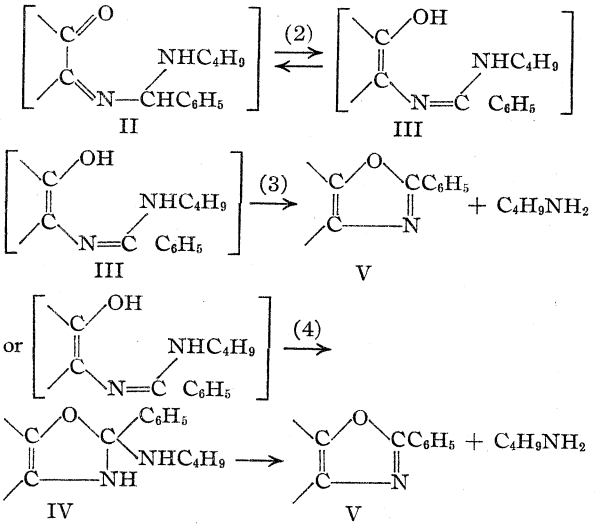
this point showed that any suggested mechanism for this reaction must meet the following requirements. (1) The reaction between the quinonimine and benzal-*n*-butylamine must evolve *n*-butylamine, equivalent in quantity to the amine (present in combined form) in the Schiff base at the start of the reaction; and (2) the substituent in position two of the oxazole ring is derived from the aldehyde portion of the Schiff base.

In accord with these requirements, a mechanism is suggested which involves an aldol-type of condensation between the aldehyde and the quinonimine (step 1). Since the hydrogen of the imino group may be said to be an active hydrogen, it appears reasonable to believe that addition to the Schiff base occurs as the initial step. Indirect evidence for this may be deduced from the fact that when retenequinone is used in place of the quinonimine, no oxazole is formed. Hence the presence of the imino group is essential for the reaction. The addition of the quinonimine to the Schiff base involves an aldol-type condensation where the base acts as an aldehyde and the quinonimine supplies the active hydrogen. The Schiff base also acts as the basic catalyst for the reaction, at least in the case where benzal-*n*-butylamine was used. Such condensations are conditioned by the basic strength of the catalyst and it is interesting to note that when benzalaniline is substituted for the benzal-*n*-butylamine, the reaction is very slow and low yields of oxazole result, unless a more basic catalyst such as piperidine is added. The initial reaction between the quinonimine and benzal-*n*-butylamine, step (1), may be written as





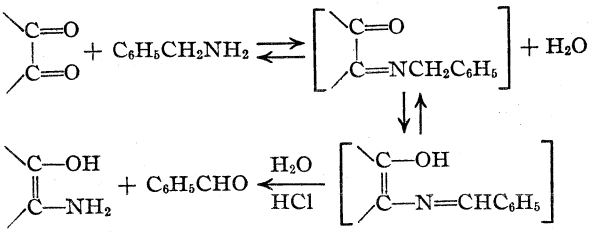
This is followed by two allylic-type shifts of hydrogen, step (2), and subsequently by the splitting out of *n*-butylamine to form the oxazole, step (3) or (4).



There is a considerable amount of information in the literature which may be offered in support of the above mechanism. The addition of various types of active hydrogen compounds to the double bond in Schiff bases has been reported by Mayer.[4] In all of the reactions reported by Mayer, the course of reaction involved addition of the active hydrogen to the nitrogen atom and addition of the other group to the unsaturated carbon atom of the Schiff base. These additions are undoubtedly basic catalyzed reactions for they occur under the influence of basic reagents.

Step (2) in the postulated mechanism also is quite reasonable, for allylic-type shifts of hydrogen would be expected in the type of structure shown. Direct evidence for this shift is difficult to obtain, but in closely related work McCoy[5] has been able to establish such a shift. The hydrolysis of the interaction products of retenequinone and benzylamine yields benzaldehyde. This can be explained only on the basis of a hydrogen shift.

(4) Mayer, *Bull. soc. chim.*, [3] **33**, 157, 395, 498 (1905).
(5) McCoy and Day, unpublished work.



In the final reaction (ring closure to form the oxazole), step (3) appears to be more reasonable in view of the close similarity between Schiff bases and aldehydes in addition reactions. Furthermore, the postulated intermediate III, being a substituted amidine, would be expected to undergo such a condensation.[6] However, step (4) cannot be ruled out. The addition of a hydroxyl group across a double bond with the formation of a heterocyclic ring has been reported in the synthesis of the tocopherols and related compounds.[7] The postulated intermediate (IV) resulting from such an addition would be a dihydroretenoxazole. Such a derivative would be expected to pass readily into the oxazole. A search of the literature disclosed the fact that in cases where 2,3-dihydro-oxazoles or 2,3-dihydroimidazoles might be expected to be the end-products, only the corresponding oxazoles or imidazoles were isolated. The last step, then, may represent spontaneous conversion (oxidation) of a dihydro-oxazole to the oxazole (with the elimination of an amine rather than hydrogen). This assumption is in agreement with the absence of 2,3-dihydro-oxazoles in the literature. Either course suggested for the last step in the reaction, (3) or (4), would explain the liberation of *n*-butylamine.

The use of different types of Schiff bases has yielded some interesting results: benzal-*n*-butylamine yielded up to 93% of 2-phenylretenoxazole; benzalaniline gave a 21% yield of 2-phenylretenoxazole; *n*-butylidene-*n*-butylamine gave only a 7% yield of 2-propylretenoxazole; and *n*-butylideneaniline gave no oxazole. In considering the variation in yields produced by the different types of Schiff bases, it was thought that a relationship might be shown between the yields of oxazole and the basic strength and (or) molecular aggregation of the Schiff bases. Since the initial reaction is a basically catalyzed condensation, the basic strength of the Schiff base should be an important factor. When retenequinonimine and benzalaniline were heated in dry alcohol solution in the presence of one equivalent of piperidine, a 90% yield of 2-phenylretenoxazole was obtained, as compared with a 21% yield in the absence of piperidine. This result agrees with the fact that benzalaniline is a weaker base than benzal-*n*-butylamine. When retenequinonimine and *n*-butylidene-*n*-butylamine were heated in dry alcohol with one equivalent of piperidine, the yield of 2-propylretenoxazole was raised from 7% to 23%. Under similar conditions *n*-butylideneaniline yielded no oxazole. In the last two cases, it is apparent that some other factor is important.

In the dimerization of certain Schiff bases[8] a hydrogen atom on the alpha carbon of the aldehyde part of the base adds to the nitrogen atom of another molecule of the Schiff base. Hence it may be assumed that alpha hydrogen is necessary for dimerization to occur. Since oxazole formation probably depends on the existence of the Schiff base monomer in the reaction mixture, lower yields or no yield of oxazole might be expected when alpha hydrogen is present in the Schiff base. As a check on this hypothesis, a qualitative study of the molecular weights of *n*-butylidene-*n*-butylamine, benzal-*n*-butylamine, and benzalaniline was made by the Rast method. *n*-Butylideneaniline has been shown previously to be a dimer.[8] Values were obtained which were sufficiently reproducible to indicate the probable state of molecular aggregation. With benzalaniline a value was obtained which indicated that the base was essentially monomeric. Benzal-*n*-butylamine gave a somewhat similar result. *n*-Butylidene-*n*-butylamine, however, proved to be trimeric. Since at temperatures of 80–100° the associations (monomer–polymer relationships) are probably reversible, the values cannot be used for a quantitative interpretation but may be used as suggestive evidence for the presence or absence of the monomeric forms at these temperatures.

These results confirm the supposition that the Schiff bases which yield appreciable quantities of oxazole exist preponderantly as the monomers, whereas those which yield little or no oxazole are mostly dimeric or more highly associated. The types $ArCH{=}NCH_2R$ and $ArCH{=}NAr$ are among the former, while the types $(RCH{=}NCH_2R)_n$ and $(RCH{=}NAr)_n$ are among the latter.

The use of phenanthraquinonimine in place of retenequinonimine gave similar results.

(6) Dains, *Ber.*, **35**, 2496 (1902).

(7) Smith, *Chem. Revs.*, **27**, 287 (1940).

(8) Kharasch, Richlin and Mayo, THIS JOURNAL, **62**, 494 (1940); Emerson, Hess and Uhle, *ibid.*, **63**, 872 (1941).

Since the completion of the above work, a general study of basically catalyzed additions to Schiff bases has been started. It is believed that such an investigation will lead to a better understanding of the factors involved and in some cases lead to improved synthetic methods.

Experimental

Analyses and Melting Points.—See previous paper.[3]

Retenequinone, Retenequinonimine, Phenanthraquinone and Phenanthraquinonimine.—These compounds were prepared by the methods noted in the previous paper.

Benzal-*n*-butylamine.—This derivative apparently has not been reported previously. Twenty-five grams (0.236 mole) of freshly distilled benzaldehyde was dissolved in 25 cc. of absolute alcohol and 19 g. (0.26 mole) of *n*-butylamine added gradually with cooling. The solution was allowed to stand over anhydrous potassium carbonate for two days. The alcohol was removed by distillation and the crude benzal-*n*-butylamine was distilled under reduced pressure, b. p. 112–113° at 14 mm., yield 34%, d^{24}_4 0.906, $n^{24}D$ 1.5229. The addition of phenylhydrazine to a solution of the benzal-*n*-butylamine in dry toluene gave no precipitate of benzaldehyde phenylhydrazone, even when heated on the water-bath for thirty minutes. A similar test carried out with freshly distilled benzaldehyde gave an immediate precipitate of the phenylhydrazone. *Anal.* Calcd. for $C_{11}H_{15}N$: N, 8.70; mol. wt. calcd. for monomer, 161, dimer 322. Found: N, 8.64; mol. wt., 220 (in naphthalene), 227 (in triphenylmethane).

Preparation of Benzalaniline.—This was prepared by the procedure described by Bigelow and Eatough.[9] It was recrystallized from 85% alcohol; yield, 84%; m. p. 51°. *Mol. wt.* Calcd.: monomer 181, dimer 362. Found: mol. wt., 216 (in naphthalene).

Preparation of *n*-Butylidene-*n*-butylamine.—At the time this work was undertaken, this compound had not been reported, but it was reported about one month later by Emerson, Hess and Uhle.[8] The method used here is a modification of the method of Chancel.[10] *n*-Butyraldehyde (21.6 g., 0.30 mole) was slowly added to 21.9 g. (0.30 mole) of cooled *n*-butylamine. After standing for one hour, the layers were separated and the upper layer dried over potassium hydroxide. The dried product was distilled at atmospheric pressure, b. p. 141–145°. *Mol. wt.* Calcd. for trimer: 383. Found: 383 and 414 (13% solution in naphthalene).

Preparation of *n*-Butylideneaniline.—This was prepared by the method of Kharasch, Richlin and Mayo;[8] yield 32%. It was reported to be a dimer.

Reactions of Retenequinonimine with Schiff Bases.—In general 2 g. (0.0076 mole) of the quinonimine and one equivalent of the Schiff base were added to 50–100 cc. of dry alcohol and refluxed for a suitable length of time on the water-bath. In most cases the solution was then cooled and the product removed by filtration.

Reaction of Retenequinonimine with Benzal-*n*-butylamine.—The solution was refluxed for nineteen minutes. The crude 2-phenylretenoxazole was recrystallized from absolute alcohol; yield 78%; m. p. 174–175°. *Anal.* Calcd. for $C_{25}H_{21}NO$: N, 3.99. Found: N, 3.96.

Reaction of Retenequinonimine with Two Equivalents of Benzal-*n*-butylamine.—The solution was refluxed for ninety minutes. The product was purified as described above; yield 93.5%; m. p. 175–177°.

Reaction of Retenequinonimine with Benzal-*n*-butylamine in Dry Toluene. (a) Test for *n*-Butylamine as a Reaction Product.—The solution was heated on the water-bath for three hours. After cooling the mixture, the 2-phenylretenoxazole was removed by filtration. The filtrate was distilled and the distillate collected in hydrochloric acid. The acid solution was evaporated to about 20 cc., made alkaline with sodium hydroxide and treated with *m*-nitrobenzenesulfonyl chloride. The filtrate on acidification yielded N-butyl-*m*-nitrobenzenesulfonamide which was recrystallized from alcohol and water; m. p. 67°. A mixed m. p. with an authentic sample showed no depression. **(b) Determination of the Amount of *n*-Butylamine Liberated.**—A run similar to the one described above was carried out in dry alcohol. At the end of the heating period the mixture was steam distilled and the distillate collected in 4% boric acid solution containing methyl red. The boric acid solution was then titrated with standard hydrochloric acid. The volume of the acid used corresponded to 96.58% of the *n*-butylamine originally held in the benzal-*n*-butylamine. In this particular experiment an 82% yield of 2-phenylretenoxazole was obtained.

Reaction of Retenequinone with Benzal-*n*-butylamine.—The solution was refluxed for one hour. No oxazole formation was observed.

Reaction of Retenequinonimine with Benzalaniline.—After refluxing for four hours, the mixture was cooled and the orange-yellow solid removed by filtration. The crude product was recrystallized from 80% dioxane–water to separate the 2-phenylretenoxazole from retenequinone. Final purification was effected from dry alcohol with the use of decolorizing carbon; yield 21.6%; m. p. 177–178.5°. *Anal.* Calcd. for $C_{25}H_{21}NO$: N, 3.99. Found: N, 3.95.

Reaction of Retenequinonimine with *n*-Butylidene-*n*-butylamine.—After refluxing for two hours, the solution was evaporated to a small volume and cooled. The crude 2-propylretenoxazole, so obtained, was recrystallized from 80% dioxane–water, with the aid of decolorizing carbon, until colorless; yield 7%; m. p. 98.5–100.5°. *Anal.* Calcd. for $C_{22}H_{23}NO$: N, 4.42. Found: N, 4.43.

Reaction of Retenequinonimine with *n*-Butylidene-aniline.—No oxazole could be isolated from the reaction mixture after refluxing for four hours.

Reaction of Retenequinonimine with Benzalaniline in the Presence of One Equivalent of Piperidine.—The solution was refluxed for four hours and the crude 2-phenylretenoxazole was recrystallized from dioxane and water; yield 90.5%; m. p. 178–180°.

Reaction of Retenequinonimine with *n*-Butylidene-*n*-butylamine in the Presence of One Equivalent of Piperidine.—After refluxing for four hours, the solution was evaporated to dryness and the gummy residue extracted with a small amount of methyl alcohol, leaving 0.65 g. of a yellow solid. Recrystallization from 80% alcohol, with

(9) Bigelow and Eatough, "Organic Syntheses," John Wiley and Sons, New York, N. Y., 1941, Coll. Vol. I, p. 80.

(10) Chancel, *Bull. soc. chim.*, [3] **11**, 933 (1894).

the use of decolorizing carbon, gave white, fluffy needles of 2-propylretenoxazole; yield 23%; m. p. 100–100.5°.

Reaction of Retenequinonimine with *n*-Butylideneaniline in the Presence of One Equivalent of Piperidine.—No oxazole could be isolated from this reaction mixture after refluxing for fourteen hours.

Reaction of Phenanthraquinonimine with Benzal-*n*-butylamine.—The solution was refluxed for forty-five minutes and the crude 2-phenylphenanthroxazole recrystallized from 80% dioxane–water using decolorizing carbon and finally alcohol; yield 79%; m. p. 205–205.8°. *Anal.* Calcd. for $C_{21}H_{13}NO$: N, 4.74. Found: N, 4.57.

Reaction of Phenanthraquinonimine with Benzalaniline.—The 2-phenylphenanthroxazole obtained after refluxing the solution for four hours was recrystallized from 80% dioxane–water with the use of decolorizing carbon; yield 21.7%; m. p. 206–207°. *Anal.* Calcd. for $C_{21}H_{13}NO$: N, 4.74. Found: N, 4.72.

Reaction of Phenanthraquinonimine with Benzalaniline in the Presence of One Equivalent of Piperidine.—In the presence of piperidine, the yield of 2-phenylphenanthroxazole increased from the 21.7% noted above to 85%, after only two hours of refluxing.

Reaction of Phenanthraquinonimine with *n*-Butylidene-*n*-butylamine.—The solution was refluxed for four hours. After three weeks of standing in the cold, a small amount of yellowish-brown solid separated and was removed. Evaporation of the filtrate yielded only an intractable gum. The crude 2-propylphenanthroxazole was recrystallized from 80% alcohol and finally from 50% alcohol and obtained as colorless needles; yield 0.8%; m. p. 84.3–86.2°. Several runs were necessary to obtain sufficient material for the analyses. *Anal.* Calcd. for $C_{18}H_{15}NO$: C, 82.73; H 5.79; N, 5.36. Found: C, 82.56; H, 5.71; N, 5.30.

Reaction of Phenanthraquinonimine with *n*-Butylidene-*n*-butylamine in the Presence of One Equivalent of Piperidine.—After refluxing for four hours, the solution was evaporated and the viscous residue stirred with 50% methyl alcohol and a few pellets of sodium hydroxide until it had solidified. The 2-propylphenanthroxazole was then recrystallized from 80% alcohol, with the aid of decolorizing carbon; yield 30%; m. p. 85–86°. *Anal.* Calcd. for $C_{18}H_{15}NO$: N, 5.36. Found: N, 5.27.

Reaction of Phenanthraquinonimine with *n*-Butylideneaniline.—No 2-propylphenanthroxazole could be isolated in the absence or the presence of piperidine, after four hours of refluxing.

Summary

1. Retenequinonimine and phenanthraquinonimine have been shown to react with most types of Schiff bases to form 2-substituted retenoxazoles or phenanthroxazoles.

2. The first step in the reaction has been shown to consist of an aldol-type of condensation, with the quinonimine supplying the labile hydrogen. Some Schiff bases are sufficiently basic to catalyze the condensation.

3. This base-catalyzed reaction is a new and useful method for the synthesis of 2-substituted retenoxazoles and phenanthroxazoles.

PHILADELPHIA, PENNA. RECEIVED JULY 14, 1942

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

Para Acylation of Polyalkylbenzophenones by Aryl 2,4,6-Trialkylbenzoates

BY REYNOLD C. FUSON, E. M. BOTTORFF, R. E. FOSTER AND S. B. SPECK

Alkylmagnesium halides and arylmagnesium halides that carry a substituent in the para position have been shown to condense with aryl mesitoates to produce ketones.[1] A much more remarkable result was obtained with arylmagnesium halides that had no substituent in the para position. *p*-Tolyl mesitoate and phenylmagnesium bromide, for example, yielded *p*-cresol and a substance that proved to be *p*-dimesitoylbenzene (III). The structure of this compound was proved by synthesizing it from terephthalyl chloride and mesitylene by the Friedel–Crafts method.

The first step in this transformation appeared to be the formation of benzoylmesitylene, which then condensed with unchanged mesitoic ester to produce the diketone (III). In confirmation of this hypothesis, it was discovered that the diketone could be made also by condensing benzoylmesitylene with *p*-tolyl mesitoate.

$$MesCO_2C_6H_4CH_3 \xrightarrow{C_6H_5MgBr} MesCOC_6H_5 \text{ and } CH_3C_6H_4OH$$

$$MesCO_2C_6H_4CH_3 + MesCOC_6H_5 \longrightarrow MesCO\text{—}C_6H_4\text{—}COMes + CH_3C_6H_4OH$$

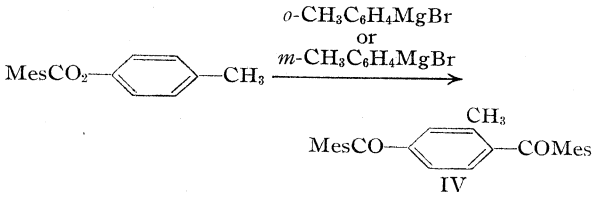
III

This condensation is without parallel. The net result is the acylation, under the influence of the Grignard reagent, of a benzene ring in the position *which is para to the meta-directing carbonyl group*. The condensation can be formulated as a Claisen reaction in which a nuclear hydrogen atom is replaced by an acyl group. This point of view is supported by the fact that the condensation between the ketone and the ester can be effected with the aid of a number of alkaline cata-

(1) Fuson, Bottorff and Speck, THIS JOURNAL, **64**, 1450 (1942).

lysts. Among these are sodium, ethylmagnesium bromide, mesitylmagnesium bromide and the binary mixture, Mg–MgI_2.[2] The binary mixture afforded the best yields, but usually gave less than 50% of the theoretical amount.

Under the influence of this reagent *p*-tolyl mesitoate condensed with *m*-toluylmesitylene, *m*-methoxybenzoylmesitylene, dibromomesityl phenyl ketone and α-naphthoylmesitylene to yield the expected diketones. It is interesting that *o*- and *m*-tolylmagnesium bromide reacted with *p*-tolyl mesitoate to yield the same diketone–1,4-dimesitoyl-2-methylbenzene (IV).



IV

The formation of 1,4-diaroylbenzenes appears to be general for highly hindered ketones. Aryl esters of 2,4,6-triethylbenzoic, 2,4,6-triisopropylbenzoic and 2,3,5,6-tetramethylbenzoic acids were found to condense with the corresponding aryl phenyl ketones to yield, respectively, 1,4-di-(2,4,6-triethylbenzoyl)-benzene, 1,4-di-(2,4,6-triisopropylbenzoyl)-benzene and 1,4-di-(2,3,5,6-tetramethylbenzoyl)-benzene.

Experimental

Synthesis of Ketones.—The ketones prepared in this work are listed in Table I, which indicates also melting points, yields, solvents and analytical data. All except the last four in the table were prepared by the condensation of the corresponding acid chloride with the appropriate hydrocarbon by the Friedel–Crafts method. A description of the preparation of *p*-dimesitoylbenzene will illustrate the procedure.

***p*-Dimesitoylbenzene.**[3]—A solution of 15 g. of terephthalyl chloride,[4] 40 cc. of carbon disulfide and 10 cc. of mesitylene was added dropwise, with stirring, at room temperature to a mixture of 26 g. of mesitylene, 28 g. of aluminum chloride and 50 cc. of carbon disulfide. The solution was refluxed gently and stirred for six hours. The dark-red reaction mixture was poured into an ice–hydrochloric acid mixture. The carbon disulfide was evaporated and the solution extracted with three portions of hot benzene. The benzene extracts were washed with hot water, hot 5% sodium hydroxide solution and again with water. A portion of the benzene was removed by distillation, and the remaining solution was allowed to cool; 12 g. of *p*-dimesitoylbenzene crystallized. The melting point after two recrystallizations from benzene was 244–246°.

Dibromomesityl Phenyl Ketone.—This compound was prepared by direct bromination of benzoylmesitylene in carbon tetrachloride.

2,4,6-Tribromophenyl Mesitoate.—This compound was prepared in 84% yield by condensing 2,4,6-tribromophenol with mesitoyl chloride. It crystallized from alcohol in colorless needles melting at 86°.

Anal.[5] Calcd. for $C_{16}H_{13}O_2Br_3$: C, 40.26; H, 2.74. Found: C, 40.56; H, 2.89.

Condensation of Hindered Esters with Aryl Grignard Reagents.—The reactions of a few hindered esters with certain aryl Grignard reagents have been studied. The arylmagnesium halides selected were those having no substituents in the para position. The results of this work are shown in Table II. Since the experimental details were very similar for all of these reactions, the procedure will be described only for one, *viz.*, that between *p*-tolyl mesitoate and phenylmagnesium bromide.

***p*-Tolyl Mesitoate and Phenylmagnesium Bromide.**—The reagent was prepared from 5 g. of magnesium and 28.2 g. of bromobenzene in 50 cc. of *n*-butyl ether. A solution of 20.4 g. of *p*-tolyl mesitoate in 60 cc. of *n*-butyl ether was added, with stirring. The clear solution slowly became a deep wine color. The mixture was heated at 100° for two hours in an atmosphere of nitrogen.

The reaction mixture was decomposed with cold dilute hydrochloric acid and the aqueous layer extracted twice with ether. The ether solution was washed once with water, then with three 100-cc. portions of 10% sodium hydroxide. The sodium hydroxide solution was washed twice with ether, acidified with hydrochloric acid and extracted with ether. The ether solution was washed with water, dried over magnesium sulfate, and freed of solvent by evaporation. The residual *p*-cresol weighed 6.4 g.

The solvent was removed from the ether solution and the oil treated with alcohol. The *p*-dimesitoylbenzene which separated was collected on a filter and washed with alcohol; yield 5 g. The filtrate was distilled under reduced pressure and small amounts of biphenyl and *p*-tolyl mesitoate were obtained.

Many of the products shown in Table II could be isolated only by distillation of the neutral portion of the reaction mixture under reduced pressure. The fractions obtained were then taken up in ethanol, and crystallization was induced.

Condensation of Hindered Esters with Diaryl Ketones.—The condensation reactions are listed in Table III. The starting materials, reaction temperatures, reagent, products and yields are given. Since the procedures used for these reactions are very similar, only two will be described in detail.

Benzoylmesitylene and *p*-Tolyl Mesitoate.—A solution of 11.2 g. of benzoylmesitylene and 12.7 g. of *p*-tolyl mesitoate in 60 cc. of 1:1 toluene–*n*-butyl ether mixture was added slowly to a solution of the binary mixture, Mg–MgI_2, prepared from 2.5 g. of magnesium and 12.7 g. of iodine in 60 cc. of 1:1 ethyl ether–*n*-butyl ether mixture. The reaction mixture was stirred in an atmosphere of nitrogen at

(2) Gomberg and Bachmann, THIS JOURNAL, **49**, 236 (1927).
(3) This experiment was carried out by Dr. C. H. McKeever.
(4) Beund and Herms, *J. prakt. Chem.*, [2] **74**, 123 (1906).
(5) The analyses reported in this paper are microanalyses. They were performed by Miss Mary S. Kreger and Mr. L. G. Fauble.

TABLE I

KETONES[a]

Ketone	Yield, %	Melting point, °C.	Solvent	Analyses, % Calcd. C	Calcd. H	Found C	Found H
MesCOTol(*m*)	91	67	Ethanol	85.64	7.64	85.97	7.97
MesCOα-$C_{10}H_7$[b]	60	159	Ethanol	87.59	6.57	87.65	6.67
DurCOC_6H_5[c]	40	119					
TipCOC_6H_5	81	97–99	Methanol	85.66	9.15	86.01	9.39
TepCOC_6H_5[d]	81	...	.....	85.70	8.28	85.41	8.40
m-MesCOC_6H_4COMes	94	149–151	Benzene–ethanol	84.30	7.08	84.33	7.00
p-MesCOC_6H_4COMes	44	244–246	Benzene	84.30	7.08	84.28	6.83
p-Mes$COC_{10}H_6$COMes	45	171	Ethanol–benzene	85.61	6.66	86.04	6.88
		193.5		85.61	6.66	85.52	6.77
p-TipCOC_6H_4COTip	50	223–225	Ethanol–chloroform	84.71	9.35	84.49	8.98
p-TepCOC_6H_4COTep[e]	67	119–120	Ethanol	84.54	8.42	84.64	8.51
p-DurCOC_6H_4CODur	67	246	Chloroform–pet. ether	84.35	7.61	84.41	7.87
Mes$COC_6H_3(CH_3)$COMes(1,3,4)	29	189	Ethanol–benzene	84.31	7.34	84.07	7.36
Br_2MesCOC_6H_5	23	113	Ethanol	50.26	3.66	50.46	3.61
p-Br_2MesCOC_6H_4COMes	27	274–277	Benzene–pet. ether	59.09	4.58	59.68	4.97
Mes$COC_6H_3(OCH_3)$COMes(1,3,4)	35	210	Ethanol–benzene	80.96	7.05	81.12	7.09

[a] The radicals tolyl, mesityl, 2,4,6-triisopropylphenyl, 2,4,6-triethylphenyl and 2,3,5,6-tetramethylphenyl are represented by Tol, Mes, Tip, Tep and Dur, respectively. [b] This compound was prepared by Dr. M. D. Armstrong from α-naphthoyl chloride and mesitylene by the Friedel–Crafts method. [c] This compound was prepared by B. C. McKusick by the Friedel–Crafts method. [d] B. p. 144–145° (3 mm.); d^{20}_{20} 1.022; $n^{20}D$ 1.5648. [e] This compound was prepared by Dr. C. H. McKeever by the method described for *p*-dimesitoylbenzene.

TABLE II

REACTIONS OF HINDERED ARYL ESTERS WITH GRIGNARD REAGENTS

Ester	Grignard reagent	Product (% yield)	Product (% yield)
MesCO_2Tol(*p*)	C_6H_5MgBr	*p*-Cresol (74)	*p*-MesCOC_6H_4COMes[a] (34)
MesCO_2Tol(*m*)[b]	C_6H_5MgBr	*m*-Cresol (80)	*p*-MesCOC_6H_4COMes (small amounts) *o*-Mes$COC_6H_4C_6H_5$[c]
MesCO_2Tol(*p*)	*o*-$CH_3C_6H_4$MgBr	*p*-Cresol	(1,3,4)Mes$COC_6H_3(CH_3)$COMes (29)
MesCO_2Tol(*p*)	*m*-$CH_3C_6H_4$MgBr	*p*-Cresol	(1,3,4)Mes$COC_6H_3(CH_3)$COMes (11)
MesCO_2Tol(*p*)	*m*-$CH_3OC_6H_4$MgBr	*p*-Cresol	(1,3,4)Mes$COC_6H_3(OCH_3)$COMes (3.5)
TipCO_2Tol(*p*)	C_6H_5MgBr	*p*-Cresol	*p*-TipCOC_6H_4COTip[a]
TepCO_2Tol(*p*)[d]	C_6H_5MgBr	*p*-Cresol	*p*-TepCOC_6H_4COTep[a]

[a] A mixed melting point with an authentic specimen prepared by the Friedel–Crafts method gave no depression. [b] This ester was made by the method[1] described earlier for the para isomer; m. p. 38–39°. *Anal.* Calcd. for $C_{17}H_{18}O_2$: C, 80.30; H, 7.10. Found: C, 80.22; H, 7.37. [c] Identified by a mixed melting point with an authentic specimen.[6] [d] This ester was made by the method[1] described earlier for *p*-tolyl mesitoate; b. p. 170–171° (3 mm.); d^{20}_{20} 1.035; $n^{20}D$ 1.5435. *Anal.* Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.10. Found: C, 81.14; H, 7.85.

115° for five hours. The color gradually became a very deep red.

The reaction mixture was decomposed with cold dilute hydrochloric acid and the aqueous layer extracted twice with ether. The ether solution was washed once with water, then with three 100-cc. portions of 10% sodium hydroxide. The sodium hydroxide solution was washed twice with ether, acidified with hydrochloric acid and extracted with ether. The ether solution was washed with water, dried over magnesium sulfate, and freed from ether by evaporation. The residual *p*-cresol weighed 4.3 g.

The solvent was removed from the original ether solution and the oil taken up in alcohol. *p*-Dimesitoylbenzene separated and was collected on a filter and washed with alcohol; yield 7.4 g. A small amount (0.45 g.) of a bright yellow compound, m. p. 189°, was isolated. It was not identified.

The filtrate was distilled under reduced pressure; 2 g. of benzoylmesitylene and 3.4 g. of *p*-tolyl mesitoate were recovered.

α-Naphthoylmesitylene and *p*-Tolyl Mesitoate.—A solution of the binary mixture, Mg–MgI_2, was prepared from 2.5 g. of magnesium and 12.7 g. of iodine in 50 cc. of 1:1 toluene–*n*-butyl ether. A solution of 13.7 g. of α-naphthoylmesitylene and 12.7 g. of *p*-tolyl mesitoate in 40 cc. of the solvent was added slowly. The mixture was stirred at 115° for three hours under an atmosphere of nitrogen. It was then treated with dilute hydrochloric acid and washed as described in the preceding experiment. *p*-Cresol was obtained from the alkaline extract.

After the solvent was removed from the neutral portion, a solid separated. The mixture was treated with alcohol, and the solid material collected on a filter and washed with alcohol. The yield was 5.7 g. of 1,4-dimesitoylnaphthalene, which melted at 171°, after many recrystallizations from an alcohol–benzene mixture, and was yellow in color.

The alcohol filtrate was distilled under reduced pressure,

(6) Fuson, Armstrong and Speck, *J. Org. Chem.*, **7**, 297 (1942).

TABLE III

CONDENSATION OF HINDERED ESTERS WITH DIARYL KETONES

Starting materials	Reagent	Temp. of reaction, °C.	Diketone	Yield, %
$MesCO_2Tol(p)$[a] and $MesCOC_6H_5$	C_2H_5MgBr	115	p-$MesCOC_6H_4COMes$[b]	14
$MesCO_2Tol(p)$ and $MesCOC_6H_5$	C_6H_5MgBr	115	p-$MesCOC_6H_4COMes$[c]	13
$MesCO_2Tol(p)$ and $MesCOC_6H_5$	MesMgBr	115	p-$MesCOC_6H_4COMes$	17
$MesCO_2Tol(p)$ and $MesCOC_6H_5$	Na	100	p-$MesCOC_6H_4COMes$[d]	8
$MesCO_2Tol(p)$[a] and $MesCOC_6H_5$[e]	$ZnCl_2$	115		
$MesCO_2Tol(p)$ and $MesCOC_6H_5$	$Mg–MgI_2$	115	p-$MesCOC_6H_4COMes$	40
$MesCO_2Tol(p)$ and $MesCOC_6H_5$	$Mg–MgI_2$	60	p-$MesCOC_6H_4COMes$	36
$MesCO_2Tol(p)$ and $Br_2MesCOC_6H_5$	$Mg–MgI_2$	60	p-$Br_2MesCOC_6H_4COMes$	27
$MesCO_2Tol(p)$ and $MesCOTol(m)$	$Mg–MgI_2$	115	$(1,3,4)MesCOC_6H_3(CH_3)COMes$	32
$MesCO_2Tol(p)$ and m-$MesCOC_6H_4OCH_3$	$Mg–MgI_2$	70	$(1,3,4)MesCOC_6H_3(OCH_3)COMes$	35
$MesCO_2Tol(p)$ and m-$MesCOC_6H_4COMes$	$Mg–MgI_2$	115	$(1,3,4)(MesCO)_3C_6H_3$	13
$MesCO_2CH_3$[f] and $MesCOC_6H_5$	$Mg–MgI_2$	115		
$MesCO_2C_6H_2Br_3(2,4,6)$ and $MesCOC_6H_5$	$Mg–MgI_2$	100	p-$MesCOC_6H_4COMes$[g]	
$MesCO_2Tol(p)$ and $MesCOC_{10}H_7(\alpha)$	$Mg–MgI_2$	115	p-$MesCOC_{10}H_6COMes$	30
$DurCO_2Tol(p)$[h] and $DurCOC_6H_5$	$Mg–MgI_2$	60	p-$DurCOC_6H_4CODur$	54
$TipCO_2Tol(p)$ and $TipCOC_6H_5$	C_2H_5MgBr	140	p-$TipCOC_6H_4COTip$	trace
$TepCO_2Tol(p)$ and $TepCOC_6H_5$	$Mg–MgI_2$	115	p-$TepCOC_6H_4COTep$	16

[a] All reactions involving esters of p-cresol yielded p-cresol as one of the products. [b] Propiomesitylene was also produced. [c] A trace of 2-mesitoylbiphenyl was formed also. [d] Mesitoic acid was formed in 13% yield. [e] p-Cresol and mesitoic acid were the only products isolated. The yields were very low. [f] A 58% yield of mesitoic acid was obtained. [g] 2,4,6-Tribromophenol was also a product. [h] This compound was prepared by B. C. McKusick from the acid chloride and p-cresol; m. p. 138°, from alcohol. *Anal.* Calcd. for $C_{18}H_{20}O_2$: C, 80.55; H, 7.47. Found: C, 80.02; H, 7.41.

and the following substances were isolated from the distillate; 3.2 g. of p-tolyl mesitoate, 2.0 g. of α-naphthoylmesitylene and 0.75 g. of 1,4-dimesitoylnaphthalene.

The 1,4-dimesitoylnaphthalene was found to have two crystalline forms. When the yellow compound was heated above its melting point (171°) for a few minutes or was treated with chromic acid in glacial acetic acid and then recrystallized from alcohol, colorless needles were obtained. This colorless form showed a definite softening point at 171° and melted sharply at 193.5° to a bright yellow liquid, which when cooled rapidly gave the yellow solid.

This compound was synthesized from 1,4-dicyanonaphthalene[7] by way of the dicarboxylic acid and the acid chloride. Hydrolysis of the dinitrile by the method of Scholl and Neumann,[8] gave a 76% yield of the crude acid. The acid was converted to the acid chloride by the method of Beund and Herms.[4] The condensation of the impure acid chloride with mesitylene produced a mixture from which the diketone melting at 193.5° could be isolated.

A by-product, melting at 134° (cor.), was found to contain nitrogen and is believed to be 1-mesitoyl-4-cyanonaphthalene. Its origin may be traced to incomplete hydrolysis of the dinitrile giving rise to 4-cyanonaphthoic acid and eventually to the cyano ketone. It was purified by recrystallization from methanol and petroleum ether. It had a bright yellow color.

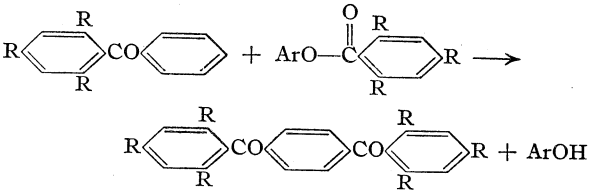
Anal. Calcd. for $C_{21}H_{17}ON$: C, 84.22; H, 5.75. Found: C, 84.36; H, 5.85.

(7) Newman, THIS JOURNAL, **59**, 2472 (1937).

(8) Scholl and Neumann, *Ber.*, **55B**, 118 (1922).

Summary

It has been shown that certain highly hindered benzophenones undergo acylation in an unsubstituted para position when treated with aryl 2,4,6-trialkylbenzoates. The generalized equation for the reaction is



The reaction takes place under the influence of Grignard reagents, the binary mixture ($Mg–MgI_2$) and certain other alkaline catalysts.

URBANA, ILLINOIS RECEIVED JULY 27, 1942

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NEW YORK STATE AGRICULTURAL EXPERIMENT (GENEVA) STATION]

Note on Invertase Activity in Identical Mixtures in the Liquid and Frozen State[1]

BY Z. I. KERTESZ

The publication of the following experiment was prompted by a recent article by Sizer and Josephson dealing with enzyme[2] kinetics as a function of temperature. These authors confirm the well-known fact that low temperatures do not inactivate the enzymes, lipase, trypsin and invertase, and state that "a sharp break in the relationship of rate to temperature appears at 0 to −2°." This observation is in harmony with and an extension of the writer's findings with invertase activity measured between +40 and −40° and part of which was reported in an article[3] dealing with the velocity of the reaction in undercooled solutions. In connection with this latter work some measurements were performed in identical reaction mixtures of the rate of invertase action in the liquid and solid (frozen) state at the same temperature. These data, heretofore unpublished, gain additional interest by the observations of Sizer and Josephson and throw light on the suspected effect of change of physical state on the velocity of the reaction.

There is little to be added to the experimental technique described in my above article.[3] If reaction mixtures containing sucrose, invertase and buffer in water solution are quickly cooled, temperatures as low as −9° may be reached without freezing the mixture. On the other hand, shaking of the test-tubes during cooling (or sometimes even moving them) is sufficient to cause a rapid solidification of the mixture. Single observations in liquid and frozen mixtures were performed at various temperatures between −2 and −8° but it was at −6.8° that the measurement of the two whole sets of determinations was most successful. These results and a few others indicating the rate of reaction at 20° and at a lower freezing temperature (−17.8°) are given in Table I.

The hydrolysis appears to be much slower in the frozen mixture than in the liquid one. The high value for the first monomolecular constant "k" in the frozen mixture at −6.8° is believed to be caused by the higher velocity of the reaction while the mixture was cooled and until it was frozen. The great difference in the velocity in the liquid and frozen state confirms the statement of Sizer and Josephson that the change in phase may be the cause of the break in the rate of enzyme action. It is also apparent that no predictions concerning the rate of a reaction in the frozen state can be made from determinations in liquid mixtures although it is not impossible that in the future some predictable relation may be found between the two factors.

The difference between the rate of hydrolysis in the liquid and frozen mixtures is also apparent in most samples of the lipase series of Sizer and Josephson, although this is not emphasized by these authors.

The reason for the drop in the velocity upon freezing may be the restricted availability of water for the hydrolysis. This may well be the case because previous observations indicated[4] that the amount of water available in invertase reaction mixtures has more effect on the velocity of the reaction than physical conditions as changes in the viscosity, for instance. The possibility of an effect of the freezing on the enzyme itself cannot be disregarded. This effect, if any, must be temporary because when frozen reaction mixtures were melted, they exhibited a normal velocity of hydrolysis.

There is some uncertainty about the significance of results obtained in enzyme reaction mixtures in the presence of glycerol, ethanol and other chemicals used in order to lower the freezing point. In the writer's work difficulties were experienced with these materials in the study of invertase action. They exerted considerable effect on the reaction above the freezing point, as is observable in the lipase hydrolysis data of Sizer and Josephson. The use of these materials would open easy avenues of approach to the problem but their effect on the reaction is definite but not constant (see the lipase table of Sizer and Josephson) and thus there is an element of unreliability about results obtained by their use. The effect of these compounds seems to be again in changing the proportion of water available for the hydroly-

(1) Article III on "Water relations of enzymes." Approved by the Director of the New York State Agricultural Experiment Station for publication as Journal Article No. 466, August 15, 1942.

(2) I. W. Sizer and E. S. Josephson, *Food Research*, **7**, 200 (1942).

(3) Z. I. Kertesz, *Z. physiol. Chem.*, **216**, 229 (1933).

(4) Z. I. Kertesz, THIS JOURNAL, **57**, 345 (1935).

TABLE I

INFLUENCE OF TEMPERATURE AND CONDITION ON THE VELOCITY OF SUCROSE HYDROLYSIS BY INVERTASE

Reaction temp., °C....	20.2		−6.8		−6.8		−17.8	
Condition.....	Liquid		Liquid		Frozen		Frozen	
	min.	$k \times 10^5$	min.	$k \times 10^5$	min.	$k \times 10^5$	min.	$k \times 10^5$
	60	259.6	120	38.30	233	(35.80)	2,820	0.265
			410	39.62			7,200	.388
	120	255.6	1038	36.35	1038	10.54	10,080	.372
			1215	36.70	1218	10.62	17,280	.404
	240	273.8	1218	37.45	1563	10.32	20,160	.393
			1395	40.35			27,350	.201
	360	222.8	1740	40.60			28,970	.221
	Av.	253.0		38.5		10.49		.321

sis rather than by altering the physical characteristics of the solutions.

Summary

The velocity of invertase action in a frozen mixture at −6.8° was only 27% of that in a like mixture in the liquid state. The diminished availability of water may be responsible for this phenomenon.

GENEVA, N. Y. RECEIVED AUGUST 20, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE STATE COLLEGE OF WASHINGTON]

Some Derivatives of 2-Propionyl-1-naphthol

BY C. M. BREWSTER AND G. G. WATTERS

Since the substitution of acyl and alkyl groups for nuclear hydrogen in phenols has given compounds with marked germicidal properties, we have extended our study in this field by preparing some derivatives of 2-propionyl-1-naphthol, with changes in side chain and nucleus.

We have compared methods of preparation of 2-propionyl-1-naphthol[1] and found little difference in yield, whether the process is carried out directly with α-naphthol or by intra-molecular rearrangement of the ester first formed through the action of the anhydride. However, the direct method requires fewer steps and we have been able to minimize the formation of purple by-products by the procedure given in the experimental part.

In attempting to prepare a di-acyl naphthol from 2-acetyl-1-naphthol by condensation with propionic acid, using zinc chloride as condensing agent, we obtained 2-propionyl-1-naphthol in good yield, the larger acyl group replacing the smaller. A similar replacement occurred when benzoic acid reacted with 2-acetyl-1-naphthol; however, the yield was very small. This replacement recalls the method of preparation of higher members of the salol series, by heating salol with eugenol or other phenols; the higher phenol replaces the lower.[2]

When examining some crystals of 2-propionyl-1-naphthol in subdued light, it was accidentally discovered that the compound shows marked triboluminescence, and this phenomenon persists whether the compound is dry or moistened with water or ethanol, even after removal of traces of impurities.

Reduction of acyl naphthols replaced the carbonyl oxygen by hydrogen and resulted in alkyl naphthols which showed an increase in germicidal activity. However, the pure reduced compounds on standing in the air slowly turned to brown oils and their preservation was difficult. It was anticipated that modification of the acyl side-chain might give compounds of greater stability, and such compounds have been made by condensation of the acyl group with aldehydes.[3] While there was marked reactivity with 2-propionyl-1-naphthol, we have been able to isolate only two derivatives in pure form. Acid condensing agents such as zinc chloride, aluminum chloride, or concentrated sulfuric acid produced marked color

(1) Witt and Braun, *Ber.*, **47**, 3216 (1914); Fries, *ibid.*, **54**, 709 (1921); Stoughton, THIS JOURNAL, **57**, 204 (1935).

(2) German Patent 111,656; also May and Dyson, "The Chemistry of Synthetic Drugs," 4th edition, 1939, p. 219.

(3) Kostanecki, *Ber.*, **31**, 705 (1898); Pfeiffer, Kalckbrenner and Levin, *J. prakt. Chem.*, **119**, 109 (1928); Cheema, Gulati and Venkataraman, *J. Chem. Soc.*, 930 (1932).

changes and complex products, while potassium hydroxide in aqueous or alcoholic solution caused less polymerization. The lower temperatures tended to inhibit the Cannizzaro reaction, and also decreased the tendency to polymerization.

The ethers of acyl and alkyl naphthols which are reported were somewhat difficult to prepare, which is characteristic of ortho substituted naphthols. They are more stable than the naphthols when heated or exposed to air.

Experimental

2-Propionyl-1-naphthol.—We have carried out numerous trials of the methods reported by Goldzweig and Kaiser,[4] by Hantzsch[5] and by Stoughton[6] and obtained best yields from the following shortened modification of Hantzsch's method. Two hundred grams of fused zinc chloride was crushed and warmed with 300 g. of propionic acid until dissolved. To the warm solution was added 300 g. of α-naphthol and the mixture heated under reflux in an oil-bath to gentle boiling (145–150°) for forty to fifty minutes. The solution became orange, then bright red; if allowed to become deep red, an undue proportion of tar is formed. The mixture was allowed to cool slowly and to stand overnight, then gently warmed to 60° and diluted with an equal volume of warm glacial acetic acid. On standing overnight large yellow-green crystals separated from the purple solution, and were filtered with suction, rinsed by suspension in 200 g. of 85% acetic acid, filtered and recrystallized from hot ethanol. A second crop of crystals was obtained from the purple mother liquor by warming with activated carbon. The hot filtrate was cooled and diluted, and the crystalline product recrystallized from ethanol. The compound may be purified by solution in ethanol and 2% sodium hydroxide, which is then warmed with activated carbon, filtered and precipitated by neutralization with hydrochloric acid. The compound may also be purified by distillation *in vacuo*. A total yield of 200 g. was obtained; m. p. 81–82°.[7]

Crystals which were formed after melting and slowly cooling the dry compound gave the greatest brilliance of luminescence; when ground to a powder no further luminescence was observed.

2-Propionyl-1-ethoxynaphthalene.—Fifteen grams of 2-propionyl-1-naphthol and 75 ml. of ethanol were heated with a solution of 3 g. of sodium hydroxide in 10 ml. of water. This mixture was heated to gentle boiling under reflux and 8 g. of ethyl bromide was added drop by drop. After six hours of heating, 6 g. more of ethyl bromide was added and heating continued for six hours more. When a test with ferric chloride showed no coloration, the solution was cooled, neutralized and the brown oily product separated with ether, dried, and distilled *in vacuo*, giving a yellow viscous oil, b. p. 175–180° (15 mm.); yield, 13 g.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.85; H, 6.9. Found: C, 78.9; H, 7.0.

2-Propionyl-1-naphthol Phenylhydrazone.—Yellow plates from acetic acid, m. p. 136°.

Anal. Calcd. for $C_{19}H_{18}ON_2$: N, 9.65. Found: N, 9.36.

2-Propyl-1-naphthol.—Preparation by the Clemmensen reduction method as given in detail by Coulthard, Marshall and Pyman[9] and reported by Stoughton[10] required heating under reflux for twelve hours. The pale yellow oil, obtained by distillation *in vacuo*, solidified on standing and gradually turned brown; m. p. 48–50°. The germicidal activity of this compound has been tested recently and reported to be superior to that of 2-propionyl-1-naphthol.[11]

2-Propyl-1-ethoxynaphthalene.—Ten grams of 2-propyl-1-naphthol and 50 ml. of methyl ethyl ketone with 2 g. of sodium hydroxide were warmed, giving a brown solution. Fifteen g. of ethyl iodide was added in small portions and heating under reflux continued for a total of fifteen hours. The solvent was distilled off, the brown oil dissolved in ether, washed with 2% sodium hydroxide, and the ether layer separated, dried and distilled. The opaque red-brown liquid was distilled twice *in vacuo*, giving a pale yellow oil, b. p. 294–296° (690 mm.).

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.11; H, 8.41. Found: C, 83.9; H. 8.5.

2-Propyl-1-*n*-butyloxynaphthalene.—Ten grams of 2-propyl-1-naphthol was dissolved in 50 ml. of methyl ethyl ketone, and warmed with a solution of 2.1 g. of sodium hydroxide in 5 ml. of ethanol and 5 ml. of water. The solution turned deep green. Powdered copper, 0.1 g., was added as catalyst, and 10 g. of *n*-butyl bromide added in small portions. The solution was boiled under reflux for twenty-four hours, the solvents removed by distillation, and the brown oily residue was washed with 2% sodium hydroxide, extracted with ether, and the ether extract dried. Distillation *in vacuo* gave a pale yellow oil, b. p. 304–306° (692 mm.).

Anal. Calcd. for $C_{17}H_{22}O$: C, 84.3; H, 9.01. Found: C, 84.0; H, 9.1.

4-Bromo-2-propionyl-1-naphthol.—Fifty grams of 2-propionyl-1-naphthol was dissolved in 125 ml. of chloroform; to this was added slowly and with vigorous stirring a solution of 50 g. of bromine in 125 ml. of chloroform. Large volumes of hydrobromic acid were given off. After standing for thirty minutes, the solution was washed with water by decantation until no longer acid. The chloroform layer was separated, the chloroform distilled off, and the yellow mass crystallized from ethanol. Yellow needles were obtained in nearly quantitative yield; m. p. and

(4) Goldzweig and Kaiser, *J. prakt. Chem.*, **43**, 95 (1891).

(5) Hantzsch, *Ber.*, **39**, 3096 (1906).

(6) Stoughton, THIS JOURNAL, **57**, 202 (1935).

(7) On cooling an alcoholic solution of the compound, a crust of large transparent yellow-green plates formed. In dislodging these with a stirring rod, in a dark room, flashes of blue light were seen as the rod broke the mass of crystals beneath the mother liquor. This triboluminescence appeared when the compound was subjected to friction or to percussion, even after repeated recrystallization. The phenomenon persisted whether the crystals were dry or suspended in water or ethanol, and seemed to be an inherent property of the compound.[8]

(8) R. Ghigi, *Gazz. chim. ital.*, **57**, 278 (1927).

(9) Coulthard, Marshall and Pyman, *J. Chem. Soc.*, 280 (1930).

(10) Stoughton, THIS JOURNAL, **57**, 204 (1935).

(11) H. L. Cole, C. C. Prouty and Emily R. Meserve, THIS JOURNAL, **63**, 3523 (1941).

m. p. when mixed with a sample prepared by Hantzsch's method,[12] 98–99°.

4-Bromo-2-propionyl-1-ethoxynaphthalene.—A mixture of 5.6 g. of 4-bromo-2-propionyl-1-naphthol with 0.8 g. of sodium hydroxide in 4 ml. of water and 50 ml. of methyl ethyl ketone was heated, and 5 g. of ethyl bromide slowly added. After eight hours of heating under reflux, 3.0 g. more of ethyl bromide was added, and heating continued for a total of sixteen hours. The solvent was then distilled off, the residue washed and crystallized from ethanol, giving a yield of 3.8 g. of pale yellow needles, m. p. 68–69°.

Anal. Calcd. for $C_{15}H_{15}O_2Br$: Br, 26.03. Found: Br, 26.10.

4-Bromo-2-propionyl-1-*n*-propyloxynaphthalene.—A mixture of 15 g. of 4-bromo-2-propionyl-1-naphthol, 50 ml. of methyl ethyl ketone, and a solution of 2.2 g. of sodium hydroxide in 10 ml. of ethanol and 10 ml. of water was heated under reflux, and 12 g. of *n*-propyl bromide was added in small portions. After forty-eight hours of heating the solvent was distilled off, the oily layer taken up in ether and washed with 2% aqueous sodium hydroxide. The ethereal layer was separated, dried and distilled *in vacuo*. The light yellow oil had a slightly sweet odor; b. p. 298–303° (690 mm.).

Anal. Calcd. for $C_{16}H_{17}O_2Br$: Br, 24.90. Found: Br, 25.23.

4-Nitro-2-propionyl-1-naphthol.—Ten grams of 2-propionyl-1-naphthol was powdered and suspended in 200 ml. of 50% acetic acid. Ten ml. of concentrated nitric acid was diluted with 30 ml. of glacial acetic acid and added slowly to the vigorously stirred suspension. After five hours the mixture was diluted, filtered, and the solid crystallized from ethanol giving fine yellow needles, m. p. 162–163°.

Anal. Calcd. for $C_{13}H_{11}O_4N$: N, 5.7. Found: N, 5.5.

The phenylhydrazone crystallized from ethanol in pale brown crystals which melted at 199–200°.

Anal. Calcd. for $C_{19}H_{17}O_3N_3$: N, 12.53. Found: N, 12.02.

2-Propionyl-β-(2-chlorobenzylidene)-1-naphthol.—Five grams of 2-propionyl-1-naphthol and 5 g. of *o*-chlorobenzaldehyde were suspended in 25 ml. of ethanol, cooled to 0°, and vigorously stirred. A solution of 50 g. of potassium hydroxide in 35 ml. of water was added slowly during a period of one hour, and stirring at 0° continued for two hours, after which the mixture was allowed to stand at room temperature out of contact with air for two days. The dark red alcoholic solution was poured into 200 ml. of ice-water and neutralized with dilute hydrochloric acid. The yellow precipitate was filtered off and crystallized from hot ethanol. Long yellow needles were obtained which melted at 93–94°.

Anal. Calcd. for $C_{20}H_{15}O_2Cl$: Cl, 11.01. Found: Cl, 11.06.

(12) Hantzsch, *Ber.*, **39**, 3097 (1906).

4-Bromo-2-propionyl-β-(2-chlorobenzylidene)-1-naphthol.—Three grams of 4-bromo-2-propionyl-1-naphthol and 1.5 g. of *o*-chlorobenzaldehyde were dissolved in 25 ml. of 1,4-dioxane, cooled to 0°, and a solution of 30 g. of potassium hydroxide in 20 ml. of water, also cooled to 0°, was added slowly over a period of two hours, with vigorous mechanical stirring. The solution turned dark red and a precipitate formed. The mixture was allowed to stand for two days out of contact with air and at room temperature, then poured into 100 ml. of ice-water and neutralized with dilute hydrochloric acid. The yellow precipitate was filtered and crystallized from ethanol, giving light yellow needles which melted at 129°.

Anal. Calcd. for $C_{20}H_{14}O_2ClBr$: Cl and Br, 28.76. Found: Cl and Br, 28.5.

As typical of the reactivity of aromatic aldehydes in the presence of condensing agents, when 10 g. of 2-propionyl-1-naphthol and 5 g. of benzaldehyde were warmed with 5 g. of fused zinc chloride the viscous mass became yellow-brown at 70°, deepening in color as the temperature rose, until at 170° there was slight effervescence and the color changed to deep crimson. The temperature was held at 170° for about ten minutes or until effervescence ceased. Upon dilution a gray-blue granular precipitate separated which was dissolved in acetic acid giving a red solution. Fractional precipitation by dilution with water gave successive portions of the gray-blue precipitate; none of the fractions contained unchanged starting material, and all sintered with decomposition when heated to 175–180°.

When concentrated sulfuric acid was used as condensing agent, a red-brown solution was obtained which on dilution with water gave a flocculent cream-colored compound, which sintered when heated to 105°. With aqueous sodium hydroxide solutions at room temperature or below, less tar was formed than when solutions were heated. On dilution and neutralization, red viscous products were obtained. The three condensing agents have been used with hydroxy and halogenated aldehydes with formation of deeply colored products, and we have been able to characterize two which were formed from *o*-chlorobenzaldehyde as described above.

Summary

1. A simplified method of preparation and purification of 2-propionyl-1-naphthol is reported. The compound shows marked triboluminescence.

2. A method of preparation involving direct replacement of a smaller by a larger acyl group is reported.

3. Ten new derivatives have been characterized, some of which are more stable than the parent acyl and alkyl naphthols.

PULLMAN, WASHINGTON RECEIVED JULY 20, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

Saponins and Sapogenins. XX. Bethogenin and Trillogenin, New Sapogenins from *Trillium Erectum*

BY S. LIEBERMAN,[1] F. C. CHANG, M. R. BARUSCH AND C. R. NOLLER

During the course of the isolation of diosgenin from commercial powdered beth root (*Trillium erectum*) by the procedure of Marker, Turner and Ulshafer[2] we have obtained a second sapogenin in an amount at least as great as the amount of diosgenin. This compound, which we have named "bethogenin," has the molecular formula $C_{27}H_{40}O_4$. It gives a yellow color with tetranitromethane and is precipitated by digitonin, suggesting that it is an unsaturated steroid sapogenin. Reaction with acetic anhydride in pyridine gave only a monoacetate, while benzoyl chloride and pyridine gave a monobenzoate. Two oxygen atoms tentatively may be assumed to be the inert oxygen atoms in the side chain characteristic of steroid sapogenins. This makes it still necessary to account for one more oxygen atom.

Attempts to dehydrate bethogenin failed, indicating that this oxygen atom is not a tertiary hydroxyl group. This was confirmed by a Zerewitinow determination which showed only one active hydrogen. On catalytic reduction in neutral alcohol solution with hydrogen and palladium catalyst, two moles of hydrogen were absorbed per mole of bethogenin. While isolation of a pure hydrogenated bethogenin has not yet been successful, acetylation of the reduction product gave a readily crystallized compound which proved to be a diacetate. From this it appears that bethogenin contains a carbonyl group.

In order to confirm this view, attempts were made to prepare a carbonyl derivative. It was found that bethogenin reacted with hydroxylamine in pyridine to give a new compound but analyses indicated that this was a dioxime. At present such behavior is difficult to explain. One possibility is that bethogenin is a diketone with one very readily enolizable carbonyl group so that it gives the reactions both of a carbonyl group and of a double bond and hydroxyl group. However, all of the usual tests for an enol group gave negative results. Another possibility is that the second molecule of hydroxylamine reacted with the side chain. Indication that the side chain of bethogenin behaves differently from that of other steroid sapogenins was obtained when it was found that bethogenin could not be converted into a pseudosapogenin.[3] Heating with acetic anhydride at 200° gave only uncrystallizable gums.

A third sapogenin has been isolated in small amount which appears to be unique among the known steroid sapogenins in that the two characteristic inert oxygen atoms are lacking. This compound has the empirical formula $C_{27}H_{48}O_4$ and yields a tetraacetate, $C_{35}H_{56}O_8$. Nothing further has been done with this compound because of the small amount of material that has been available. One is inclined to speculate that the customary side chain has been reduced with the formation of an open chain and two free hydroxyl groups. For this substance we suggest the name "trillogenin."

A very small amount of a fourth sapogenin, which appears to be identical with chlorogenin, also has been isolated.

The authors are indebted to Dr. L. F. Fieser for his interest in this problem and for permitting one of us (F. C. C.) to spend some time in this Laboratory working on the problem.

Experimental

Diosgenin and Trillin.—Ten pounds of powdered beth root[4] was extracted and hydrolyzed according to the procedure of Marker, Turner and Ulshafer.[2] The crude diosgenin was filtered from the second hydrolysis mixture and weighed only 15 g. It could not be purified readily by crystallization but on extraction in a Soxhlet apparatus with 60–70° ligroin, the diosgenin was removed and then readily purified by crystallization from acetone.

The unextracted residue amounting to 2.7 g. was purified by crystallization from glacial acetic acid and melted at 269.5°–271° when the capillary tube was placed in a preheated bath; $[\alpha]^{26}D$ −103.4°, $[\alpha]^{26}Hg$ −127.2° in dioxane. This substance is the "trillin" of Marker and Krueger[5] as shown by analysis, conversion to the acetate, and further hydrolysis to diosgenin. Our analysis checks better for the anhydrous compound than for the hemihydrate of Marker and Krueger.

Anal. Calcd. for $C_{33}H_{52}O_8$: C, 68.7; H, 9.1. Found: C, 69.3; H, 9.0.

(1) Research Assistant on funds from the Rockefeller Foundation.

(2) Marker, Turner and Ulshafer, THIS JOURNAL, **62**, 2542 (1940).

(3) Marker and co-workers, *ibid.*, **62**, 518, 648, 898 (1940).

(4) Purchased from S. B. Penick and Company and described in their price list as "*Trillium erectum* and species."

(5) Marker and Krueger, THIS JOURNAL, **62**, 2548 (1940).

The **acetate**, m. p. 204–205°, has a rotation of $[\alpha]^{30}D$ −71.4°; $[\alpha]^{30}Hg$ −80.2° in dioxane.

Chlorogenin.—The aqueous alcoholic acid filtrate and washings from the crude diosgenin after standing for several days deposited about 0.2 g. of material which, after several recrystallizations from methyl alcohol, melted at 262–272° and did not depress the melting point of chlorogenin, m. p. 270–274°, but depressed the melting point of gitogenin and of trillin. Conversion to the acetate did not give enough product to purify to a melting point above 130°.

Bethogenin.—When the above alcoholic filtrates were poured into a large volume of water, a black tar precipitated. This was dissolved in 500 cc. of alcohol, just sufficient water added to prevent miscibility with 60–70° ligroin and the solution exhaustively extracted in a continuous liquid extractor with 60–70° ligroin. The ligroin extract on concentration left a yellow semi-solid residue weighing 20 g. which on repeated crystallization from methyl alcohol gave long white needles with a maximum melting point of 182–185°. Purification takes place more readily from a diluted rather than from a hot saturated solution. If the bethogenin was prepared by hydrolysis of the acetate with methyl alcoholic potassium hydroxide solution or by recrystallization from alcohol containing potassium hydroxide, a product was obtained melting at 193–194°. When this was recrystallized from pure methyl alcohol, the melting point dropped to 184–186° and on a second recrystallization to 163–182°. A sample which melted at 180–184° when first prepared melted at 160–173° after standing two weeks. The first two analyses given below are on material which had been purified by crystallization from methyl alcohol alone, while the second two are on samples that had been crystallized from alkaline alcohol. Bethogenin as obtained by crystallization from methyl alcohol contains solvent of crystallization. All samples were dried for analysis at 110° and 20 mm. to constant weight.

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.67; H, 9.40; one OH, 3.97; mol. wt., 428.6. Found: C, 75.60, 75.06, 75.55, 75.60; H, 9.70, 9.87, 9.50, 9.96; OH (Zerewitinow), 3.84; mol. wt. (Rast), 442; $[\alpha]^{24}D$ −98.4° in dioxane.

Bethogenin gives a yellow color with tetranitromethane and is precipitated from alcoholic solution with digitonin. The ferric chloride test for enols, the Legal test, the Rosenheim test and the Zimmermann–Jaffee reaction were all negative. In the Lieberman test, a red color was formed which slowly darkened to a deep green.

The **acetate** was prepared by adding 12 cc. of acetic anhydride to 1.97 g. of bethogenin dissolved in 20 cc. of pyridine and allowing the solution to stand for one hour. The product crystallized and was filtered, washed with water and crystallized twice from a mixture of four parts ethyl alcohol and one part benzene. It melted at 230–232° and gave a yellow color with tetranitromethane.

Anal. Calcd. for $C_{29}H_{42}O_5$: C, 74.01; H, 8.99. Found: C, 73.50, 74.00, 74.62; H, 9.70, 9.89, 9.00; $[\alpha]^{24}D$ −94.4° in dioxane.

When 1 g. of bethogenin in 6 cc. of acetic anhydride and 6 cc. of pyridine was heated in a sealed tube at 100° for twenty hours,[6] a brownish colored solution resulted from which only the monoacetate could be isolated.

(6) Steiger and Reichstein, *Helv. Chim. Acta*, **20**, 823 (1937).

A solution of 0.24 g. of bethogenin in 10 cc. of dry pyridine was treated with 3 cc. of benzoyl chloride and allowed to stand overnight. After removing the pyridine under reduced pressure, water was added and the precipitate washed with hot water to remove benzoic acid. The residue was crystallized from methyl alcohol and gave 0.15 g. of the **benzoate** as needles, m. p. 190–191. Three more crystallizations from 1:4 benzene–methyl alcohol mixture raised the melting point to 212–215°.

Anal. Calcd. for $C_{34}H_{44}O_5$: C, 76.65; H, 8.33. Found: C, 76.97; H, 9.10; $[\alpha]^{24}D$ −65.1° in dioxane.

Tetrahydrobethogenin Diacetate.—A mixture of 1.5 g. of bethogenin, 0.3 g. of palladium oxide and 200 cc. of ethyl alcohol was shaken overnight under hydrogen at a pressure of 30 pounds per square inch. The mixture was filtered to remove the palladium and the filtrate evaporated to dryness. This product could not be crystallized readily from any of the common organic solvents. Crystallization did take place from 75% aqueous methyl alcohol but constant melting material could not be obtained even after thirteen crystallizations.

Acetylation of 0.86 g. of the crude product with 5 cc. of acetic anhydride in 7 cc. of pyridine gave 0.77 g., m. p. 126–129°. After fourteen crystallizations from ligroin (60–70°) the melting point was constant at 141–144°. It gave a negative test for unsaturation with tetranitromethane.

Anal. Calcd. for $C_{31}H_{48}O_6$: C, 72.05; H, 9.37. Found: C, 71.87, 72.30; H, 9.25, 9.66; $[\alpha]^{24}D$ −156° in dioxane.

A smaller sample of bethogenin in a semi-micro apparatus showed absorption of four atoms of hydrogen per mole.

Reaction of Bethogenin with Hydroxylamine.—A solution of 0.5 g. of bethogenin and 0.4 g. of hydroxylamine hydrochloride in 4 cc. of pyridine and 4 cc. of absolute alcohol was heated on the steam-bath for one hour and the flask allowed to stand overnight. The precipitate was filtered, washed with 95% alcohol and crystallized from absolute alcohol to a constant melting point of 241–243°.

Anal. Calcd. for $C_{27}H_{42}O_4N_2$: C, 70.72; H, 9.22; N, 6.11. Found: C, 70.42, 70.40; H, 9.54, 9.96; N, 5.94, 5.92.

Attempts to hydrolyze the reaction product to the original compound were unsuccessful.

Attempts to Prepare a Pseudobethogenin.—Three attempts were made to convert bethogenin into a pseudobethogenin. In the first bethogenin was heated with acetic anhydride at 200°, in the second bethogenin acetate was heated with acetic anhydride at 165° and in the third run bethogenin acetate and acetic anhydride were heated at 200°. Only unchanged acetate or resinous products could be isolated.

Trillogenin.—After standing for several months, the methyl alcohol solution which had been extracted with ligroin deposited a few tenths of a gram of precipitate which, after several crystallizations from methyl alcohol, melted at 206–210°; $[\alpha]^{24}D$ −41.6; $[\alpha]^{24}Hg$ −54.3 in dioxane. The substance does not give a color with tetranitromethane and gives marked depressions in melting point when mixed with diosgenin or tigogenin.

Anal. Calcd. for $C_{27}H_{48}O_4$: C, 74.26; H, 11.08. Found: C, 73.74, 74.17; H, 11.05, 11.08.

The compound was recovered unchanged after several hours of refluxing with alcoholic hydrochloric acid, proving that it is not a prosapogenin. When refluxed with acetic anhydride and sodium acetate, an acetate was obtained which, after several crystallizations from aqueous methyl alcohol, melted at 102–103°; $[\alpha]^{24}D$ 0°; $[\alpha]^{24}Hg$ −3.5° in dioxane.

Anal. Calcd. for $C_{27}H_{44}O_4(CH_3CO)_4$: C, 69.51; H, 9.33; acetyl, 28.48. Found: C, 69.97; H, 9.28; acetyl, 29.86, 29.52.

Summary

Bethogenin, a new sapogenin having the empirical formula $C_{27}H_{40}O_4$, has been isolated from the hydrolysis products of extracts of powdered beth root (*Trillium erectum*). It appears to be an unsaturated steroid sapogenin with one hydroxyl group and one carbonyl group.

Another new sapogenin, trillogenin, having the empirical formula $C_{27}H_{48}O_4$, has been obtained in very small amount. This compound is saturated and is unique among the known steroid sapogenins because it lacks the two characteristic inert oxygen atoms, all four oxygen atoms being accounted for by hydroxyl groups.

STANFORD UNIV., CALIF. RECEIVED NOVEMBER 5, 1941

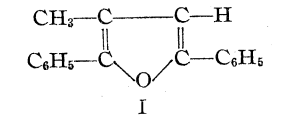
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Halogen Compounds Derived from 4-Methyl-2,5-diphenylfuran

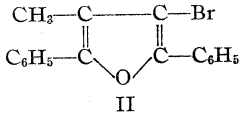
BY ROBERT E. LUTZ AND C. EDWARD MCGINN[1]

The bromination of this furan was of interest in connection with orientation[2] and the synthesis of certain brominated *cis* unsaturated diketones which could not easily be made otherwise.

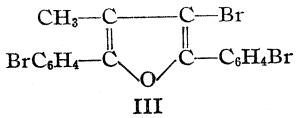
The bromination of methyldiphenylfuran (I) proceeded stepwise with the formation successively of the mono,[3] tri and tetrabromo derivatives (II, III and IV).



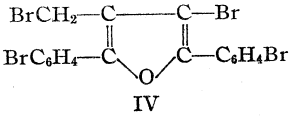
I



II

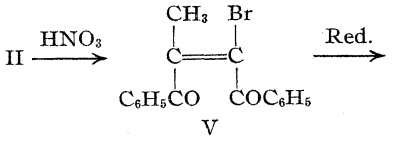


III

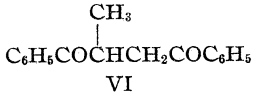


IV

Zinc and acetic acid reduced only the tetrabromo derivative and eliminated but one bromine to give the tribromo compound. The last bromine introduced therefore must have been aliphatic and located on the methyl group; and the three bromines of the tribromo compound must be aromatic. The tribromo compound on oxidation first with nitric acid and then with potassium permanganate gave more than one molecule of *p*-bromobenzoic acid, showing that two of the halogens occupied the two phenyl para positions. The remaining bromine atom, evidently the first introduced, must, therefore, be in the furan β-position (*cf.* II). This was confirmed by nitric acid oxidation of the monobromo derivative (II) to the unsaturated bromo 1,4-diketone[3] (V) and reduction of this to the saturated diketone (VI) with loss of the bromine. The structures of the three bromination products therefore are as represented in formulas II, III and IV.



V



VI

Each of the three brominated furans (II, III and IV) could be oxidized by the nitric–acetic acid reagent to the corresponding unsaturated 1,4-diketones (V, VII and IX) which are presumed to be *cis* from the mode of formation. The first of these oxidation products (V) already has been reported.[3] The other two (VII and IX) could be converted into the saturated diketone (VIII) by reduction with zinc and acetic acid and into the furan (X) by reduction under dehydrating conditions.

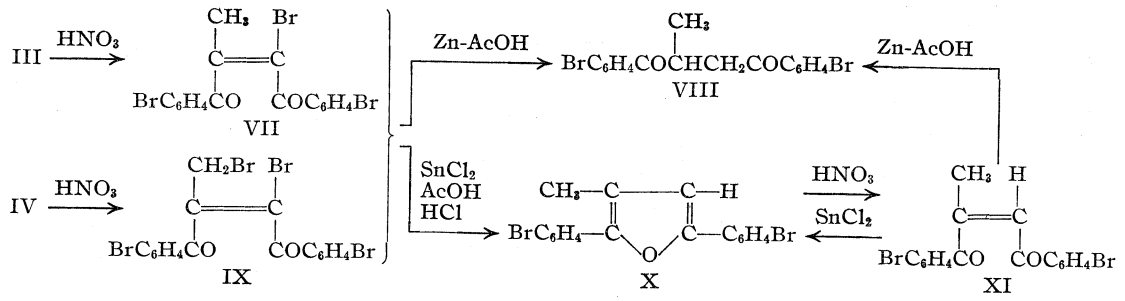
The *cis*-di-[bromobenzoyl]-propylene (XI) has become available through oxidation of the corresponding furan (X). This new unsaturated diketone in turn was reduced to the saturated diketone (VIII) and to the furan (X).

Unfortunately, it has not yet been possible to

(1) Present location, National Aniline Division, Allied Chemical and Dye Corp., Buffalo.

(2) Lutz and Kibler, THIS JOURNAL, **62**, 1520 (1940).

(3) Lutz and Stuart, *ibid.*, **59**, 2316 (1937).



make any of the corresponding *trans*-compounds in this series. One important approach which should have led directly to the *trans*-isomer of XI was blocked by the failure of the Friedel–Crafts reaction between bromobenzene and mesaconyl chloride to go beyond the first stage, namely, the formation of β-bromobenzoyl-β-methylacrylic acid.[4]

Experimental

3-Methyl-2,5-di(*p*-bromophenyl)-furan (X).—This furan was obtained in excellent yields by the stannous chloride reduction of 1-bromo-1,2-di-(*p*-bromobenzoyl)-propylene (VII), 1,2-di-(*p*-bromobenzoyl)-propylene (XI), and 1,3-dibromo-1,2-di-(*p*-bromobenzoyl)-propylene (IX). The following procedure is general.

A mixture of 30 ml. of concd. acetic acid, 25 ml. of concd. hydrochloric acid and 18 g. of stannous chloride was heated to boiling under mechanical stirring; 5 g. of (XI) in 15 ml. of concd. acetic acid was added; heating was continued for five minutes; and cooling and dilution with water gave a crystalline product. Recrystallizations from ethyl acetate raised the melting point to 158–159°. The yield of nearly pure product was 3.1 g.

Anal. Calcd. for $C_{17}H_{12}Br_2O$: C, 52.07; H, 3.09. Found: C, 52.12; H, 3.87.

3-Bromo-2,5-di-(*p*-bromophenyl)-4-methyl-furan (III). This compound was obtained directly by bromination of 3-methyl-2,5-diphenylfuran (I) by the calculated amount of bromine in chloroform solution but the method was impractical because of the difficultly separable mixture of bromination products which was obtained. The preparation is as follows:

A mixture of 2 g. of 3-bromo-4-bromomethyl-2,5-di-(*p*-bromophenyl)-furan and 2 g. of zinc dust in 70 ml. of concd. acetic acid was refluxed for five minutes and filtered. Upon dilution with water and crystallizing the resulting precipitate from a chloroform–ethanol mixture, 1.6 g. of nearly pure product (III) was obtained. Repeated crystallizations from chloroform–ethanol mixtures raised the melting point to 168–169°.

Anal. Calcd. for $C_{17}H_{11}Br_3O$: C, 43.35; H, 2.36. Found: C, 43.04, 43.03; H, 2.66, 2.66.

Zinc dust and boiling concd. acetic acid was without action on this compound.

3-Bromo-4-bromomethyl-2,5-di-(*p*-bromophenyl)-furan (IV).—A solution of 30 g. (4.1 moles) of bromine in 50 ml. of chloroform was added to 10 g. of methyldiphenylfuran (I) in 100 ml. of chloroform. The mixture was allowed to stand for twenty hours at room temperature, during which time hydrogen bromide was evolved, and a colorless crystalline product separated. Filtration, evaporation and finally dilution with ethanol gave successive crops totalling 17.9 g. (75%). After repeated crystallization it melted at 212–213°.

Anal. Calcd. for $C_{17}H_{10}Br_4O$: Br, 58.15. Found: Br, 58.33.

***cis*-1,4-Di-(*p*-bromophenyl)-2-methyl-2-butenedione-1,4 (XI).**—A mixture of 5 ml. of concd. nitric acid and 15 ml. of concd. acetic acid was added to a suspension of 2,5-di-(*p*-bromophenyl)-3-methylfuran (X) in 20 ml. of concd. acetic acid. After one hour at room temperature the mixture was diluted with water and the product crystallized from ethanol (yield 1.8 g.). Repeated crystallization from this solvent brought the melting point to 115–116°.

Anal. Calcd. for $C_{17}H_{12}Br_2O_2$: C, 50.0; H, 2.96. Found: C, 49.71; H, 3.08.

Sunlight was without action on a chloroform–iodine solution of this compound.

***cis*-1-Bromo-1,4-di-(*p*-bromophenyl)-2-methyl-2-butenedione-1,4 (VII).**—A mixture of 5 ml. of concd. nitric acid and 15 ml. of concd. acetic acid was added to a suspension of 5 g. of the furan (III) in 25 ml. of concd. acetic acid. After heating for one hour at 50°, diluting with ice-water and crystallizing the product from ethanol, 4.7 g. (91%) of VII was obtained. Recrystallization from ethanol brought the melting point to 119.5–120°.

Anal. Calcd. for $C_{17}H_{11}Br_3O_2$: C, 41.90; H, 2.28; Br, 49.23. Found: C, 41.46; H, 2.40; Br, 48.83.

***cis*-1-Bromo-2-(bromomethyl)-1,4-di-(*p*-bromophenyl)-2-butenedione-1,4 (IX).**—A mixture of 10 ml. of concd. nitric and 30 ml. of concd. acetic acids added to a suspension of 5 g. of IV, was heated for one hour at 50° and diluted with water. The product was crystallized from ethanol (4.5 g., 90%), and after further crystallization it melted at 117–117.5°.

Anal. Calcd. for $C_{17}H_{10}Br_4O_2$: C, 36.1; H, 1.78; Br, 56.40. Found: C, 35.77; H, 2.13; Br, 56.83.

Sunlight was without action on a chloroform–iodine solution.

1,4-Di-(*p*-bromophenyl)-2-methylbutanedione-1,4 (VIII).—The following procedure was employed using at will, VII, IX or XI.

A mixture of 5 g. of VII, 5 g. of zinc dust and 100 ml. of concd. acetic acid was refluxed for fifteen minutes, filtered and diluted with water. Extraction with ether, washing

(4) Lutz and Taylor, THIS JOURNAL, **55**, 1168 (1933).

the extract with water, evaporation and crystallization of the residue gave 3 g. of colorless prisms which after repeated crystallizations from ethanol melted at 120–120.5°.

Anal. Calcd. for $C_{17}H_{14}Br_2O_2$: Br, 39.0. Found: Br, 38.93.

Summary

Bromination of 3-methyl-2,5-diphenylfuran involves successive substitutions in the furan β-position, the phenyl para positions and in the methyl group.

The various brominated furans of this series have been oxidized to *cis* unsaturated diketones and these in turn have been reduced. The diketones of the di-*p*-bromophenyl series have become available through these reactions.

CHARLOTTESVILLE, VA. RECEIVED JULY 16, 1942

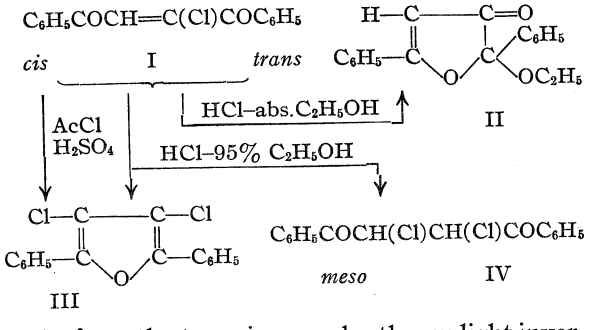
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

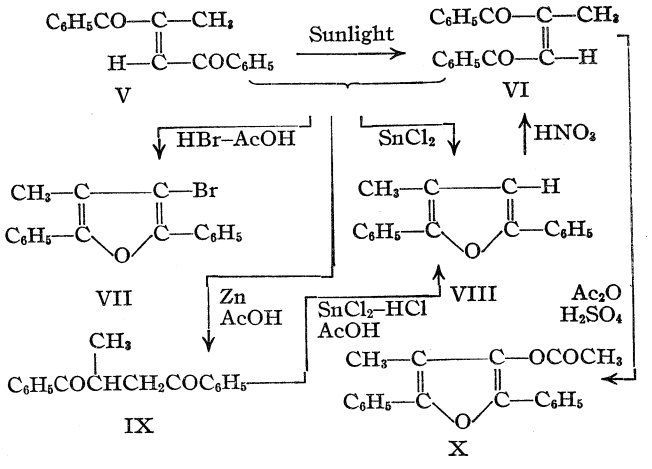
The Conversion of Unsaturated 1,4-Diketones into Furans and Hydroxyfuranones

BY ROBERT E. LUTZ AND C. EDWARD MCGINN[1]

It would be expected that *cis* unsaturated 1,4-diketones would be somewhat more reactive than *trans*. This is the case with the stereoisomeric dibenzoylchloroethylenes (I) where only the *cis*-isomer reacts under the usual conditions with acetic anhydride and with acetyl chloride (with sulfuric acid as catalyst) to give, respectively, the acetoxychlorodiphenylfuran and dichlorodiphenylfuran (III).[2] However, both the *cis*- and *trans*-dibenzoylchloroethylenes react easily with hydrogen chloride in 95% ethanol to give the same mixture of dichlorodiketone (IV) and furan (III)[3], and in absolute ethanol to give the ethoxyfuranone (II).[4] This report deals with more reactions of these types.

Certain of the *cis* unsaturated diketones which have been difficult if not impossible to make from the *trans*-isomers by the sunlight inversion can now be made in good yield through the corresponding furan by oxidation by means of nitric acid. This method has been applied successfully in the preparation in quantity of *cis*-dibenzoylmethylethylene (VI) as is outlined in the diagram.





The *cis*- and *trans*-dibenzoylmethylethylenes (VI and V) are converted readily into the bromofuran (VII) by hydrogen bromide in acetic acid, but it has not been possible under the experimental conditions to determine the relative ease of reaction in the two cases. In the reaction with acetic anhydride and sulfuric acid at room temperature, on the other hand, the *trans*-compound did not react whereas the *cis*-isomer was converted in good yield into the acetoxyfuran (X). Similarly the *trans*-compound did not react with benzoic anhydride and sulfuric acid whereas the *cis*-isomer did (although, unfortunately, not to give a crystalline product). Incidentally, it has since been found that in the medium acetic anhydride, acetic acid and zinc chloride, *trans*-dimesitoylethylene is reduced catalytically to the saturated diketone in the normal fashion whereas the *cis*-isomer in-

(1) Present location, National Aniline Division, Allied Chemical and Dye Corp., Buffalo.

(2) Lutz, Stuart, Wilder and Connor, THIS JOURNAL, **59**, 2314 (1937).

(3) Lutz and Wilder, *ibid.*, **56**, 1193 (1934).

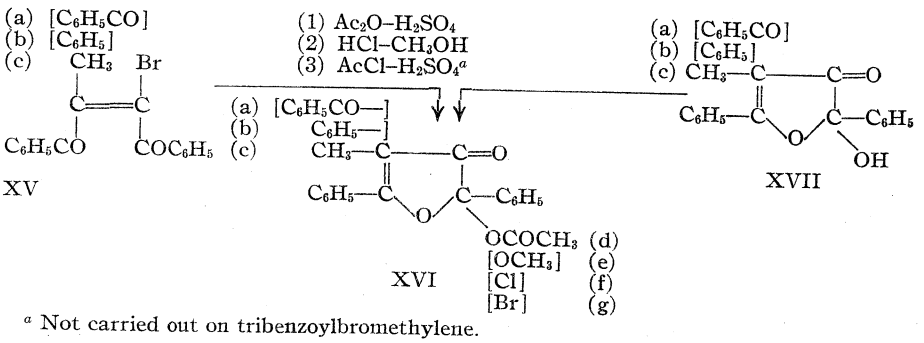
(4) Lutz, Wilder and Parrish, *ibid.*, **56**, 1980 (1934).

stead is converted into the acetoxyfuran by addition and dehydration.[5]

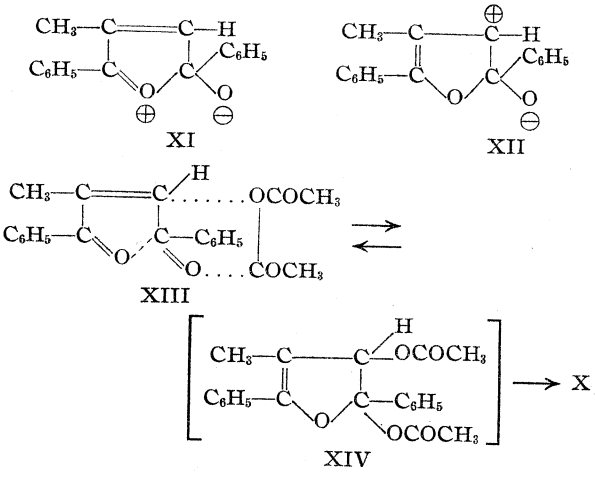
There probably is some special reason, other than the slightly higher energy content, for the greater reactivity of the *cis* as compared with the *trans* unsaturated 1,4-diketone. Possibly actual interaction of the two spatially proximate carbonyl groups is involved to give resonance hybrids such as XI and XII, which might facilitate the reaction with acetic anhydride or combination with the catalyst (*cf.* XIII, XIV).[6]

Each of the compounds discussed above carries in the chain position a hydrogen atom which makes possible elimination of an acid molecule or its equivalent to form the double bond needed to complete the conjugated system of the furan nucleus (*cf.* XIV). If this chain hydrogen were not available, as is the case with completely substituted unsaturated diketones such as XV, the formation of a furan would be impossible. However, with an oxygen or halogen atom at one of these chain positions, a reaction still could proceed by a mechanism similar to that suggested above but with the formation in the end of a 2,3-hydroxyfuranone derivative of the type XVI or XVII. This latter type of reaction has in fact been observed even when a chain hydrogen is available and where both the furan and the hydroxyfuranone theoretically might result [*cf.* the conversion of the *cis*- and *trans*-dibenzoylchloroethylenes (I) into the ethoxyfuranone (II[3,4])].

The formation of hydroxyfuranone types from suitably substituted unsaturated 1,4-diketones has already been utilized in a method of synthesis of 4-benzoyl-2-hydroxy-2,5-diphenylfuranone-3.[7] Other examples of this type of reaction have been sought and found; these reactions, including both old and new ones, are illustrated in the following diagram.



[a] Not carried out on tribenzoylbromethylene.



The *trans* unsaturated diketones corresponding to XV-b and c are not known and work is being undertaken to complete some suitably substituted *cis–trans* pairs for comparison with respect to relative facility of this type of reaction.

Experimental

***trans*-2-Methyl-1,4-diphenyl-2-butenedione-1,4 (V).**—Earlier preparations[8] were not satisfactory. From a long series of experiments carried out under varied conditions, it was found that temperature control and rapid working-up of the product were very important factors. The directions finally evolved were practically identical with those which have since been published.[9]

***cis*-2-Methyl-1,4-diphenyl-2-butenedione-1,4 (VI).**—A mixture of 10 ml. of concd. nitric and 30 ml. of concd. acetic acids at 10° was added to a solution of 10 g. of the furan (VIII) in 50 ml. of concd. acetic acid (also at 10°). Immediate reaction occurred with evolution of oxides of nitrogen, and after standing for five minutes 200 ml. of water was added. The viscous resinous precipitate was isolated by extraction with ether and evaporating. The product crystallized from ethanol; 8.7 g. (81%). It was identified by mixture melting point with a sample made by the sunlight inversion method.[10] The yields were lowered when the reactions were carried out at higher temperatures or over longer periods of time.

Reduction with zinc dust and concd. acetic acid at 100° gave the saturated diketone (IX) in excellent yields.

(5) Lutz, Reveley and Mattox, THIS JOURNAL, **63**, 3171 (1941).

(6) The idea of interaction of the two carbonyls to give a ring form in an equilibrium or oscillating system is not new [*cf.* the peroxide formula for *cis*-dibenzoylethylene suggested by Smedley [*J. Chem. Soc.*, **75**, 219 (1909)].

(7) Lutz and Smith, THIS JOURNAL, **63**, 1148 (1941).

(8) Lutz and Taylor, *ibid.*, **55**, 1177 (1933); Stuart, Dissertation, University of Virginia, 1936, p. 100.

(9) Fuson, Fleming and Johnson, *ibid.*, **60**, 1994 (1938).

(10) Lutz and Taylor, *ibid.*, **55**, 1168 (1933).

Attempts to obtain a crystalline ethylene oxide from the *cis*-compound (VI) by the action of hydrogen peroxide were unsuccessful and only non-crystalline products were obtained.

3-Methyl-2,5-diphenylfuran (VIII).—A mixture of 250 ml. of concd. acetic acid and 200 ml. of concd. hydrochloric acid was heated to boiling, and 128 g. of stannous chloride was added, followed by 35 g. of *trans*-dibenzoylmethylethylene (V) in 100 ml. of concd. acetic acid. Heating was continued for five minutes during which time an oil separated. Upon cooling and diluting with 700 ml. of water and crystallizing the product once from ethanol, 31.3 g. (96%) of nearly pure furan was obtained (m. p. 58–59°). This melting point corresponds with that given in the literature.[11]

Equally good results were obtained using the *cis* unsaturated diketone (VI).

3-Bromo-2,5-diphenyl-4-methylfuran (VII).[12]—A solution of 1 g. of the furan (VIII) in 20 ml. of chloroform was treated with 0.8 ml. of bromine. The bromine color was discharged and hydrogen bromide was evolved. Evaporation and crystallization of the residue from ethanol gave 1.1 g. of the bromofuran (VII).

In another experiment, 5 g. of the *cis* unsaturated diketone (VI) was suspended in 50 ml. of acetic anhydride and treated with 10 ml. of 30% hydrogen bromide in concd. acetic acid at 0°. Three drops of concd. sulfuric acid were added and after fifteen minutes the mixture was hydrolyzed with water. The product was crystallized from ethanol and identified as the bromofuran (VII) (yield 5.1 g.).

3-Acetoxy-4-methyl-2,5-diphenylfuran (X).—A solution of 5 g. of the *cis* unsaturated diketone (VI) in 20 ml. of acetic anhydride was cooled to −5° and three drops of concd. sulfuric acid were added. The temperature was not allowed to rise above −1°. After standing for five minutes the solution was poured into 200 ml. of water. When crystallization was complete the product was recrystallized from isopropanol (yield 3.7 g. or 68%).

In a similar experiment on a larger scale in which the temperature was allowed to rise to 25° the yield was lower (about 50%).

The compound crystallizes as yellowish needles but undergoes vacuum evaporation onto a cold-finger condenser as colorless needles of m. p. 94–95°.

Anal. Calcd. for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 78.18; H, 5.58.

Attempts to obtain a chlorofuranone from this compound by means of phosphorus pentachloride, thionyl chloride and phenyliodochloride produced only non-crystalline materials. In the case of thionyl chloride a small yield (5%) of the dimolecular oxidation product, 2-bis-(4-methyl-2,5-diphenylfuranone-3), was obtained and identified by mixture m. p.[12]

2-Bromo-4-methyl-2,5-diphenylfuranone-3 (*cf.* XVI-c,g).—A solution of 0.8 g. of bromine in 8 ml. of carbon tetrachloride was added to a solution of 1.0 g. of the acetoxyfuran (X) in 15 ml. of the same solvent. The color was discharged by refluxing for a short time. Evaporation and crystallization of the residue from ligroin gave 1 g. of colorless prisms which after repeated crystallizations from ligroin melted at 88–89°.

Anal. Calcd. for $C_{17}H_{13}BrO_2$: C, 62.02; H, 3.98. Found: C, 62.98, 62.67; H, 4.22, 4.33. (The high values for carbon and hydrogen are accounted for by the instability of the compound and evident loss of some of the bromine through hydrolysis.)

When treated immediately with ethanol under refluxing for five minutes, the ethoxyfuranone was obtained in good yield and identified by mixture melting point.

***cis*-2-Bromo-3-methyl-1,4-diphenyl-2-butenedione-1,4**[12] **(XV-c).**—A mixture of 5 ml. of concd. nitric and 15 ml. of concd. acetic acid was added to a solution of 5.1 g. of the bromofuran (VII) in 25 ml. of concd. acetic acid with heating at 80° for one hour. Dilution with water gave 4.2 g. of nearly pure *cis* unsaturated diketone (XV-c).

A suspension of 1 g. of (XV-c) in 10 ml. of acetic anhydride at 0° was treated with two drops of concd. sulfuric acid. After fifteen minutes at this temperature, the solution was hydrolyzed with a large volume of water. The resulting oil was crystallized from ethanol (0.5 g.) and identified as the acetoxyfuranone (XVI-c,d).

A drop of concd. sulfuric acid was added to a suspension of 1 g. of (XV-c) in 10 ml. of acetyl chloride at 0° and the mixture was allowed to stand at this temperature for fifteen minutes and hydrolyzed in an excess of water. The resulting yellow solid was crystallized from ligroin (0.2 g.) and identified as the chlorofuranone (XVI-c,f).

A solution of 1 g. of the bromo unsaturated diketone (XV-c) in 20 ml. of 99% of methanol saturated with dry hydrogen chloride was allowed to stand at room temperature for twenty hours in a glass-stoppered flask. Upon cooling 0.6 g. of the methoxyfuranone (XVI-c,e) crystallized and was identified.

3-Bromo-2,4,5-triphenylfuran[13] was prepared in excellent yield by the action of 30% hydrogen bromide in concd. acetic acid on dibenzoylphenylethylene. The reaction was complete within two to three minutes at room temperature and the product crystallized on cooling.

***cis*-2-Bromo-1,2,4-triphenyl-2-butenedione-1,4**[14] **(XV-b)** was prepared by adding a mixture of 50 ml. of concd. nitric and 30 ml. of concd. acetic acids to a solution of 10 g. of 3-bromotriphenylfuran in 50 ml. of concd. acetic acid. The mixture was heated for fifteen minutes at 100° and poured into cold water. The product was crystallized from ethanol (7.2 g.).

Two drops of concd. sulfuric acid were added to a solution of 1 g. of (XV-b) in 10 cc. of acetic anhydride. The mixture was allowed to stand for fifteen minutes at room temperature and was hydrolyzed in an excess of water. Crystallization of the product from isopropanol gave 0.73 g. of the acetoxyfuranone (XVI-b,d).

In a similar experiment, using acetyl chloride instead of acetic anhydride, the chlorofuranone (XVI-b,f) was obtained in 85% yield.

A solution of 0.5 g. of (XV-b) in 10 ml. of methanol saturated with hydrogen chloride was allowed to stand for eighteen hours in a glass-stoppered flask; 0.3 g. of methoxyfuranone (XVI-b,e) was obtained.

(11) Lauer and Spielman, THIS JOURNAL, **55**, 4924 (1933).

(12) Lutz and Stuart, *ibid.*, **59**, 2316 (1937).

(13) Japp and Klingemann, *J. Chem. Soc.*, **57**, 674 (1890); Allen, THIS JOURNAL, **49**, 2110 (1927).

(14) Lutz, Tyson, Sanders and Fink, THIS JOURNAL, **56**, 2679 (1934).

Summary

Several *cis* unsaturated 1,4-diketones are shown to be much more susceptible than the *trans* isomers toward furanization through addition and dehydration. A mechanism is suggested to account for this.

The analogy between these furanizations and the formation of 2,3-hydroxyfuranones is considered and new examples of the latter reaction are described.

CHARLOTTESVILLE, VA. RECEIVED JULY 16, 1942

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

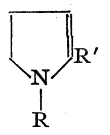
Basicity Studies of Tertiary Vinyl Amines

BY ROGER ADAMS AND J. E. MAHAN

The introduction of a double bond into a primary or secondary amine lowers the basic strength constant, that is, decreases the degree of ionization.[1] Hixon and co-workers[2] measured the ionization constants of several 2-alkyl substituted 4,5-dihydropyrroles (2-ethyl, 2-benzyl, 2-phenyl, and 2-cyclohexyl-Δ^2-pyrrolines) and of the corresponding saturated compounds (pyrrolidines). The saturated molecules were, in all cases, stronger bases than the unsaturated by 2.4 to 3.3 pK_H units.[2a] In the case of tertiary amines the same general effect as for primary and secondary amines might be expected but no examples were found in the literature. Vinyl tertiary amines, excluding the pseudo bases or anhydro bases formed from pyridinium type salts which are not entirely comparable have also, with one exception, not been studied. The normal assumption would be that they are weaker bases than the corresponding saturated amines.

An attempt to locate the relative position of a double bond to the nitrogen atom in retronecine, a base from the plants of the genera *Crotalaria*, *Senecio* and *Trichodesma*, was initiated by comparative basicity studies[3] of retronecine, desoxyretronecine and their reduction products. These substances were all tertiary amines containing pyrrolizidine rings. For purposes of comparison, a variety of tertiary vinyl amines and the corresponding reduced compounds have been synthesized and their relative basicity measurements made.

A series of 1,2-dialkyl-Δ^2-pyrrolines (I–IV) was first investigated, since such molecules are very closely related in structure to the products under



I. R = CH_3; R′ = CH_3
II. R = CH_3; R′ = C_4H_9
III. R = C_2H_5; R′ = CH_3
IV. R = C_4H_9; R′ = CH_3

study. The basic strengths of these pyrrolines and the analogous pyrrolidines are shown in Table I. It is to be noticed that in every case the unsaturated compound is more basic than the saturated. This interesting observation stimulated us to study analogous 6-membered ring compounds, namely, 1,2-dialkyl-Δ^2-tetrahydropyridines and the corresponding piperidines.

TABLE I

Name	Obs. pK_H	T, °C.	pK_H (25°)[4]	Diff.	Lit.
1,2-Dimethyl-Δ^2-pyrroline	11.94	25	11.94		
1,2-Dimethylpyrrolidine	10.24	26	10.26	1.68	9.8[5]
1-Methyl-2-*n*-butyl-Δ^2-pyrroline	11.88	26	11.90		
1-Methyl-2-*n*-butylpyrrolidine	10.24	25	10.24	1.66	9.8[5]
1-Ethyl-2-methyl-Δ^2-pyrroline	11.88	27	11.92		
1-Ethyl-2-methylpyrrolidine	10.60	27	10.64	1.28	
1-*n*-Butyl-2-methyl-Δ^2-pyrroline	11.90[a]	26			
1-*n*-Butyl-2-methylpyrrolidine	10.43[a]	28		1.47	

[a] Taken in 25% aqueous methanol.

(1) Hixon and Johns, THIS JOURNAL, **49**, 1786 (1927).

(2) Craig and Hixon, *ibid.*, **53**, 4367 (1931); Starr, Bulbrook and Hixon, *ibid.*, **54**, 3971 (1932).

(2a) The constant pK_H will be used in this paper to indicate the basic strengths. It is related to the more usual constant K_{ion}, by the expression $pK_H = pK_w - pK_{ion}$, where K_w is the ion product for water.

(3) Adams, Carmack, and Mahan, *ibid.*, **64**, 2593 (1942).

(4) Corrected to 25° employing the negative temperature coefficient of the constant as given by Hall and Sprinkle, *ibid.*, **54**, 3469 (1932), for amines of various basicity. Since these data are valid only for aqueous solutions the pK_H constants measured in aqueous methanol were not corrected to 25°.

(5) Craig, *ibid.*, **55**, 2543 (1933).

The results are shown in Table II. Here again the unsaturated tertiary amines are more basic than the saturated.

TABLE II

Name	Obs. pK_H	T, °C.	pK_H (25°)[4]	Lit.
1,2-Dimethyl-Δ^2-tetrahydropyridine	11.42	25.5	11.43	
1,2-Dimethylpiperidine	10.26	25	10.26	
1-Ethyl-2-methyl-Δ^2-tetrahydropyridine	11.57	25	11.57	
1-Ethyl-2-methylpiperidine	10.70	25	10.70	10.68[4]
ω-Dimethylamino-*n*-butyl methyl ketone	9.66	24.5	9.67	

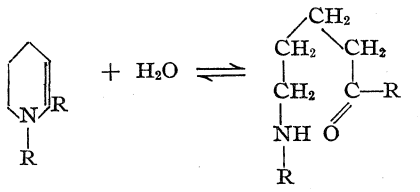
A similar comparison has been carried to 1-propenylpiperidine and 1-*n*-propylpiperidine, as well as to a pair of straight chain compounds, 1-diethylamino-*n*-heptene-1 and 1-diethylamino-*n*-heptane (Table III). The basic strength determinations of these two sets of molecules were carried out in the former case in 25% methanol and in the latter in 50% methanol because of the fact that the unsaturated molecules are not sufficiently soluble in water. The phenomenon still holds that the unsaturated molecules are more basic than the saturated, though to a lesser degree than in the Δ^2-pyrroline and Δ^2-tetrahydropyridine series.

TABLE III

Name	Obs. pK_H	T, °C.	Diff.
1-Propenylpiperidine	10.66[a]	28	
1-Propylpiperidine	10.23[a]	25	0.43
1-Diethylamino-*n*-heptene-1	10.38[b]	28	
1-Diethylamino-*n*-heptane	9.94[b]	26	.44
Piperidine (in 25% methanol which contained over an equivalent of propionaldehyde)	10.77	27	
Diethylamine (in 50% methanol which contained over an equivalent of heptaldehyde)	10.50	27	

[a] In 25% aqueous methanol. [b] In 50% aqueous methanol.

In experiments of this kind the question may be raised in the case of the pyrrolines and tetrahydropyridines whether the basic strength as determined is a measure of the molecules in cyclic form or whether of possible open chain hydrolytic products; in the case of the 1-propenylpiperidine and 1-diethylamino-*n*-heptene-1, whether the basic strength is that of the original molecules or of a mixture of the secondary amine and corresponding aldehyde. The smooth titration curves, described in the experimental part, support the supposition that only a single basic molecule is being titrated in each instance. Lipp and Widnmann[6] reported that when a Δ^2-tetrahydropyridine (V) (Table II) is dissolved in water, it is immediately hydrolyzed to some extent to give an open chain secondary amino ketone (VI). This was based



V VI

on immediate reaction of the compounds with carbonyl reagents to give derivatives of the open chain amine.

The basic strength of ω-dimethylamino-*n*-butyl methyl ketone, which is a tertiary amino ketone and thus cannot ring close to a Δ^2-tetrahydropyridine, gave a pK_H value of 9.68, which is relatively low and which led to the deduction that the strong basicity of aqueous solutions of the Δ^2-tetrahydropyridines is not due to the open-chain form of the equilibrium mixture.

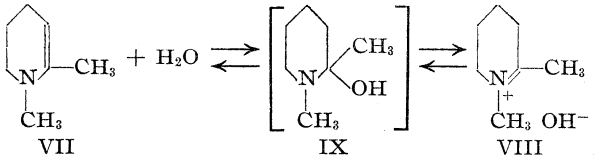
Marz[7] observed that 2-methyl-Δ^2-pyrroline would react with hydroxylamine, semicarbazide and phenylhydrazine in aqueous solution, and hence concluded that a similar equilibrium existed in the Δ^2-pyrroline series. Craig,[8] however, prepared and studied several 1-methyl-2-alkyl-Δ^2-pyrrolines and because of their apparent non-reactivity with semicarbazide or phenylhydrazine assumed that hydrolysis did not occur to any great extent in aqueous solution.

Mannich and Davidsen[9] pointed out that vinyl tertiary amines in which the double bond is not a part of a ring are readily hydrolyzed in the presence of mineral acids to the corresponding aldehyde and secondary amine. If rapid hydrolysis occurs during the titration in the present basic strength studies, the resulting curve and pK_H value should be that of piperidine in the case of 1-propenylpiperidine, and that of diethylamine in the case of 1-diethylamino-*n*-heptene-1. Piperidine and diethylamine were titrated (Table III) in aqueous methanol in the presence of slightly over an equivalent of the appropriate aldehyde, approximating as nearly as possible those conditions used in the titration of the 1-propenylpiperi-

(6) Lipp and Widnmann, *Ann.*, **409**, 79 (1915).
(7) Marz, Diss. Techn. Hochsch., München, 1913.
(8) Craig, THIS JOURNAL, **55**, 295 (1933).
(9) Mannich and Davidsen, *Ber.*, **69**, 2106 (1936).

dine and the 1-diethylamino-heptene-1. The mixture of the aldehyde and base gave a slightly higher basicity than the molecules which were prepared from them, though the difference was far less than expected.

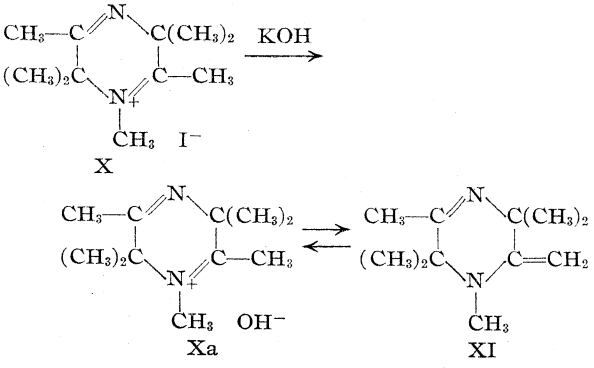
A possible explanation of the increased basicity of the vinyl tertiary amines compared with their saturated homologs lies in the assumption that an equilibrium exists in aqueous solution between the vinyl amine and a hydration product, the corresponding quaternary hydroxide as shown in formulas VII and VIII for 1,2-dimethyl-Δ^2-tetrahydropyridine as a representative of all the vinyl amines studied. The quaternary ammonium



VII IX VIII

hydroxides are known to be strong bases which exceed in basicity all the tertiary amines. Since pseudo bases in general are weak, no appreciable amount of pseudo base (IX) can be present in the solution when titrated.

Aston[10] studied the action of alkali on 1,2,3,-5,5,6-heptamethyldihydropyrazinium iodide (X) and obtained a strong base (Xa) (pK_H at 25°, 11.6) of a quaternary ammonium type which is in equilibrium in aqueous solution with the tertiary base XI. This coincides with the explanation offered for the basicity of the simple vinyl tertiary amines studied in this investigation.



X Xa XI

Vinyl primary or secondary amines if they undergo a similar rearrangement would form ammonium bases, not quaternary ammonium bases. Hence a lower basicity of the vinyl primary or secondary amines as compared with the corresponding saturated compounds would be expected and this agrees with the experimental facts. In Table IV, it may be noted that 2-methyl-Δ^2-tetrahydropyridine, a secondary vinyl amine, is less basic than 2-methylpiperidine, a fact which is in harmony with the above statement and the observations of Hixon and co-workers[2] on 2-alkyl-Δ^2-pyrrolines.

TABLE IV

Name	Obs. pK_H	T, °C.	pK_H (25°)[4]	Lit.
2-Methylpiperidine	10.99	25	10.99	10.98[4]
2-Methyl-Δ^2-tetrahydropyridine	9.57	24	9.55	

Although it has been generally assumed that unsaturated tertiary amines with the double bond not in the vinyl position are less basic than the corresponding saturated, it was deemed advisable to test two pairs of such molecules which are related to the amines under investigation. These are shown (Table V) by a comparison of 1-methyl-Δ^3-pyrroline with 1-methylpyrrolidine and 1-allylpiperidine with 1-*n*-propylpiperidine. The saturated molecules are more basic than the unsaturated.

TABLE V

Name	Obs. pK_H	T, °C.	pK_H (25°)[4]	Diff.	Lit.
1-Methylpyrrolidine	10.36	25	10.36		10.18[5]
1-Methyl-Δ^3-pyrroline	9.92	25	9.92	0.44	
Propylpiperidine	10.45	26.5	10.48		
Allylpiperidine	9.65	27	9.69	.89	

A few effects of substitution were noted in this work which have not been previously mentioned in the literature. When an N-methyl group is replaced by an N-ethyl group on the pyrrolidine or piperidine ring there is an increase in basicity of about 0.4 unit. This effect is exemplified in Table VI; compare 2 with 4, and 8 with 9. However, increasing the size of the alkyl group from ethyl to butyl has little effect on the pK_H value of the resulting base; compare 1 with 2, 7 with 8, 11 with 12 and 13. The close parallel of pK_H values of compounds of the pyrrolidine series with analogous substituted compounds of the piperidine series may be worthy of note; compare 1 with 9, 2 with 10, 4 with 11, and 8 with 16.

Craig, Shedlovsky, Gould and Jacobs[11] assigned the double bond in lysergic acid (XII) to the 5,10-position because this acid and ergome-

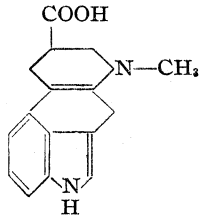
(10) Aston, THIS JOURNAL, **52**, 5254 (1930); **53**, 1448 (1931); Aston and Montgomery, *ibid.*, **53**, 4298 (1931); Aston and Lasselle, *ibid.*, **56**, 426 (1934).

(11) Craig, Shedlovsky, Gould and Jacobs, *J. Biol. Chem.*, **125**, 289 (1938).

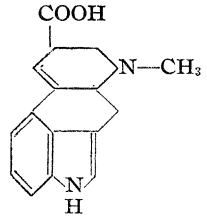
TABLE VI

Name	Obs. pK_H	T, °C.	pK_H (25°)[4]	Lit.
(1) 1-*n*-Butyl-2-methylpyrrolidine	10.65	27	10.69	
(2) 1-Ethyl-2-methylpyrrolidine	10.61	27	10.64	
(3) 1-Methyl-2-*n*-butylpyrrolidine	10.24	25	10.24	9.8[5]
(4) 1,2-Dimethylpyrrolidine	10.24	26	10.26	9.8[5]
(5) 1-Methylpyrrolidine	10.36	25	10.36	10.18[5]
(6) Pyrrolidine				11.99[2]
(7) 1-*n*-Butyl-2-methylpiperidine				10.72[4]
(8) 1-Ethyl-2-methylpiperidine	10.70	25	10.70	10.68[4]
(9) 1,2-Dimethylpiperidine	10.26	25	10.26	
(10) 2-Methylpiperidine	10.99	25	10.99	10.98[4]
(11) 1-Ethylpiperidine				10.41[4]
(12) 1-*n*-Propylpiperidine	10.45	26.5	10.48	
(13) 1-*n*-Butylpiperidine	10.47	26	10.49	10.48[4]
(14) Piperidine	11.11	24.5	11.12	11.13[4]

trine, a parent alkaloid, exhibited weaker basic properties than *iso*-lysergic acid (XIII) and ergometrinine. The double bond in *iso*-lysergic acid was then assigned to the 9,10-position. In view of the results obtained on the basic strengths of vinyl tertiary amines, it appears questionable whether the deductions of the authors were justified and whether the assignment of the formulas should not possibly be reversed.



XII



XIII

Experimental

Determination of Basic Strength Constants.—A sample of the base calculated to require between 20 to 30 cc. of 0.10 *N* hydrochloric acid was dissolved in 90 cc. of conductivity water. While the solution was continuously stirred by means of a small air-driven stirrer, the base was titrated by adding appropriate increments of standard 0.1 *N* hydrochloric acid. After each addition of acid the *p*H was carefully measured with a Hellige glass electrode *p*H meter (no. 7040). The *p*H of the solution when exactly half of the base had been neutralized (pK_H value) was read from the titration curve (*p*H *vs.* cc. of acid). Duplicate or triplicate measurements were made in all cases. The curves obtained were smooth and showed only the characteristic sharp break at the end-point. For compounds not sufficiently soluble in water, 90 cc. of an aqueous solution was used which contained the calculated amount of methanol to make a 25 or 50% solution just at the point when half the titer had been added. All of the amines studied were carefully fractionated in a carbon dioxide-free atmosphere immediately before use, and all boiled within a range of 1° or less.

Basicity measurements were made on several compounds for which values have been recorded in the literature by Hall and Sprinkle[4] who used a hydrogen electrode in their *p*H determinations. The close agreement (see tables) in all cases with their values indicates that no great error has been introduced by the use of a glass electrode in the basicity studies.[12] Before each titration the electrodes were washed, the half-cell tip flushed with fresh saturated potassium chloride solution, and the meter standardized with 0.05 *M* potassium acid phthalate. Each day that the *p*H meter was put in service it was further checked by titration of ammonia (pK_H (25°) 9.27).[4]

Δ^2-Pyrrolines.—1,2-Dimethyl-Δ^2-pyrroline and 1-methyl-2-*n*-butyl-Δ^2-pyrroline were prepared according to the method of Craig.[8] The reaction of methylmagnesium iodide on N-methylpyrrolidone-2 led apparently only to the formation of 1,2-dimethyl-Δ^2-pyrroline, as none of the 1,2,2-trimethylpyrrolidine reported by Lukeš[13] could be found. However, the reversible dimerization mentioned by Craig[8] was encountered. In the synthesis of 1-methyl-2-*n*-butyl-Δ^2-pyrroline by an analogous reaction using butylmagnesium bromide, 1-methyl-2,2-di-*n*-butylpyrrolidine was isolated from the mixture of by-products in 14% yield. In preliminary attempts to prepare 1-*n*-butyl-2-methyl-Δ^2-pyrroline, it was found that the reaction of methylmagnesium iodide on N-*n*-butylpyrrolidone-2 was incomplete and did not lead to the formation of any appreciable quantity of the desired pyrroline.

A second procedure proved to be more satisfactory for the general preparation of pyrrolines in which alkyl groups larger than methyl were attached to the nitrogen. This consisted in treatment of 3-bromo-*n*-propyl methyl ketone with the appropriate primary amine[14,15] in aqueous solution. If ethanol instead of water is used as a solvent, the resulting homogeneous mixture undergoes reaction rapidly at room temperature, thus eliminating the necessity of longer periods of agitation. The yields in the case of 1-*n*-butyl and 1-ethyl-2-methyl-Δ^2-pyrroline were increased from 15% to 40–50% by this modification.

1-Methyl-2-*n*-butyl-Δ^2-pyrroline and 1-Methyl-2,2-*n*-dibutylpyrrolidine.—To the Grignard reagent, prepared

(12) It is only in the presence of certain metallic ions that there is a serious error introduced by the use of a glass electrode in alkaline solutions. See Dole, "The Glass Electrode," John Wiley and Sons, Inc., New York, N. Y., 1941, Chapter 7.

(13) Lukeš, *Coll. Czechoslov. Chem. Comm.*, **2**, 531 (1930); *Chem. Listy*, **27**, 97, 121 (1933).

(14) Hielscher, *Ber.*, **31**, 277 (1898).

(15) Markwalder, *J. prakt. Chem.*, **75**, 329 (1907).

from 31.6 g. (1.30 moles) of magnesium, 1200 cc. of dry ether, and 185 g. (1.34 moles) of *n*-butyl bromide, was added with stirring under nitrogen 63.5 g. (0.642 mole) of N-methylpyrrolidone-2[16] over a period of three hours. The mixture was stirred at room temperature for five hours when it became necessary to stop the stirrer due to the formation of a solid complex. After standing for twenty hours the mixture was hydrolyzed with an excess of 3 *N* hydrochloric acid. The aqueous layer was separated, made alkaline with 30% aqueous sodium hydroxide and steam distilled. The steam distillate (600–700 cc.) was neutralized with dilute hydrochloric acid, the solvent removed *in vacuo* on a water-bath and the residual sirup taken up in 60 cc. of water. This solution was made basic with sodium hydroxide, extracted with ether, and the ethereal extract dried over anhydrous magnesium sulfate. After removal of ether the product was fractionated. The main portion consisted of 1-methyl-2-*n*-butyl-Δ^2-pyrroline,[8] b. p. 88.5° (30 mm.); yield 48 g. (54%).

A second smaller fraction, 1-methyl-2,2-*n*-dibutylpyrrolidine, boiled at 122° (18 mm.); $n^{20}D$ 1.4567; d^{20}_4 0.846; yield 18 g. (14%). This substance, a colorless liquid, is only slightly soluble in water, but is readily soluble in all common organic solvents.

Anal. Calcd. for $C_{13}H_{27}N$: C, 79.12; H, 13.79. Found: C, 79.53; H, 13.69.

1-Methyl-2,2-dibutylpyrrolidine Methiodide.—This substance was prepared by treating a dry ether solution of the base with the calculated amount of methyl iodide. It was purified by recrystallization from ethanol–ether; white plates, m. p. 211° (cor.), unchanged on further recrystallization from methanol–ether.

Anal. Calcd. for $C_{13}H_{27}N\cdot CH_3I$: C, 49.55; H, 8.91; N, 4.13. Found: C, 49.67; H, 9.09; N, 4.22.

1-Ethyl-2-methyl-Δ^2-pyrroline.—To a solution cooled to 0° of 44 g. (0.68 mole) of 70% ethylamine in 110 cc. of absolute ethanol contained in a pressure bottle was added 55.9 g. (0.34 mole) of ω-bromo-*n*-propyl methyl ketone. The bottle was tightly stoppered and the contents permitted to warm up gradually; at 15° reaction set in and cooling was again necessary as the temperature rose quickly to 50–60°. When the reaction had subsided, as judged by a decrease in temperature, the mixture was shaken for fifteen to twenty minutes and then acidified with dilute hydrochloric acid. The solvent was removed *in vacuo* on a water-bath and the resulting sirup taken up in 100 cc. of water, made strongly alkaline with sodium hydroxide, and steam distilled. A part of the amine fraction would not steam distil as in all runs there was several cc. of very high boiling, brown, viscous oil which remained behind. The clear steam distillate (300–400 cc.) was made more strongly alkaline with 50% sodium hydroxide solution and the pyrroline extracted with ether. After drying and removal of ether the product was fractionated; b. p. 73.5–74.5° (55 mm.); $n^{20}D$ 1.4945; d^{20}_4 0.896; yield 19.5 g. (52%). When water was used as the reaction solvent and the mixture allowed to stand (occasional shaking) for twenty-four to forty-eight hours, the yields were decreased to 10–15%. 1-Ethyl-2-methyl-Δ^2-pyrroline is a colorless liquid which turns yellow and deposits an insoluble red viscous oil when exposed to the air. However, when sealed under nitrogen it will remain colorless indefinitely.

Anal. Calcd. for $C_7H_{13}N$: C, 75.62; H, 11.78. Found: C, 75.54; H, 11.80.

1-*n*-Butyl-2-methyl-Δ^2-pyrroline.—The procedure employed was that as described above for 1-ethyl-2-methyl-Δ^2-pyrroline. From 55.3 g. (0.335 mole) of ω-bromo-*n*-propyl methyl ketone and 49.5 g. (0.68 mole) of *n*-butyl amine was obtained 18.3 g. (39%) of product; b. p. 82–83.5° (16 mm.); $n^{20}D$ 1.4865; d^{20}_4 0.904. 1-Butyl-2-methyl-Δ^2-pyrroline is a colorless liquid which, like all vinyl tertiary amines, soon colors up when exposed to the air. It is only slightly soluble in water (1 part in 300–400 parts water), but is readily miscible with the common organic solvents.

Anal. Calcd. for $C_9H_{17}N$: C, 77.63; H, 12.31. Found: C, 77.50; H, 12.37.

1-Methyl-Δ^3-pyrroline.—This was prepared in 80% yield by the partial reduction[17] of 1-methylpyrrole.

Pyrrolidines.—All of the disubstituted pyrrolidines were synthesized by catalytic reduction of the corresponding unsaturated Δ^2-pyrrolines in ethanol with Raney nickel and hydrogen at two to three atmospheres pressure. The constants agreed essentially with those in the literature: 1,2-dimethylpyrrolidine,[5] b. p. 98–99°; 1-methyl-2-butylpyrrolidine,[5] b. p. 170.5°; 1-ethyl-2-methylpyrrolidine,[18] b. p. 118.5–119.5°; 1-*n*-butyl-2-methylpyrrolidine,[19] b. p. 86–86.5° (57 mm.). 1-Methylpyrrolidine was obtained by catalytic reduction of 1-methylpyrrole with platinum oxide.[20]

Δ^2-Tetrahydropyridines.—The Δ^2-tetrahydropyridines and ω-dimethylamino-*n*-butyl methyl ketone were synthesized from ω-bromo-*n*-butyl methyl ketone and the appropriate amine according to the directions of Lipp[6,21] and of Ladenburg.[22] Considerable decomposition occurs when ω-bromo-*n*-butyl methyl ketone is distilled at atmospheric pressure. By distilling under reduced pressure, b. p. 104–106° (17 mm.), this decomposition can be avoided.

1,2-Dialkylpiperidines.—These compounds were prepared by reduction of the corresponding tetrahydropyridines in ethanol with Raney nickel at two to three atmospheres of hydrogen.

1-Propenylpiperidine and 1-Diethylamino-*n*-heptene-1.—These vinyl tertiary amines were prepared according to the directions of Mannich and Davidsen.[9] 1-Propenylpiperidine was found to boil at 51–53° (10 mm.) instead of 61–63° (10 mm.) as previously reported.

1-Propylpiperidine and 1-Diethylamino-*n*-heptane.—These substances resulted when the corresponding vinyl amines were reduced in ethanol with Raney nickel and hydrogen at two to three atmospheres pressure.

1-Allylpiperidine[23] and 1-*n*-Butylpiperidine.—Refluxing one mole of bromide with two moles of piperidine in benzene solution resulted in good yields of the products.

(16) Späth and Lintner, *Ber.*, **69**, 2727 (1936).

(17) Andrews and McElvain, THIS JOURNAL, **51**, 887 (1929).

(18) Signaigo and Adkins, *ibid.*, **58**, 715 (1936).

(19) Tsuda, *J. Pharm. Soc. Japan*, **56**, 359 (1936).

(20) Craig and Hixon, THIS JOURNAL, **53**, 187 (1931).

(21) Lipp, *Ann.*, **289**, 209 (1896).

(22) Ladenburg, *ibid.*, **304**, 54 (1899).

(23) Menshutkin, *J. Russ. Phys.-Chem. Soc.*, **31**, 43 (1899); *Chem. Zentr.*, **70**, 1066 (1899).

N-*n*-Butylpyrrolidone-2.—This substance was prepared by the general method of Späth and Lintner.[16] A mixture of 50 g. (0.58 mole) of butyrolactone and 46 g. (0.64 mole) of *n*-butylamine was heated at 280° for four hours. After cooling, the reaction mixture was dissolved in 50 cc. of 6 *N* hydrochloric acid and the aqueous solution continuously extracted with ether for fifteen hours to remove the N-*n*-butylpyrrolidone-2, which is exceedingly soluble in water. After drying and removal of the ether the product was distilled; b. p. 121° (16 mm.); $n^{20}D$ 1.4650; d^{20}_4 0.964; yield 78 g. (95%).

Anal. Calcd. for $C_8H_{15}ON$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.03; H, 10.75; N, 10.18.

Summary

1. A variety of cyclic and straight chained vinyl tertiary amines have been synthesized as well as the corresponding saturated molecules.

2. Comparative basicity studies demonstrated that the vinyl tertiary amines were in all cases more basic than the corresponding saturated compounds.

3. This is explained by assuming hydration and rearrangement to a quaternary ammonium base.

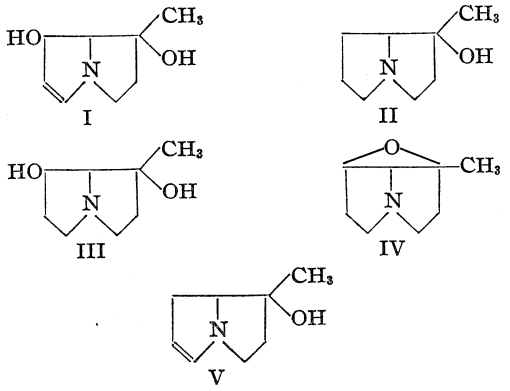
URBANA, ILLINOIS RECEIVED JULY 30, 1942

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

Structure of Monocrotaline. VII.[1] Structure of Retronecine and Related Bases

BY ROGER ADAMS, MARVIN CARMACK AND J. E. MAHAN

Structure I, previously suggested for retronecine, was deduced on the basis of (a) the validity of structure II for oxyheliotridane, a stereoisomer[2] of retronecanol, as proposed by Menshikov,[3] and (b) the reduction characteristics of retronecine and the reactivity of the hydroxyls in retronecine and related molecules. No structure other than I will explain as satisfactorily all the available experimental facts. The formulation of platynecine as III, anhydroplatynecine as IV, and desoxyretronecine as V will then result.



The most objectionable feature to structure I for retronecine, as pointed out in a previous paper, lies in the results obtained upon esterification. One hydroxyl in retronecine esterifies very readily, more readily than would be anticipated from the usual secondary alcohol, and the other esterifies with difficulty, but with more facility than is observed with any ordinary tertiary alcohol. Moreover, retronecanol (II) dehydrates more sluggishly than would be expected on the basis of a tertiary hydroxyl group.

Direct chemical proof for the positions of the hydroxyls and double bond in retronecine (I) was undertaken. The evidence for a pyrrolizidine nucleus and for a methyl group in the 1-position is indisputable. A complete assembly of the facts concerning known vinyl tertiary amines revealed that in no instance where the vinyl amine structure was established unequivocally was the molecule stable both to alkali and acid; hydrolysis occurs with one or the other especially when warmed with the reagent. Retronecine is stable to both even on boiling. Further evidence that the presence of a vinyl amine structure is unlikely was obtained through basicity studies. The following table gives the pK_H values for retronecine and its related compounds.

TABLE I

BASICITY OF RETRONECINE AND RELATED COMPOUNDS

Name	pK_H	*T*, °C.	pK_H (25°)
Retronecine	8.92	26	8.94
Platynecine	10.24	24	10.22
Desoxyretronecine	9.55	25	9.55
Retronecanol	10.92	24.5	10.91
Anhydroplatynecine	9.44	24	9.42
Heliotridane	11.44	27	11.48
Heliotridene	10.59	25.5	10.60
Isoretronecanol[5]	10.87	25.5	10.88

It is to be noted that the saturated molecules on the basis of the postulated structures (I–V)

(1) VI, Adams and Rogers, THIS JOURNAL, **63**, 537 (1941).

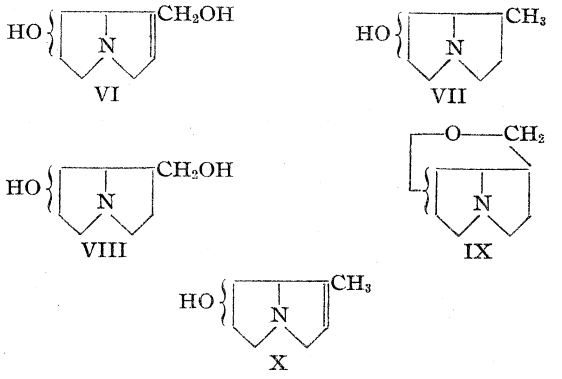
(2) Konovalova and Orekhov, *Bull. soc. chim.*, [5] **4**, 1285 (1937); *Ber.*, **69B**, 1908 (1936).

(3) Menshikov, *Bull. acad. sci. U. S. S. R.*, Classe sci. math., Ser. chim., 978 (1936).

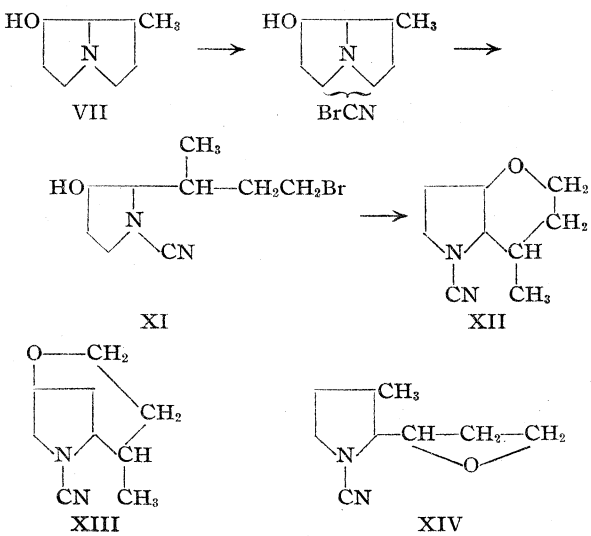
are more basic than the unsaturated—platynecine (III) is more basic than retronecine (I) and retronecanol (II) is more basic than desoxyretronecine (V). These results are in direct contradiction to what would be expected. Vinyl tertiary amines are more basic than the corresponding saturated molecules.[4]

The weight of this evidence and that derived from the stability experiments was sufficient to warrant the assumption that the vinyl amine structures for retronecine and desoxyretronecine were very probably incorrect. Assignment of the double bond in retronecine to any other non-vinyl position and retention at the same time of the positions shown in formula I for the hydroxyls gives molecular structures which will explain almost none of the important reactions of the molecule. It was thus obvious that a complete revision of the orientation of the double bond and hydroxyl groups in retronecine was necessary.

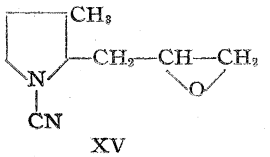
The experiments of Menshikov on oxyheliotridane, from which he deduced structure II, leave much to be desired. He performed a series of exhaustive methylations and reductions until a nitrogen-free compound was obtained. The final product was described[3] as a tertiary octanol. However, in this degradation no intermediates were isolated or purified, the characterization of the tertiary octanol was doubtful and no detailed description of his procedure was published. In view of this, the oxyheliotridane (stereoisomeric with retronecanol) structure reported by Menshikov was disregarded and a new set of structures for retronecine and its related compounds was formulated. The two hydroxyls and the double bond were introduced into the 1-methylpyrrolizidine nucleus in such a way that the following established experimental facts were satisfied: (a) difference in the rate of esterification of the two hydroxyls, which would more nearly agree with one secondary and one primary hydroxyl than with one secondary and one tertiary; (b) the ease of hydrogenolysis of one hydroxyl under very mild conditions; (c) the relative difficulty in dehydration of retronecanol which resembles more a secondary than a tertiary hydroxyl; (d) the resistance to hydrogenolysis of either hydroxyl in platynecine; (e) the ease of dehydration of platynecine to anhydroplatynecine; and (f) the absence of a vinyl amine linkage. The postulation of a primary hydroxyl limits its position to a substitution of a hydrogen atom on the methyl group of the 1-methylpyrrolizidine nucleus and this automatically, when the other conditions are fulfilled, establishes retronecine as having one of two structures (VI). Retronecanol would then be assigned structures VII, platynecine VIII, anhydroplatynecine IX, and desoxyretronecine X.



The readily hydrogenolyzed hydroxyl, the primary one, is shown as an allylic type. Construction of models indicates the structures represented by IX to involve very little strain whether the secondary hydroxyl is in the 6- or 7-position. The 7-position is favored on the basis of experiments involving the degradation of retronecanol (VII) by bromocyanogen. An addition compound is formed with this reagent which on rearrangement and treatment with alkali yields a halogen-free compound postulated as an ether (XII). Only the cyanide group is removed on hydrolysis with hot sulfuric acid; there is no cleavage of the cyclic ether. The mechanism of formation is postulated as follows



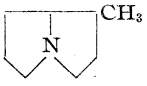
(4) Adams and Mahan, THIS JOURNAL, 64, 2588 (1942).



XV

The cleavage is believed to take place in the ring containing the methyl group; assuming the 7-position for the hydroxyl group a six-membered ether (XII) is produced, or assuming the 6-position a much less likely structure (XIII) would result. Cleavage of the unmethylated ring in VII would yield an ether of structure XIV or XV, depending on the position of the hydroxyl group. Either of these would be expected to hydrolyze upon treatment with hot sulfuric acid.

The changes in basicity of retronecine and related compounds, as influenced by the presence or absence of an hydroxyl group or double bond, are surprisingly parallel. These are shown in Table II. The structure of heliotridane is XVI, and the structure of isoretronecanol is XVII.



XVI



XVII

TABLE II

BASICITY COMPARISONS OF RETRONECINE AND RELATED COMPOUNDS; pK_H VALUES

(a) Effect of removal of primary hydroxyl	
Desoxyretronecine (X)	9.6
Retronecine (VI)	8.9
	0.7
Retronecanol (VII)	10.9
Platynecine (VIII)	10.2
	0.7
Heliotridane (XVI)	11.5
Isoretronecanol (XVII)[5]	10.9
	0.6
(b) Effect of removal of secondary hydroxyl	
Heliotridane (XVI)	11.5
Retronecanol (VII)	10.9
	0.6
(c) Effect of removal of double bond	
Platynecine (VIII)	10.2
Retronecine (VI)	8.9
	1.3
Retronecanol (VII)	10.9
Desoxyretronecine (X)	9.6
	1.3

(5) Adams and Hamlin, THIS JOURNAL, 64, 2597 (1942).

As shown in Table II, the removal of the primary or secondary hydroxyl results in an increase in basicity of about 0.7 pK_H unit; the removal of the double bond in an increase in basicity of 1.3 pK_H unit.

Experiments to establish whether the structures in series VI–X are correct are now under way and the first results are reported in this communication. A comparison of structures I–V and VI–X reveals that I–V all contain C–CH_3 groups, whereas such groups exist in the series VI–X only in structures VII and X. The determination of C–CH_3 in each of these molecules was undertaken and none could be found in retronecine (VI), platynecine (VIII), or anhydroplatynecine (X), but one was present in both retronecanol (VII) and desoxyretronecine (IX). As observed by those who have studied extensively this quantitative method, the amount of acetic acid produced upon oxidation of a molecule with a C–CH_3 group is never quantitative but varies in degree with the character of the molecule as a whole and especially on the substituents present on the carbon holding the methyl groups. The results are shown in Table III.

TABLE III

ACETIC ACID BY OXIDATION OF RETRONECINE AND RELATED BASES

Substance	Moles HOAc per mole of substance
Retronecine	None
Platynecine	None
Anhydroplatynecine	None
Retronecanol	0.69
Desoxyretronecine	.66
Heliotridane	.58
Heliotridene	.40
Isoretronecanol	None

These analytical data conform to the new structures VI–X which may be accepted provisionally in place of those previously proposed (I–V). None of the known experimental facts are in disagreement with present postulated formulas.

Experimental

Determination of Basic Strength Constants.—The procedure employed for the determination of the pK_H values was that previously described.[3] All solid amines were recrystallized to constant melting point, and the three liquid amines were freshly distilled in a carbon dioxide-free atmosphere immediately before use. The basicity measurements were taken at temperatures within the range 23 to 27° and the observed constant corrected to 25° employing the value of the negative temperature coefficient of the constant as given by Hall and Sprinkle.[6] Duplicate meas-

(6) Hall and Sprinkle, *ibid.*, 54, 3469 (1932).

urements were made on all of the substances listed in Tables I and II.

Carbon–Methyl Analysis.—The procedure used for carbon–methyl determinations was a macro modification adapted from the micro procedure of Kuhn and Roth,[7] and the macro method of Kuhn and L'Orsa.[8] That the acidity of the distillate after chromic acid oxidation was due to acetic acid was shown by conversion of the acid component to its *p*-bromophenacyl ester, m. p. 85°. The reported melting point of *p*-bromophenacyl acetate is 85°.[9]

Thymol was used as a control and gave 1.31 moles of acetic acid per mole of substance. Kuhn and L'Orsa[8] reported a value of 1.40.

Conversion of Retronecanol to the Cyanamide Ether (XII).—A solution of 8 g. of cyanogen bromide in 60 cc. of dry ether was cooled in a dry-ice–acetone mixture. To this was added slowly and with constant swirling a solution of 10 g. of retronecanol in 140 cc. of dry ether. A voluminous white precipitate separated instantly. The reaction mixture was allowed to warm up gradually (constant swirling) and at a point just below room temperature the white solid changed into a viscous oil. When the mixture had reached room temperature, 15 cc. of water was added to dissolve the sirup, the ether layer was then separated and washed once with very dilute hydrochloric acid to remove any unreacted retronecanol. The aqueous layer and acid washings were both extracted with ether and the ether washings combined with the ether layer from the original reaction mixture. The ethereal solution was dried over anhydrous magnesium sulfate and the solvent removed by distillation. The pale yellow viscous oil which remained was heated on the water-bath under reduced pressure to remove remaining solvent and any excess of cyanogen bromide; yield 11.3 g. All attempts to crystallize the sirup failed. It is probable that this product consisted of a mixture of bromocyanamides.

A sample of the bromocyanamide oil which had stood at 2° for several days deposited a small amount of crystalline material. A further quantity of this substance was obtained by dissolving the viscous residue in methanol, cooling in a dry-ice–acetone bath, seeding, and filtering rapidly through a precooled funnel. Pure material was obtained by recrystallization from water; m. p. 94.5–95° (cor.). Qualitative tests showed the absence of halogen. A solution in carbon tetrachloride did not decolorize bromine, and a solution in acetone–water did not decolorize 1% potassium permanganate solution.

Anal. Calcd. for $C_9H_{14}ON_2$: C, 65.03; H, 8.49; N, 16.86. Found: C, 65.14; H, 8.37; N, 16.89.

Rotation. 53.7 mg. made up to 2.50 cc. with absolute ethanol at 28° gave $\alpha^{31}D$ −4.63°; *l*, 2; $[\alpha]^{31}D$ −107.6°.

This substance was obtained in better yields as follows. A sample of 5.8 g. of the crude liquid bromocyanamide dissolved in 20 cc. of dry pyridine was refluxed for thirty minutes. The solution, which had turned deep red in color, was cooled, diluted with an equal volume of water, treated with Norite, and the solvent removed by distillation *in vacuo*. The residual brown viscous oil was diluted with a little water and on seeding crystallization ensued. Thus in two crops 1.08 g. was obtained; m. p. 92–94° (18% from retronecanol, or 28% from the crude bromocyanamide). Refluxing in pyridine for longer periods of time than thirty minutes did not increase the yield. The cyanamide ether could also be formed in approximately the same yield by warming the crude bromocyanamide with methanolic potassium hydroxide.

Hydrolysis of the Cyanamide Ether to a Secondary Amine.—A mixture of 0.88 g. of the cyanamide ether and 15 cc. of 15% sulfuric acid was refluxed for fifty-five hours. The solution was decolorized with Norite, cooled, made strongly alkaline with potassium hydroxide and the precipitated salts removed by filtration through glass wool. The filtrate was extracted thoroughly with ether and the ether extract dried over sodium carbonate. After removal of solvent the residue was distilled at 20 mm. and a bath temperature of 110–120°; yield 0.64 g. of colorless liquid. Although this product was not analyzed as such its identity as a secondary amine was shown by conversion to the following three analyzed derivatives.

Reconversion to Cyanamide Ether.—A sample of 68 mg. of the liquid amine was warmed with excess cyanogen bromide in ether for ten minutes. After evaporation of the solvent the residue was taken up in warm water and the solution seeded; yield 20 mg.; m. p. 92–93°, mixed melting point with an authentic sample of cyanamide ether produced no depression.

Picrate.—A sample of 68 mg. of liquid amine from the acid hydrolysis of the cyanamide ether was treated with 130 mg. of picric acid containing 15% water dissolved in 1 cc. of hot ethanol. After cooling in the ice-bath for fifteen minutes, 141 mg. of picrate was filtered; glistening yellow plates, m. p. 121.5–122.5° (cor.). Further recrystallization did not raise the melting point.

Anal. Calcd. for $C_8H_{15}ON \cdot C_6H_3O_7N_3$: C, 45.41; H, 4.90; N, 15.13. Found: C, 45.36; H, 5.01; N, 15.07.

N-Methyl Hydroiodide.—To a solution of 0.64 g. of the liquid amine in a mixture of 1 cc. of dry acetone and 1 cc. of dry ether was added gradually 1 cc. of methyl iodide. After the original vigorous reaction had subsided the mixture was refluxed on the steam-bath for ten minutes. On cooling crystallization occurred; yield 0.44 g. (in two crops). Two recrystallizations from acetone yielded pure material; long fine prisms, m. p. 195–196° (cor.).

Anal. Calcd. for $C_9H_{18}ONI$: C, 38.17; H, 6.41; N, 4.95. Found: C, 38.29; H, 6.54; N, 4.69.

Rotation. 15.7 mg. made up to 0.500 cc. with absolute ethanol at 33° gave $\alpha^{33}D$ −0.54°; *l*, 1; $[\alpha]^{33}D$ −17.2°.

Although this substance has the same molecular formula as retronecanol methiodide (m. p. 193°) a mixed melting point between the two gave a depression to 145–148°.

Summary

1. New structures are proposed for retronecine, retronecanol, platynecine and desoxyretronecine which agree with all the pertinent experimental data.

2. Basic strength constants and carbon–

(7) Kuhn and Roth, *Ber.*, **66**, 1274 (1933); Pregl, "Quantitative Organic Microanalysis," P. Blakiston's Son and Co., Inc., Philadelphia, Pa., 1937, pp. 201–204.

(8) Kuhn and L'Orsa, *Z. angew. Chem.*, **44**, 847 (1931).

(9) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2nd ed., 1940, p. 181.

methyl analyses on these substances tend to confirm the proposed formulas and prove the incorrectness of the old formulas.

3. A von Braun degradation of retronecanol with cyanogen bromide yielded a cyanamide ether which can be explained very satisfactorily on the basis of the new formula.

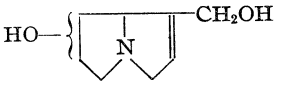
URBANA, ILLINOIS RECEIVED JULY 30, 1942

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

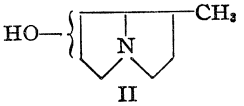
Structure of Monocrotaline. VIII. The Proof of Primary and Secondary Hydroxyl Groups in Retronecine[1]

BY ROGER ADAMS AND K. E. HAMLIN, JR.

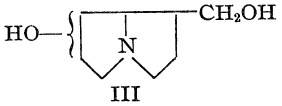
Direct experimental evidence for the structures postulated for retronecine (I), retronecanol (II) platynecine (III), anhydroplatynecine (IV) and desoxyretronecine (V) is being investigated. This



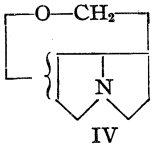
I



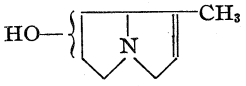
II



III

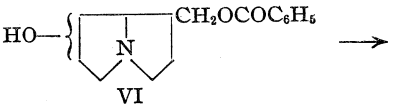


IV

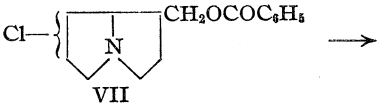


V

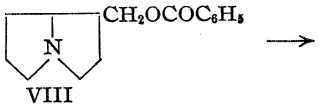
communication describes work which has served to establish beyond dispute (1) the presence of a CH_2OH group in compound I and in its reduction product (III), and (2) the presence of a secondary hydroxyl group in retronecanol (II). Since all attempts to obtain tractable oxidation products from retronecine and its associated molecules have failed, it was concluded that the molecules probably were rendered sensitive to oxidation by the presence of an hydroxyl group substituted in the nucleus. Platynecine (III), synthesized from retronecine (I), was selected for study and the monobenzoate (VI) was prepared. This was converted to the corresponding chloride (VII) according to the directions of Konovalova and Orekhov.[2] These investigators reported failure in attempts to replace the chlorine by hydrogen in this molecule but in our experiments no difficulty was encountered by the use of Raney nickel and hydrogen in ethanol solution. Thus, a molecule (VIII) was produced which was the benzoate of a



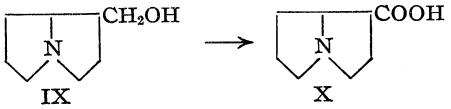
VI



VII



VIII



IX X

new base, herein designated as isoretronecanol (IX). Upon hydrolysis, isoretronecanol (IX) was obtained. Structurally this resembles lupinine and differs from it merely in that the CH_2OH group is attached to a pyrrolizidine nucleus, a fusion of two five-membered rings, rather than to a norlupinane nucleus, consisting of two analogously fused six-membered rings. The procedure described for oxidizing lupinine to lupininic acid[3] was followed for the conversion of isoretronecanol (IX) to 1-carboxypyrrolizidine (X) and proved to be entirely satisfactory. The oily degradation products encountered in the oxidation of retronecine, *et al.*, were absent and a readily purified derivative with the properties of an amino acid was isolated. Analyses of the pure compound, its picrate and derivatives of the betaine, prepared from the reaction of diazomethane on the amino acid, were used for identification.

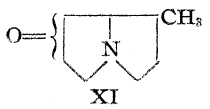
On the basis of structure II, retronecanol contains a secondary hydroxyl group. It has now been found that aluminum *t*-butoxide in the presence of cyclohexanone oxidizes the molecule without degradation and with the formation of the corresponding ketone, retronecanone (XI). The

(1) For previous paper see Adams, Carmack and Mahan, THIS JOURNAL, **64**, 2593 (1942).

(2) Konovalova and Orekhov, *Ber.*, **69**, 1908 (1936).

(3) Willstätter and Fourneau, *ibid.*, **35**, 1917 (1902).

ketone group was identified through its semicarbazone and its oxime.



XI

By these experiments the presence of a CH_2OH group and a secondary hydroxyl have been established directly in retronecine. The results serve to support the structures I–V postulated on the C–CH_3 determinations and the chemical properties of these molecules.

Experimental

Monobenzoylplatynecine (VI).—This was prepared from platynecine as described by Orekhov, Konovalova and Tiedebel.[4] It crystallized from ether–petroleum ether (b. p. 30–60°) in colorless prisms m. p. 118–119° (cor.). The reported melting point is 119–120°.

Rotation. 0.4081 g. made up to 15 cc. with absolute ethanol at 29° gave α_D −2.41; *l*, 1; $[\alpha]^{29}D$ −88.6°. The reported value is $[\alpha]_D$ −87.9° in ethanol.

Monobenzoylplatynecine Chloride (VII).—This was prepared as described by Konovalova and Orekhov.[2] Recrystallization from petroleum ether (b. p. 30–60°) gave colorless tufts of needles, m. p. 72–73° (cor.). The reported melting point is 73–74°.

Rotation. 0.6092 g. made up to 15 cc. with absolute ethanol at 29° gave α_D −0.59; *l*, 1; $[\alpha]^{29}D$ −14.5°.

Benzoylisoretronecanol Hydrochloride.—A solution of 7 g. of monobenzoylplatynecine chloride in 100 cc. of ethanol, to which was added about 4 g. of Raney nickel, was hydrogenated at 2–3 atm. pressure. Hydrogen was absorbed to the theoretical end-point in four and one-half hours. After filtration, the solution was made just acid to congo and the solvent removed *in vacuo*. The highly colored crystalline residue was taken up in chloroform, boiled with Darco, and the solution filtered. The colorless chloroform solution was treated with anhydrous ether until it became cloudy. The hydrochloride separated as fine colorless needles; recrystallized from chloroform–ether, m. p. 181–182° (cor.); yield, 6.02 g. (86%).

Anal. Calcd. for $C_{15}H_{19}O_2N \cdot HCl$: C, 63.91; H, 7.16; N, 4.97. Found: C, 63.84; H, 7.12; N, 4.80.

Rotation. 0.5056 g. made up to 15 cc. with absolute ethanol at 28° gave α_D −1.62; *l*, 1; $[\alpha]^{28}D$ −48.6°.

Benzoylisoretronecanol (VIII).—A solution of the base hydrochloride in water was treated with one equivalent of *N* aqueous sodium hydroxide. The mixture was thoroughly extracted with ether and the ethereal solution dried over anhydrous potassium carbonate. After carefully distilling off the ether, the residue was distilled *in vacuo*, b. p. 161.5–162.5° (1–2 mm.). The colorless, mobile distillate readily crystallized on cooling in a dry-ice–acetone bath. The crystalline product could be recrystallized from petroleum ether (b. p. 30–60°); large prisms, m. p. 56–57° (cor.).

Anal. Calcd. for $C_{15}H_{19}O_2N$: C, 73.42; H, 7.81; N, 5.71. Found: C, 73.51; H, 7.86; N, 5.70.

(4) Orekhov, Konovalova and Tiedebel, *Ber.*, **68**, 1886 (1935).

Rotation. 0.1578 g. made up to 5 cc. with absolute ethanol at 28° gave α_D −1.92; *l*, 1; $[\alpha]^{28}D$ −60.8°.

Benzoylisoretronecanol Picrate.—Prepared in and recrystallized from ethanol, the picrate formed yellow needles, m. p. 130–131° (cor.) with decomposition.

Anal. Calcd. for $C_{21}H_{22}O_9N_4$: C, 53.14; H, 4.67; N, 11.81. Found: C, 53.32; H, 4.82; N, 11.81.

Isoretronecanol (IX).—An aqueous solution of 4.4 g. of benzoylisoretronecanol hydrochloride was refluxed for three hours with 100 cc. of 10% aqueous sodium hydroxide. The alkaline solution thus obtained was extracted continuously with ether for twenty-four hours. On acidification of the residual alkaline layer, white crystals were obtained which were identified by melting point as benzoic acid.

The ethereal extract was dried well over anhydrous sodium carbonate and the ether removed by distillation. The oily residue was distilled *in vacuo*, b. p. 115–116° (1–2 mm.); yield 1.62 g. (74%). The colorless viscous distillate crystallized readily on cooling in dry-ice–acetone bath; m. p. 39–40° (cor.).

Anal. Calcd. for $C_8H_{15}ON$: C, 68.02; H, 10.71; N, 9.93. Found: C, 68.11; H, 10.69; N, 10.07.

Rotation. 0.1407 g. made up to 5 cc. with absolute ethanol at 27° gave α_D −2.20; *l*, 1; $[\alpha]^{27}D$ −78.2°.

Isoretronecanol Methiodide.—This product was prepared by treating a dry ether solution of isoretronecanol with an excess of methyl iodide. It was purified from methanol–ether; white needles, m. p. 281–282° (cor.) with decomposition.

Anal. Calcd. for $C_8H_{15}ON \cdot CH_3I$: C, 38.14; H, 6.41; N, 4.95. Found: C, 38.21; H, 6.50; N, 4.78.

Rotation. 0.0725 g. made up to 5 cc. with absolute ethanol at 26° gave α_D −0.44; *l*, 1; $[\alpha]^{26}D$ −31.0°.

Isoretronecanol Picrate.—Prepared in and recrystallized from ethanol, the picrate formed yellow needles, m. p. 194–195° (cor.) with decomposition.

Anal. Calcd. for $C_{14}H_{18}O_8N_4$: C, 45.34; H, 4.90; N, 15.12. Found: C, 45.51; H, 5.00; N, 15.02.

1-Carboxypyrrolizidine (X).—Following the procedure described by Willstätter and Fourneau[3] for oxidizing lupinine to lupininic acid, 0.5 g. of isoretronecanol was dissolved in a solution of 0.15 g. of sulfuric acid (sp. gr. 1.84) in 2 cc. of water. This mixture was added carefully to a cooled solution of 0.3 g. of chromic anhydride in 0.35 g. of sulfuric acid and 4 cc. of water. After warming this mixture a few minutes on a steam-cone until reduction of the chromic anhydride was complete, a second charge of the oxidizing mixture described above was added. The solution was now heated on a steam-cone for one and one-half hours. From this point the degradation product was worked up as described for lupininic acid. Before recrystallization, 0.22 g. of 1-carboxypyrrolizidine was isolated. After dissolving in absolute ethanol, boiling with a Darco-Norite mixture and filtering, excess dry acetone was added. At this point white flat plates crystallized, m. p. 228–229° (cor.) with decomposition.

Anal. Calcd. for $C_8H_{13}O_2N$: C, 61.91; H, 8.45; N, 9.03. Found: C, 62.06; H, 8.66; N, 9.13.

Rotation. 0.0996 g. made up to 5 cc. with absolute ethanol at 28° gave α_D −1.31; *l*, 1; $[\alpha]^{28}D$ −65.8°.

The amino acid was very soluble in water, fairly soluble in ethanol but insoluble in acetone, ether, and chloroform.

1-Carboxypyrrolizidine Picrate.—Prepared in and recrystallized from ethanol, the picrate formed beautiful yellow needles, m. p. 220–221° (cor.) with decomposition.

Anal. Calcd. for $C_{14}H_{16}O_9N_4$: C, 43.75; H, 4.20; N, 14.58. Found: C, 44.02; H, 4.25; N, 14.54.

Action of Diazomethane on 1-Carboxypyrrolizidine.—Following the procedure of Kuhn and Brydowna,[5] 0.1 g. of the 1-carboxypyrrolizidine was treated with a large excess of a moist ethereal solution of diazomethane. An immediate evolution of nitrogen took place which continued until the solid amino acid disappeared. After standing overnight, the ether was decanted from the small aqueous layer which appeared. The latter was diluted to about 1 cc. with water. The product was found to be predominantly in this aqueous portion. Identification of the compound as the betaine of the amino acid was made by analyses of the chloroaurate and the picrate.

Chloroaurate of the Betaine.—The gold salt was prepared from 10% aqueous auric chloride and an acidified (with hydrochloric acid) portion of the above aqueous solution of the betaine. Recrystallized from water, the yellow crystalline chloroaurate melted at 224–225° (cor.) with decomposition.

Anal. Calcd. for $C_9H_{16}O_2NAuCl_4$: C, 21.23; H, 3.17; Au, 38.73. Found: C, 21.72; H, 3.38; Au, 39.30.

Picrate of the Betaine.—The yellow crystalline picrate was prepared by adding a saturated ethanolic solution of picric acid to the aqueous solution of the betaine. After recrystallization from ethanol, the product melted at 194–195° (cor.) with decomposition.

Anal. Calcd. for $C_{15}H_{18}O_9N_4$: N, 14.06. Found: N, 13.81.

Retronecanone (XI).—A mixture of 5 g. of retronecanol, 15 g. of aluminum *t*-butoxide, 200 cc. of dry cyclohexanone and 700 cc. of dry toluene was refluxed for six hours. After cooling, the orange suspension was carefully extracted with 10% sulfuric acid. The acid extract, after washing well with ether to remove unchanged cyclohexanone, was treated with an excess of 50% sodium hydroxide. The basic solution was extracted continuously with ether for twenty-four hours and the ethereal extract dried over anhydrous magnesium sulfate. After carefully removing the ether, the residue was distilled *in vacuo;* the fraction boiling between 94 and 100° (15 mm.) was collected, yield 1.5 g. (30%). The pure amino ketone is a colorless, mobile liquid, distilling at 95–96° (15 mm.); $n^{20}D$ 1.4818; d^{20}_4 1.030.

Anal. Calcd. for $C_8H_{13}ON$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.76; H, 9.46; N, 10.14.

Rotation. 0.1127 g. made up to 5 cc. with absolute ethanol at 30° gave α_D −2.18; *l*, 1; $[\alpha]^{30}D$ −96.7°.

Retronecanone is not stable and tends to decompose readily even when kept at 0°, protected from light and moisture.

(5) Kuhn and Brydowna, *Ber.*, **70B**, 1333 (1937).

Retronecanone Picrate.—Prepared in and recrystallized from ethanol, the picrate formed fine yellow needles, m. p. 195° (cor.) with decomposition.

Anal. Calcd. for $C_8H_{13}ON \cdot C_6H_3O_7N_3$: C, 45.65; H, 4.38; N, 15.21. Found: C, 45.99; H, 4.36; N, 15.34.

A mixed melting point with an authentic sample of retronecanol picrate (m. p. 214°) gave a depression to 182–183°.

Retronecanone Semicarbazone.—A solution of 0.7 g. of semicarbazide hydrochloride and 1.5 g. of sodium acetate in 10 cc. of water was added to 0.5 g. of retronecanone. After heating in a water-bath for one hour and then cooling, the solution was made alkaline to litmus. On further cooling and scratching, the crystalline derivative precipitated. After recrystallization from a mixture of chloroform–petroleum ether, the semicarbazone was obtained as white platelets, m. p. 209–210° (cor.) with decomposition.

Anal. Calcd. for $C_9H_{16}ON_4$: C, 55.08; H, 8.22; N, 28.55. Found: C, 55.01; H, 8.23; N, 28.31.

Retronecanone Oxime—To a solution of 1 g. of hydroxylamine hydrochloride in 6 cc. of 10% aqueous sodium hydroxide was added 0.6 g. of retronecanone. After heating twenty minutes on a steam-cone, the solution was cooled and the *p*H adjusted to about 8.5. The oxime was removed from the mixture by continuous ether extraction for twenty-four hours. After drying the ethereal extract and removing the solvent, a yield of 0.5 g. (75%) of the oxime was obtained. The most practical means of purification was found to be vacuum sublimation; small, white needles, m. p. 167–168° (cor.).

Anal. Calcd. for $C_8H_{14}ON_2$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.59; H, 9.16; N, 18.36.

Rotation. 0.0204 g. made up to 5 cc. with absolute ethanol at 26° gave α_D −0.31; *l*, 1; $[\alpha]^{26}D$ −76.0°.

Summary

1. The base, isoretronecanol, has been prepared by the removal of the stable hydroxyl from platynecine. It has the formula $C_8H_{15}ON$. Isoretronecanol undergoes chromic acid oxidation to yield an optically active amino acid. Since there is no loss of carbon atoms, this product has been designated as 1-carboxypyrrolizidine (X) and thus establishes beyond doubt the presence of a CH_2OH group in retronecine (I) and platynecine (III).

2. Retronecanol by oxidation with aluminum *t*-butoxide and cyclohexanone gives retronecanone from which typical ketone reagent derivatives were prepared.

3. These experiments confirm the presence of a primary and a secondary hydroxyl group in retronecine.

URBANA, ILLINOIS RECEIVED JULY 30, 1942

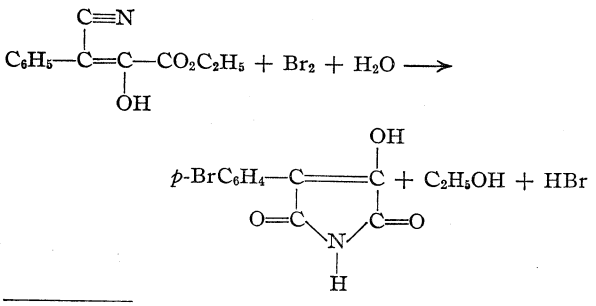
[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF DELAWARE]

p-Bromophenylhydroxymaleic Imide

BY GLENN S. SKINNER, C. A. COGHLAN AND A. S. BERLIN

Bromine reacts with ethyl cyanophenylpyruvate in chloroform solution to give a colorless unstable addition product. The initial reaction is followed by the loss of hydrogen bromide. The products then undergo a series of reactions to yield *p*-bromophenylhydroxymaleic imide. This is a lemon-yellow crystalline substance whose brick-red sodium salt reacts with benzyl chloride in alcohol to give a benzyl derivative. The silver salt reacts with ethyl iodide in absolute ether to give an ethyl derivative. The nature of the reaction product is further attested by its oxidation to *p*-bromobenzoic acid and its alkaline hydrolysis to *p*-bromophenylacetic acid.

As to the mechanism of its formation, the first step in the breakdown of the addition product involves the loss of hydrogen bromide and the formation of the amide. The tertiary bromine atom then rearranges to the ring at this point or during cyclization. It is significant that this bromine atom appears exclusively in the para position since this is typical of the rearrangement of many similarly placed atoms or groups in the aromatic series. Ring formation takes place through the loss of alcohol. In the case of ethyl cyanomethylpyruvate[1] ethyl alcohol is not lost and the final product is ethyl β-bromo-β-carbamido-α-ketobutyrate. The last two steps are similar to the formation of phenylhydroxymaleic imide from the unbrominated ester by the action of cold concentrated sulfuric acid in alcohol.[2] The cyclization and bromination may also proceed partly in the reverse order as the same product is obtained by bromination of phenylhydroxymaleic imide. The reaction may be formulated as follows



(1) Wislicenus and Silberstein, *Ber.*, **43**, 1834 (1910).
(2) Bougault, *J. Pharm. Chem.*, **10**, 297 (1914).

Experimental

Bromination of Ethyl Cyanophenylpyruvate.—A hot solution of 21.7 g. of the ester in 80 cc. of dry chloroform contained in a 250-cc. bulb connected to a condenser by a glass joint was rapidly cooled to 45–50° in a water-bath. Water (1.8 cc.) and dry bromine (5.3 cc.) were added simultaneously with good mixing in the course of a few minutes. The reaction was rapid with the evolution of hydrogen bromide and initially a colorless almost entirely liquid layer may separate at the bottom in the absence of continued agitation. The mixture was kept at approximately 50° for six hours and then allowed to stand for two days at room temperature. A slight excess of bromine remained at the end of the reaction. The chloroform was decanted and the crystalline product was crystallized from boiling alcohol. The yield of lemon-yellow crystals was 22 g.; m. p. 239–240°.

Anal. Calcd. for $C_{10}H_6O_3NBr$: N, 5.22. Found: N, 5.15.

There was no lachrymatory effect of bromobenzyl cyanide from the residues in the mother liquor when the experiment was conducted in the above manner. The yield dropped to about 9 g. when the added water was omitted. In this case the residues had a powerful lachrymatory effect. Small amounts of ammonium bromide were always formed. The product was obtained in approximately the same yield from the methyl and *n*-butyl esters. An equivalent amount of the alcohol was isolated by extraction of the chloroform with water followed by salting out with potassium carbonate. Ethyl alcohol was further identified as a reaction product of the ethyl ester by conversion to the 3,5-dinitrobenzoate; m. p. 78–79°. No *o*-bromophenylhydroxymaleic imide could be isolated from the combined mother liquors.

Characterization of *p*-Bromophenylhydroxymaleic Imide.—The imide is slowly soluble in cold sodium bicarbonate solution and very soluble in ether. It is stable to cold dilute permanganate and to bromine water. The sodium salt was obtained in 88% yield by the following procedure: *p*-bromophenylhydroxymaleic imide (53.6 g.) was dissolved in a hot solution of 12.4 g. of sodium carbonate in 150 cc. of water. The solution was filtered hot and allowed to crystallize. The brick-red crystals were filtered with suction and washed with a 1:2 alcohol–ether mixture. The product was recrystallized from an alcohol–water mixture. The salt decomposes at 321°. For the analysis it was dried to constant weight at 110°.

Anal. Calcd. for $C_{10}H_5O_3NBrNa$: Na, 7.93. Found: Na, 7.92.

The brick-red gelatinous silver salt was precipitated quantitatively from an aqueous solution of the sodium salt. It was dried in a vacuum desiccator protected from light under the influence of which its color changes to chocolate-brown.

The N-ethyl derivative was made by gently refluxing for three days a mixture of 6.7 g. of the dry silver salt, 3.7 g. of ethyl iodide and 50 cc. of absolute ether. The unchanged imide was removed by extraction with sodium bicarbonate solution. The insoluble portion was dissolved in ether, 10 cc. of alcohol was added and the product was crystallized repeatedly by evaporation of the ether; yield, 1.4 g.; m. p. 191–192°.

The N-benzyl derivative was made by refluxing overnight a solution of 5.8 g. of the sodium salt and 2.53 g. of benzyl chloride in 25 cc. of alcohol. Crystallized from alcohol it melts at 169–170°; yield, 5.6 g.

Anal. Calcd. for $C_{17}H_{12}O_3NBr$: N, 3.91. Found: N, 3.89.

A sample of the imide (1.34 g.) oxidized by a boiling mixture of 5 cc. of nitric acid (1.42) and 5 cc. of water gave 0.8 g. of *p*-bromobenzoic acid which after crystallization from alcohol melted at 254°. The same acid was obtained by refluxing a solution of the imide (0.67 g.) prepared from 0.21 g. of sodium bicarbonate and 10 cc. of water, while 200 cc. of a 1% solution of potassium permanganate was added during a period of 2.5 hours.

To an ice-cold solution of 1.2 g. of sodium hydroxide in 10 cc. of water was added 2.68 g. of *p*-bromophenylhydroxymaleic imide. As it was stirred the red solution became colorless. The mixture was allowed to stand for one day. The products were ammonia, sodium oxalate and *p*-bromophenylacetic acid; m. p. 113–114°.

Phenylhydroxymaleic imide prepared by the method of Bougault was dissolved in 75 cc. of nitrobenzene. To this solution was added 1.8 cc. of bromine. After heating a short time the mixture was allowed to stand for three days at room temperature. The crystals were separated from the mother liquor by decantation and recrystallized from alcohol; yield, 4.3 g.; m. p. 239–240°.

Summary

The action of bromine on ethyl cyanophenylpyruvate leads to the formation of *p*-bromophenylhydroxymaleic imide. The identity of the product has been established by its hydrolysis to *p*-bromophenylacetic acid, its oxidation to *p*-bromobenzoic acid and its formation by the action of bromine on phenylhydroxymaleic imide.

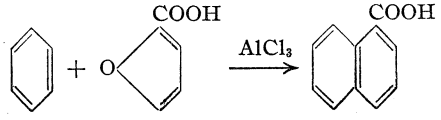
NEWARK, DELAWARE RECEIVED AUGUST 10, 1942

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

The Reaction of Furoic Acid with Tetralin

BY CHARLES C. PRICE AND NORMAN C. DENO

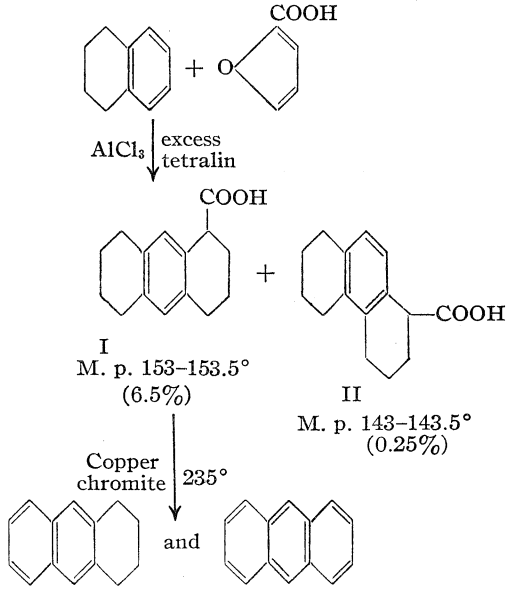
Since the reaction of furoic acid and aluminum chloride with various aromatic compounds of the benzene series was found to produce naphthoic acids,[1] the reaction has been extended to the



naphthalene series, in the expectation of obtaining phenanthroic or anthroic acids.

From naphthalene, furoic acid and aluminum chloride, the only product obtained was an intractable amorphous, neutral black powder, but from the condensation of tetralin and furoic acid it was possible to isolate two isomeric crystalline acids. These acids had four more hydrogen atoms than the expected tetrahydroanthroic or phenanthroic acids. Evidently, disproportionation of hydrogen occurred with the excess tetralin used as solvent for the condensation.

The crystalline product obtained in greater yield (6.5%), shiny white plates melting at 153–153.5°, has been shown by simultaneous decarboxylation and dehydrogenation with copper chromite catalyst to contain an anthracene nucleus and thus appears to be *sym*-octahydro-1-anthroic acid (I). The most likely structure for the isomeric product, slender needles melting at



(1) Gilman, McCorkle and Calloway, THIS JOURNAL, **56**, 745 (1934); McCorkle and Turck, *Proc. Iowa Acad. Sci.*, **43**, 205 (1936); Price, Chapin, Goldman, Krebs and Shafer, THIS JOURNAL, **63**, 1857 (1941).

143–143.5°, would appear to be that of *sym*-octahydro-1-phenanthroic acid (II).

Although the crystalline acids isolated represented only about one-tenth of the total acidic product formed in the reaction, no other crystalline material could be isolated from the residue.

Experimental[2]

***sym*-Octahydro-1-anthroic Acid (I).**—A suspension of 48 g. (0.43 mole) of furoic acid in 400 cc. of tetralin was stirred in an ice-bath while 120 g. (0.90 mole) of aluminum chloride was added in small portions. After the aluminum chloride had been added, the deep red-black viscous reaction mixture was stirred at 50–60° for twelve hours or at room temperature for forty hours. The reaction mixture was poured into 400 cc. of hydrochloric acid and 400 g. of ice and was stirred at 50–60° for six hours to complete hydrolysis. One liter of benzene was added and the deep red, green-fluorescent solution was extracted with sodium bicarbonate solution; 0.3 g. of *sym*-octahydro-1-anthroic acid was recovered from this extract by acidification. The benzene was then extracted with three 200-cc. portions of 2% sodium hydroxide and the red, blue-fluorescent extract was acidified; 68 g. of a pale tan tacky solid precipitated. This material, which had a neutral equivalent of 335, was redissolved in alkali and fractionally precipitated, either with hydrochloric acid or carbon dioxide. The brown gum first precipitated was removed by filtration. Further acidification gave about 10 g. of white solid which was recrystallized three times from 50% ethyl alcohol, yield, 6.2 g. (6.3%) of shiny white plates of ***sym*-octahydro-1-anthroic acid (I)**, m. p. 153–153.5°.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24; neut. eq., 226. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.87; neut. eq., 230. Found: C, 78.31; H, 8.01; neut. eq., 230.

Treatment of this acid (I) by the procedure used for the dinitration of durene[3] gave an acid melting from 230 to 235° with a neutral equivalent of 333. The neutral equivalent for 9,10-dinitro-octahydro-1-anthroic acid should be 320.

Decarboxylation.—A solution of 0.5 g. of the anthroic acid (I) in 5 cc. of quinoline was heated for eighteen hours at 235° in the presence of 0.2 g. of copper chromite catalyst. The mixture was cooled, ether was added and the solution washed with several portions of dilute hydrochloric acid and sodium hydroxide. The ether was dried, treated with Norite, which removed most of the color, and then evaporated. The **tetrahydroanthracene**, 0.2 g., was recrystallized from 70% alcohol as white plates, m. p. 102–104°.[4] Because of the similarity of melting point and appearance, a mixture of the decarboxylation product and phenanthrene, m. p. 101–102°, was prepared; it melted at 84–99°. A second decarboxylation, apparently identical with that described above, gave some anthracene, identified by melting point and mixed melting point.

When one gram of the anthroic acid was heated with 0.56 g. of sulfur at 180–190° for ten hours, hydrogen sulfide was evolved copiously. The residue was dissolved in 50 cc. of benzene and the solution was filtered and extracted with sodium bicarbonate. Acidification of this extract precipitated 0.4 g. of orange-yellow powder, m. p. 216–226°. Purification of this material could not be effected by crystallization from alcohol, acetic acid or benzene. Sublimation at 205–210° yielded beautiful long, slender, clear-yellow needles,[5] but the melting point was the same as that of the crude product. Qualitative tests for sulfur by sodium fusion were negative.

***sym*-Octahydro-1-phenanthroic Acid (II).**—When the mother liquor from the first recrystallizaton of the octahydroanthroic acid (I) was allowed to evaporate slowly clusters of needles separated among the plates. After mechanical separation and six recrystallizations from 50% alcohol, the slender shiny needles obtained (0.25 g. or 0.25%) melted at 143–143.5°.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.87; neut. eq., 230. Found: C, 78.46; H, 7.56; neut. eq., 233.

Summary

The reaction of furoic acid with tetralin in the presence of aluminum chloride gave a considerable amount of acidic product from which two isomeric crystalline acids were obtained in small yield. These acids contained four more hydrogen atoms than had been expected and are believed to be *sym*-octahydro-1-anthroic and 1-phenanthroic acids.

URBANA, ILLINOIS RECEIVED JULY 8, 1942

(2) Microanalyses by L. G. Fauble and Theta Spoor.

(3) Smith, "Org. Syntheses," **10**, 40 (1930).

(4) Schroeter [*Ber.*, **57**, 2013 (1924)] has reported the melting point of tethracene (tetrahydroanthracene) as 103–105°.

(5) Graebe and Blumenfeld, *ibid.*, **30**, 1118 (1897), and Liebermann and Pleus, *ibid.*, **37**, 648 (1904), report that 1-anthroic acid sublimes as clear yellow needles melting at 245°.

[CONTRIBUTION FROM THE PURDUE UNIVERSITY AGRICULTURAL EXPERIMENT STATION AND THE BUREAU OF PLANT INDUSTRY, U. S. DEPARTMENT OF AGRICULTURE]

The Carotenoids of Yellow Corn Grain[1]

BY JONATHAN W. WHITE, JR., F. P. ZSCHEILE AND ARTHUR M. BRUNSON

It has only recently been recognized that the following carotenoids, other than "carotene" and "xanthophyll," often occur in the grain of yellow corn (*Zea mays L.*): zeaxanthol,[2] cryptoxanthol[3] β-carotene, α-carotene, K carotene and neocryptoxanthol.[4] It has been shown that the isomerization products neo-β-carotene,[5,6] neocryptoxanthol,[6] and neozeaxanthols A, B and C[7,8] are present under ordinary conditions in solutions containing β-carotene, cryptoxanthol, and zeaxanthol, respectively. Nagy[9] recently studied the carotenoid pigments of corn gluten meal and noted the formation of numerous isomeric forms, particularly of zeaxanthol, under acid conditions. The degree of isomerization of carotenoids during and after extraction from natural sources will depend upon experimental conditions. In quantitative analysis of corn grain pigments, Fraps and Kemmerer[4] considered the presence of neocryptoxanthol. Beadle and Zscheile[10] showed the necessity for inclusion of neo-β-carotene in the analysis of vegetable carotenoids.

In order to analyze solutions containing these neo-type pigments by spectroscopic methods, it is necessary that their identity and quantitative absorption spectra be known. Data given in this paper form the foundation for such a system of analysis which will be presented later.

During an investigation of the carotenoids of corn grain, several pigments were separated that had not previously been observed there.

Luteol.—Chromatography from ether on MgO–Supercel[11] of the saponified carotenol fraction of yellow corn showed in every case the presence of a zone immediately below the zeaxanthol zone. An ethanolic solution of the pigment from this zone had a characteristic absorption spectrum identical with that of luteol. Absorption spectra were determined on a photoelectric spectrophotometer previously employed for pigment studies.[10,11,12] The only other known carotenoid (except luteol esters) with an absorption spectrum of this type is α-carotene. When α-carotene and this pigment from corn grain were mixed in ether and adsorbed on magnesia, two zones were formed, indicating that the corn pigment was not α-carotene. From the above considerations it is concluded that this pigment is luteol.

Unnamed Carotene 1.—A spectrophotometric study was made of the carotene fraction of corn carotenoids, prepared from an extract by partition between hexane and 78.5% diacetone alcohol [which removed the carotenols, except cryptoxanthol] followed by partition between hexane and 92% 2-methyl-2,4-pentanediol as recommended by White and Zscheile.[13] In addition to other deviations from the absorption spectra of the pure pigments believed to be present, it was noted that a shelf [in some preparations a maximum] was present at 4250 Å. Chromatography on magnesia (three times), followed successively by adsorption on calcium hydroxide and on Brockmann's alumina gave a product with the absorption spectrum shown in Fig. 1 as curve I. A short heating of the[14] solution had no effect on the spectrum. The quantity of the compound was too small to permit the establishment of quantitative values for absorption coefficients or to permit chemical analysis. Strain[15] described a carotenoid from carrots with absorption maxima at 4250 and 4000 Å. A preparation of this carotenoid was made from carrots following Strain's directions. Its absorption spectrum had maxima at 4250, 4000, 3790, and 3600 Å. and a pronounced minimum at 4150 Å.

γ-Carotene.—Investigation of the cause in corn carotene fractions of relatively high absorption on the long wave length side of the 4780 Å. maximum of β-carotene resulted in the separation of a pigment with absorption maxima [4900, 4600, and 4300 Å. in hexane] in good agreement with those of γ-carotene.[16] It was adsorbed from hexane solution on magnesia above β-carotene. Quantities were too small to permit the most accurate determination of absorption values. The characteristic spectrum in hexane solution is shown in Fig. 1 as curve II.

Carotenoid with Properties Expected of a Monohydroxy-α-carotene.—The cryptoxanthol fraction of several inbred lines of yellow corn was found to produce from four to eight distinct zones on a magnesia adsorption column when absorbed from hexane and washed with ether.

(1) Studies on the Carotenoids. IV. Journal Paper Number 34 of the Purdue University Agricultural Experiment Station.

(2) P. Karrer, H. Salomon and H. Wehrli, *Helv. Chim. Acta*, **12**, 790 (1929).

(3) R. Kuhn and C. Grundmann, *Ber.*, **67**, 593 (1934).

(4) G. S. Fraps and A. R. Kemmerer, *Ind. Eng. Chem., Anal. Ed.*, **13**, 806 (1941).

(5) A. E. Gillam and M. S. El Ridi, *Biochem. J.*, **30**, 1735 (1936).

(6) L. Zechmeister and P. Tuzson, *ibid.*, **32**, 1305 (1938).

(7) L. Zechmeister and P. Tuzson, *Ber.*, **72**, 1340 (1939).

(8) L. Zechmeister, L. v. Cholnoky and A. Polgar, *ibid.*, **72**, 1678 (1939).

(9) D. Nagy, *Iowa State Coll. J. Sci.*, **15**, 89 (1940).

(10) B. W. Beadle and F. P. Zscheile, *J. Biol. Chem.*, **144**, 21 (1942).

(11) F. P. Zscheile, J. W. White, Jr., B. W. Beadle, and J. R. Roach, *Plant Physiol.*, **17**, 331 (1942).

(12) F. P. Zscheile and C. L. Comar, *Bot. Gaz.*, **102**, 463 (1941).

(13) J. W. White, Jr., and F. P. Zscheile, THIS JOURNAL, **64**, 1440 (1942).

(14) T. R. Hogness and V. R. Potter, *Ann. Rev. Biochem.*, **10**, 509 (1941).

(15) H. H. Strain, *J. Biol. Chem.*, **127**, 191 (1939).

(16) R. Kuhn and H. Brockmann, *Ber.*, **66**, 407 (1933).

In all cases but one, the zones other than those due to cryptoxanthol and to small amounts of β-carotene (not removed by the partition process) were too small to be isolated. In the case of inbred M4B[17] a buff zone was found immediately below the cryptoxanthol layer. These two zones were of approximately equal thickness. After washing with ether and elution with ethanolic hexane, the characteristic absorption spectrum of the pigment in this lower zone was determined in hexane. It agreed well with that of α-carotene, having maxima at 4740, 4450 and 4250 Å., and a deep minimum at 4625 Å.

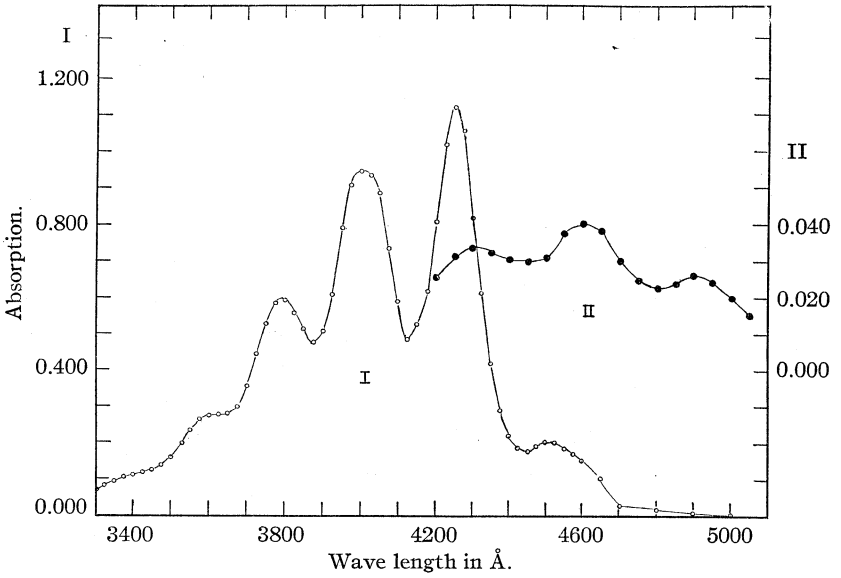


Fig. 1.—Absorption spectra in hexane: I, unnamed carotene 1; II, γ-carotene preparation from corn. Absorption = $\log_{10}(I_0/I)/l$.[14]

Portions of the solution were mixed with solutions of α-carotene in hexane and with luteol in ether. The resulting solutions each produced two zones when adsorbed on magnesia. The same results were obtained after the unknown compound was boiled for twenty minutes with alcoholic alkali, which indicated that it was not an ester of luteol. The mixed chromatograms showed that the compound was neither α-carotene nor luteol. In view of its occurrence in the cryptoxanthol fraction, its position of adsorption immediately below cryptoxanthol (α-carotene is adsorbed immediately below β-carotene), and its nonidentity with α-carotene and luteol, it is suggested that the compound may be a monohydroxy-α-carotene. Quantities available were too small for chemical analysis.

Neocryptoxanthol.—A hexane solution of pure cryptoxanthol was heated in an amber glass flask under reflux for twenty-four hours, cooled, and adsorbed on $Ca(OH)_2$-Supercel (1:1). After washing with 20% ether in hexane, two zones were found. No oxidation products were evident. The upper one contained cryptoxanthol, the lower neocryptoxanthol. After elution the latter was readsorbed, eluted, and made to volume. Its absorption spectrum was determined. An aliquot of this neocryptoxanthol solution was evaporated to dryness *in vacuo*, made to the original volume, and its spectrum redetermined. As shown in Fig. 2, the absorption of a solution of the material after drying decreased over the range from 3800 to 4157 and increased over the range from 4157 to 5000 Å. It is well known that the change cryptoxanthol-to-neocryptoxanthol is reversible.[6] The absorption coefficient at 4157 Å. did not change, indicating that the absorption coefficients of cryptoxanthol and of neocryptoxanthol are identical at this wave length. This makes it possible to establish the absorption spectrum of neocryptoxanthol on a quantitative basis.[18] It was necessary that the above procedure be used because the quantities of neocryptoxanthol available were too small to be weighed accurately. Also plotted in Fig. 2 is the characteristic spectrum of cryptoxanthol, recalculated from earlier data,[10] placed to intersect the other two curves at 4157 Å. It will be noted that the curve of the dried preparation falls at a proportional distance between the other two curves over the entire range. Determinations of the intersection point with several preparations (intersection points, 4137, 4157, and 4177 Å. gave the quantitative absorption spectrum of neocryptoxanthol shown in Fig. 3. The maximum deviation from this curve of absorption values of six preparations is ±3%. This curve bears a relation to cryptoxanthol which is strikingly similar to that between neo-β- and

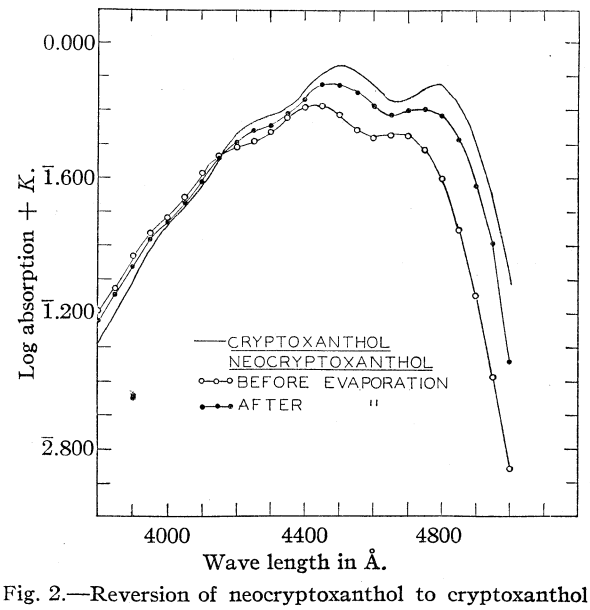


Fig. 2.—Reversion of neocryptoxanthol to cryptoxanthol in hexane solution.

(17) The designation of the various inbred lines is purely arbitrary and has no significance as to type of plant or chemical composition.

(18) In the case of neo-β-carotene, this method gave results which agreed with data obtained with weighed samples.[9]

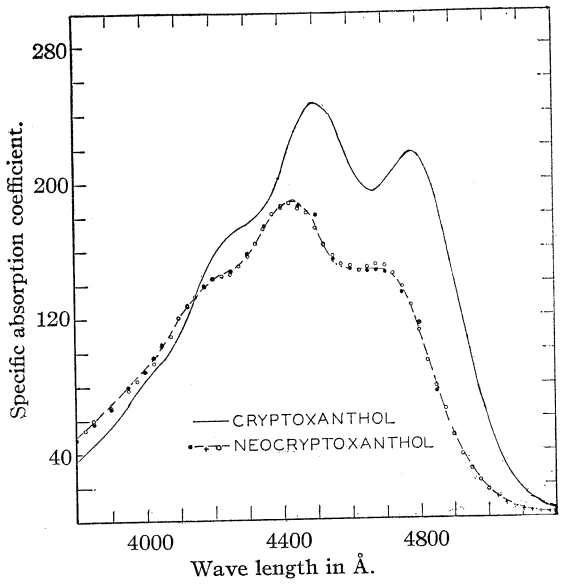


Fig. 3.—Absorption spectra of neocryptoxanthol and cryptoxanthol[11] in hexane.

β-carotenes.[10] Table I presents absorption values for two preparations of neocryptoxanthol in hexane solution.

TABLE I

ABSORPTION VALUES OF NEOCRYPTOXANTHOL IN HEXANE SOLUTION

Wave length, Å.	Specific absorption coefficient, liters/g. cm. 1	2
4650 Shelf	147	148
4425 Maximum	185	187
4150–4160 Region of intersection	133–135	133–135

Neozeaxanthols.—An ethanol solution of pure zeaxanthol was heated in an amber glass flask under reflux for twenty-four hours, the pigment transferred to a 50% solution of ether in hexane, and adsorbed on $Ca(OH)_2$–Supercel as before. Three zones were found. Spectra of the eluted pigments were determined, and the pigment from zone 2 was identified as zeaxanthol. The other two curves had maxima shifted toward shorter wave lengths than those of zeaxanthol. Since the relation of these two neo- pigments to neozeaxanthols A, B, and C of Zechmeister and Tuzson[7,8] was not clear, they were named neozeaxanthol I (more strongly adsorbed) and neozeaxanthol II (less strongly adsorbed). The neo-isomers were purified by further adsorption and attempts were made to apply the intersection-point method used with neocryptoxanthol. A short heating of the solutions was used instead of evaporation to dryness. When compared to the absorption curve before heating, the curve of the solution of neozeaxanthol I after heating decreased over the range 4350 to 5000 Å., increased over the range 3800 to 4200 Å., and did not change over the range 4200 to 4350 Å. Under similar treatment the absorption spectrum of neozeaxanthol II changed as follows: it increased over the range 4407 to 5000 Å., decreased over the range 3800 to 4407 Å., and did not change at 4250 Å. Adsorption showed three compounds in the solution.

In order to obtain a provisional value for the absorption spectra of these two compounds, it was assumed that the isomerization of neozeaxanthol I was to neozeaxanthol II and that of neozeaxanthol II was to zeaxanthol. It is on these assumptions that the absorption spectra of the neozeaxanthols shown in Fig. 4 were determined. These curves are only first approximations.

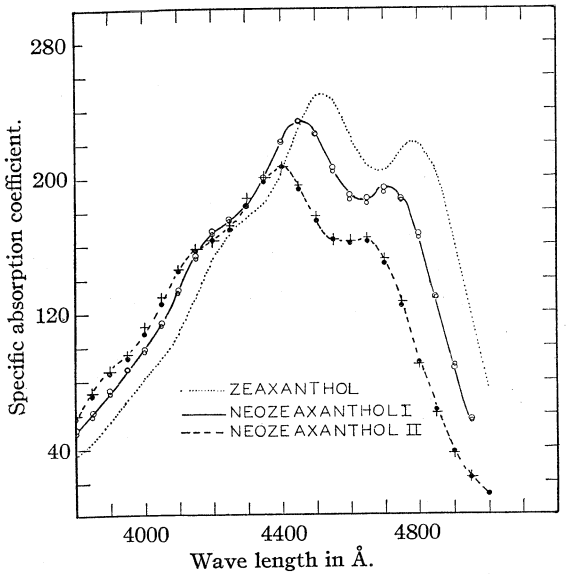


Fig. 4.—Absorption spectra of neozeaxanthols I and II in ethanol; spectrum of zeaxanthol in ethanol from earlier data.[11]

Discussion

If the method of measurement of pigment concentration used for the determination of the carotenoids of corn is sensitive enough to detect the presence of the neocarotenoids, it is necessary that proper account be taken of their possible presence. Likewise, if the other pigments reported here are present in high enough concentation, they must be considered. Determination of the carotenoids of corn is usually made for estimation of provitamin A potency. From this point of view the provitamin A potency of neocryptoxanthol and of the carotenoid with maxima at 4250 and 4000 Å. must be determined. Fraps and Kemmerer[4] reported neocryptoxanthol to be nearly as potent as cryptoxanthol.

In the same paper, Fraps and Kemmerer reported the presence in corn of a compound which they call K carotene and to which they assign provitamin A activity. They presented a qualitative absorption spectrum for the pigment with maxima at 4250 and 3970 Å. and a prominent shelf at 4450 to 4500 Å. Strain[15] reported the isolation of a pigment from carrot roots which he termed "flavoxanthin-like carotene." Its spec-

trum had maxima at 4250 and at 4000 Å. He also noted that his product was apparently identical with a pigment isolated by van Stolk, Guilbert, and Penau in 1932. In the spectrum of this compound as separated in this Laboratory, there was no trace of a shelf or maximum at 4500 Å. The spectrum was quite similar to that of unnamed carotene 1 as shown in Fig. 1, except for the absence of the maximum at 4500 Å. This maximum is not due to contamination of unnamed carotene 1 by β-carotene since absorption at 4800 Å. is too low. No preparation of unnamed carotene 1 from corn failed to show a maximum at 4500 Å. Since Fraps and Kemmerer's[4] curve for K carotene shows neither the 3790 Å. maximum nor the 3600 Å. shelf, it is possible that K carotene and un-named carotene 1 may not be identical.

Fraps and Kemmerer also stated that α-carotene was found in all but one of twenty-two corn varieties. The authors have never observed α-carotene in corn (six inbreds, several sweet corn varieties, and two hybrids were studied). The adsorbent used by Fraps and Kemmerer was capable of separating cryptoxanthol from neocryptoxanthol and might be expected to separate β-carotene from neo-β-carotene. However, they did not report neo-β-carotene in their corn extracts. They identified their α-carotene spectrophotometrically and by mixed chromatography. In this connection, it should be pointed out that Gillam and El Ridi[5] were unable to distinguish spectroscopically between α-carotene and neo-β-carotene. They found that α-carotene and neo-β-carotene formed a single zone when adsorbed on alumina from the carotene fraction of butter.[19] Examination of the spectra of α-carotene and neo-β-carotene by a very sensitive photoelectric spectrophotometer[10,11] shows that they can be differentiated spectroscopically with an instrument of sufficient accuracy. The experience of Gillam and El Ridi illustrates that failure of a mixture of two compounds to form two zones on a given adsorbent does not necessarily indicate that the compounds are identical. The writers consider it possible that the pigment identified by Fraps and Kemmerer as α-carotene might have been neo-β-carotene.

Summary

1. Luteol, γ-carotene and a compound tentatively identified as a hydroxy-α-carotene were found in yellow corn grain for the first time.

2. A compound having some properties like Fraps and Kemmerer's K carotene was also separated from yellow corn grain.

3. Preliminary quantitative absorption spectra of neocryptoxanthol and two neozeaxanthol isomers are presented.

(19) A. E. Gillam and M. S. El Ridi, *Nature*, **136**, 914 (1935).

LAFAYETTE, INDIANA RECEIVED JUNE 24, 1942

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

The Malonic Ester Synthesis and Walden Inversion

BY WILLIAM E. GRIGSBY,[1] JOHN HIND, JACOB CHANLEY AND F. H. WESTHEIMER

It has been suggested recently that the reaction of alkyl halides and olefin oxides with the sodium salt of malonic ester is an example of the normal displacement reaction.[2,3] If this is the case, the reaction should proceed with Walden inversion about the carbon atom to which the halogen (or oxygen) atom is attached. An experimental demonstration of this inversion has now been established for the reaction of cyclopentene oxide with sodium malonic ester.

In all the previously known reactions of sodium malonic ester with an oxide—ethylene oxide,[4] epichlorhydrin,[4] cyclohexene oxide[5] and others[6]—the reaction product is a lactone. With ethylene oxide, for example, the product is α-carbethoxy-γ-butyrolactone. If the reaction with cyclopentene oxide had proceeded without inversion, the product would have been the lactone of the mono-

(1) Du Pont Fellow, 1941–1942.

(2) Hind, Dissertation, Chicago, 1939.

(3) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chap. VI, see also p. 143.

(4) Traube and Lehmann, *Ber.*, **34**, 1971 (1901).

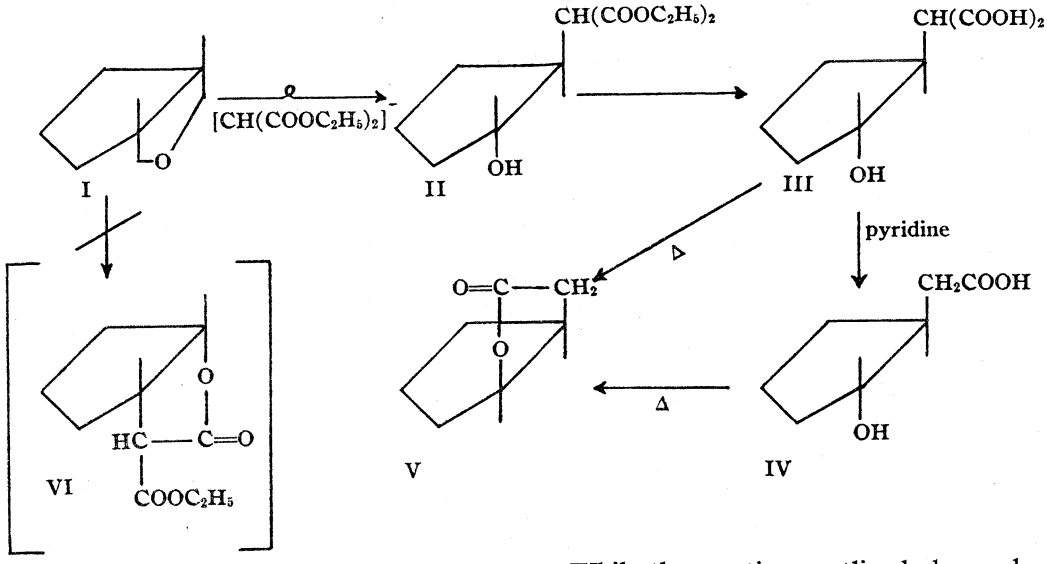
(5) Coffey, *Rec. trav. chim.*, **42**, 387 (1923).

(6) Kötz and Hoffman, *J. prakt. Chem.*, **110**, 101 (1925); Rothstein, *Bull. soc. chim.*, [5] **2**, 1936 (1935); Haller and Blanc, *Compt. rend.*, **142**, 1471 (1906). The reactions recorded in the literature were carried out between equimolar quantities of oxide, malonic ester, and sodium ethylate. However, repetition of the work of Traube and Lehmann, using two moles of malonic ester for each mole of sodium ethylate, showed that, in this case, excess malonic ester is without effect on the composition of the product obtained.

ethyl ester of *cis*-cyclopentanol-2-malonic acid (VI). In actual fact, inversion occurred and the product proved to be the diethyl ester of *trans*-cyclopentanol-2-malonic acid (II). Lactone formation in this case was precluded, since it would involve fusing two five-membered rings together in the *trans*-positions. Such a configuration involves a great deal of strain, and has been accomplished only once, and then with a carbocyclic compound.[7]

It is interesting to contrast the behavior of cyclopentene oxide with that of cyclohexene oxide. When cyclohexene oxide reacts with equivalent quantities of malonic ester and sodium ethylate, a lactone is formed.[5] No stereochemical conclusion can, however, be drawn from this fact. Many examples are known in which a six and a five membered ring are fused together in the *trans* positions.[8] As a matter of fact, lactones of both the *cis*- and the *trans*-cyclohexanol-2-acetic acids are known.[9]

Under favorable experimental conditions, the reaction between cyclopentene oxide and sodium malonic ester gave a 70–75% yield of the *trans*-diester. The ester was a liquid which could be purified by molecular distillation; saponification equivalent, and carbon, hydrogen and ethoxyl analyses all clearly showed that the compound was the *trans*-diester, II, not the *cis*-lactone, VI.



The fact that the liquid ester was *trans* was confirmed by transforming it to a derivative the structure and configuration of which are known. On refluxing with dilute alkali, the ester was converted into the salt of a diacid. The acid was obtained in 80–90% yield as a crystalline solid which evidently did not contain water of crystallization. The analytical data agree with those calculated for *trans*-cyclopentanol-2-malonic acid (III), but are not in agreement with those for the corresponding *cis*-lactone. It seems improbable that the saponification altered the configuration of the molecule, since there was no asymmetric carbon atom in a position alpha to a carbonyl group; inversion by enolization is therefore ruled out.[10]

The *trans*-diacid was decarboxylated by refluxing for ten minutes in pyridine solution; carbon dioxide and *trans*-cyclopentanol-2-acetic acid (IV) were obtained in excellent yields. By neutral equivalent, melting point, solubility behavior and analysis, the compound was shown to be identical with that previously prepared by an entirely independent method by Hückel and Gelmroth.[11] The configuration of this acid is not in doubt; the corresponding *cis*-compound exists only in the form of a lactone (V), melting at −14°.[12]

Evidence that the decarboxylation does not involve a change in configuration is offered by the fact that the lactone (V) of *cis*-cyclopentanol-2-acetic acid can be heated with pyridine and subsequently recovered unchanged.

While the reactions outlined above almost cer-

(7) Linstead and Meade, *J. Chem. Soc.*, 935 (1934).

(8) Baeyer, *Ann.*, **258**, 145 (1890); Windaus, Hückel and Reverey, *Ber.*, **56**, 91 (1923); Cook and Linstead, *J. Chem. Soc.*, 956 (1934); Hückel and Friedrich, *Ann.*, **451**, 132 (1927).

(9) M. Newman, private communication.

(10) Hammett, *op. cit.*, Chap. VIII.

(11) Hückel and Gelmroth, *Ann.*, **514**, 233 (1934).

(12) Only in the case of a beta lactone has ring opening accompanied by Walden inversion been observed; Olson and Miller, THIS JOURNAL, **60**, 2687 (1938); see also Day and Ingold, *Trans. Faraday Soc.*, **37**, 686 (1941).

tainly did not involve a change in configuration, it is possible by more drastic means to rearrange the *trans*-compounds to the *cis*. Prolonged pyrolysis of the *trans*-diacid (fifty hours at 160°) was necessary to cause decarboxylation in the absence of pyridine and the product obtained was V, the lactone of *cis*-cyclopentanol-2-acetic acid. Under similar conditions, *trans*-cyclopentanol-2-acetic acid (IV) rearranged to the *cis*-lactone (V). The mechanism of this rearrangement may involve the acid-catalyzed dehydration of an hydroxy acid, followed by lactonization of the olefinic acid; it is possible, however, that the isomerization occurred without the actual formation of the unsaturated compound.

The series of reactions outlined above clearly shows that the reaction between cyclopentene oxide and sodium malonic ester occurs with Walden inversion. The facts are, therefore, consistent with the hypothesis that the reaction is a nucleophilic displacement on carbon involving the malonic ester anion $(C_2H_5O_2CCHCO_2C_2H_5)^-$. This general theory is also supported by the older observation of Wislicenus[13] that sodium malonic ester reacts much more readily with primary than with secondary halides.[14]

While the results of the present investigation were quite satisfactory, some experimental difficulties encountered during the research are worth discussing.

An interesting phenomenon was noticed regarding the saponification of the diester, II. The saponification took place more readily with dilute than with concentrated alkali, although of course complete saponification always led to the formation of the *trans*-diacid (III). Michael[15] noted a similar peculiarity in the saponification of some other mono substituted malonic esters, and Goldschmidt and Oslan[16] successfully explained why the rate of saponification of acetoacetic ester is independent of the alkali concentration.

It is also necessary to call attention to the fact that, in the reaction between sodium malonic ester and cyclopentene oxide, good yields were obtained only in alcoholic solution and in the presence of excess malonic ester. When benzene was used as a solvent, the yield fell to 30%. Furthermore, unless two molar equivalents of malonic ester were used, none of the pure *trans*-diester could be isolated, and neither the configuration nor the structure of the products obtained has yet been established.

It is a fact, however, that reactions of sodium malonic ester are frequently improved by the addition of malonic ester. In the condensations with either halides or oxides, excess malonic ester greatly increases the yield of monosubstitution product,[17] while the abnormal Michael[18] reaction occurs only when the amount of sodium present is equivalent to the malonic ester used. It seems probable that the malonic ester functions as an acid, and removes the reactive anion of the substituted malonic ester from solution. This explanation seems reasonable in the present case, since experiments showed that the anion of *trans*-cyclopentanol-2-malonic ester decomposed on refluxing in alcohol. Although its decomposition did not give the same products as were obtained from the cyclopentene oxide reaction without excess malonic ester, the instability of the anion was evident.

Experimental

Reaction of Sodium Malonic Ester with Cyclopentene Oxide.—About 125 cc. of absolute ethanol and 2.3 g. (0.1 mole) of sodium were placed in a 500-cc. three-necked flask, to which were attached a dropping funnel and a reflux condenser fitted with a calcium chloride tube. When all the metal had reacted, 31.5 g. (0.2 mole) of malonic ester was added. The solution was refluxed, 8.4 g. (0.1 mole) of cyclopentene oxide[19] was added over a period of an hour, and the solution refluxed for an additional three hours. The ethanol was removed by distillation, and a quantity of 10% sulfuric acid was added which was equivalent to the sodium used. The sodium sulfate was filtered and washed with ether, and the filtrate was extracted three times with ether. The combined ether extracts were washed, the ether distilled, and the excess malonic ester removed by vacuum distillation. The residue of pale yellow, crude *trans*-cyclopentanol-2-malonic ester corresponded to a yield of 70–75% and had a saponification equivalent of 110–115.[20] For identification and characterization, it was purified by molecular distillation in a Hickman still. At a pressure of 10^{-4} mm., a colorless oil came over at 75°; if the pressure rose to 10^{-2} mm., the product passed over at 150–160° with slight decomposition.

Anal. Calcd. for $C_{12}H_{20}O_5$(II): C, 58.98; H, 8.20; C_2H_5O, 36.86; sap. eq., 122. (Calcd. for $C_{10}H_{14}O_4$ (V): C, 60.58; H, 7.12; C_2H_5O, 22.72; sap. eq., 99.) Found: C, 59.01, 59.43; H, 7.93, 8.00; C_2H_5O, 37.01; sap. eq.,

(13) Wislicenus, *Ann.*, **212**, 239 (1882).
(14) Hammett, *op. cit.*, pp. 152–154.
(15) Michael, *J. prakt. Chem.*, [2] **72**, 537 (1905).
(16) Goldschmidt and Oslan, *Ber.*, **32**, 3390 (1899).
(17) Leuchs, *ibid.*, **44**, 1507 (1911); see also Cohen, Marshall and Woodman, *J. Chem. Soc.*, **107**, 887 (1915); and Brigl, *Z. physiol. Chem.*, **95**, 161 (1915).
(18) Michael and Ross, THIS JOURNAL, **52**, 4598 (1930).
(19) Verkade, Coops, Maan and Verkade-Sandbergen, *Ann.*, **467**, 217 (1928).
(20) Mulliken, "The Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1904, Vol. I, p. 111.

120, 122; $n^{20}D$ 1.4564; $d^{4}_{21.5}$, 1.109. The micro Zeisel analysis was performed by Dr. J. A. Alicino, Fordham University, New York, N. Y.

A similar reaction, carried out with benzene as solvent, gave a 27% yield of diester (II), identified by saponification, and isolation of the diacid, (III).

Saponification of the Diester, II.—The diester was saponified by refluxing the crude, undistilled ester for four hours with twice the calculated amount of 1.0 *N* sodium hydroxide. An amount of hydrochloric acid exactly equivalent to the sodium hydroxide was then added to this solution. Since it was impossible to extract the acid, because of its great solubility in water, the solution was evaporated to dryness *in vacuo* at room temperature. Unless solutions of the free acid were kept cool, they showed a marked tendency to precipitate out an insoluble polymer. The dry salt-cake was extracted with acetone and the acetone evaporated *in vacuo* at room temperature, leaving a 95% yield of a colorless oil. On stirring with benzene, this oil solidified (yields of 90% were obtained using only 1 g. of ester). The crude powder melted 20–30° lower than the best material finally obtained. The compound was difficult to recrystallize because it was extremely soluble in water, methanol, ethanol, acetone, ether and dioxane, was insoluble in benzene, chloroform, and ligroin, and precipitated as an oil from mixed solvents. However, it was possible to effect a purification by dissolving the compound in the minimum quantity of ethyl acetate or amyl alcohol, centrifuging to remove insoluble matter, and then removing most of the solvent with a stream of dry air. After a few days, the crystals were centrifuged, rapidly washed several times with ethyl acetate, and dried *in vacuo*. The melting point, after several recrystallizations from ethyl acetate, was 118.4–118.7° (with dec., cor.). Before analysis, the purified crystals were dried for a week in a vacuum desiccator over phosphorus pentoxide or over sulfuric acid. In no case did drying affect the melting point or neutral equivalent.

The yield on the recrystallization of the crude diacid was only about 50%; it seems reasonable to assume, however, that the crude material was essentially pure. The crude acid had a neutral equivalent which did not change on recrystallization and which was close to the theoretical value. Furthermore, subsequent decarboxylation gave yields of 80% of pure *trans*-cyclopentanol-2-acetic acid.

Anal. Calcd. for $C_8H_{12}O_5$ (III): C, 51.04; H, 6.39; neut. eq., 94.0. Found: C, 51.27; H, 6.49; neut. eq. (semi-micro), 94.9, 95.0.

Saponification with Concentrated Alkali.—About 1.2 g. of *trans*-cyclopentanol-2-malonic ester (II) was refluxed for nine hours with twice the calculated amount of 5.5 *N* sodium hydroxide. The acid recovered from this treatment had a neutral equivalent of 136, and a saponification equivalent of 99. Further saponification with 1.0 *N* alkali gave an 85% yield of solid *trans*-diacid, (III).

Decarboxylation.—One gram of crude diacid was dissolved in 10 cc. of pyridine, refluxed for ten minutes, and then poured into slightly more 1 *N* sodium hydroxide than the amount calculated for the neutralization of the resulting acid. The pyridine and water were removed at room temperature, and the residue acidified with an amount of 1 *N* hydrochloric acid which was exactly equivalent to the alkali previously added. The water was removed *in vacuo*, and the residue extracted with acetone. The extract was filtered, and the acetone removed at reduced pressure, to avoid polymerization of the acid.[11] This gave an 80% yield of an oil which solidified on scratching. The reported melting point for the *trans*-acid (IV) is 52.5–53.5°. The observed melting point of the recrystallized acid was 53.3–54.3° (cor.).

Anal. Calcd. for $C_7H_{12}O_3$ (IV): C, 58.29; H, 8.40; neut. eq., 144.1 (calcd. for $C_7H_{10}O_2$ (VI): C, 66.67; H, 7.94; neut. eq., 126). Found: C, 58.30; H, 8.00; neut. eq. (semi-micro), 145.9, 145.6.

Treatment of *cis*-Cyclopentanol-2-acetic Acid Lactone with Pyridine.—A solution of 0.5 g. of the lactone in several cc. of pyridine was refluxed for fifteen minutes. Five cc. of 1 *N* sodium hydroxide was added, and the refluxing continued for another fifteen minutes. After evaporation to dryness, acid was added and the lactone recovered unchanged.

Thermal *trans–cis* Isomerization.—Two grams of crude *trans*-cyclopentanol-2-malonic acid was heated for fifty hours at 160°. After two vacuum distillations, 0.6 g. of *cis*-cyclopentanol-2-acetic acid lactone was obtained. The material melted at −14°, while Hückel and Gelmroth[11] reported −17°. When 1.5 g. of *trans*-cyclopentanol-2-acetic acid was heated in a similar fashion and distilled twice, the resulting product, in 40% yield, was the same lactone. These samples of lactone were further identified by boiling point, saponification equivalent, analysis, and by determining the melting point of a mixture of the compound with a sample prepared according to Hückel and Gelmroth.[11]

Reaction without Excess Malonic Ester.—The reaction was carried out as previously described, except that two molar proportions of sodium and malonic ester were used for one of cyclopentene oxide, or else equal proportions of all reactants were used. The product in this case was obtained in only 20–40% yields, and had a saponification equivalent of 165. After prolonged saponification, the resulting acid was partitioned between benzene and water. The water layer contained an acid of neutral equivalent 120–140, while the benzene soluble portion of the mixture had a neutral equivalent of about 200. Clearly, the saponification product was a mixture. The products obtained here have not yet been identified.

Stability of the Anion of the Diester (II).—A gram of *trans*-cyclopentanol-2-malonic ester was dissolved in absolute alcohol, 0.1 g. of sodium added, and the solution refluxed for two hours. At the end of this period of time, only 25% of the *trans* diester could be recovered; the rest had been converted into water soluble compounds. If the solution was refluxed for seven hours, the recovery was only 8%.

Summary

1. A stereochemical study of the reaction of sodium malonic ester with cyclopentene oxide in the presence of excess malonic ester has shown that the reaction involves Walden inversion about one of the carbon atoms of the oxide ring.

2. This is the result which would be anticipated if the reaction proceeded by the usual mechanism for displacement reactions.

CHICAGO, ILLINOIS RECEIVED JULY 23, 1942

[CONTRIBUTION FROM THE SANDERS LABORATORY OF CHEMISTRY, VASSAR COLLEGE]

The Sorption of Carbon Monoxide by Metals. Temperature Variation Experiments

BY CARROLL W. GRIFFIN

Introduction

The identification of two types of adsorption, namely, physical and activated, has been definitely established for gases on many solids. The existence of a third sorptive force has long been suspected and that this might be solution was mentioned by the author in the case of hydrogen and massive copper.[1] Further evidence to support this belief was obtained in studies of the sorption of hydrogen on supported copper,[2] on massive nickel,[3] on supported nickel,[4] and particularly by the "experiments with temperature variation."[5] In the last two studies the attack has consisted of bringing the gas into sorptive equilibrium with the metal at −78.5°, raising the temperature to 0° and, after measuring the equilibrium conditions, returning the temperature to −78.5°. In this manner it was revealed that the sorption at −78.5° is followed first by a rapid desorption at 0° and then by a slower process (solution) at 0°. Upon cooling again to −78.5° the sorption is found to be greater than the original sorption at this temperature to an extent equal to the volume slowly taken up at 0°.

The success of this method of study of course depends upon selecting two temperatures, one at which the secondary sorptive force, thought to be solution, is absent or is at a minimum, and the other at which it manifests itself distinctly. The amount of solution, and not simply its rate, will be greater at the higher temperature and also at higher pressures. These facts hold for the studies already cited.

It is obvious that −78.5 and 0° might not always be the temperature at which the two sorptive forces would distinguish themselves best. Thus, although Benton and White do not specifically so label the experiment immediately under their Table IV,[6] this is really a run "with temperature variation," the variation here being from 110 to 210°. In connection with their study of carbon monoxide on massive copper it might be emphasized that the authors did not find, after noting the desorption coming with the elevated temperature, any resorption (solution) as evidenced by a drop in pressure. Yet, when the temperature was again brought to 110°, the sorption of carbon monoxide amounted to 15.00 ml. as compared with an original 14.43 ml. It therefore seems, in the writer's opinion, since 0.57 ml. is more than ten times their experimental error, that actually solution of over half a milliliter did take place at 210°, in excess of any dissolved at 110°, but it occurred simultaneously with the desorption of the activated carbon monoxide molecules and *was overshadowed by the desorption.* For as long as both processes are taking place and the rate of desorption exceeds the rate of solution there can be no observable evidence of the latter, save the greater total sorption when return is made to the lower temperature. Only when the desorption at the higher temperature is completed quickly or is relatively small may one observe the pressure reversal which indicates that solution is taking place.

Sorption studies with temperature variation have been confined to hydrogen on metals with the exception that Benton and White have shown the general behavior of carbon monoxide on massive copper. Therefore, the present work was undertaken to learn whether or not the effects observed with hydrogen are common also to other gases. Platinum and copper were the metals selected and, since little or no solution can be expected with supported metals, both forms have been employed with platinum. With copper only the supported metal was used. Since it has already been shown that solution of carbon monoxide in massive copper becomes appreciable only above 0°, the temperatures selected for the supported copper

(1) Griffin, THIS JOURNAL, **49**, 2136 (1927).
(2) Griffin, *ibid.*, **57**, 1206 (1935).
(3) White and Benton, *J. Phys. Chem.*, **35**, 1784 (1931).
(4) Griffin, THIS JOURNAL, **61**, 270 (1939).
(5) Benton and White, *ibid.*, **54**, 1373 (1932); Griffin, *ibid.*, **63**, 2957 (1941).
(6) Benton and White, *ibid.*, **54**, 1373 (1932).

were 0 and 100°. Those for the two platinum sorbents were −78.5 and 0°, for von Hemptinne[7] found that a marked increase in the sorption of carbon monoxide on platinum takes place around −40°.

Experimental

The apparatus[8] and general method of making the runs[9] and the purification of carbon monoxide[1] have been described. The supported copper sample was the same as in a previous study.[2] The platinum samples also had been used before and their preparation reported.[10] Since it is not possible completely to remove adsorbed carbon monoxide from platinum surfaces by simple evacuation, its removal was accomplished by burning off with oxygen at 250° between runs. The oxygen was then washed off with hydrogen and the latter removed by pumping off at 250°. As usual, helium was employed as a reference gas.

Results

On each of the three sorbents a run was first made to measure the sorption at the lower temperature (0° for copper; −78.5° for platinum) at several pressures up to one atmosphere. Then a run was made at the higher temperature (100° for copper; 0° for platinum). After this three runs were made on each sorbent with temperature variation, using progressively greater volumes of carbon monoxide. The results are summarized in the tables and figures. Table I lists the data obtained with supported copper, and Tables II and III give the results for the platinum sorbents. The values in Row (2) of the tables represent the adsorption at the higher temperature for a given experiment (plus solution, if any, at the lower temperature). The differences given in Row (4) are the volumes of carbon monoxide dissolved at the higher temperature and at pressures of Row (2), while the differences given in Row (8) are the volumes dissolved at the higher temperature at pressures of Row (5). The sums of adsorption and solution are found in Rows (3) and (5).[9]

TABLE I

EFFECT OF CHANGING TEMPERATURE ON SORPTION OF CARBON MONOXIDE BY SUPPORTED COPPER (10.2 G. Cu ON 40 G. OF BRICK)

(1) Gas taken up at 0°	Press.	88.4	362.2	512.9
	Vol.	3.00	3.55	3.63
(2) Initial value after warming to 100°	Press.	159.9	522.5	739.9
	Vol.	1.88	2.78	2.99
(3) Total sorption at 100° at pressures given in (2)		1.98	2.94	3.15
(4) Differences of (2) and (3)		0.10	0.16	0.16
(5) Final values reached at 100°	Press.	158.0	518.7	736.1
	Vol.	1.94	2.91	3.10
(6) After cooling to 0°	Press.	86.5	351.8	509.2
	Vol.	3.09	3.69	3.79
(7) Direct values at 0° at pressures given in (6)		2.98	3.54	3.63
(8) Differences of (6) and (7)		0.11	0.15	0.16

TABLE II

EFFECT OF CHANGING TEMPERATURE ON SORPTION OF CARBON MONOXIDE BY 5 G. OF MASSIVE PLATINUM

(1) Gas taken up at −78.5°	Press.	15.1	249.5	462.6
	Vol.	3.97	4.58	4.59
(2) Initial values after warming to 0°	Press.	45.1	398.1	696.8
	Vol.	3.44	3.50	3.52
(3) Total sorption at 0° at pressures given in (2)		3.79	4.16	4.22
(4) Differences of (2) and (3)		0.35	0.66	0.70
(5) Final values reached at 0°	Press.	34.5	371.4	666.5
	Vol.	3.68	4.10	4.20
(6) After cooling to −78.5°	Press.	8.5	233.6	440.1
	Vol.	4.18	5.22	5.30
(7) Direct values at −78.5° at pressures given in (6)		3.86	4.58	4.61
(8) Differences of (6) and (7)		0.32	0.64	0.69

TABLE III

EFFECT OF CHANGING TEMPERATURE ON SORPTION OF CARBON MONOXIDE BY SUPPORTED PLATINUM (3.9 G. Pt ON 10 G. OF BRICK)

(1) Gas taken up at −78.5°	Press.	32.8	286.1	426.2
	Vol.	1.03	1.25	1.27
(2) Initial values after warming to 0°	Press.	51.4	400.6	592.4
	Vol.	0.82	0.97	0.99
(3) Total sorption at 0° at pressures given in (2)		0.85	1.02	1.06
(4) Differences of (2) and (3)		0.03	0.05	0.07
(5) Final values reached at 0°	Press.	49.8	399.0	590.2
	Vol.	0.87	1.02	1.06
(6) After cooling to −78.5°	Press.	32.4	284.6	424.4
	Vol.	1.05	1.32	1.35
(7) Direct values at −78.5° at pressures given in (6)		1.03	1.26	1.28
(8) Differences of (6) and (7)		0.02	0.06	0.07

The data of the three tables are brought together in the figures. Curve 3 in all the figures, giving the adsorption at the higher temperature, is obtained by subtracting the amount of dissolved carbon monoxide at a given pressure from the total sorption at that pressure as found from Curve 2.

As in the case of hydrogen[10] the extent of solution of carbon monoxide in supported metals is

(7) von Hemptinne, *Z. physik. Chem.*, **27**, 429 (1898).
(8) Pease, THIS JOURNAL, **45**, 1196 (1923).
(9) Benton and White, *ibid.*, **54**, 1379 (1932).
(10) Griffin, *ibid.*, **63**, 2957 (1941).

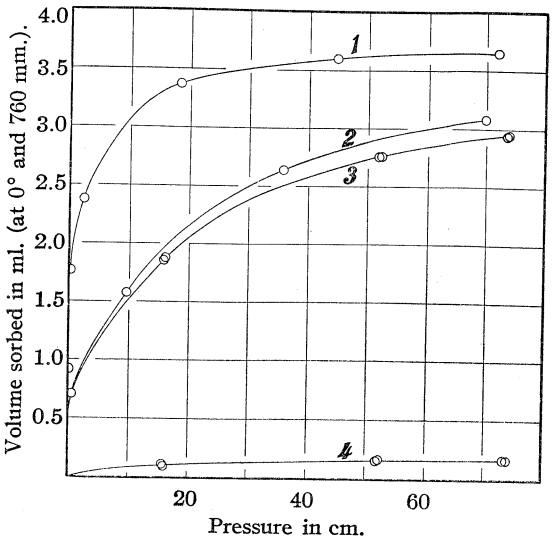


Fig. 1.—Sorption of carbon monoxide on supported copper, four moles of copper per 1000 g. of brick: curve 1, total sorption at 0°; 2, total sorption at 100°; 3, adsorption at 100°; 4, solution at 100°.

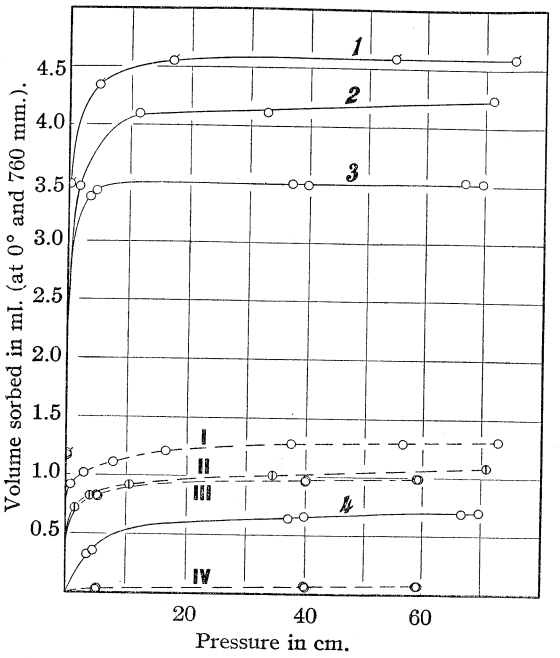


Fig. 2.—Sorption of carbon monoxide on platinum. Solid curves indicate massive platinum; broken curves indicate supported platinum, two moles of platinum per 1000 g. of brick: curves 1 and I, total sorption at −78.5°; 2 and II, total sorption at 0°; 3 and III, adsorption at 0°; 4 and IV, solution at 0°.

distinctly less than in massive metals. Thus, for carbon monoxide in platinum at 500 mm. pressure, the solution process accounts for 17% of the total 0° sorption for the massive form, and for only 5% for the supported form. For supported copper at 100° the figure is 5% both at 500 mm. and at 300 mm. pressure, whereas Benton and White found that for massive copper at 300 mm. pressure over 50% of the 100° sorption is due to solution.[11] The 17% solution for massive platinum is the smallest percentage yet found for a massive metal as may be seen from Table V of an earlier study.[10] Nevertheless, the present evidence substantiates the conclusion that when the sorbent is spread largely as surface the solution factor is much reduced.

The rate of sorption was rapid at low pressures for all three sorbents and somewhat slower at atmospheric pressure. The rate was about the same for massive as for supported platinum; this, as well as the rather unexpectedly low 17% solution for massive platinum, is believed due to the probability that there was a much greater amount of surface metal in this sorbent than is found in massive metals reduced from oxides in wire form. At atmospheric pressure two hours sufficed for equilibrium. This differs from the case of massive copper at 110° or higher under which conditions several days may not bring about equilibrium.

The rate of desorption of carbon monoxide on the two platinum sorbents when the temperature is elevated from −78.5 to 0° was slower than for hydrogen on platinum. As a result, the "initial sorption after warming to 0°," which is computed from the maximum pressure shown when the temperature is increased to 0°, (and which for hydrogen on platinum is almost immediate) was effected in about three or four minutes. Had the total desorption been immediate it follows that the "Initial values after warming to 0°" as shown in Row (2) of these tables would have been slightly higher for the observed pressures and thus somewhat lower for the calculated volumes. In turn this would mean that the values of Row (4), representing solution, would be rather greater. Because of these considerations the values in Row (8) for a given series of experiments should be more trustworthy than those of Row (4), and the fact that good checks have been obtained in Rows (4) and (8) (note that the pressures corresponding to the volumes for the two rows differ somewhat) indicates that in these particular experiments the maximum pressures of Row (2) did not materially differ from the actual values, had the latter been obtainable, which prevailed before the solution process had attained a finite value.

(11) Benton and White, THIS JOURNAL, 54, 1373 (1932), see Fig. 7.

Summary

Measurements with temperature variation have been made for the sorption of carbon monoxide on supported copper and on massive and supported platinum. The results are qualitatively similar to like measurements of hydrogen on massive and supported metals and show that the presence of a secondary sorptive force is probably a general characteristic of metallic sorbents. This factor, apparently solution, manifests itself only to a small extent with supported sorbents where the metal is largely exposed as surface. With massive metals and carbon monoxide the secondary action is over three times as great in the case of platinum, and about ten times as great in the case of copper, when compared with their respective supported forms.

POUGHKEEPSIE, N. Y. RECEIVED AUGUST 11, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Chemical Separation of the Isotopes of Hydrogen by the Addition of Metals and Compounds of Metals to Water, Acids and Bases. I. Relative Efficiencies of Specific Reactions. The Effects of Certain Factors other than Temperature[1]

BY HERRICK L. JOHNSTON AND CLYDE O. DAVIS

The possibility of obtaining separation of isotopes of hydrogen by displacement reactions of metals with acids was suggested by Washburn and Urey.[2] The first experimental results on displacement reactions were reported independently by L. and A. Farkas[3] and by ourselves.[4] Horiuti and Szabo[5] confirmed our own value of 2.5 for the separation coefficient in the Na–H_2O reaction, in experiments in which they introduced water vapor onto metallic sodium. More extensive observations at 90° have been reported by Hughes, Ingold and Wilson,[6] whose data differ somewhat from our own. Recently, Reyerson, Johnson and Bemmels[7] have reported qualitative data on the isotope separation which results when calcium carbide is treated with water.

The present paper describes quantitative investigations of the reactions of lithium, sodium, potassium, calcium, calcium carbide and aluminum carbide with water; magnesium, granulated and mossy zinc, C. P. and commercial iron, manganese, aluminum and ferrous sulfide with sulfuric acid; and aluminum with sodium hydroxide. In a following paper[8] the results of an investigation of temperature coefficients of the separation factors in several of the reactions are presented.

In both this and the following paper the specific gravity of pure D_2O at 27° is taken to be $d^{27}_{27} = 1.10768$[9] and that of pure protium water with the normal oxygen isotope ratio $d^{27}_{27} = 0.999982$.[10] Account is also taken of the slight non-additivity of H_2O and D_2O volumes reported by Luten.[11] This makes the equation for the specific gravity of a D_2O–H_2O mixture, in terms of the absolute mole fraction of D

$$S_{27^\circ} = 0.999982 + 0.10770\ N_D - 0.0012\ N_H N_D \quad (1)$$

While equation (1) is set up for 27°, it is applicable with high accuracy for moderate concentrations of D for the whole temperature range between 25 and 30°.

Experimental Description

(a) **The Reaction System.**—A diagram of an improved form[12] of the reaction system is shown in Fig. 1.

At the beginning of each run a weighed quantity (400–800 g.) of water, acid or base, with an enriched D content, was placed in the reaction vessel A, and a weighed quantity of the solid reagent (in small pieces) was placed in C.

(1) Except for slight modification for newer values of oxygen isotope abnormality in the electrolyte and in air and for the densities of pure D_2O and pure protium oxide, the values in this paper were presented before the Division of Physical and Inorganic Chemistry at the Cleveland Meeting of the American Chemical Society (September, 1934) and the Symposium on Deuterium, held with the Pittsburgh Meeting of the American Association for the Advancement of Science (December, 1934). Original manuscript received September 19, 1941.

(2) E. W. Washburn and H. C. Urey, *Proc. Natl. Acad. Sci. U. S.*, **18**, 496 (1932).

(3) L. Farkas and A. Farkas, *Nature*, **133**, 139 (1934).

(4) C. O. Davis and H. L. Johnston, THIS JOURNAL, **56**, 492 (1934).

(5) J. Horiuti and A. L. Szabo, *Nature*, **133**, 327 (1934).

(6) E. D. Hughes, C. K. Ingold and C. L. Wilson, *ibid.*, **133**, 291 (1934); *J. Chem. Soc.*, 493 (1934).

(7) L. H. Reyerson, O. Johnson and C. Bemmels, THIS JOURNAL, **61**, 1594 (1939).

(8) H. L. Johnston and W. H. Hall, manuscript in preparation.

(9) H. L. Johnston, THIS JOURNAL, **61**, 878 (1939).

(10) H. L. Johnston, *ibid.*, **57**, 484 (1935).

(11) D. B. Luten, *Phys. Rev.*, **45**, 161 (1934).

(12) This is actually a diagram of the reaction system used by Johnston and Hall.[8] In the original design the reaction flask was not thermostatted but was either exposed to air, or sprayed with a continuous stream of tap water (*cf. seq.*). The semi-automatic levelling bulbs (H, H) and calibrated flowmeters (J, J) were not included in the original design.

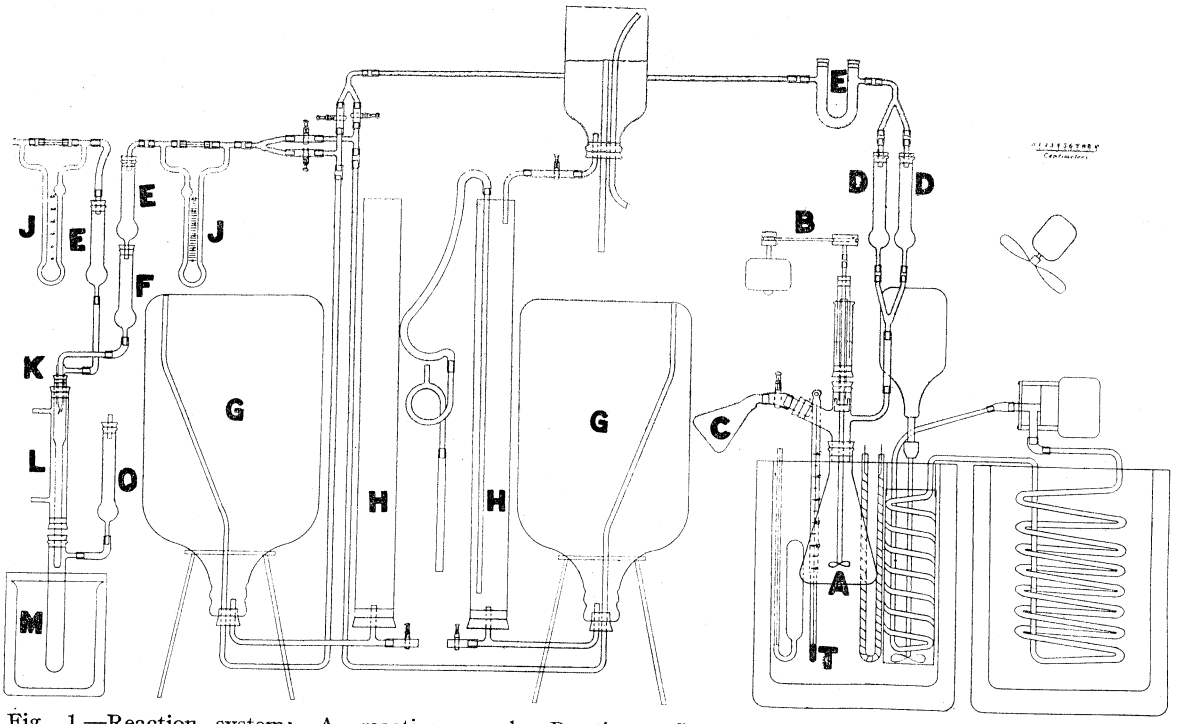


Fig. 1.—Reaction system: A, reaction vessel; B, stirrer; C, reagent flask; D,D,O, weighed $CaCl_2$ drying tubes; E,E,E, unweighed $CaCl_2$ drying tubes; F, sand trap; G, gas storage carboys; H,H, water levelling tubes to control pressure heads in the carboys; J,J, calibrated flowmeters; K, Pyrex oxyhydrogen torch; L, Pyrex condenser; M, ice-jacketed receiver; T, thermostat.

During the run the solid reagent was added slowly to the rapidly stirred liquid in the reaction vessel, and the evolved gas was: (1) dried, (2) collected over water (hydrogen sulfide and acetylene were collected over mercury), (3) redried and (4) burned in an excess of dry, tank oxygen.

Runs were permitted to go to completion (*i. e.*, until all of the weighed solid reagent had reacted). Twenty-four to sixty grams of combustion water was formed in each run and, since the reagents were added slowly for the faster reactions, the duration of each run was from twelve to forty-eight hours.

Full gravimetric data were taken (*cf.* Table III) and isotopic analyses were carried out for: (1) the initial water, acid or base and (2) the water formed by combustion. In a few instances densities were taken on water from the residual solution but these were not essential since the change in the deuterium concentration in the reaction flask can be determined more accurately from the mass and the D concentration of the water produced by combustion of the evolved gas than by a direct measurement. Correction was applied for the gas that remained in the reaction vessel or other portions of the reaction system.

(b) Densimetric Analyses with the Buoyancy Balance.—Analyses were based on the specific gravities of purified water samples and were made by the "free submerged float" method,[13] in which the temperature of the water sample is varied until the density matches that of a calibrated glass float. This is a method which we have used extensively in this Laboratory with excellent results.[4,8,10,14]

The 1.5-cc. Pyrex float was calibrated at frequent intervals against purified samples of Columbus tap water, and the calibration points were graphed against time. When first made the float came to equilibrium in pure normal water at 26.773° but the calibration temperature rose steadily over a period of several months. We attribute this to gradual solution of the outer surface of the float.[15]

Flotation temperatures of samples analyzed, relative to normal water, are considered reliable to within ±0.001 to 0.002° (2 to 5 γ in density). The densities of normal water between 25 and 30° were taken from the "International Critical Tables."[16] In computing the density differences correction was applied for the thermal expansion of the Pyrex float.[17]

It has been our experience that the limiting factor in the accuracy attainable with the buoyancy balance is ordinarily the purification of water samples for analysis. In this work we repeated the purification of samples until constant density (to within 1 p. p. m.) was obtained.

(13) T. W. Richards and G. W. Harris, THIS JOURNAL, **38**, 1000 (1916); G. N. Lewis and R. T. Macdonald, *J. Chem. Phys.*, **1**, 341 (1933).

(14) (a) R. D. Snow and H. L. Johnston, *Science*, **80**, 210 (1934); (b) W. H. Hall and H. L. Johnston, THIS JOURNAL, **57**, 1515 (1935); (c) *ibid.*, **58**, 1920 (1936). A more detailed description of our procedures in densimetric analyses will be published in the *Journal of the Ohio Academy of Science*.

(15) There appears to be some relation between this behavior and the dimensions of the float. Earlier calibrations of an 8-cc. Pyrex float showed little change in a period of several weeks.

(16) "International Critical Tables," McGraw-Hill Book Co., Inc., New York, N. Y., 1927, Vol. III, p. 25.

(17) R. M. Buffington, THIS JOURNAL, **48**, 2305 (1926).

Table I is an illustration for a particularly troublesome sample, for which the density changed by about 8 p. p. m. in the second and third processings.

TABLE I

PURIFICATION RECORD OF A TROUBLESOME SAMPLE

Processings	1	2	3	4	5
Flotation temp. (Beckmann), °C.	3.695	3.675	3.664	3.663	3.664

(c) **Reagents.**—**The deuterium-rich water** used in this investigation was prepared by ourselves out of old electrolyte from electrolytic hydrogen cells of the Capital City Products Co. of Columbus. Water distilled from this electrolyte was further electrolyzed between nickel or iron electrodes in potassium hydroxide solution to a volume fraction of approximately $^1/_{16}$, which resulted in water whose hydrogen content was approximately 0.5% in D. The alkaline solution was neutralized with excess carbon dioxide and the water distilled away from the sodium bicarbonate in a copper still and redistilled in Pyrex. While the O^{18} abnormality must have amounted to about 9 p. p. m. on the density of the water at the end of the electrolyses,[10] the carbon dioxide treatment must have nearly or completely removed this abnormality.[14c] We have therefore taken the initial water in the several runs as normal in its oxygen isotope ratio.

The acid solution was prepared by adding Baker and Adamson C. P. fuming sulfuric acid to a weighed amount of deuterium-rich water. A sufficient amount was prepared at one time to serve for all of the runs with metals. Its concentration was found, by titration with standard base, to be 6.983 equivalents per 1000 g. of acid. Its deuterium content was 0.400 atomic % of hydrogen. The latter was determined: (1) by a direct density measurement on a middle fraction of water distilled from the sulfuric acid solution and (2) by deuterium analysis on the original water and computation of the amount of dilution by normal hydrogen from the fuming sulfuric acid. The two analyses agreed to within 1 p. p. m. on the measured and computed densities.

A second quantity of acid was prepared in a similar manner for the ferrous sulfide run.

The **basic solution** was prepared with C. P. sodium hydroxide, in a similar manner. The strength of the solution was 3.340 equivalents per 1000 g. of base.

The oxygen used in the combustions was from a commercial cylinder and had been prepared from air by the Linde process. Its oxygen isotope composition, relative to air, was determined by comparison of densities of two water samples—one prepared by combustion of tank hydrogen in an excess of the tank oxygen, the other by combustion of the same tank hydrogen in air. The combustions were brought about in the burner K. This manner of combustion will, in itself, have produced no change in the isotopic composition of either the hydrogen or the oxygen.[14c] The two water samples agreed in density to within 0.5 p. p. m. Our combustion samples must, therefore, have possessed the same oxygen abnormality as oxygen in air. We have accordingly applied a correction of −6.5 p. p. m.[14c,18] to densities of *combustion waters only*.

(18) M. Dole, *J. Chem. Phys.*, **4**, 268 (1936). See also Table VI of the recent paper by Swartout and Dole, THIS JOURNAL, **61**, 2025 (1939).

Coleman and Bell standard laboratory quality sodium and potassium were employed. Thick slices of the outer surface were cut away, in an atmosphere of nitrogen, and the metals cut into small pellets. The lithium was a reputedly pure metal supplied by A. D. Mackay of New York. The calcium metal was in the form of thick, silvery chips and was packaged, without analysis, for a local supply house.

Two C. P. samples of zinc were employed. The granular zinc was a J. T. Baker product and bore an analysis on the label which showed only 0.024% of total impurity, of which 0.02% was Pb. The mossy sample was Baker and Adamson's C. P. mossy zinc with an analysis on the label which showed 0.05% Pb and 0.002% of other impurities.

Also two samples of iron were employed. One was a 99.8% pure sample, from J. T. Baker, while the other was from a stock supply of "commercial iron filings" and contained 10 to 15% of impurities, principally carbon.

The aluminum was a granular C. P. product of Coleman and Bell and the magnesium was purchased from a local supply house as "A1 turnings for Grignard reagent." Manganese, calcium carbide, aluminum carbide and ferrous sulfide were stock chemicals of unknown origin and purity. The three last, in particular, may have contained considerable impurity.

(d) **Temperatures.**—No effort was made to thermostat the reactions. However, most of the runs were carried out at room temperature, which usually varied between 25 and 30° during the period of the experiments, and can be directly compared. The other reactions were carried out by spraying hot water from the laboratory pipes (55–60°) onto the wall of the reaction flask in order to accelerate otherwise sluggish rates. This was done in both of the runs with aluminum in acid; in the second lithium run, in which lithium was added to an already strong solution of lithium sulfate; in both runs with granular zinc and in both runs with C. P. iron. Cold tap water was sprayed onto the reaction vessel during the runs with sodium and with potassium in order to maintain the reaction mixtures close to room temperature.

Because the reactions were run relatively slowly, the temperatures of the reaction mixtures can seldom have differed by as much as 5° from the wall of the flask.

Because of the extreme slowness with which aluminum reacted with the acid a small quantity of mercury was added to promote the reaction. For the same reason copper strips were added to the reaction vessel in Run 11, with granular zinc.

Experimental Data

(a) **Sample Data and Calculations for a Typical Run.**—Table II contains the data obtained in a typical run (magnesium with sulfuric acid).

The separation coefficient, α, is defined by the equation

$$d \ln H = \alpha d \ln D \qquad (2)$$

with the symbols H and D used to represent the H_2O and D_2O equivalents of the quantities of

TABLE II

SAMPLE DATA AND CALCULATIONS

Run 18, 42.50 g. of Mg added to an excess of 6.983 *N* H_2SO_4.

	Initial acid	Combustion H_2O	Residue in reaction flask
Weight, g.	958.27	31.35 (obs.)[19]	995.57[25]
Water equivalent, g.	690.48	31.49 (calcd.)[20]	
ΔT of flotation, °C.	1.500	0.917[22]	
Specific gravity	1.0004081	1.0002470	
Mole fraction of D	0.004001	0.002467	
Wt. fraction of D[23]	.004446	.002742	
Quantity of D (as D_2O)	3.06987	.08635	2.98352[24]
Quantity of H (as H_2O)	687.41013[21]	31.40365[20]	656.00648[24]

$$\alpha = \frac{\log (656.00648/687.41013)}{\log (2.98352/3.06987)} = 1.640$$

H and D, respectively, in the acid solution. The equation is integrated between initial and final amounts.

The good agreement between the observed[19] and calculated[20] weights of combustion water, and likewise the check on the gravimetric data through the observed and calculated weights of residue,[25] are good evidence against any significant amount of reduction by the reaction[26]

$$Mg + 2H_2SO_4 = Mg^{++} + SO_4^{=} + 2H_2O + SO_2 \quad (3)$$

Failure to observe an odor of sulfur dioxide in the slow streams of excess oxygen from the burner is further confirmation of this.

(b) Complete Tabulation for All Fifteen Reactions in Water of Approximate 0.5% D Content.—Complete tabulations of the essential experimental data for all runs in the fifteen reactions investigated, together with the values of α, are given in Table III. Except as noted, calculations were carried out in the same manner as illustrated by the run recorded in Table II. Temperatures were approximately 30°, with the exception of certain runs in which the reaction flask was heated to about 55°. These runs were referred to previously.

Run 1 is the preliminary run with sodium, previously reported.[4] Its value of α has been recomputed with corrections made for oxygen isotope abnormality in both the combustion water and the initial water and for the improved H/D ratio in ordinary water.

Comparisons[25] of the weight of residue found in the reaction vessel with that calculated from the initial weighings and the quantity of hydrogen (or hydrogen bearing gas) evolved are not included in the table. With few exceptions[27] calculated and observed weighings of residue agreed to within a few tenths of a gram. This can be considered to be within experimental limits of error. However, the observed amount of *combustion water* was usually *less* than the calculated weight. In some instances this was due to known accidental losses of hydrogen while the apparatus was allowed to run overnight, or to impurities in certain of the reagents (commercial iron, aluminum carbide and possibly calcium carbide, calcium and ferrous sulfide as examples). However, it can easily be shown that even relatively large errors in the *amounts* of combustion water, should they exist, do not affect the values of α significantly.

The precision with which α may be determined depends primarily on the precision with which compositions of Initial Water and of Combustion Water are determined. It can be shown, simply, that any percentage error in either of these compositions will influence α in the same proportion.

(19) The sum of: 29.55 g. collected in M (Fig. 1); 1.25 g. collected in O (no ice was on hand when this run was made); and 0.55 g. computed as the H_2O equivalent of an approximate 800 cc. of unburned H_2 left in the apparatus at the end of the run.

(20) Calculated from the weight of metal reacted.

(21) Corrected by 0.65 g. for loss of 1.31 g. of vapor to drying tube D.

(22) Corrected by 0.023° for the O^{18} abnormality of the tank oxygen.

(23) Wt. fractions were computed with the molecular weight values: H_2O = 18.0156, D_2O = 20.0283.

(24) Computed by difference between entries in the "Initial Acid" and "Combustion H_2O" columns.

(25) This weighing was taken as a check on the gravimetric data. It compares with the calculated value 996.06. The latter makes allowance for the 1.31-g. vapor loss to the drying tube D (ref. 21) and for the 3.60 g. of H_2 (0.25% in D) represented by the 31.35 g. of H_2O collected.

(26) The good gravimetric check on the weight of residue is significant in ruling out this reaction since SO_2 is 32 times as heavy as the equivalent amount of hydrogen. For example, in the run recorded in Table II, 100% reaction by (3) rather than by displacement would have liberated 32 × 3.60 = 115.2 g. of SO_2, a weight difference of 112.6 g., and 1% reaction by (3) would have therefore, introduced an error of +1.13 g. in the computed weight of residue. The observed discrepancy is only 0.5 g. and is within limits of error.

(27) Among the reactions that evolve H_2 (Runs 1 to 26 inclusive) only Runs 9, 10 and 13 showed disagreements in the gravimetric data amounting to more than 1 g. The average disagreement in this group (Runs 9, 10 and 13 not included) was ±0.4 g. In Run 13 the disagreement was 2.9 g. and for the combined K runs it was 11 g. The 11-g. disagreement in the gravimetric data for the K runs may be due in part to the presence of K_2O, which would not have been distinguished from 2K in the titrations of residue. We also encountered experimental difficulties resulting from explosions of small pieces of potassium in the reaction vessel, that caused some losses of material and weakened the validity of any gravimetric comparison. It can easily be shown, however, that the experimental values of α cannot have been influenced by these difficulties by more than a few hundredths of a unit.

The gravimetric check was less accurate with the residues from runs 27–32 inclusive. With CaC_2 the average disagreement was 3 g.; with Al_4C_3, 1 g.; and with FeS, 10 g. With CaC_2 and Al_4C_3 the disagreements may be accounted for by not unreasonable losses of hydrocarbon gases from the stirrer or gas train. It is possible that soluble impurities in the FeS may have been responsible, in whole or in part, for the relatively large discrepancy in the observed and calculated weight of residue in that reaction.

TABLE III

GRAVIMETRIC AND DENSITY DATA, AND VALUES OF THE ISOTOPIC SEPARATION FACTOR, FOR ALL RUNS WITH APPROXIMATE 0.5% D CONTENT IN THE INITIAL WATER[28]

Run	Reaction	Amounts, grams: Metal[29] (or compound)	Amounts, grams: Initial liquid	Relative flotation temps., °C.: Combustion water[30]	Relative flotation temps., °C.: Initial water	Relative flotation temps., °C.: Combustion water[22]	α
1	$Na + H_2O$	150.0	389.2	57.3	0.532	0.156	2.6
2	$Na + H_2O$	369.9[31]	849.67[31]	42.62	1.666[31]	.616	2.55
3	$Na + H_2O$	....	.....	52.94	....	.627	2.59
4	$Na + H_2O$	....	.....	47.21	....	.638	2.66
5	$Li + H_2O$	58.3[31]	810.17[31]	44.73	1.699[31]	.922	1.84
6	$Li + H_2O$	....	.....	31.04	....	.930	1.86
7	$Ca + H_2O$	120.79	641.80	54.28	1.521	1.082	1.41
8	$Ca + H_2O$	119.26	700.72	53.60	1.521	1.090	1.40
9	$K + H_2O$	391[31]	568.56[31]	31.53	1.705[31]	1.206	1.42
10	$K + H_2O$	....	.....	32.02	....	1.190	1.46
11	Zn (gran.) $+ H_2SO_4$	127.90	840.80	34.33	1.500	0.269	4.89
12	Zn (gran.) $+ H_2SO_4$	129.53	815.10	35.69	1.500	.247	5.24
13	Zn (mossy) $+ H_2SO_4$	132.92	889.40	36.62	1.500	.199	6.19
14	Zn (mossy) $+ H_2SO_4$	100.17	843.30	27.62	1.500	.200	6.12
15	$Al + H_2SO_4$	36.03	806.09	36.03	1.500	.303	4.45
16	$Al + H_2SO_4$	30.21	818.19	30.21	1.500	.295	4.52
17	$Mg + H_2SO_4$	36.78	792.48	25.80	1.500	.903	1.65
18	$Mg + H_2SO_4$	42.50	958.27	31.35	1.500	.917	1.64
19	Fe (c. p.) $+ H_2SO_4$	101.27	587.94	32.67	1.500	.185	6.60
20	Fe (c. p.) $+ H_2SO_4$	101.36	692.97	32.65	1.500	.188	6.48
21	Fe (Comm) $+ H_2SO_4$	103.27	822.63	29.26	1.500	.215	5.81
22	Fe (Comm) $+ H_2SO_4$	101.27	672.20	30.03	1.500	.228	5.56
23	$Mn + H_2SO_4$	102.67	580.90	33.57	1.500	.366	3.81
24	$Mn + H_2SO_4$	102.96	487.41	33.73	1.500	.360	3.89
25	$Al + NaOH$	30.20	570.60	30.20	1.669	.301	5.07
26	$Al + NaOH$	54.09	510.74	29.40	1.669	.308	4.87
27	$CaC_2 + H_2O$	117.57	550.94	24.31	1.728	.772	2.21
28	$CaC_2 + H_2O$	213.83	453.91	43.80	1.728	.732	2.36
29	$Al_4C_3 + H_2O$	123.35	488.00	27.40	1.728	.691	2.46
30	$Al_4C_3 + H_2O$	118.87	496.76	29.92	1.728	.705	2.42
31	$FeS + H_2SO_4$	183.31	674.09	32.90	1.690	.603	2.46
32	$FeS + H_2SO_4$	179.96	586.61	37.53	1.690	.609	2.46

If we take the ΔT's of flotation to be reliable to within about 0.004° (equivalent to 1 p. p. m. in density) in the present group of runs, this would amount to about ±2% in the precision of the values for α, for the majority of runs. This corresponds pretty closely to the reproducibilities observed in the experimental α's. Other factors, including inaccuracies in temperatures for certain of the runs, may increase the limits of error to ± about 5% for purposes of comparison with other work.

(28) Acid and basic concentrations of solutions used were as follows: Runs 11–24, 3.492 moles of H_2SO_4 per 1000 g. of acid; Runs 25–26, 3.340 moles of NaOH per 100 g. of base; Runs 31–32, 3.487 moles of H_2SO_4 per 1000 g. of acid.

(29) The amounts of Na, Li and K used in runs with the alkali metals were determined by titrations of the alkaline solutions left in the reaction vessel. Except for K, which may have been contaminated with K_2O, these calculations agree well with those based on the amounts of combustion water collected as well as with those based on the weights of residues in the reaction flask.

(30) The values recorded in this column for runs with the alkali metals, *commercial* iron, and the compounds CaC_2, Al_4C_3 and FeS are the observed weights of combustion water (with corrections applied for water collected in the drying tube O and for the water equivalent of unburned gas in the apparatus). Values for all other runs were computed from the weights of reacted metal.

(31) Runs 2, 3 and 4 with Na form a single series which were carried out by adding successive portions of metal to an original 849.7 g. of water, and collecting three successive fractions of combustion water. The residue was weighed and titrated only after all 367.9 g. of Na had been added. In computing α's we have calculated the amounts of H and of D present in the reaction vessel after removal of each of the three fractions of combustion water, by subtracting from the original amounts the quantities of H and D collected in the receiver (corrected for losses to the $CaCl_2$ tubes and for H_2 in the apparatus). Each α is therefore an individual value at the mean alkalinity of each of the three successive runs—not a cumulative value. Runs 5 and 6, with Li, and 9 and 10, with K, were carried out in a similar manner except for the fact that only two fractions of combustion water were taken.

Hughes, Ingold and Wilson[6] criticized the accuracy of our preliminary determination[4] of α for the Na–H_2O reaction (Run 1 of Table III) on the grounds that it was somewhat sensitive to the choice of the H/D ratio in ordinary water. Due to improvements in the determination of the latter ratio, which is now known to within relatively close limits,[10,32] and to three-fold increase in the deuterium concentration of the starting water, the inaccuracy from this source cannot exceed 1 or 2% in the least favorable runs reported in the present paper (Run 1 not included).

(c) **Reaction at High Concentration of Deuterium.**—A. and L. Farkas[3] have published results for displacement reactions with water and acid 25 mole % in deuterium. For calcium they obtained a value for α (1.5) close to our own with 0.5% D. But with sodium, zinc and aluminum, respectively, their values of α were only about one-half of ours.

To check whether or not these results were due to a real dependence on the deuterium composition we carried out a single careful run with sodium in water of approximately 30 mole % deuterium. The reaction was carried out in the same manner as for the 0.5% D runs except that a smaller reaction vessel was employed and that no cooling water was used. Although special care was taken to add the sodium slowly the (undetermined) temperature of the reaction mixture must have been somewhat above that of the previous, water-cooled sodium runs. Specific gravities of the initial water and of the combustion water were made by pycnometer, in an approximate 11-cc. pycnometer of special design. The significant data of this run are entered in Table IV, together with the value of α.

TABLE IV

DATA ON REACTION OF Na WITH WATER 31.083 MOLE % IN D (56.12 G. OF Na ADDED TO 116.21 G. OF INITIAL WATER)

	Amounts, grams	Sp. gravity, d^{26}_{26}	Composition, wt. per cent. of D
Initial water	115.70[33]	1.03372	33.396
Combustion water	20.64 (obs.)[34]	1.01780	17.893
Final residue water	95.06[35]		36.761[35]

α = 2.473.

Aside from the possible influence of a small temperature coefficient in the separation efficiency the value of α obtained from this run should be reliable to the four figures recorded. It is seen that the results do not agree with those of A. and L. Farkas with 25% heavy water (α = 1.2, which corresponds to only 13% of the separation efficiency observed by ourselves) but agree well with our own results in water of 0.5% D.

We made no check of the Farkas values for zinc and aluminum in acid of high D content.

Discussion of Results

It is apparent that the displacement reactions, and the reactions with the carbides and with ferrous sulfide, bring about isotopic separations that are properly characterized by definite coefficients (α's) that are relatively insensitive to experimental conditions other than temperature[8] and the purity of reagents. The values of these coefficients lie on both sides of the equilibrium α for the exchange equilibrium between gaseous and liquid phases, which is close to 3.0 at 30°.[36] From this it is apparent that differences in reaction *rates* contribute to the separation.

There appear to be definite, though small, increases in α with increase in alkalinity of the reaction mixture for the alkali metal–water reactions. This conclusion is based on trends observed in series of runs with sodium (Runs 2–4), lithium (Runs 5–6) and potassium (Runs 9–10). The trends are within error limits but seem too often repeated to be fortuitous. There is nothing to distinguish between *p*H and ionic strength as cause for the trends, but the point of greatest significance appears to be that neither of these factors has more than a barely significant influence on α. For example, in the series of runs with sodium the sodium hydroxide concentration varied from 0 at the initiation of the runs to 28.3 *M* at their conclusion. Average sodium hydroxide molalities for the three successive runs were 3.07, 11.1 and 22.2, respectively. Yet α changed by only 0.1 unit.

We confirm the observations of Ingold and coworkers regarding the relatively large influence of impurities in the reacting metals. The α's

(32) Tronstad, Nordhagen and Brun, *Nature*, **136**, 515 (1935); Tronstad and Brun, *Trans. Faraday Soc.*, **34**, 766 (1938); Morita and Titani, *Bull. Chem. Soc. Japan*, **11**, 403 (1936); *ibid.*, **13**, 419 (1938); Hall and Jones, THIS JOURNAL, **58**, 1915 (1936); Gabbard and Dole, *ibid.*, **59**, 181 (1937); Swartout and Dole, *ibid.*, **61**, 2025 (1939).

(33) This includes a correction of 0.51 g. for 1.02 g. of water vaporized during the run.

(34) This compares with a calculated value of 22.4 on the basis of 56.1 g. of Na, assumed pure.

(35) Computed from the data for initial and combustion waters. The computed and observed values of total residue in the reaction flask agree well for this run. Thus, the computed value of the residue is 169.01 g. while the observed value was 168.90 g.

(36) L. and A. Farkas, *Trans. Faraday Soc.*, **30**, 1071 (1934).

in Runs 21 and 22, with impure iron, are almost a full unit below those in Runs 19 and 20, with pure iron. The α's in our Runs 23 and 24, with impure manganese, are lower than the value obtained by the extrapolation of Johnston and Hall's data,[8] who used pure manganese, by about the same amount. Accidental entrance of mercury into the reaction vessel during Runs 14 (Zn, H_2SO_4) and 26 (Al, NaOH) do not appear to have influenced the α's beyond the limits of experimental accuracy, but the mercury may not have become intimately mixed with the metals.

The order of the α's, among the displacement reactions, at 30° is: Ca, K, Mg, Li, Na, Al, Mn (pure[8]), Zn, Fe. This follows the order found by Hughes, Ingold and Wilson, at 90°: Li, Ca, K, Mg, Na, Al, Fe, Mn, Zn, except for the positions of Li and of Fe. Extrapolation of the curves of Johnston and Hall[8] to higher temperatures would give the order Zn, Mn, Fe at 90°, which is the reverse of the order reported by Hughes, Ingold and Wilson.

It is interesting to observe that the α's for the three metathetic reactions (CaC_2, H_2O; Al_4C_3, H_2O; FeS, H_2SO_4) are nearly identical.

There have been direct comparisons of heterogeneous reaction velocities with H_2O and D_2O, respectively, for the Al_4C_3–H_2O reaction. Urey and Price[37] reported the very high value of 23 for the ratio of reaction rates at 80°. This is ten times higher than our measured α at 30°. However, Barrer,[38] who used a more careful procedure obtained a reaction velocity ratio of 3.9 at 0°.

One of us has taken some preliminary data on reaction rates of aluminum with 4.5 *N* sulfuric acid, at 50°, as a function of the H/D ratio in the aqueous acid.

The results of these experiments are shown in graphical form in Fig. 2, where the rates are shown relative to the rate with ordinary 4.5 *N* sulfuric acid taken as unity. Each point on this graph is the average of two independent rate determinations with the same lot of acid. It is apparent that the reaction rate is linear with the D concentration, to within the limits of error, and that extrapolation to 100% D gives a reaction rate of about half that with acid 100% in H. This does not compare very accurately with the α of 4.5 found by us in the Al–H_2SO_4 reaction. However, the conditions of reaction may not have been comparable, due to the presence of mercury in runs (15–16). Probably, both in this comparison and in that with aluminum carbide, the agreements obtained are as close as could be expected under the conditions of experiment. Investigations on reactions more suitably chosen for this comparison are in progress in this Laboratory.

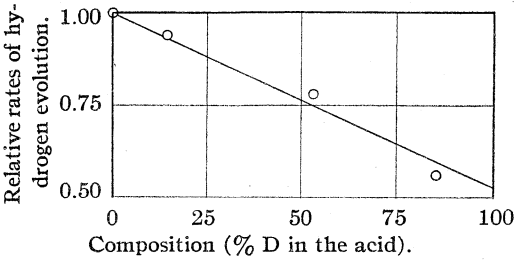


Fig. 2.—Relative velocities of the dissolution of aluminum in 4.5 *N* sulfuric acid, at 50°, as a function of the H/D ratio in the acid.

We accept the suggestion of Horiuti and Szabo[5] that the α's of displacement reactions are not necessarily the ratios of reaction velocities in pure H and pure D media, respectively, since the character of the reaction mechanism may lead to rates that are not strictly proportional to the relative numbers of H and D atoms. However, we fail to perceive the validity of their argument that the α for sodium cannot be the ratio of reaction rates since they obtained the same degree of isotopic separation in the reaction of water vapor with *excess* sodium as we had obtained in the reaction with excess liquid water. In view of our observation that α remains constant, within error limits, between 0.5 and 30% heavy water, it appears that the relative reactivities of OH and OD linkages remain the same when OH and OD are in the same molecule (*i. e.*, HDO) as when they exist in different molecules (*i. e.*, H_2O and D_2O).

To us, it seems of greater significance to stress the observation that Horiuti and Szabo obtained nearly the same α's[39] with *water vapor* as we obtained with *liquid water*, since the reaction with water vapor is clearly a molecular, as distinct from an ionic, mechanism. This implies that the reaction of the alkali metals with *liquid water* occurs by a molecular mechanism—a conclusion reached by Hughes, Ingold and Wilson by other reasoning, and previously suggested by Polanyi, who pic-

(37) H. C. Urey and D. Price, *J. Chem. Phys.*, **2**, 300 (1934).
(38) R. M. Barrer, *Trans. Faraday Soc.*, **32**, 486 (1936).
(39) Horiuti and Szabo did not compute α's for their four runs (two with sodium in excess and two with water vapor in excess) but tabulate data which we have used to compute their α's. The four runs yield an average α of about 2.2, with extremes of about 2.0 and 2.4, respectively.

tures[6] "the attachment of water molecules through their oxygen atoms to the metallic surface, and the subsequent elimination of hydrogen from two bound molecules in accordance with the (bond activation) mechanism of Horiuti and Szabo."

A fuller discussion of mechanisms will be left to the following paper.[8]

Summary

Quantitative data were secured on the extent of isotopic separation which occurs in the following respective reactions which liberate hydrogen or gaseous hydrides: Li, Na, K, Ca, CaC_2 and Al_4C with water; Mg, Zn, Fe, Mn, Al and FeS with aqueous sulfuric acid; and aluminum with aqueous sodium hydroxide. With a few exceptions the runs were made at or near room temperature. The hydrogen and hydrides were burned in a flame, with a slight excess of tank oxygen, and the water of combustion carefully purified and analyzed for its hydrogen isotope proportions by the free submerged float method. Correction was applied for the O^{18} abnormality of the tank oxygen, which was separately determined.

The data were quite reproducible, for a given set of reagents, and confirm the applicability of the quantitative relationship $d \ln [H] = \alpha d \ln [D]$, in which [H] and [D] are instantaneous values of the amounts of protium and deuterium, respectively, in the liquid phase, and α is the "isotopic separation factor," different for each reaction. The form of this relationship is identical with that which pertains to the isotopic separations by electrolysis.

A discussion of regularities observed in the results, and their bearing on some phases of the reaction mechanism is included.

COLUMBUS, OHIO RECEIVED AUGUST 13, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

Iodine Monochloride. IV. The System Potassium Chloride–Iodine Monochloride[1]

BY JACOB CORNOG AND ELDON E. BAUER[2]

This paper describes a series of studies in which existing vapor pressure data of iodine monochloride have been extended, the system potassium chloride–iodine monochloride has been formulated, and earlier work with the polyhalides potassium dichloroiodide, KCl·ICl or $KICl_2$, and potassium dibromoiodide, KBr·IBr or $KIBr_2$, has been reviewed.

1. The Vapor Pressure of Iodine Monochloride.—The vapor pressure of iodine monochloride was measured by Cornog and Karges,[3] who used the static method of Smith and Menzies[4] for measurements within the temperature range 35 to 70°. A modified form of the dynamic method of Pearce and Snow[5] was used to measure all of the vapor pressure data included in this paper. The vapor pressure of iodine monochloride was measured between the temperatures −15 and 50°. This served both to validate the method and to extend existing data. The iodine monochloride used in these measurements froze at 27.3°. Measurements were made in a thermostat in which temperatures were constant within ±0.02°. Vapor pressure measurements were reproducible within ±0.1 mm. at low pressures and ±0.3 mm. at higher pressures. The vapor pressure data for iodine monochloride are shown in Table I and are graphically represented in Fig. 1.

TABLE I

VAPOR PRESSURE OF SOLID AND LIQUID IODINE MONOCHLORIDE

1	2	3	4
Temp., °C.	V. p. liq. ICl, mm.	V. p. solid ICl, mm.	V. p. liq. ICl by Cornog and Karges, mm.
−15		1.2	
−10		2.0	
− 5		3.1	
0		4.6	
5		6.8	
10	12	9.9	
15	16.3	14.3	
20	21.9	20.4	
25	29.3	28.3	
27.3	33.2	33.2	
30	38.4		
35	50.2		48.0
40	64.4		62.5
45	84.5		81.0
50	107.1		103.6

Each value in columns 2 and 3, Table I, is the average of from two to six observations. Comparison of the values shown in columns 2 and 4, Table I, shows reasonable agreement between current and previous observations. In the course of these experiments considerable time and ef-

(1) A summary of a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, in the Department of Chemistry, in the Graduate College of the State University of Iowa, May, 1942.

(2) Present address, Eastman Kodak Co., Rochester, N. Y.

(3) Cornog and Karges, THIS JOURNAL, **54**, 1882 (1932).

(4) Smith and Menzies, *ibid.*, **32**, 1427 (1910).

(5) Pearce and Snow, *J. Phys. Chem.*, **31**, 231 (1927).

fort was expended in attempts to measure the vapor pressures of the labile beta form of iodine monochloride. While the labile form was readily obtained, transformation to the stable form was too rapid to permit vapor pressure measurements by this method.

The data in Table I may be used to calculate the heats of vaporization, sublimation and fusion of iodine monochloride by use of the Clausius–Clapeyron equation. By this means the heat of vaporization of iodine monochloride was found to be 9950 cal./mole, the heat of sublimation was 11,800 cal./mole. By difference the heat of fusion was found to be 1850 cal./mole.

2. Potassium Dichloroiodide, KCl·ICl or $KICl_2$.—Some earlier workers[6,7,8] have applied this name and formula to a compound, perhaps the hydrate, having a much lower melting point than the product obtained in this Laboratory. The hydrate is discussed in Part 7. Anhydrous potassium dichloroiodide is formed when equal molecular quantities of potassium chloride and iodine monochloride are joined in a glass-stoppered bottle and maintained at or somewhat above room temperature for several weeks. The initial mixture, nearly black in color, slowly changes to the bright orange-yellow characteristic of this compound. This compound melts sharply at 195° in a closed glass tube, and is so stable that a specimen was kept in a glass-stoppered bottle for more than one year with less than 1% loss in weight. The dissociation pressure of potassium dichloroiodide was measured by use of the method mentioned in Section 1 (see Table II).

TABLE II

THE DISSOCIATION PRESSURE OF POTASSIUM DICHLOROIODIDE

1 Temperature, °C.	2 Dissociation pressure, mm.
25	0.20
35	.40
40	.55
45	.70
50	1.00
55	1.35
60	1.80

The probable limit of accuracy of the figures in column 2 is 0.05 mm.

3. Potassium Trichlorodiiodide, KCl·2ICl or KI_2Cl_3.—This compound has not been reported previously. It is the stable solid phase formed when solutions of potassium chloride in iodine monochloride are brought to crystallization at temperatures below 45°. The needle-like crystals are nearly black when viewed in masses but are ruby-red in thin sections. In a closed tube these crystals melt at 45° but when exposed to the air at room temperature they decompose rapidly into potassium dichloroiodide crystals and iodine monochloride vapor. The composition of these crystals was determined by (a) determining the loss of weight on heating and (b) determining the iodine monochloride content. The latter was accomplished by converting the iodine monochloride in the crystals to free iodine by means of potassium iodide and titrating the free

(6) Wells and Wheeler, *Z. anorg. Chem.*, **1**, 442 (1892).
(7) Ephraim, *Ber.*, **50**, 1069 (1917).
(8) Cremer and Duncan, *J. Chem. Soc.*, 1857 (1931).

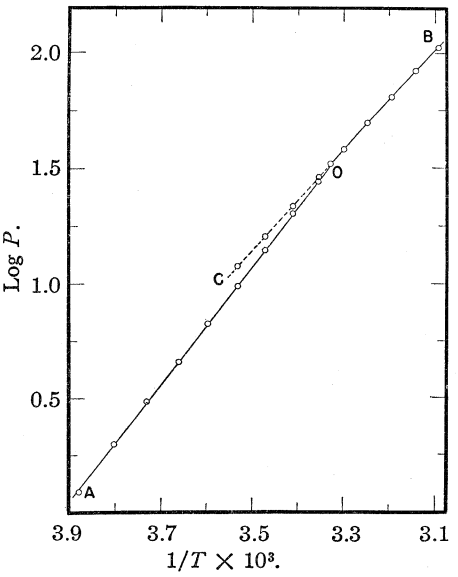


Fig. 1.—Vapor pressure of iodine monochloride: Point O is 27.3° the m. p. of ICl, AO vapor pressure solid ICl, OB is the vapor pressure of liquid ICl above the m. p., OC is the vapor pressure of undercooled ICl.

iodine with sodium thiosulfate solution. These data are shown in Table III.

TABLE III

(a) Loss of weight on heating	Run 1	Run 2
Sample taken, g.	0.954	0.351
Wt. KCl obtained, g.	.1726	.064
Calcd. wt. KCl·2ICl	.924	.343
(b) By $Na_2S_2O_3$ titration		
Wt. of sample, g.	0.200	
Vol. 0.0966 N $Na_2S_2O_3$, ml.	21.67	
Equiv. of oxidizing halogen	0.00209	
Calcd. equiv. of oxidizing halogen	.00200	

Inspection of Table III part (a) shows that the "Sample taken" is greater than the "Calculated weight of KCl·2ICl" by 3% in Run 1 and by 2% in Run 2. This discrepancy is probably caused by the fact that the potassium dichloroiodide crystals are very fine needles and were crystallized from iodine monochloride solution, some of which adhered to the crystals and was lost when the crystals were heated.

The method mentioned in Section 1 was used to get the dissociation pressure data shown in Table IV, which are represented graphically in Fig. 2.

In Fig. 2 the line OB represents the vapor pressure of the univariant system potassium trichlorodiiodide–potassium dichloroiodide–vapor. The line OA represents the univariant system potassium trichlorodiiodide–solution–vapor. The point O (45°) represents the invariant system potassium trichlorodiiodide–potassium dichloroiodide–solution–vapor. Below 45° potassium trichlorodiiodide is the stable phase in equilibrium, while above 45° potassium dichloroiodide (*cf.* Section 4) is the stable phase in equilibrium with saturated solutions. The apparent melting that occurs when potassium trichlorodiiodide is heated to 45° in a closed tube is, in reality, the decomposition of

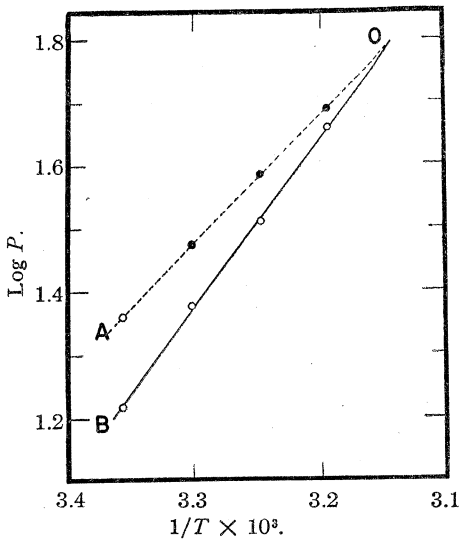


Fig. 2.—The line OB, dissociation pressure of KI_2Cl_3, intersects the dotted line, vapor pressure of saturated KI_2Cl_3 solution, at 45° the melting point of KI_2Cl_3.

solid potassium trichlorodiiodide into solid potassium dichloriodide and saturated solution of potassium dichloroiodide in iodine monochloride. Cremer and Duncan[9] have suggested similar ideas regarding the melting points of polyhalide compounds.

TABLE IV

DISSOCIATION PRESSURE OF POTASSIUM TRICHLORODIIODIDE

1	2	3
Temp., °C.	Dissociation pressure KI_2Cl_3, mm.	V. p. satd. soln. KI_2Cl_3 in ICl, mm.
15	8.3	...
25	16.5	23.05
30	23.8	29.8[a]
35	32.5	38.5[a]
40	45.6	48.5[a]

[a] Calculated by assuming that vapor pressure lowering is proportional both to the quantity of dissolved potassium chloride and to the vapor pressure lowering at 25° and by applying this assumption to the experimental data in Tables I, V and VI.

4. The Potassium Trichlorodiiodide–Potassium Dichloroiodide Transition Temperature.—The location of this transition temperature was learned by getting the solubility curves of the tri and pentahalide compounds and observing where the two curves intersected (see Table V and Fig. 3). Each solubility datum in Table V was obtained by saturating iodine monochloride, contained in a flask, with potassium chloride at a temperature well above that at which solubility was later measured. The flask containing the saturated solution was plugged with glass wool and placed in a thermostat in which the temperature variation did not exceed ±0.02°. Equilibrium between the solid and the solution was assumed to exist when the potassium chloride content of successive portions of saturated solution removed at twenty-four to forty-eight hour intervals were in agreement. The glass wool plugs served as filters in removing such portions. The potassium chloride content of portions thus removed was determined by weighing the portion, removing iodine chloride by heating and weighing the potassium chloride residue. Separate experiments were performed to establish the identity of the solid phases by methods previously described by Cornog and Olson[10] (see Table V and Fig. 3).

TABLE V

SOLUBILITY OF POTASSIUM CHLORIDE IN IODINE MONOCHLORIDE

1	2	3
	G. KCl dissolved in 100 g. ICl	
Temp., °C.	Solid phase KCl·2ICl	Solid phase KCl·ICl
15	4.70	
20	4.90	
25	5.20	
30	5.55	
35	5.95	
40	6.45	6.80
45		6.95
50		7.20
55		7.40
60		7.70
65		8.05

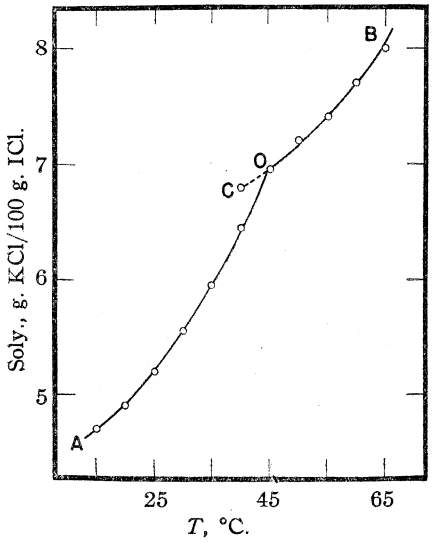


Fig. 3.—The solubility of potassium chloride in iodine monochloride: KCl·2ICl is the stable solid phase represented by AO. The point O (45°) is the transition temperature between KCl·2ICl and KCl·ICl. The line CO represents metastable and OB, stable, KCl·ICl.

5. The Vapor Pressure of Solutions of Potassium Chloride in Iodine Monochloride.—The general procedure described in Part 1 was used to obtain the vapor pressure of solutions of potassium chloride in iodine monochloride as recorded in Table VI and graphically represented in Fig. 4.

The calculations used in getting the figures in column 5 Table VI and the dotted line in Fig. 4 are based on the assumption that the dissolved potassium chloride, or the derived solute, is dissociated into two ions, each of which

(9) Cremer and Duncan, *J. Chem. Soc.*, 2251 (1931).

(10) Cornog and Olson, THIS JOURNAL, **62**, 3328 (1940).

TABLE VI

THE VAPOR PRESSURE OF SOLUTIONS OF POTASSIUM CHLORIDE IN IODINE MONOCHLORIDE AT 25°

1 Mole fraction KCl	2 P, mm.	3 $^{a}P_0 - P$, mm.	4 $(P_0 - P)/P_0$	5 $(P_0 - P)/P_0$ calcd.
0.005	29.00	0.30	0.010	0.0099
.02	28.30	1.00	.034	.0392
.04	27.25	2.05	.070	.0769
.05	26.45	2.85	.097	.0952
.06	25.85	3.45	.118	.1131
.0875	24.05	5.25	.197	.1608
.1015[b]	23.05	6.25	.213	.1843

[a] $P_0 = 29.3$ (Table I). [b] Saturated.

acts as a perfect solute. At the lower concentrations, the observed vapor pressure lowering is less than, and at higher concentrations, greater than the calculated values.

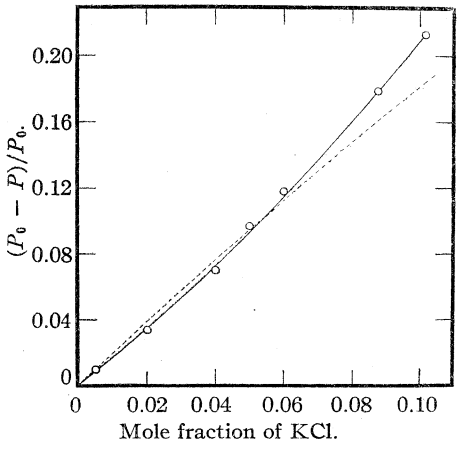


Fig. 4.—The vapor pressure of KCl–ICl solutions. The solid line represents experimentally determined values of vapor pressure lowerings. The dotted line represents calculated vapor pressure lowerings assuming dissociation of the solute into two different ions.

Although these data are probably insufficient in quantity and precision to warrant calculations of activities, they serve as the basis of the tentative conclusion that potassium chloride, or its derivative, is ionized in iodine monochloride. Further, since the crystalline material separating from the solution at 25° is represented by the formula KI_2Cl_3, the tentative inference is drawn that the ions in solution are probably represented by the formula K^+ and $I_2Cl_3^-$. The data in Table VI are also used in plotting curve AB Fig. 5, Section 6.

6. The System Potassium Chloride–Iodine Monochloride.—The vapor pressure data in the preceding sections have been used to construct the vapor pressure–composition diagram of the system potassium chloride–iodine monochloride at 25° as shown in Fig. 5.

The similarity in general outline between Fig. 5 and corresponding diagrams for hydrate systems is obvious.

7. Potassium Dichloroiodide Monohydrate, $KCl{\cdot}ICl{\cdot}H_2O$.—This compound is obtained when the product mentioned in Section 2 is recrystallized from water solution. The hydrated crystals thus obtained are much like potassium dichromate in general appearance and melt at 43°

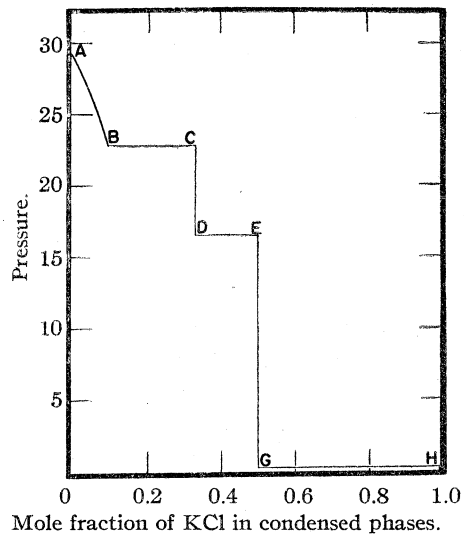


Fig. 5.—Vapor pressure–composition diagram of the system KCl–ICl at 25°: AB represents the vapor pressure of unsaturated solutions of KCl in ICl. At B solid KI_2Cl_3 begins to form and continues to C where the liquid phase disappears. DE represents the KI_2Cl_3–$KICl_2$ equilibrium at constant pressure. At E only $KICl_2$ is present. GH represents the $KICl_2$–KCl equilibrium at constant pressure. At H only KCl is present.

in a closed tube. The composition of the hydrated crystals was estimated by heating weighed portions in an oven at 110° to constant weight. These data follow.

	1	2
Weight of sample taken, g.	3.572	2.342
Weight of KCl residue, g.	1.045	0.686
Calcd. corresponding wt. $KICl_2$	3.321	2.180
Calcd. corresponding wt. $KICl_2{\cdot}H_2O$	3.573	2.346

An indication of the water content of the hydrated crystals was given by the weight of the residue obtained when crystals were dried in a desiccator over phosphorus pentoxide.

Weight of sample, g.	1.570
Weight of residue from drying with P_2O_5	1.452
Weight of sample calcd. from wt. residue	1.562

The melting point of the material changed from 43° before drying to approximately 195° after drying. A small quantity of iodine monochloride was doubtless lost in drying.

The dissociation pressure of the monohydrate, Table VII, was measured in such a way as to distinguish between the partial pressures of water and of iodine monochloride.

The segregation and estimation of the partial pressures of water vapor and iodine monochloride vapor which together made up the dissociation pressure of the monohydrate, was accomplished by passing the vapor from dissociation through two absorbers arranged in series. The first absorber, containing phosphoric anhydride, retained water vapor but passed iodine monochloride vapor, while the second absorber contained soda lime and retained iodine monochloride vapor.

TABLE VII

THE DISSOCIATION PRESSURE OF $KCl \cdot ICl \cdot H_2O$

1	2	3	4	5
Temp., °C.	P_{ICl}, mm.	P_{H_2O}, mm.	$P = P_{ICl} + P_{H_2O}$, mm.	Interpolated Cremer and Duncan dissociation pressure, mm.
25	0.1	9.9	10.0	9.2
30	.2	15.0	15.2	14.2
35	.4	20.6	21.0	20.6
40	.7	29.6	30.3	29.5

The data in column 2 show that the partial pressure of iodine monochloride in the hydrated compound is virtually the same as the dissociation pressure of anhydrous potassium dichloroiodide (see Part 2). Comparison of columns 2 and 3 indicates that the dissociation pressure of the hydrate is due almost entirely to the partial pressure of water vapor. Comparison of columns 4 and 5 indicates that the substance measured by Cremer and Duncan[11] was probably the hydrate.

The preparative methods described by Ephraim[7] were repeated in this Laboratory. The compound thus obtained was identical in properties with the monohydrate described above.

8. Potassium Dibromoiodide, $KBr \cdot IBr$ or $KIBr_2$, and Potassium Dibromoiodide Monohydrate, $KBr \cdot IBr \cdot H_2O$ or $KIBr_2 \cdot H_2O$.—Potassium dibromoiodide was prepared by Cremer and Duncan[1] by exposing "dry" potassium iodide to bromine vapors in a desiccator for three days. The product thus obtained melted at 58–60° and was converted to potassium dichloroiodide by chlorination. When this work was repeated in this Laboratory, several weeks were required for potassium iodide to absorb the theoretically required quantity of bromine, the resulting potassium dibromoiodide melted in a closed tube at 180° and the rate of conversion to the dichloroiodide by chlorination was so slow as to render the method impractical. Upon recrystallizing the potassium dibromoiodide of melting point 180° from water solution, the resulting crystals melted at 58° in a closed tube. The composition of the material crystallized from water solution is indicated by the following data.

A. Loss of weight on heating crystals ($KIBr_2 \cdot H_2O$)

Weight of sample taken, g.	0.961
Weight of KBr residue, g.	.332
Calculated weight assuming $KIBr_2$	.910
Calculated weight assuming $KIBr_2 \cdot H_2O$	.960

B. Loss of weight $KIBr_2 \cdot H_2O$ by drying over P_2O_5

Weight of sample taken, g.	3.290
Weight of residue after drying with P_2O_5	3.104
Weight of sample computed from wt. of residue assuming $KIBr_2H_2O$	3.280

These data and the melting point data together indicate that the low melting substance is potassium dibromoiodide monohydrate while the high melting substance is potassium dibromoiodide.

Potassium dibromoiodide of melting point 180° is expeditiously prepared by joining equivalent quantities of potassium iodide and bromine in a glass-stoppered bottle, at room temperature. The initially nearly black mixture begins to assume the bright red color of potassium dibromoiodide in a day or two and the reaction goes to completion in about a week.

(11) Cremer and Duncan, *J. Chem. Soc.*, 2245 (1931).

Summary

1. A dynamic method has been used to measure the vapor pressure of iodine monochloride between −15 and 50°. These data have been used to compute the heats of fusion, vaporization and sublimation of iodine monochloride.

2. Potassium dichloroiodide has been prepared by the direct union of iodine monochloride and potassium chloride. The dissociation pressure of this compound has been measured.

3. A new compound, potassium trichlorodiiodide, has been prepared by direct union of iodine monochloride and potassium chloride at temperatures below 45°. The dissociation pressure of the compound has been measured.

4. Solubility curves for potassium dichloroiodide and potassium trichlorodiiodide in iodine monochloride have been plotted and the transition temperature between these compounds has been established at 45° from the intersection of these curves.

5. The vapor pressure–composition relations for the system potassium chloride–iodine monochloride have been formulated.

6. Methods for preparing both the anhydrous and hydrated forms of potassium dichloroiodide and potassium dibromoiodide have been described. The melting points of all four different compounds have been determined.

IOWA CITY, IOWA RECEIVED JUNE 1, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE STATE COLLEGE OF WASHINGTON]

Compound Formation between the Isomeric Phenylphenols and Pyridine

BY STEWART E. HAZLET AND RAYMOND W. MORROW

In the course of some synthetic work which was reported earlier,[1] heat changes were noted when the phenylphenols were dissolved in pyridine, and the effects for the isomeric phenols were different: (a) with *o*-phenylphenol, there was evidence of a definitely exothermic reaction; (b) practically no temperature change was noted when the meta isomer was dissolved in the base; (c) the temperature was lowered slightly upon dissolving *p*-phenylphenol in pyridine.

In an attempt to gain some insight into the types of changes involved in these situations, especially to determine the character of compound formation if any, thermal analyses of the three binary systems were made—freezing point-concentration curves were obtained—in much the same manner as in Kendall's studies.[2]

Experimental Part[3]

A. Purification of Materials

Pyridine.—Pyridine was allowed to stand over sodium hydroxide pellets for from six to eight weeks and then distilled through a 30-cm. Vigreux column. The middle fraction with a boiling range of not over 0.5° was collected. Different lots had $n^{21}D$ varying between 1.5089 and 1.5087.[4] It was stored in a brown glass-stoppered bottle, and over a period of two months the change in $n^{21}D$ was never more than 0.0002. The freezing point (from cooling curve) was −41.7°.[5]

***o*-Phenylphenol.**—Eastman Kodak Company best grade product was recrystallized from ligroin, which had been dried over sodium hydroxide pellets and distilled from 70 to 80°. After standing in a vacuum desiccator containing paraffin shavings, the product had a freezing point (from cooling curve) of 57.1°.[6]

***m*-Phenylphenol.**[7]—The *m*-phenylphenol was recrystallized from carbon tetrachloride ("analytical reagent") and allowed to stand in a vacuum desiccator in the same manner as described for the ortho isomer. The freezing point (from cooling curve) of the product was 75.3°.[8]

***p*-Phenylphenol.**—Eastman Kodak Co. *p*-phenylphenol was recrystallized from carefully dried and redistilled benzene and placed in a desiccator as indicated for the other phenols. The freezing point (from cooling curve) of this material was 165.1°.[9]

B. Apparatus

The apparatus used in this work was essentially the same as that conventionally employed in such experiments. It consisted of a 2 cm. × 15 cm. "Pyrex" test-tube fitted with a two-hole cork covered with tin foil. Through one hole there was the appropriate thermometer and through the other there was a short glass sleeve through which the stirrer passed. This inner vessel was surrounded by another test-tube with a diameter about 7 mm. greater than the smaller one; this provided an air jacket to smooth out and to retard the rate of cooling or heating. The whole apparatus was securely clamped in a larger beaker or unsilvered Dewar flask which served as a control bath. The materials in this bath were varied to suit the range of temperatures involved; in order of decreasing temperature they were: cottonseed oil, water, ice–water, ice–salt–water, and ethyl acetate–methanol–solid carbon dioxide. For temperatures above −10°, a set of 15-cm. Anschütz pre-

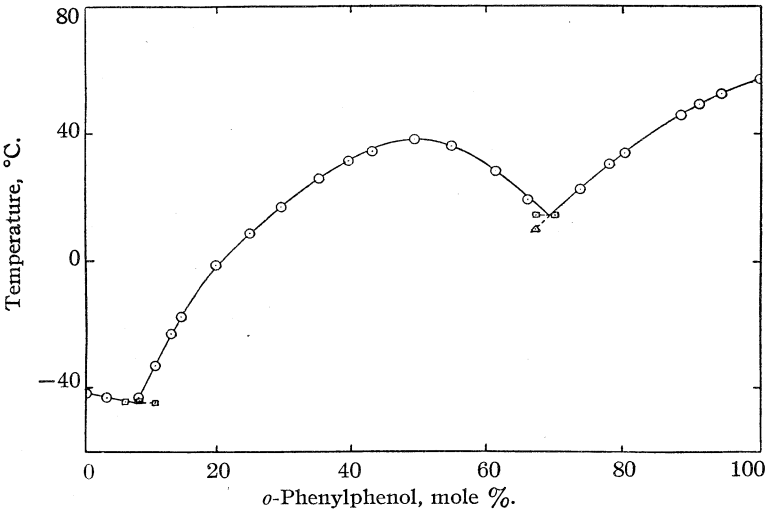


Fig. 1.—*o*-Phenylphenol + pyridine: ⊙, freezing point; ⊡, eutectic temperature; △, freezing point, metastable state.

(1) Hazlet, THIS JOURNAL, **59**, 287 (1937).

(2) Kendall, *ibid.*, **36**, 1222 (1914).

(3) All temperatures, unless otherwise indicated, are corrected.

(4) (a) Brühl, *Z. physik. Chem.*, **16**, 215 (1895), reported $n^{21}D$ 1.50919. (b) The values reported here were determined in the same manner and with the same apparatus as other data reported by Schutz, THIS JOURNAL, **61**, 2691 (1939).

(5) The reported freezing point is −42°; Zawidzki, *Chem. Zeit.*, **30**, 299 (1906), and Weger, *Z. anorg. Chem.*, **22**, 394 (1900); "Beilstein's Handbuch der organischen Chemie," 4th ed., Julius Springer, Berlin, 1935, Vol. 20, p. 183.

(6) Jacobson, Franz and Hönigsberger, *Ber.*, **36**, 4080 (1903), reported m. p. 56°.

(7) The *m*-phenylphenol used in this work was generously furnished by the Dow Chemical Company, Midland, Michigan.

(8) Briner and Bron, *Helv. Chim. Acta*, **15**, 1239 (1932), reported m. p. 76°.

(9) Latschinoff and Engelhardt, *Ber.*, **6**, 194 (1873), reported m. p. 164–165°.

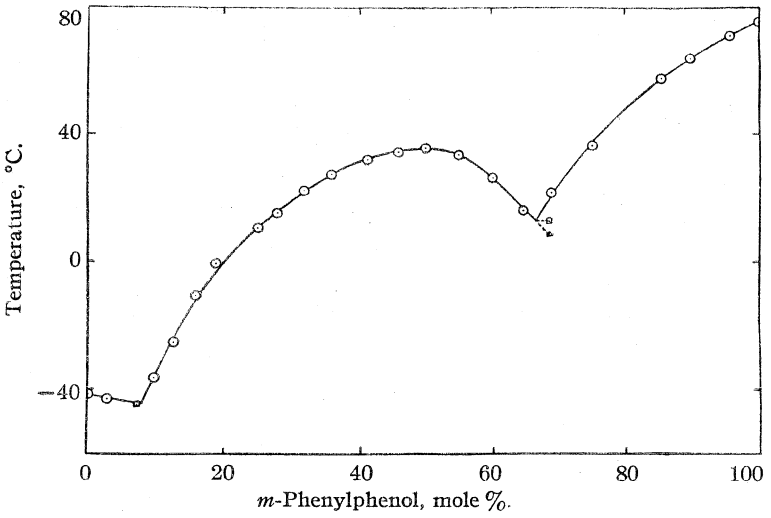


Fig. 2.—*m*-Phenylphenol + pyridine: ⊙, freezing point; ⊡, eutectic temperature; ⧋, freezing point, metastable state.

cision thermometers graduated in one-fifth degrees was used for determining freezing points. These were calibrated against a thermometer certified by the United States Bureau of Standards. For temperatures below −10°, a −50 to 50° alcohol thermometer graduated in one-fifth degrees was used. This thermometer was calibrated against the freezing points of mercury and water. The temperature of the outer bath was determined by an ordinary laboratory thermometer when above 0° and by a copper–constantan thermocouple when below that temperature. As an aid in observing temperatures, which were read to the nearest 0.1° through a magnifying glass, and the condition of the material in the reaction tube, a source of light was placed in the rear of the apparatus. In the study of the *p*-phenylphenol–pyridine system where temperatures near or above the boiling point of pyridine were involved, the stirrer was dispensed with and only a thermometer in a tight-fitting cork was used; mixing was accomplished by shaking the melted material; no loss of pyridine was detected.

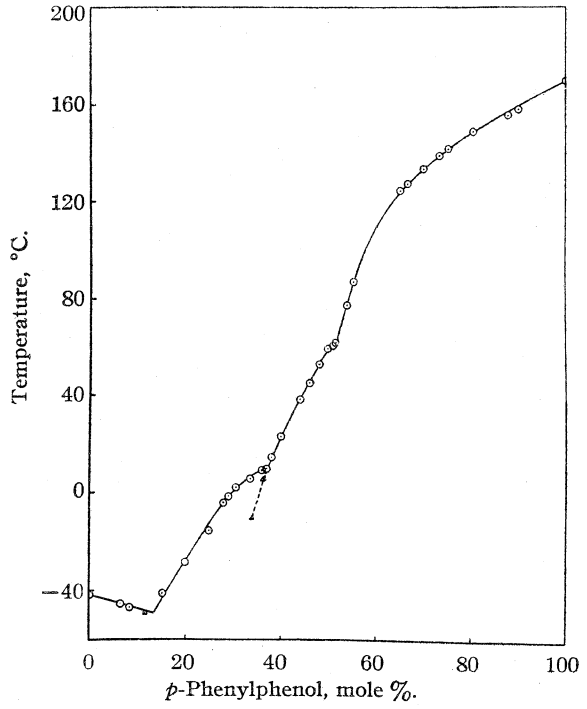


Fig. 3.—*p*-Phenylphenol + pyridine: ⊙, freezing point; ⊡, eutectic temperature; ⧋, freezing point, metastable state.

C. Procedure

The phenols were weighed by difference and placed in the freezing point apparatus. The approximate quantity of pyridine was delivered to the apparatus from a weight buret, and the exact weight of the sample was determined by difference. In general, the weight of each mixture was 6 to 8 g., but for those samples with compositions within 10 mole % on either side of eutectics the amount was doubled or trebled.

A mixture was warmed slightly if necessary to effect solution, thoroughly stirred, and, while stirring was continued, cooled slowly to obtain an approximate freezing point. From the information thus obtained, the bath was regulated to an appropriate temperature, and the freezing point of the mixture was determined from the cooling curve.

For compositions representing a nearly pure compound there was very little tendency to supercool, but for other compositions considerable supercooling was encountered. To induce crystallization, seeding with a crystal of the solid phase was done at approximately the expected freezing point.

D. Results

Below in tabular and graphical form the experimental data are shown. Compositions, as indicated, are shown in mole %.

Discussion

From the graphical representations of the three systems studied the following conclusions can be drawn.

A. Pyridine and *o*-phenylphenol form a compound, $C_5H_5N \cdot C_{12}H_{10}O$, f. p. 38.2°, which appears to be quite stable. The two eutectics are: (1) 7.5 mole % *o*-phenylphenol, f. p. −44.7°, and (2) 69.3 mole % *o*-phenylphenol, f. p. 14.3°. The determination of freezing points near the eutectic at 69.3 mole % was difficult; supercooling often caused the phenol to crystallize in the metastable state.

B. Pyridine and *m*-phenylphenol form one compound, $C_5H_5N \cdot C_{12}H_{10}O$, f. p. 35.5°, much the same as the ortho isomer. In this case the two

TABLE I

THE SYSTEM: PYRIDINE AND *o*-PHENYLPHENOL

o-Phenylphenol, mole %	F. p., °C.[a]	*o*-Phenylphenol, mole %	F. p., °C.[a]
0.00	−41.7	49.39	38.2
3.21	−43.3	54.88	36.0
(5.17)	(−44.7)(E_1)	61.39	28.2
8.10	−43.1	66.26	19.1
(8.10)	(−44.4)(E_1)	(67.22)	(9.8)(M)
10.52	−33.1	(67.22)	(14.4)(E_2)
(10.52)	(−44.8)(E_1)	(70.13)	(14.3)(E_2)
13.05	−23.0	73.88	22.4
14.54	−17.8	78.11	30.4
19.81	− 1.4	80.34	33.9
24.86	8.8	88.53	45.9
29.52	17.0	91.24	49.4
35.10	25.8	94.41	52.5
39.65	31.5	100.00	57.1
43.11	34.5		

[a] In this table (E_1) refers to the first eutectic temperature obtained from the mixture with composition as shown, (E_2) to the second, and (M) to the temperature for the crystallization of the component in the metastable state.

TABLE II

THE SYSTEM: PYRIDINE AND *m*-PHENYLPHENOL

m-Phenylphenol, mole %	F. p., °C.[a]	*m*-Phenylphenol, mole %	F. p., °C.[a]
0.00	−41.7	45.68	34.3
2.87	−43.0	49.75	35.5
(7.21)	(−44.3)(E_1)	54.87	33.3
9.76	−36.3	59.86	26.0
12.54	−25.3	64.61	15.7
15.92	−10.9	(68.68)	(8.8)(M)[b]
18.71	− 0.9	(68.68)	(12.6)(E_2)
24.97	10.4	68.98	21.5
27.67	15.2	74.92	36.5
31.62	22.2	85.36	57.9
35.75	27.2	89.87	64.0
41.19	31.9	95.72	71.1
		100.00	75.3

[a] See note, Table I. [b] Obtained by seeding the mixture with compound $C_6H_5N \cdot C_{12}H_{10}O$.

eutectics are: (1) 8 mole % *m*-phenylphenol, f. p. −44.3° and (2) 66.5 mole % *m*-phenylphenol, f. p. 12.6°. Freezing points of mixtures with between 30 and 70 mole % *m*-phenylphenol were got only by seeding the liquid with a sample of material obtained by freezing a mixture of the latter composition in carbon dioxide–ethyl acetate.

C. Pyridine and *p*-phenylphenol appear, from the shape of the graph, to form two compounds. Both are unstable at their melting points and crystallize only from solutions containing an excess of pyridine. A sample (approximately 7 g.) of one of these, apparently $C_5H_5N \cdot C_{12}H_{10}O$, was cooled to −5° (uncor.); at this temperature it

TABLE III

THE SYSTEM: PYRIDINE AND *p*-PHENYLPHENOL

p-Phenylphenol, mole %	F. p., °C.[a]	*p*-Phenylphenol, mole %	F. p., °C.[a]
0.00	−41.7	44.00	38.7
6.34	−45.5	46.03	45.6
8.40	−46.8	48.12	53.0
(11.42)	(−49.3)(E_1)	49.83	59.7
15.20	−41.3	51.13	61.0
19.98	−28.4	51.64	62.1
25.14	−15.2	53.80	77.4
28.13	− 3.3	55.31	87.1
29.28	− 1.1	65.09	124.2
30.86	2.5	66.64	127.0
33.76	6.0	69.84	133.0
(33.97)	(−10.5)(M)	73.12	138.5
36.13	9.8	74.86	141.4
(36.57)	(6.0)(M)	80.46	148.4
37.15	10.4	87.77	155.5[b]
38.15	15.2	90.06	157.6[b]
40.05	23.6	100.00	165.1

[a] See note, Table I. [b] Uncorrected.

was in the form of a crumbly, snow-white solid. It was allowed to warm slowly. At 8–9° (uncor.) it showed signs of softening—the snow-white solid became rather glassy; this corresponds approximately to the incongruent melting point. As the temperature was increased, the material became soft and sticky at 15–17° (uncor.); this may be the approximate melting point of the compound. Between 55 and 60° (uncor.), which corresponds approximately to a composition of 50 mole % *p*-phenylphenol as read from the freezing point curve of the system, the last crystals disappeared. A small sample of the other material, apparently $C_5H_5N \cdot 2C_{12}H_{10}O$, was isolated, excess pyridine was absorbed on porous plate, and its melting range was determined in a capillary tube. It softened at 62–64° (uncor.) which corresponds to its incongruent melting point. On raising the temperature, the material showed signs of further change over the range of 85–90° (uncor.); possibly this corresponds to the approximate melting point of the material. Above 90° the system behaved as an equilibrium mixture and the last crystals disappeared at 125–128° (uncor.), which corresponds to the freezing point of the system containing approximately 67 mole % of the phenol. The only eutectic is 13.3 mole % *p*-phenylphenol, f. p. −49.3°.

Summary

The freezing point–composition diagrams have been determined for the two component systems of pyridine and of the three isomeric phenyl-

phenols. With (1) pyridine and *o*-phenylphenol: one compound, $C_5H_5N \cdot C_{12}H_{10}O$, is formed; (2) pyridine and *m*-phenylphenol: one compound, $C_5H_5N \cdot C_{12}H_{10}O$, is formed; (3) pyridine and *p*-phenylphenol: two compounds, (a) $C_5H_5N \cdot C_{12}H_{10}O$ and (b) $C_5H_5N \cdot 2C_{12}H_{10}O$, are formed; both are unstable at their melting points.

PULLMAN, WASHINGTON RECEIVED JULY 20, 1942

[CONTRIBUTION FROM THE GENERAL LABORATORIES OF THE UNITED STATES RUBBER COMPANY, PASSAIC, NEW JERSEY]

An Electrophoretic Study of the Proteins in Rubber Latex Serum

BY CHARLES P. ROE AND ROSWELL H. EWART

The proteins in rubber latex serum (*Hevea brasiliensis*) have been the subject of several researches during the past fifteen years. Some of this work has been concerned with the chemical properties of the proteins[1] and some with their electrophoretic properties.[2] Recently, the improvements introduced by Tiselius[3] in the electrophoretic technique have made it possible to increase the precision and significance of electrophoretic measurements very considerably. The work here reported is part of a program of electrophoretic research on latex proteins. This program was initiated in an attempt to obtain information which would be helpful in correlating protein behavior with the colloidal and other properties of latex.

Experimental

The Electrophoresis Apparatus.—The apparatus was supplied by the Klett Manufacturing Company of New York City and was built according to specifications furnished by Dr. L. G. Longsworth of the Rockefeller Institute in New York. Details may be found in Longsworth's publications.[4] A few modifications of the apparatus are described in the following paragraphs.

Illumination System.—Many latex serum samples used in this work did not transmit the visible lines of the mercury spectrum very well. In some cases this was on account of slight turbidity, in others, on account of color. The transmission coefficient of such solutions was found to be much greater in the red. Consequently, the mercury arc supplied with the apparatus was replaced by a 500-watt Tungsten filament projection lamp in conjunction with a Corning no. 246 lighthouse red filter. The object of this arrangement was to produce the most uniform possible exposure of photographic plate over the entire length of the cell image when the cell contained either a turbid or colored protein solution separated from a colorless buffer solution by a boundary in the exposed part of the cell. This expedient did not in all cases yield perfect results, but it was much more generally practicable than the use of the mercury arc, and well-defined Schlieren patterns were obtained.[5] Wratten and Wainwright Contrast Thin Coated Panchromatic plates were used. They are insensitive at wave lengths greater than 6800 Å. and the red filter cuts out all light of wave length less than 5600 Å. These figures are extreme values. The range of practical intensities lies between 5800 and 6600 Å.

In using the mercury arc in cases where this was feasible, it was found advantageous to introduce a Corning yellow–yellow filter in order to filter out the violet part of the mercury spectrum. This resulted in the production of straighter base lines in the schlieren diagrams through the elimination of a small dispersion effect due to some undetermined cause in the optical system.

The Electrodes and Source of Potential.—The silver–silver chloride electrodes were replaced by copper electrodes dipping into a concentrated copper sulfate solution. These electrodes are perfectly reversible and are easier to prepare than the silver–silver chloride system. In addition, they require no special care or attention after they are made. The authors used no. 14 copper wire wound into a compact flat coil and soldered to a small copper tube which was cemented to a piece of glass tubing just as in the case of the silver electrodes. When an alkaline buffer solution was used, a layer of saturated sodium sulfate solution was introduced between the buffer and copper sulfate solutions in order to prevent the formation of insoluble basic copper compounds at the liquid junction.

The potential difference applied to the electrophoresis cell and electrodes was furnished by a bank of 45-volt heavy duty B batteries. Conditions were always adjusted so as to make the power consumption less than three watts in the cell and electrode system.

The field strength within the electrophoresis cell was calculated from measured values of the current passing, the specific conductance of the solution and the cross section of the cell.

The Compensating Device for Shifting Boundaries.—The motor-driven compensating device was replaced by a gravity feed through a one-meter U-shaped length of capillary glass tubing of 1-mm. inside diameter which was connected at one end to the closed electrode vessel and at the other end to a separatory funnel which served as a reservoir.

(1) Bishop, *Malayan Agr. J.*, **15**, 27 (1927); Bondy and Freundlich, *Rubber Age*, **44**, 377 (1938); Kemp and Straitiff, *J. Phys. Chem.*, **44**, 788 (1940).

(2) I. Kemp and Twiss, *Trans. Faraday Soc.*, **32**, 890 (1936).

(3) Tiselius, *ibid.*, **33**, 524 (1937).

(4) Longsworth, THIS JOURNAL, **61**, 529 (1939); Longsworth and MacInnes, *Chem. Rev.*, **24**, 271 (1939).

(5) Verbal communication from Prof. J. W. Williams has informed the writers that a similar expedient has also been used successfully in his laboratory.

Ammonia Preserved Serum from Sumatra Normal Latex.—This was a one-gallon lot which was prepared on the plantations of the U. S. Rubber Company in Sumatra by freezing fresh unpreserved normal Hevea latex. Freezing caused complete coagulation of the rubber into a coherent clot. After thawing, the rubber-free serum was expressed, preserved with 2% ammonia and shipped to America in a stoppered glass container.

Serum from Unpreserved Sumatra Normal Latex.—Fresh unpreserved normal Hevea latex was frozen on the plantations in Sumatra and shipped in the frozen state to America. After this material had been thawed, the rubber-free serum was expressed and refrozen as quickly as possible to prevent deterioration. Serum thus prepared and containing no chemical preservative had a light straw color and a perfectly sweet odor. Its *p*H value was 6.4 at 25°. When kept stored in glass in the frozen state at −20° it retained these characteristics over a period of months with no signs of any deterioration.

Serum from Unpreserved Normal Florida Latex.—This latex (Hevea) was treated exactly like that prepared in Sumatra but it originated in the Plant Introduction Garden of the United States Department of Agriculture, Coconut Grove, Florida. The *p*H value of this serum was also 6.4 at 25°.

Direct Preparation of Latex Serum for Electrophoresis.—All electrophoresis determinations were made in solutions which were well buffered so as to secure adequate *p*H control. Each serum sample was, therefore, dialyzed exhaustively against the appropriate buffer solution at the temperature of the Tiselius thermostat. Conductance measurements were used to determine the extent of dialysis. Conductance and *p*H measurements (glass electrode) were made at the temperature of the cold thermostat which was held at +1°.

Concentration of Latex Serum Proteins.—It was necessary in several cases to have a more concentrated solution of the serum proteins than that in which they naturally occur in serum from frozen latex. For this purpose dry serum solids were prepared by the technique of vacuum sublimation of rubber-free frozen serum. This technique has been used extensively in the past by workers with animal sera.[6] The latex serum solids thus obtained contained some hygroscopic material which could be largely removed by dialysis with distilled water for twenty-four hours before starting the vacuum sublimation process. Dialysis could not be carried farther than this without causing partial flocculation and denaturation of the proteins. When properly prepared, the dried serum solids showed no outward signs of deterioration and could be completely redissolved in aqueous solutions at all *p*H values at which the original serum was stable. All concentrated latex protein solutions used in this work were prepared from completely vacuum dried samples. Dialysis against buffer solutions was carried out prior to electrophoresis in the case of these concentrated solutions just as in the case of the native serum samples.

Buffer Solutions.—All buffer solutions were made by use of uni-univalent electrolytes at an ionic strength equal to 0.1. In the following table the acid–base combinations used to cover the various segments of the *p*H interval between 2.0 and 10.5 are listed. *p*H values were measured

*p*H Interval	Acid	Base
2 – 4	HCl	Glycine
4 – 5.5	Acetic	NaOH
5.5– 7	Cacodylic	NaOH
7 – 8.5	HCl	Triethanolamine
9 –10.5	Glycine	NaOH

with the glass electrode at 1°. In order to calibrate the electrode, it was assumed, following Harned and Ehlers[7] that the ionization constant of acetic acid at 0° was $10^{-4.79}$ at an ionic strength of 0.1.

Results and Discussion

General Remarks on the Interpretation of Schlieren Diagrams.—The detailed theory of the schlieren scanning method of measuring refractive index gradients has been described elsewhere[4,8] It will be recalled that in electrophoretic schlieren diagrams the position and the time rate of displacement of a given peak along the axis of abscissas give, respectively, a direct index of the position and the rate of motion of the corresponding protein boundary within the cell. From this may be calculated the electrophoretic mobility by the introduction of the appropriate magnification and electric field factors. Each peak corresponds to a separate boundary. The ordinate of a schlieren diagram is proportional to the gradient of refractive index, and hence the area under the diagram included between two abscissas is proportional to the total refractive index change between the two abscissas. If the relationship between concentration and refractive index is known, then the area under a schlieren diagram, upon introduction of the proper optical factors, gives a measure of the concentration change of solute from one part of the cell to another.

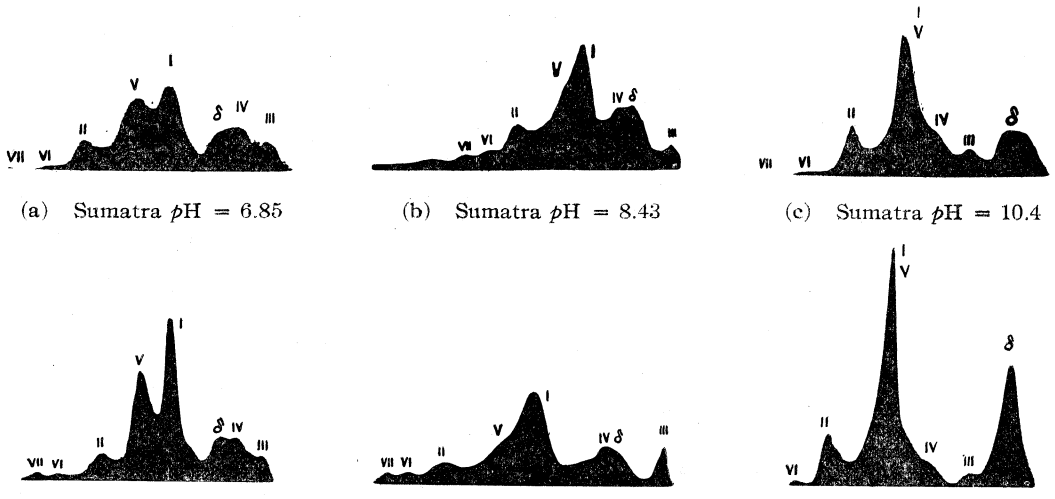
Protein Components of Latex Serum.—Figure 1 shows electrophoretic schlieren diagrams (rising boundaries) at three *p*H levels for each of two samples of protein from Sumatra and Florida unpreserved whole latex serum. The presence of seven resolvable components is evidenced by inspection at the *p*H values of 6.85 and 8.43. Only six components are resolvable at *p*H 10.4, since I and V have the same mobility at this point.

Complete electrophoretic schlieren diagrams for the proteins in whole latex serum can be obtained only with concentrated serum, since two of the minor components (VI and VII) are present in such small quantities that they are not detect-

(6) Mudd, Reichel, Flosdorf and Eagle, *J. Immunol.*, **26**, 341 (1934).

(7) Harned and Ehlers, THIS JOURNAL, **54**, 1350 (1932).

(8) Lamm, *Z. physik. Chem.*, **A138**, 313–331 (1928).



(a) Sumatra *p*H = 6.85 (b) Sumatra *p*H = 8.43 (c) Sumatra *p*H = 10.4

(d) Florida *p*H = 6.85 (e) Florida *p*H = 8.43 (f) Florida *p*H = 10.4

Fig. 1.—Schlieren diagrams showing comparison of Florida and Sumatra latex serum proteins, all samples concentrated 3/1.

able at their natural concentrations in serum from frozen latex.

It is not known at present how to classify these electrophoretically resolvable components in terms of usual protein nomenclature. So far as the authors are aware, the only classification which has ever been made depends upon the separation of the whole protein into the so-called glutelin, globulin and albumin fractions.[1] Probably the protein components of unpreserved latex serum can be fitted into this classification, but it will require a combination of analytical results with those of electrophoresis experiments.

Comparison of Florida and Sumatra Latex Serum Proteins.—The schlieren diagrams of Fig. 1 show that the Florida and Sumatra protein samples are electrophoretically very similar in most respects. The number of resolvable components is the same, and the mobilities and relative abundance of the various components are nearly the same. The mobility figures are given in Table I and are represented graphically in Fig. 2.

Inspection of the diagrams in Fig. 1 shows that the relative abundance is about the same in the sera from the two sources and also that the total protein content is not much different in the two cases. A quantitative comparison of the areas under the schlieren diagrams is impossible since through an unfortunate oversight base line photographs were not recorded in all cases. No attempt has been made to fit the correct base lines in any case, since no use is made of them. The principal difference between the Florida and Sumatra diagrams lies in the sharpness of the peaks. The sharper peaks in the Florida sample indicate a greater degree of electrophoretic homogeneity of the several components in this than in the Sumatra sample. The cause is not definitely known, but the difference probably indicates more sanitary handling and less incipient deterioration before freezing on the Florida experimental plot than on the Sumatra plantation.

TABLE I

MOBILITY *versus* *p*H VALUES FOR TOTAL SERUM PROTEINS FROM SUMATRA AND FLORIDA LATEX

	Mobility in microns per second per volt per cm.					
	*p*H = 6.85		*p*H = 8.43		*p*H = 10.4[a]	
Component	Sumatra	Florida	Sumatra	Florida	Sumatra	Florida
I	−0.200	−0.210	−0.355	−0.335	−0.575	−0.580
II	− .590	− .615	− .690	− .680	− .880	− .980
III	+ .255	+ .240	+ .120	+ .110	− .230	− .165
IV	+ .090	+ .120	− .150	− .160	Not resolved	
V	− .335	− .360	Not resolved		− .575	− .580
VI	− .800	− .825	− .850	− .825	−1.18	−1.21
VII	− .955	− .915	− .985	− .915	−1.39	−1.53

[a] This *p*H value is actually an average figure. The Sumatra values were measured at *p*H 10.2 and the Florida values at 10.6.

The similarity of schlieren patterns obtained from latex sera with such widely different geographical origins is not surprising. Workers with human sera[9] have found that the schlieren pattern of normal human serum is nearly independent of the source of the serum and that only abnormal or pathological conditions cause large departures from the characteristic normal pattern. The results here reported on latex serum proteins are not sufficiently extensive to be accepted as proof that the geographical origin of latex from a healthy tree has no effect on the schlieren pattern of the serum proteins, but the close similarity of the patterns here presented, taken together with the findings of investigators in other related fields, makes such an assumption seem plausible. If this is true, it is a matter of some practical interest in latex technology. It would indicate that variations in normal latex from healthy trees cannot be ascribed to qualitative variations in the protein content of the serum prior to tapping. Variations traceable to the proteins must be due, then, to variations in handling conditions and preservation procedures.

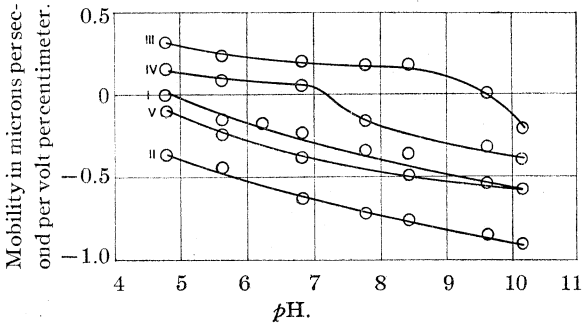


Fig. 2.—Mobility–*p*H curves for five protein components of latex serum.

Relationship between *p*H and Electrophoretic Mobility.—Figure 2 shows the mobility–*p*H curves for five of the seven protein components of whole unpreserved latex serum. These curves were plotted from data obtained from the electrophoresis of unconcentrated serum before the discovery of the minor components VI and VII, which were detectable only after concentration. It was found impossible to follow these curves below *p*H 4.79. Some insoluble material was precipitated below *p*H 5.7, but schlieren diagrams continued to exhibit peaks corresponding in an orderly way to five components down to *p*H 4.79. Below this level it is not possible on the basis of data in hand to correlate the diagrams obtained with the behavior of the proteins above *p*H 4.79.

(9) Longsworth, Shedlovsky and MacInnes, *J. Exptl. Med.*, **70**, 399–413 (1939); Moore and Lynn, *J. Biol. Chem.*, **141**, 819 (1941).

TABLE II

MOBILITY *versus* *p*H DATA ON SUMATRA LATEX SERUM PROTEINS

*p*H	Component..I	II	III	IV	V
4.79	0	−0.360	+0.330	+0.160	−0.105
5.66	− .150	− .445	+ .245	+ .089	− .245
6.85	− .230	− .630	+ .200	+ .064	− .385
7.81	− .340	− .735	+ .170	− .170	.....
8.43	− .365	− .755	+ .177	.....	− .495
9.67	− .530	− .850		− .325	− .530
10.18	− .575	− .910	− .212	− .395	− .575

The wide distribution of isoelectric points on the *p*H scale is a matter of interest. Since two of these isoelectric points occur at *p*H 7.2 and *p*H 9.7, the persistence of positively charged protein components at high *p*H values is demonstrated. This may be accountable for the known stability of fresh unpreserved latex toward the addition of acid, whereas the negative components stabilize with respect to added alkali.

Effect of Ammonia Treatment of Latex Serum.—The progressive effects of free ammonia at high *p*H levels on the proteins from unpreserved latex serum are shown by a comparison of the schlieren diagrams (falling boundaries at *p*H 6.85) contained in Fig. 3. The final effect of am-

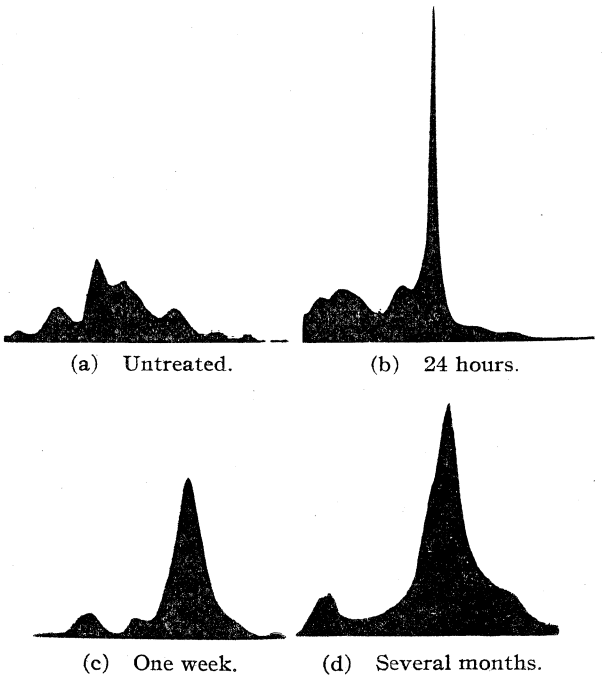


Fig. 3.—Schlieren diagrams showing effects of treatment of latex serum with 1% NH_3 for various lengths of time: (a), (b), (c) concentrated 3/1; (d) concentrated 5/1; *p*H = 6.85.

monia treatment is to reduce the number of resolvable components from seven to two.

Ammonia is of interest because of its commercial importance as a latex preservative. In its effect on latex proteins the presence of ammonia constitutes an abnormal condition in the serum and would be expected to produce departures from the characteristic normal pattern for untreated latex serum. It has been found that pathological conditions in human sera sometimes cause an abnormal change in the ratios of the various protein components of the sera. Although the detailed nature of the change in latex protein dissolved in ammonia solution is not known, one important observation may be made. The principal component of the exhaustively ammoniated protein solution has a higher numerical value of negative mobility than the principal component of unpreserved latex protein on the alkaline side of the isoelectric point. This is shown in Table III and probably accounts at least in part for the well-known rise in mechanical stability of latex within a short time after ammonia preservation is applied on the plantations.

TABLE III

MOBILITY VALUES OF PRINCIPAL PROTEIN COMPONENT OF LATEX SERUM AFTER VARIOUS LENGTHS OF TIME IN 1% NH_3 SOLUTION *p*H 6.85

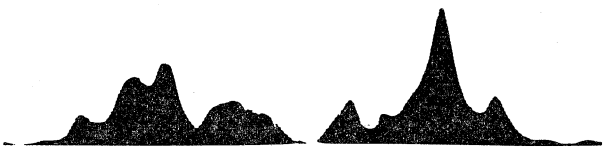
Time in 1% NH_3	Mobility in microns per sec. per volt per cm.
Untreated	−0.210
24 hours	− .332
7 days	− .565
Several months	− .465

It should be noted that soaps produced by the hydrolysis of resins may also be partially responsible for this increase in stability.

These experiments were all carried out on vacuum dried protein redissolved at a concentration three times that occurring in serum from frozen latex, except as indicated in Fig. 3.



Unconcentrated, *p*H = 6.85. Unconcentrated, *p*H = 10.18.



Concentrated, *p*H = 6.85. Concentrated, *p*H = 10.18.

Fig. 4.—Schlieren diagrams showing effects of vacuum sublimation on latex serum proteins.

Effects of Vacuum Sublimation.—Figure 4 shows a comparison of schlieren diagrams obtained with unconcentrated serum and diagrams obtained with concentrated solutions of vacuum dried serum solids.

The diagrams made in experiments with concentrated protein solutions show more detail than those made with dilute solutions, and tend to confirm the latter. The correspondence of the peaks representing the various components is taken to be an indication that no important change in the electrophoretic properties of the proteins was produced by the sublimation process.

Acknowledgment.—The writers wish to acknowledge their indebtedness to Mr. H. F. Loomis, of the United States Department of Agriculture, for his courtesy and coöperation in furnishing the fresh unpreserved latex from Florida. The writers are also indebted to Dr. L. G. Longsworth, Dr. Dan Moore and Dr. E. J. Cohn for helpful discussions of experimental methods.

Summary

1. The serum from unpreserved rubber latex (*Hevea brasiliensis*) contains seven electrophoretically distinct protein components. The proteins from whole serum originating in Sumatra and Florida give very similar results in electrophoresis experiments.

2. The relationship between electrophoretic mobility and *p*H has been determined for five of the seven protein components of unpreserved total latex serum. The results are considerably different from those reported by workers with ammonia preserved latex, and tend to clarify observed differences in the stability behavior of unpreserved and preserved latex.

3. Ammonia preservation treatment rapidly alters the electrophoretic behavior of the native protein components of latex serum and reduces the number of resolvable components from seven to two.

4. The preparation of dry latex protein from rubber free latex serum can be accomplished by the vacuum sublimation of frozen serum. This process does not appear to produce important changes in the electrophoretic properties of the total serum proteins.

5. Minor modifications of the electrodes and of the standard illumination system in the electrophoresis apparatus are described.

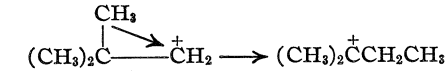
PASSAIC, NEW JERSEY RECEIVED JULY 24, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

The Reactions of Certain Neopentyl Systems with Electrophilic Reagents[1]

BY PHILIP SKELL AND CHARLES R. HAUSER

Whitmore and co-workers have shown that neopentyl systems react with electrophilic reagents to yield largely rearranged products. Thus, neopentyl alcohol with hydrogen bromide gives mainly *t*-amyl bromide,[2] while neopentyl iodide with silver nitrate or mercuric chloride yields largely *t*-amyl alcohol.[3] These reactions have been considered to involve the removal of X (hydroxyl or halogen) with its complete octet of electrons, leaving a carbon atom with only a sextet of electrons.[4] This carbon atom is stabilized by acquiring an electron pair from the adjacent carbon atom, the shifting electron pair carrying with it the attached methyl group.



The tertiary carbonium ion thus formed acquires the bromide or hydroxyl ion from the medium, yielding the *t*-amyl bromide or alcohol.

A corollary to this theory (applied to various carbon skeletons) might be that the ease of rearrangement is dependent upon the relative electron-attraction of the α-carbon atom in the positive fragment and upon the ease of migration of the electron pair with its attached group. On this basis one might expect that the tendency to rearrangement in the neopentyl system would be decreased if the hydrogens on the α-carbon atom were substituted by electron donating groups, such as alkyl or phenyl groups.[5] That the substitution of two alkyl groups on the α-carbon atom may impede rearrangement in the neopentyl system is indicated by the fact that, in contrast to α-methylneopentyl alcohol which on dehydration gives mainly rearranged olefins,[6] α,α′-methylethylneopentyl and α,α′-dimethylneohexyl alcohols on dehydration yield mainly unrearranged olefins.[7] We have demonstrated that even one α-phenyl substituent stabilizes the neopentyl system.

In contrast to the reactions of unsubstituted neopentyl systems, α-phenylneopentyl alcohol reacts with hydrogen bromide to yield largely the corresponding bromide, and this bromide reacts with silver nitrate to regenerate mainly the original alcohol. Other workers have shown that α,α-diphenylneopentyl systems can similarly be made to undergo "metathetical" reactions with electrophilic reagents to yield largely unrearranged products,[8] although rearrangement products have also been obtained under certain conditions.[9] Thus, α,α-diphenylneopentyl alcohol with thionyl chloride gives the corresponding chloride which with silver acetate yields the corresponding acetate; the latter on hydrolysis regenerates an alcohol which may be converted to the original chloride.[8]

The first step in these reactions probably involves the formation of a coördination complex between the alcohol or halide and the electrophilic reagent (ROH_2^+ or $RBr \rightarrow Ag^+$). This facilitates the removal of X with its complete octet of electrons. With neopentyl systems having at least one phenyl or two alkyl groups (in which the unrearranged product is formed) the complex decomposes probably yielding the carbonium ion as intermediate[10] which then acquires an anion (halide or hydroxyl) from the medium. The reaction of α-phenylneopentyl bromide with silver ion, for example, may be represented as

$$(CH_3)_3CCH(C_6H_5)Br \longrightarrow Ag^+ \xrightarrow{-AgBr} [(CH_3)_3CCHC_6H_5]^+ \xrightarrow{+OH^-} (CH_3)_3CCH(C_6H_5)OH$$

With neopentyl alcohol or halide, however, the

(1) This paper is taken from a portion of a Ph.D. thesis by Philip Skell.

(2) Whitmore and Rothrock, THIS JOURNAL, **54**, 3431 (1932).

(3) Whitmore, Wittle and Popkin, *ibid.*, **61**, 1586 (1939).

(4) Whitmore, *ibid.*, **54**, 3274 (1932).

(5) That alkyl and phenyl function as electron donating groups when present on the α-carbon atom of alkyl halides is demonstrated by the increased tendency to ionization of the halides; see, especially, Hughes, Ingold, Masterman and McNulty, *J. Chem. Soc.*, 899 (1940).

(6) Whitmore and Meunier, THIS JOURNAL, **55**, 3721 (1933).

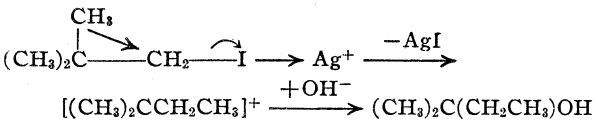
(7) Whitmore and Laughlin, *ibid.*, **54**, 4011 (1932). While the rearrangements may be precluded to some extent because of the dehydration (possibly involving the simultaneous elimination of the elements of water from adjacent atoms) it would appear that the tendency to rearrangements is less with these alcohols, since the α-methylneopentyl alcohol which also has the required structure for dehydration without rearrangement, nevertheless mainly rearranges. Moreover, Bartlett and Knox (THIS JOURNAL, **61**, 3191 (1939)) have shown that, in contrast to the reaction of neopentyl alcohol with hydrogen bromide, α,α′-diethylneopentyl alcohol reacts with anhydrous hydrogen chloride apparently without rearrangement.

(8) Ramart-Lucas, *Compt. rend.*, **154**, 1088 (1912); *Ann. chim. phys.*, [8] **30**, 368 (1913).

(9) Marvel and Bateman, THIS JOURNAL, **49**, 2914 (1927).

(10) In this connection see especially Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, pp. 139–140; "Annual Reports," *J. Chem. Soc.*, 236–247 (1940).

complex may never actually yield the neopentyl carbonium ion, but may produce directly the more stable tertiary amyl carbonium ion, the removal of X and the shift of the electron pair and its methyl group occurring simultaneously. This modification of the original hypothesis would account for the apparent absence of unrearranged products. The reaction of neopentyl iodide and silver ion, for example, may be illustrated as follows.



Since the phenyl group is known to migrate more easily than the methyl group, it might be expected that if the three methyl groups of the α-phenylneopentyl system were replaced by three phenyl groups, the resulting compound would exhibit a greater tendency to rearrangement. In agreement with this, it has been found that asymmetrical tetraphenylethyl alcohol on treatment with hydrogen bromide readily undergoes rearrangement, accompanied by elimination, yielding tetraphenylethylene. The alcohol is also dehydrated very readily by sulfuric acid, tetraphenylethylene being formed rapidly even at room temperature. Schmidlin[11] has reported that asymmetrical tetraphenylethyl bromide with aluminum chloride in benzene or even with boiling water undergoes rearrangement eliminating hydrogen bromide to yield tetraphenylethylene.

Experimental[12]

α-Phenylneopentyl Bromide.—α-Phenylneopentyl alcohol, contaminated with phenyl *t*-butyl ketone[13] (detected as its 2,4-dinitrophenylhydrazone), was prepared from *t*-butylmagnesium chloride and benzaldehyde, essentially as described by Conant and Blatt.[14] A solution of 36.0 g. of the slightly impure alcohol (b. p. 96–98° at 6 mm.) in 50 cc. of purified petroleum ether (b. p. 52–58°) was saturated with dry hydrogen bromide (the solution acquiring a yellow color immediately and a heavy yellow layer soon separating) at 0° for one hour and at room temperature for four hours. Anhydrous calcium bromide was added and the mixture filtered. After removing the solvent *in vacuo*, the residue on fractionation through a 6-inch Vigreux column yielded 37.5 g. (75%) of α-phenylneopentyl bromide, b. p. 103–104° at 7.5 mm. (reported, b. p. 106–112° at 9 mm.)[14]; d. 1.24.

(11) Schmidlin, "Das Triphenylmethyl," Verlag von Ferdinand Enke, Stuttgart, 1914, p. 146.

(12) Melting and boiling points are corrected.

(13) Reduction of the ketone with aluminum isopropoxide and isopropyl alcohol yielded the pure α-phenylneopentyl alcohol, boiling at 111.0–111.3° at 15 mm., and freezing sharply at 42°.

(14) Conant and Blatt, THIS JOURNAL, **50**, 551 (1928).

The bromide is hydrolyzed very slowly by water, is converted in high yield to the corresponding methyl ether (b. p. 94–95° at 20 mm.) by treatment with methanol in the presence of anhydrous potassium carbonate, and is converted to the corresponding acetate (b. p. 123–124° at 16 mm.) by refluxing with anhydrous potassium acetate in glacial acetic acid.

Reaction of α-Phenylneopentyl Bromide with Aqueous Silver Nitrate.—To a solution of 10 g. (0.059 mole) of silver nitrate in 50 cc. of distilled water was added 9.3 g. (0.41 mole) of α-phenylneopentyl bromide. Silver bromide separated immediately and the solution warmed perceptibly. After wrapping in paper (as a protection against light) the flask (with a ground glass stopper) was shaken mechanically overnight. The colorless organic layer was extracted with pure ether, and the ethereal solution was washed well with water and dried with anhydrous potassium carbonate. The solvent was removed through a 12-inch Vigreux column. The residue on fractionation *in vacuo* through a 6-inch Vigreux column yielded 6.2 g. (92%) of distillate (A), boiling at 96–101° (mainly at 99–100°) at 7.5 mm., leaving 0.5 cc. of yellow residue. The distillate (A) (which was solid at room temperature, the last crystal disappearing at 27°) was shown to consist mainly of α-phenylneopentyl alcohol. Pressing (A) between filter paper and washing it with a little petroleum ether yielded the alcohol melting at 38–41° (m. p. of the pure alcohol is 42°) which on oxidation with chromic anhydride in glacial acetic acid gave phenyl *t*-butyl ketone; the latter was identified as its oxime (m. p. 164–165°) and as its 2,4-dinitrophenylhydrazone (m. p. 190–191°). The freezing point constant of α-phenylneopentyl alcohol was determined by adding 0.264 g. of benzene to 4.152 g. of the pure alcohol (m. p. 42.0°), the last crystal disappearing at 37.4°; this indicated a depression of 5.6° for one mole of solute per 1000 g. of the alcohol. On this basis, the distillate (A) (m. p. 27°) contained 0.43 mole of "impurity" to 1.0 mole of α-phenylneopentyl alcohol. Assuming that all of the "impurity" was an isomeric alcohol, the maximum extent of rearranged product in (A) was only 30%.

Reaction of Asymmetrical Tetraphenylethyl Alcohol with Hydrogen Bromide.—Asymmetrical tetraphenylethyl alcohol (m. p. 151°) was prepared from sodium triphenylmethyl and benzaldehyde essentially as described by Schlenk and Ochs.[15]

A solution of 9.90 g. (0.0282 mole) of the alcohol in 100 cc. of pure anhydrous benzene (containing "Drierite" to absorb the water formed during the reaction) was saturated at 0° with dry hydrogen bromide (the solution acquiring immediately a deep yellow color which faded to a light yellow within one-half hour). No color change was observed on standing seven hours at room temperature. The solution was filtered in a dry-box and the solvent removed (at 40°) *in vacuo*. The residue after washing with purified petroleum ether yielded 8.0 g. (85%) of tetraphenylethylene (m. p. 225°), identified by its tetrabromide (m. p. 248°) and by ozonolysis to benzophenone (good yield) which was isolated as its 2,4-dinitrophenylhydrazone.

Asymmetrical tetraphenylethyl alcohol has also been dis-

(15) Schlenk and Ochs, *Ber.*, **49**, 611 (1916).

solved in concentrated sulfuric acid at room temperature. A momentary flash of bright yellow was produced and on pouring the solution into water a high yield of pure tetraphenylethylene was obtained.

Summary

1. In contrast to unsubstituted neopentyl systems, α-phenylneopentyl systems react with electrophilic reagents to yield largely unrearranged products. α-Phenylneopentyl alcohol with hydrogen bromide yields largely the corresponding bromide, and the latter with silver nitrate regenerates mainly the original alcohol.

2. Asymmetrical tetraphenylethyl alcohol with hydrogen bromide or concentrated sulfuric acid at room temperature yields tetraphenyl ethylene.

3. The effect of substituents on the tendency to rearrangement of neopentyl systems is discussed.

DURHAM, NORTH CAROLINA RECEIVED JUNE 26, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY AND OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Acetylenic Ethers. III.[1] Halogen Derivatives of Phenoxyacetylene

BY THOMAS L. JACOBS AND WENDELL J. WHITCHER[2]

At the outset of our study of acetylenic ethers it seemed possible that these compounds would exhibit many of the peculiarities of halogenated acetylenes since in both classes the carbon–carbon triple bond is directly attached to an atom bearing unshared pairs of electrons. Actually very few close similarities have been observed. The only one worthy of mention is the great tendency toward polymerization exhibited in both series by those members which have an acetylenic hydrogen (HC≡COR and HC≡CX); compounds in which this hydrogen is replaced by an alkyl group are relatively stable. Dihalogenated acetylenes, XC≡CX, are likewise characterized by ready polymerization. The preparation of halogenated phenoxyacetylenes, $C_6H_5OC{\equiv}CX$, was therefore undertaken in order to compare these two series more closely and to examine further the reactions of acetylenic ethers. Since phenoxyacetylene was the most readily available of these ethers it was used throughout this investigation.

Three general methods have been used for the preparation of halogenated acetylenes: the action of halogens or certain halogenating agents on metallic derivatives of acetylenes, the reaction between hypohalite ion and acetylenes, and the treatment of dihaloethylenes with alkaline reagents.

Iodoacetylenes have been prepared in excellent yield by the action of iodine on acetylenic Grignard reagents; at 0° neither diacetylene formation nor iodine addition occurred.[3] Sodium, copper and silver acetylides have also been used and the iodination of the first of these in liquid ammonia is a good synthetic method.[4] Diiodoacetylene has been prepared in excellent yield by passing acetylene into potassium hydroxide solution while iodine in potassium iodide solution was being added.[5] This reaction has not been applied to the synthesis of substituted iodoacetylenes.

All of these methods were tried unsuccessfully in an attempt to prepare iodophenoxyacetylene. The reaction of phenoxyethynylmagnesium bromide with the theoretical amount of iodine at 0° failed to give this compound. Phenoxytriiodoethylene was obtained in fair yield and was the only product isolated. Sodium phenoxyacetylide was similarly treated with iodine and only a small amount of phenoxytriiodoethylene resulted. The main product polymerized when distillation was attempted at 4 mm. pressure, but at much lower pressures a clear distillate was obtained. This was a mixture containing phenoxyacetylene and unstable iodo compounds. Treatment with iodine gave only phenoxyacetylene diiodide and no phenoxytriiodoethylene. The distillate darkened rapidly and could not be purified successfully. An attempt to hydrate the undistilled product with mercuric acetate and hydrochloric acid was unsuccessful.

(1) For the second paper of this series see Jacobs, Cramer and Hanson, THIS JOURNAL, **64**, 223 (1942).

(2) The greater part of this paper is taken from a thesis presented by Wendell J. Whitcher to the Faculty of Arts and Sciences of Harvard University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Mr. Whitcher's present address is E. I. du Pont de Nemours and Co., Wilmington, Delaware.

(3) Grignard and Perrichon, *Ann. chim.*, **5**, 5 (1926).

(4) Vaughn and Nieuwland, THIS JOURNAL, **55**, 2150 (1933).

(5) Biltz and Küppers, *Ber.*, **37**, 4412 (1904).

Phenoxyacetylene and iodine in potassium iodide solution were added simultaneously to cold potassium hydroxide solution. Phenoxytriiodoethylene was isolated from the reaction mixture by ether extraction and concentration. The residual liquid polymerized when distillation was attempted. The formation of the triiodo compound is accounted for readily only on the assumption that the iodoacetylenic ether is first produced and that iodine is then added.

The synthesis of bromophenoxyacetylene was attempted next in the hope that this compound could be isolated more readily. An early report of its preparation[6] by the action of alcoholic potassium hydroxide on dibromovinyl phenyl ether could not be confirmed by later workers[7,8] who obtained only phenol and ethyl bromoacetate (1).

$$\underset{\text{I}}{BrHC{=}CBrOC_6H_5} \xrightarrow[C_2H_5OH]{KOH} CH_2BrCO_2C_2H_5 + C_6H_5OH \quad (1)$$

$$\xrightarrow{H^+} CH_2BrCO_2H + C_6H_5OH \quad (2)$$

$$\xrightarrow{HNO_3} CHBr_2CO_2C_6H_3(NO_2)_2 \quad (3)$$

$$\underset{\text{II}}{Br_2C{=}CHOC_6H_5} \xrightarrow{H^+} (CHBr_2CHO) \xrightarrow[\text{phenylhydrazine}]{\text{2,4-Dinitro-}} \underset{\text{phenylosazone}}{\text{Glyoxal 2,4-dinitro-}} \quad (4)$$

$$\xrightarrow{KOH} C_6H_5OCH_2CO_2H + \text{polymer} \quad (5)$$

$$\xrightarrow{O_2} C_6H_5OCHBrCOBr \xrightarrow{C_6H_5OK} (C_6H_5O)_2CHCO_2C_6H_5 \quad (6)$$

Lawrie tried many alkaline reagents including powdered potassium hydroxide, but was unable to isolate any of the bromoacetylenic ether. All of these workers believed their starting material, prepared by the reaction of tribromoethylene and potassium phenolate, was 2,2-dibromovinyl phenyl ether, II, because it was converted by fuming nitric acid to dinitrophenyl dibromoacetate, (3). Biltz[9] pointed out that the compound was almost certainly 1,2-dibromovinyl phenyl ether, I, since on hydrolysis it yielded a derivative of (mono)bromoacetic acid, (2). He explained the formation during the nitric acid reaction of a compound with both bromines on one carbon as an oxidative rearrangement. It is interesting that Nef's acetylidene theory[8,10] was based largely on structural evidence invalidated by such rearrangements. Since phenoxyacetylene dibromide[11] is identical with the dibromovinyl phenyl ether described above, it would have been assigned an acetylidene structure, $C_6H_5OCH{=}C$, by Nef. These early workers explained the hydrolytic reactions on the basis of the 2,2-dibromovinyl phenyl ether structure by postulating the intermediate formation of bromophenoxyacetylene and assuming that it added water rapidly

$$Br_2C{=}CHOC_6H_5 \longrightarrow BrC{\equiv}COC_6H_5 \xrightarrow{H_2O} CH_2BrCO_2H + C_6H_5OH$$

The removal of hydrogen bromide in acid solution to produce a triple bond is of course very unlikely.

Slimmer[7] synthesized a second dibromovinyl phenyl ether by the reactions

$$C_6H_5OCH{=}CHBr + Br_2 \longrightarrow C_6H_5OCHBrCHBr_2 \xrightarrow{KOH} C_6H_5OCH{=}CBr_2$$

Since the 2,2-dibromo- structure had already been assigned to the compound prepared earlier, he assumed this second one had the 1,2-dibromo- structure. We repeated his synthesis and proved that the compound was 2,2-dibromovinyl phenyl ether, II, by hydrolysis to derivatives of glyoxal, (4).

An attempt to prepare bromophenoxyacetylene from this second dibromo ether by distillation from potassium hydroxide under reduced pressure was not successful. The products were tar and a little phenol and phenoxyacetic acid. The acid was probably formed by hydrolysis of the vinyl ether, but it might also have been produced by hydration of bromophenoxyacetylene, since bromoacetylenes are known to give acids by refluxing with alcoholic potassium hydroxide.[12]

The action of fuming nitric acid at −10° on 2,2-dibromovinyl phenyl ether was very vigorous and the only products isolated were 2,4-dinitrophenol and picric acid. We had no difficulty in confirming the report[8] that under the same conditions 1,2-dibromovinyl phenyl ether underwent a smooth oxidative rearrangement to a dinitrophenyl ester of dibromoacetic acid. It was observed that the 2,2-dibromo compound autoxidized rapidly in the air. It was, therefore, shaken with dry oxygen and the oxidation product treated with potassium phenolate yielding phenyl diphenoxyacetate by an oxidative rearrangement, (6). Foster[13] obtained ethyl diethoxyacetate in a

(6) Sabanejeff and Dworkowitsch, *Ann.*, **216**, 279 (1883).
(7) Slimmer, *Ber.*, **36**, 289 (1903).
(8) Lawrie, *Am. Chem. J.*, **36**, 487 (1906).
(9) Biltz, *Ber.*, **46**, 143 (1913).
(10) Nef, *Ann.*, **298**, 202 (1897).
(11) Jacobs, Cramer and Weiss, THIS JOURNAL, **62**, 1849 (1940).
(12) Nef, *Ann.*, **308**, 314 (1899).
(13) Foster, THIS JOURNAL, **31**, 596 (1909).

similar manner from 2,2-dichlorovinyl ethyl ether which was prepared by a method that left no question regarding its structure.

Since 1,2-dibromovinyl phenyl ether, m. p. 38–39°, should exist in *cis*- and *trans*-forms, an attempt was made to isomerize it by irradiation with ultraviolet light.[14] The product was a liquid from which only a third of the starting material could be recovered. A similar liquid mixture with the composition of dibromovinyl phenyl ether was obtained by adding bromine to phenoxyacetylene.[11] Irradiation of 2,2-dibromovinyl phenyl ether produced no change.

The preparation of bromo- and chloro-acetylenes by the reaction of halogens and acetylenic Grignard reagents is complicated by the ease of addition of the halogen to the triple bond. In view of the isolation of phenoxytriiodoethylene during the addition of iodine to metallic derivatives of phenoxyacetylene, no attempt was made to prepare bromophenoxyacetylene by this method. Since phenoxyacetylene is stable to cold potassium hydroxide its reaction with hypobromite ion in alkaline solution[15] was investigated. Some polymerization of the phenoxyacetylene occurred during the reaction, but the darkening was hardly more than observed with phenoxyacetylene alone. Distillation of the product even at 0° with a mercury vapor pump usually resulted in polymerization to a black, solid mass with evolution of heat. On one occasion this polymerization occurred almost explosively while the distilling flask was standing at 0° at atmospheric pressure. One successful distillation was carried out yielding a substance which darkened rapidly. Addition of bromine to this distillate gave phenoxytribromoethylene and a little phenoxyacetylene dibromide. Undistilled bromophenoxyacetylene gave phenoxytribromoethylene on addition of bromine, and phenyl bromoacetate on hydration.

These experiments show that bromophenoxyacetylene can be prepared, but that purification is very difficult due to polymerization.

Experimental Part

Phenoxytriiodoethylene.—Phenoxyethynylmagnesium bromide[11] from 8.0 g. (0.068 mole) of phenoxyacetylene was cooled to 0° under nitrogen and treated with stirring with 17.2 g. (0.068 mole) of iodine in 150 cc. of ether during two and one-half hours. Stirring was continued for twenty minutes and the solution was hydrolyzed with cold 5% ammonium chloride solution, washed with water and dried over sodium sulfate. On concentration under reduced pressure a total of 10.3 g. (60% yield) of phenoxytriiodoethylene was deposited in several fractions, m. p. 120–122.5° and 124–126°. These were recrystallized several times from ether and petroleum ether, m. p. 129–129.5°.

Anal. Calcd. for $C_8H_5OI_3$: C, 19.30; H, 1.01; I, 76.48. Found: C, 19.63; H, 1.04; I, 76.66.

Similar addition of iodine to sodium phenoxyacetylide[11] gave phenoxytriiodoethylene in only 1% yield; the main product was an unstable liquid which was distilled using a mercury vapor pump. The distillate was crystalline at −80°, but melted to a colorless liquid at room temperature and rapidly turned green. Analysis showed only 34.28% iodine as compared with 52.00% calculated for iodophenoxyacetylene. The addition of iodine to an ether solution of this liquid gave a little impure phenoxyacetylene diiodide; there was no evidence for phenoxytriodoethylene which is less soluble than the diiodide and readily separated from it.

The yield of phenoxytriiodoethylene obtained by the simultaneous addition of phenoxyacetylene and iodine in potassium iodide solution to cold potassium hydroxide solution was 28.5%.

2,2-Dibromovinyl phenyl ether was prepared according to Slimmer's direction[7] except that a nitrogen atmosphere was maintained throughout. The product was an oil which was carefully fractionated through a small Podbielniak column packed with a spiral of platinum wire; b. p. 117–118° (6 mm.), $n^{20}D$ 1.6046; yield 48%. This material solidified on standing in the cold; m. p. 29–29.5°. A mixed m. p. with 1,2-dibromovinyl phenyl ether, m. p. 38–39°, showed a depression.

Anal. Calcd. for $C_8H_6Br_2$: Br, 57.50. Found: Br, 56.89.

Hydrolysis.—Only partial hydrolysis resulted when 1.7 g. (0.006 mole) of 2,2-dibromovinyl phenyl ether was refluxed for four hours with 2.4 g. (0.012 mole) of 2,4-dinitrophenylhydrazine and 20 cc. of concd. hydrochloric acid in 50 cc. of alcohol. A yellow precipitate formed rapidly but even at the end of the reaction the solid present was a mixture with a broad melting point. The odor of unchanged dibromoether was apparent. The reaction mixture was filtered and soluble impurities partly removed from the precipitate by refluxing in ethyl acetate and filtering. The insoluble portion was recrystallized from nitrobenzene giving reddish-orange needles, m. p. 311–312°; Strain[16] reported m. p. 326–328°.

Anal. Calcd. for $C_{14}H_{10}N_8O_8$: C, 40.20; H, 2.41. Found: C, 40.29; H, 2.66.

Autoxidation.—Dry oxygen was passed slowly through 10 g. of 2,2-dibromovinyl phenyl ether with shaking during three days. The product was taken up in 75 cc. of dry benzene and added dropwise to a suspension of 10.5 g. of potassium phenolate in 50 cc. of benzene with cooling. The reaction mixture was stirred and allowed to come to room temperature during two hours and finally refluxed for twenty-five minutes. The benzene solution was washed with water, dried and concentrated. Addition of

(14) These experiments were carried out by Mr. Eugene V. Kleber.

(15) Straus, Kollek and Heyn, *Ber.*, **63**, 1868 (1930).

(16) Strain, THIS JOURNAL, **57**, 758 (1935).

ligroin gave 2.9 g. of phenyl diphenoxyacetate (25% yield). It was recrystallized from benzene and ligroin, m. p. 94.5–95° in good agreement with recorded values.[17]

Anal. Calcd. for $C_{20}H_{16}O_4$: C, 74.99; H, 5.04. Found: C, 74.81; H, 4.92.

Bromophenoxyacetylene.—A mixture of 0.112 mole of phenoxyacetylene and 200 cc. of 0.56 *M* potassium hypobromite solution containing potassium hydroxide (2.2 *M*)[15] was stirred under nitrogen at −5 to −8° for three hours. The product was taken up in ether and the ether solution washed with cold 5% potassium hydroxide and water. After drying over sodium sulfate the ether was partly removed and the solution was transferred to a 25-cc. Claisen flask which had a side arm 2 cm. in diameter bent into a U-shape to serve as a receiver. The flask was partly filled with glass wool to prevent bumping and the remaining ether and unchanged phenoxyacetylene were removed with an oil pump and collected in a trap cooled with acetone and dry-ice. Readmission of air to the flask at this point resulted in polymerization, sometimes almost explosively. Polymerization usually resulted even when distillation was continued without interruption simply by cooling the U-tube side arm in dry-ice and starting the mercury vapor pump. One successful distillation was accomplished yielding 8 g. of a lachrymatory almost colorless substance which was a liquid even at −80°. Small samples rapidly turned green and then black when allowed to warm up to room temperature. Purified carbon tetrachloride was, therefore, added to the remaining material and this solution in an ice-bath was treated dropwise with 3.4 cc. of bromine in carbon tetrachloride. At first, each drop of bromine solution reacted vigorously producing white fumes. The dark solution was washed with water and cold 5% potassium hydroxide. After drying over calcium chloride the carbon tetrachloride was removed under reduced pressure and the product distilled at 2 mm. The first fraction was phenoxyacetylene dibromide (3.65 g.) and the second tribromophenoxyethylene (3.85 g.), m. p. 92–93.5° as shown by a mixed m. p. Polymer accounted for the rest of the starting material.

Bromine in carbon tetrachloride was added similarly to the crude undistilled bromophenoxyacetylene from 14 g. of phenoxyacetylene, yielding 18.5 g. (43%) of phenoxytribromoethylene. There was no evidence of phenoxyacetylene dibromide in this experiment.

A concentrated ether solution of undistilled bromophenoxyacetylene from 7.6 g. of phenoxyacetylene was shaken with a solution of 65 g. of mercuric acetate and 3 cc. of concd. hydrochloric acid in 140 cc. of water at 10°. A greenish, flocculent solid separated, but this redissolved with continued shaking for twenty minutes and intermittent addition of concd. hydrochloric acid (total of 50 cc.). The ether solution was washed with water, dried and the ether removed under reduced pressure. Two distillations of the residue gave 4.2 g. (30% yield) of phenyl bromoacetate, b. p. 140–142° (25 mm.), m. p. 28–28.5°.

(17) Scheibler and Depner, *Ber.*, **68**, 2139 (1935).

Summary

1. Iodophenoxyacetylene could not be obtained by the action of iodine on phenylethynylmagnesium bromide or sodium phenoxyacetylide; triiodophenoxyethylene was the main product in the first case. Phenoxyacetylene and iodine reacted in alkaline solution yielding triiodophenoxyethylene. Liquids which polymerized rapidly were obtained in each instance.

2. The dibromovinyl phenyl ether prepared by Slimmer was shown to be 2,2-dibromo-1-phenoxyethylene. It yielded no bromophenoxyacetylene when distilled from potassium hydroxide.

3. Bromophenoxyacetylene was obtained by the action of potassium hypobromite in alkaline solution on phenoxyacetylene. It polymerized very readily, was successfully distilled only at very low pressures and could not be purified. It was hydrated yielding phenyl bromoacetate; the addition of bromine gave tribromophenoxyethylene.

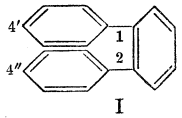
LOS ANGELES, CALIFORNIA RECEIVED AUGUST 3, 1942

[COMMUNICATION NO. 872 FROM THE EASTMAN KODAK RESEARCH LABORATORIES]

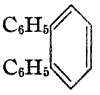
The Chemistry of *o*-Terphenyl. II. Derivatives Prepared from the Hydrocarbon

BY C. F. H. ALLEN AND F. P. PINGERT

The chemical behavior of *o*-terphenyl has not hitherto been determined, mainly on account of its inaccessibility.[1] All derivatives reported in the literature have contained the substituent groups in the central ring. They have resulted from degradation of more complex molecules or from diene syntheses.[2] Indeed, this last reaction furnishes the most suitable procedure for synthesizing such derivatives. Having accumulated a supply of the hydrocarbon,[3] its reactions were investigated, using standard procedures. Predictions as to the position to be taken by entering groups would vary according to which mode of representation was used. Thus, formula Ia would lead one to expect substitution on the central ring, while I would suggest the more likely possibilities of groups entering the side rings. The system of numbering adopted regards the side rings as substituents, and the numbers are, therefore, primed.[3]



I



Ia

The Friedel–Crafts reaction was of particular interest because the first simple degradation product previously secured had been a benzoyl-*o*-terphenyl[2a]; this was not identical with the ketone found by the action of benzoyl chloride upon *o*-terphenyl in the presence of anhydrous aluminum chloride. Since the latter reagent, by itself or in a melt with sodium chloride gives rise to side reactions,[3] a mixture of products usually results.

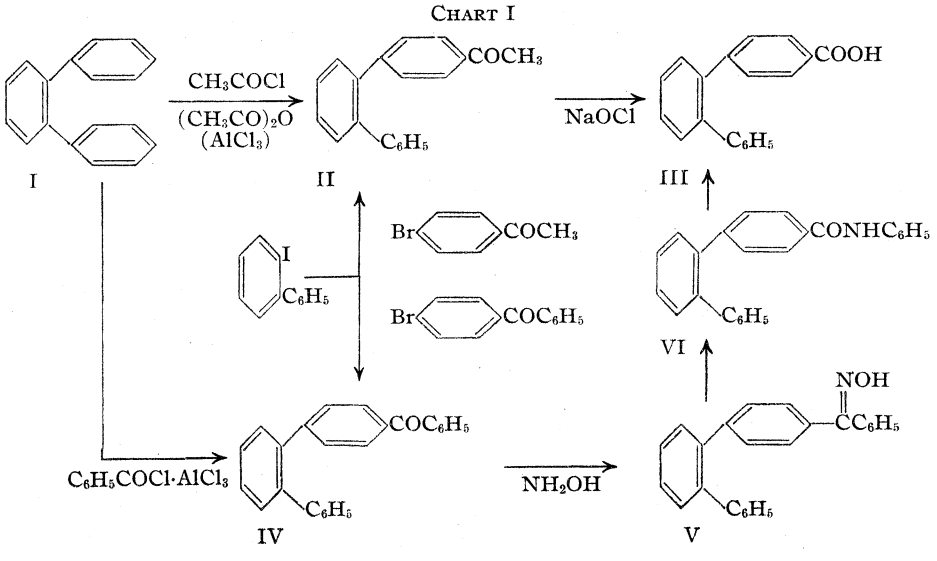
4'-Acetyl-*o*-terphenyl II is secured by the action of acetyl chloride or acetic anhydride upon the hydrocarbon in the presence of anhydrous aluminum chloride. It was also synthesized by a Wurtz reaction from *o*-iodobiphenyl and *p*-bromoacetophenone, to confirm its structure. By means of sodium hypochlorite, it was converted to the 4'-carboxylic acid III.

When benzoyl chloride was employed, a difficultly separable mixture resulted, but by using the Perrier double compound, $C_6H_5COCl \cdot AlCl_3$, a phenyl ketone IV was obtained in high yield and purity. The same ketone was also secured by a Wurtz synthesis. This ketone gave an oxime V, which formed an anilide VI by the Beckmann rearrangement; hydrolysis of the anilide furnished 4'-carboxy-*o*-terphenyl III and aniline. These reactions are summarized in Chart I.

Bromination, as would be anticipated, gave a mixture, but by variations in technique it was possible to isolate several homogeneous substitution products. The first homogeneous product is 4',4''-dibromo-*o*-terphenyl, VII. The structure was determined by oxidation, when *p*-bromobenzoic acid was secured; therefore, in the dibromo derivative the bromine atoms are in the para position.

The further action of bromine gave first a tribromo and then a tetrabromo substitution prod-

CHART I

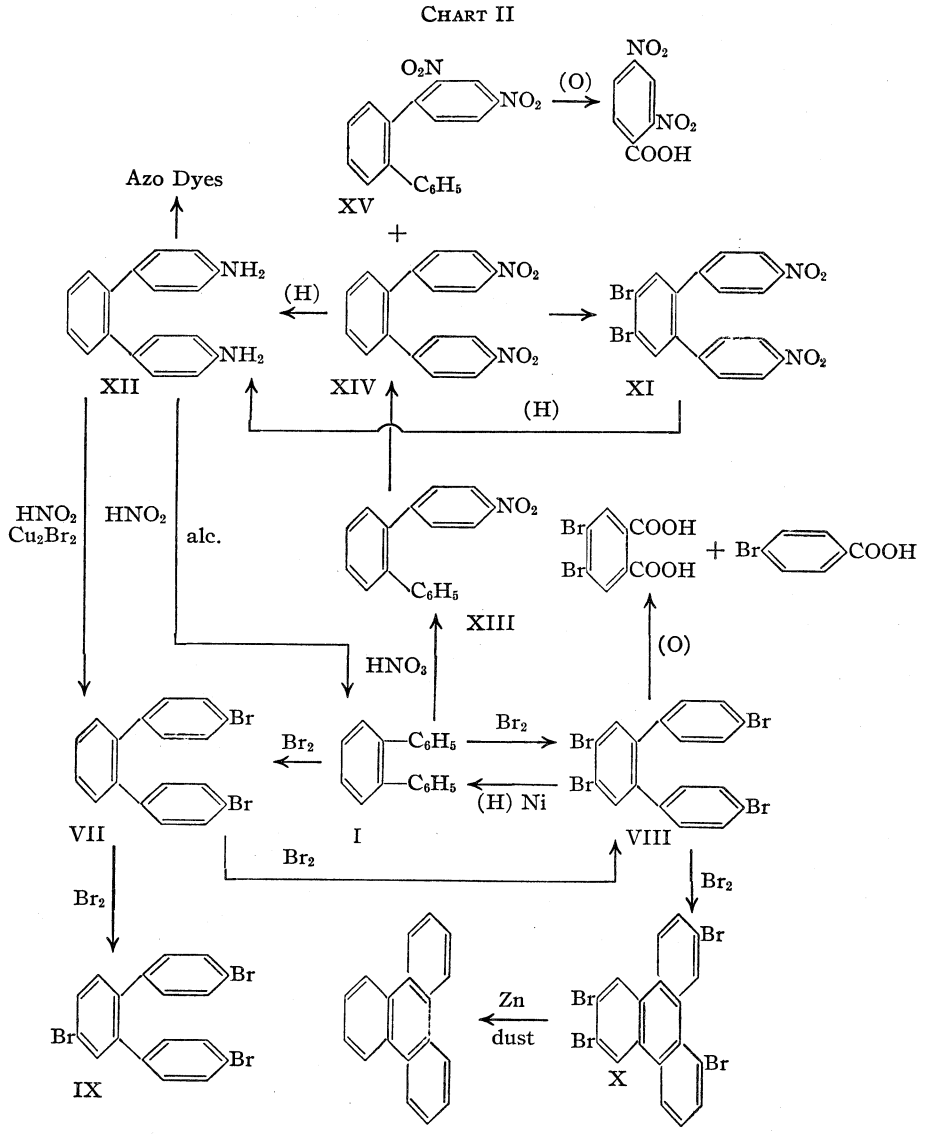


(1) It has recently been called to our attention by Dr. R. L. Jenkins, of the Monsanto Chemical Company that their product, "Santowax O," is about 85% *o*-terphenyl.

(2) (a) Allen and Spanagel, THIS JOURNAL, **55**, 3773 (1933); (b) Allen, Bell, Bell and VanAllan, *ibid.*, **62**, 656 (1940); (c) Allen and VanAllan, *ibid.*, **64**, 1260 (1942).

(3) Allen and Pingert, *ibid.*, **64**, 1365 (1942).

CHART II



uct. Upon oxidation of the latter a large amount of *p*-bromobenzoic acid and a small quantity of 4,5-dibromophthalic acid were produced; the substance is, therefore, 4,4′,4″,5-tetrabromo-*o*-terphenyl, VIII. The tribromo derivative, IX, has the bromine atoms in the 4,4′,4″-positions, for (a) further bromination gives the tetrabromo-*o*-terphenyl, and (b) oxidation gives a high yield of *p*-bromobenzoic acid. The end-product of the action of bromine is 3,5,10,11-tetrabromotriphenylene, X, the halogen acting as a dehydrogenating agent, upon the tetrabromo-*o*-terphenyl. That the four-ring system is present is shown by the formation of triphenylene on zinc dust distillation.

4′,4″-Dinitro-*o*-terphenyl gives a dibromo derivative, XI, upon bromination, which presumably has the bromine atoms in the same positions as the tetrabromo compound, for it has the same general appearance and physical properties. The melting points are identical and there is no depression on admixture—one of the uncommon instances in which two different substances have no effect on their respective melting points. On reduction by hydrogen in the presence of Raney nickel, the bromine is removed and the corresponding amine, XII, is found—thus triphenylene ring closure has not occurred. Attempts to synthesize 4′,4″-dicyano-*o*-terphenyl by the Rosenmund method were unsuccessful. The reactions are shown in Chart II.

Nitration gives first the 4′-nitro derivative, XIII, and then a mixture of two isomeric dinitro-*o*-terphenyls; the nature of the product is largely controllable according to the experimental conditions. One of the dinitro derivatives is the 4′,4″-isomer, XIV, and the other is the 2′,4′-isomer, XV, since upon oxidation the former gives only *p*-nitrobenzoic acid, and the latter, 2,4-dinitrobenzoic acid. Mixed acid gave a mixture of products that appeared to contain some of a trinitro derivative.

Reduction of the nitro compounds yields the corresponding amines; the 4′,4″-diamine, XII, was converted by means of the diazo reaction into (a) *o*-terphenyl, showing the ring system was still intact, and (b) 4′,4″-dibromo-*o*-terphenyl, VII, thus affording additional proof of structure in

both series. The diamine was also diazotized and coupled with some of the common naphthalene dye intermediates to give azo dyes.

Experimental

The behavior of *o*-terphenyl in chemical reactions is very subject to slight changes in technique, and an understanding of certain of its peculiarities is essential for successful repetition of the procedures. Under comparable conditions, it is less active than the meta- and para-isomers, so that some degree of forcing may be necessary to initiate a reaction. However, complications due to isomerization and ring closure[3] render it important not to drive the reactions to completion in most instances. Mixtures are thus produced, the separation of which is not always readily accomplished; if the conditions are such as to favor the formation of products in molecular proportions, the mixed crystals may defy as many as twenty fractional crystallizations from several solvents.

One of the obscure factors that may influence the experimental results is the solvent from which the hydrocarbon was crystallized. This effect is not understood. As an example, traces of moisture or alcohol favor polybromination; this is in line with the view that aromatic halogenation proceeds through an ionic mechanism.[4] *o*-Terphenyl and some of its derivatives retain traces of solvent very tenaciously; one-quarter to one-half per cent. of ethanol is not removed over a long period of time *in vacuo;* this affects analytical results only slightly, but may determine the course of substitution to a large degree. Small amounts of acetic acid have a strong inhibiting effect upon bromination and nitration; it is also possible to boil glacial acetic acid solutions of the hydrocarbon with bromine or fuming nitric acid without appreciable substitution.

A. The Ketones, I; 4′-Benzoyl-*o*-terphenyl; 4-*o*-Xenylbenzophenone, II. (a). Friedel–Crafts Synthesis.—To the Perrier double compound from 1.4 g. each of benzoyl chloride and aluminum chloride in 8 cc. of carbon disulfide was added 2.3 g. of *o*-terphenyl, and the mixture was refluxed for a half hour, left at room temperature for several hours and again refluxed a half hour. It was then decomposed in the usual manner, extracting with ether; on evaporation, the residue, 3.3 g., was steam-distilled from a solution made alkaline by 1 g. of potassium carbonate—only a trace of unchanged hydrocarbon was removed. The ketone was taken up in ether, treated with decolorizing carbon, and the solvent removed. After recrystallization from absolute ethanol, the ketone formed compact prisms, m. p. 111°. It crystallizes readily from dry methanol and benzene.

Anal. Calcd. for $C_{25}H_{18}O$: C, 89.8; H, 5.4. Found: C, 89.3; H, 5.3.

(b) **Ullmann Synthesis.**—An intimate mixture of 5 g. each of *p*-bromobenzophenone and *o*-iodobiphenyl, and 10 g. of copper bronze[5] was heated in a sealed tube at 240° for four hours. The contents were then extracted with benzene in a Soxhlet apparatus, and the extract distilled *in vacuo*, collecting the portion boiling above 190° at 3 mm. After a redistillation, the substance was fractionally crystallized from absolute ethanol, when 0.35 g. of *o*-xenylbenzophenone was secured. There was no depression of melting point when mixed with the ketone described in (a).

(c) **The Oxime, V.**—This was obtained in two modifications, the lower-melting form first obtained changing into the higher-melting on standing, or inoculating, or in the presence of hydrochloric acid. Once the higher-melting point had been obtained, it was thereafter impossible to isolate the low-melting form again.

A solution of 200 mg. of the purest ketone in 7 cc. of ethanol was mixed with an equal weight of hydroxylamine hydrochloride, and 15 drops of 35% sodium hydroxide was added. After gently refluxing for four hours, it was diluted with 28 cc. of water and acidified to litmus with *sulfuric* acid (*hydrochloric* acid gave the higher-melting form at once). After a thorough washing it was recrystallized from absolute ethanol, and then from petroleum ether at −60°. The oxime (210 mg.) then had a melting point of 68°. As described above, it changed to another form, which melted at 138°, showing a barely perceptible shrinking at about 68°. Both oximes gave the same anilide.

Anal. Calcd. for $C_{25}H_{19}ON$: N, 4.0. Found: N, 4.2, 4.0.

(d) **Hydrolysis of the Anilide to 4′-Carboxy-*o*-terphenyl, III.**—The anilide was not easily hydrolyzed without resinification. The best procedure was to reflux a mixture of 0.15 g. of anilide, 50 cc. of ethanol, and 15 cc. of 40% sodium hydroxide for seventy-two hours. After acidification and three recrystallizations, the acid (yield, 0.1 g.) was pure; m. p. 203°.

II. 4′-Acetyl-*o*-terphenyl, II.—(a) **Direct acetylation of the hydrocarbon** in solution invariably leads to mixtures, the aluminum chloride causing rearrangements.[3] Until a pure specimen is available for inoculation, it is almost a hopeless task to try to separate the mixtures. When acetic anhydride in nitrobenzene was used, the decomposed reaction product was extracted with ether, and this extract shaken two hours with Norite (without this treatment crystallization did not take place). The yield of ketone was 2.1 g., m. p. 94°; from 9.2 g. of *o*-terphenyl. After two months, 2.6 g. more of the less pure ketone, m. p. 93°, had separated, making the total yield 43%. Acetyl chloride, or carbon disulfide as a solvent, resulted in low-melting ketone.

Anal. Calcd. for $C_{20}H_{16}O$: C, 88.2; H, 5.9. Found: C, 88.0; H, 5.8.

(b) **Ullmann Synthesis.**—A mixture of 22 g. of *o*-iodobiphenyl and 19.4 g. of *p*-iodoacetophenone was heated

(4) Price, *Chem. Rev.*, **29**, 39 (1941).

(5) "Org. Syntheses," **20**, 46 (1940).

TABLE I

PROPERTIES OF BROMINATED HYDROCARBONS

No.	Substituents	M. p., °C.	Crystal form	Empirical formula	Analyses, % Calcd.	Found
VII	4′,4″-Dibromo-	170[a]	Rods or leaflets	$C_{18}H_{12}Br_2$	41.2	41.1
IX	4,4′,4″-Tribromo-	170[a,e]	Rods	$C_{18}H_{11}Br_3$	51.4	52.2
VIII	4,4′,4″,5-Tetrabromo-	228[b,d]	Prisms	$C_{18}H_{10}Br_4$	58.3	58.2
X	3,5,10,11-Tetrabromotriphenylene	+450[c]	Microcrystalline powder	$C_{18}H_8Br_4$	58.8	58.7

[a] Mixed melting point, about 155°. [b] In one instance, an isomer, m. p. 120°, with previous sintering, was isolated—it contained 58.4% bromine. [c] On a copper block; a specimen, synthesized from triphenylene, melted at the same point under the same conditions. [d] A 1:1 mixture of tri- and tetrabromo compounds, m. p. 212–214°, often crystallized—it could not be separated by crystallization. [e] Mol. wt. calcd., 467; found (in benzene) 469, 479.

with stirring in an oil-bath until the temperature had reached 220°. Then 40 g. of activated[5] copper bronze was added over a period of one hour. After cooling, the acetone extract was distilled in a Hickman vacuum (at about 3 micra). The fraction that passed over at 200–205° was fractionally crystallized from absolute ethanol; the yield was 6.7 g.

(c) **Oxidation with sodium hypochlorite** in aqueous methanol gave 4′-carboxy-*o*-terphenyl, m. p. 203°, identical with the product from the phenyl ketone, described above.

B. Bromination.—The three isomeric terphenyls in the crystalline state in aqueous suspension react readily with bromine; *o*-terphenyl exhibits this behavior more strongly than the isomers. Furthermore, it is practically impossible to brominate *o*-terphenyl dissolved in an organic solvent, though there is no difficulty with the isomers. The products of the bromination are mixtures, whatever the technique, but certain individuals predominate in each variation. In some instances, elution by a solvent removes a considerable quantity of undesirable by-products. In practically every case it is essential to submit the mixture of products to systematic fractional crystallization.[6] Glacial acetic acid seems to be the most generally useful solvent. In some instances, polybrominated products are very soluble and are largely removable in the first wash, along with unreacted hydrocarbon. Since space requirements prohibit the complete detailed procedures, only a brief description of the more essential features of each bromination will be given.

i.—Solid *o*-terphenyl and dry bromine vapor in a closed vessel at room temperature gave mainly di-, tri-, and tetrabromo-*o*-terphenyls. The hydrocarbon slowly liquefies and resolidifies; at this point the yield of 4′,4″-dibromo-*o*-terphenyl is at the maximum. The time (two to twenty hours) depends upon variable factors, such as size of the run.

ii.—Similar conditions but in the presence of water vapor; here the tribromo compound predominates. The same result is attained if the hydrocarbon is ground in a mortar with water, and triturated with bromine for short periods of time. A curious but unexplained observation is that in the presence of water the tribromo compound is the end-product.

iii.—Longer exposure (one to thirty days) to bromine by either of the foregoing procedures; in this case the tetrabromo-*o*-terphenyl predominates. If this is desired as a principal product, it can be obtained very quickly by adding solid hydrocarbon to excess liquid bromine, evaporating to dryness, and separating the polybromotriphenylenes.

iv.—Further exposure of the lower bromo compounds to bromine either as vapor or liquid first gives the tetrabromotriphenylene, X, *quantitatively* which is further very slowly polybrominated, but no other pure individual substance was isolated. The triphenylene derivatives have high melting points (450–600°) and are easily removed because of their relative insolubility.

The properties of the various brominated products are collected in Table I.

Ring closure of the tetrabromo-*o*-terphenyl to the tetrabromotriphenylene was brought about by heating with nitrating acid, and separating the resinous mixture by suitable manipulations. This reaction thus affords confirmatory proof that the tetrabromo-*o*-terphenyl is still open-chained; *i. e.*, the ring has not been closed in the brominations.

V. Proofs of Structure.—(a) **4′,4″-Dibromo-*o*-terphenyl** was oxidized in the usual manner, using chromium trioxide in acetic acid for forty-eight hours. The yield of *p*-bromobenzoic acid was 58%; it was identified by comparison with an available specimen.

(b) **4,4′,4″,5-Tetrabromo-*o*-terphenyl** was synthesized by further bromination of 4′,4″-dibromo-*o*-terphenyl, thus locating two of the bromine atoms. Upon oxidation with chromium trioxide in acetic acid for four days and appropriate manipulation, a 60% yield of *p*-bromobenzoic acid was isolated, showing that none of the additional bromine had entered the end rings already containing bromine. There was also isolated a small amount of 4,5-dibromophthalic acid, identified by conversion to the anhydride, m. p. 215°, and identical with a sample at hand.[7]

(c) **3,5,10,11-Tetrabromotriphenylene** was reduced by heating micro samples with zinc dust in a 10-in. capillary tube; the triphenylene sublimed into the upper end of the tube. This was cut off and the hydrocarbon identified as such by comparison with an authentic sample. The ordinary macro zinc dust distillation takes place too slowly and yields mixtures.

VI. 3,6-Dimethyl-4,4′,4″,5-tetrabromo-*o*-terphenyl, m. p. 205°, was prepared by a similar procedure from some available 3,6-dimethyl-*o*-terphenyl.[2c]

Anal. Calcd. for $C_{20}H_{14}Br_4$: Br, 55.8. Found: Br, 55.8.

Upon oxidation only *p*-bromobenzoic acid was isolated. In this substance, the bromine atoms can only be in the

(6) The material losses are prohibitive unless the purification is carried out in accordance with some such procedure, recombining all mother liquors and recovering all residues.

(7) We are indebted to Dr. C. V. Wilson for this authentic specimen.

4,5-positions of the central ring, the 3 and 6 positions being occupied by methyl groups.

C. Nitration. I. 4'-Nitro-*o*-terphenyl, XIII, and Related Products.—(a) To a solution of 23 g. of *o*-terphenyl in 150 cc. of 99–100% acetic anhydride below 0° was added, dropwise, and with stirring, 8.5 cc. of nitric acid (sp. gr. 1.44). The temperature was kept below 5° for two hours, then allowed to rise to room temperature and stirred overnight. It was then poured upon ice and sodium carbonate, and, when all the acid had been neutralized, extracted with ether. The dried ether extract was concentrated and 2–3 g. of dinitro derivatives filtered; a small further amount was filtered on further concentration, rinsing the solid with dry ether. The combined filtrate and rinse was redried over anhydrous magnesium sulfate and the residual oil after removal of the solvent distilled *in vacuo*. After recovering about 1 g. of hydrocarbon, the fraction, b. p. 180–200° (3 mm.), was collected and redistilled (b. p. 191–193° (3 mm.)); the yield was 21.6 g. (78%) of a thick oil which solidified to a honey-colored glass. After one year, during which it was remelted and resolidified several times, it crystallized. It separates in flakes from acetic acid, m. p. 105–106°.

Anal. Calcd. for $C_{14}H_{13}O_2N$: N, 5.1. Found: N, 5.3.

(b) **4'-Amino-*o*-terphenyl.**—Reduction was carried out in alcoholic solution in the presence of a Raney nickel catalyst. It crystallizes in rosets of fine needles; the melting point, at first 108°, drops, on standing, to 103–104° and the amine becomes slightly pasty.

Anal. Calcd. for $C_{18}H_{15}N$: N, 5.8. Found: N, 6.1.

The benzoyl derivative, obtained through a Schotten–Baumann reaction, formed needles when crystallized from absolute ethanol; m. p. 175°.

Anal. Calcd. for $C_{25}H_{19}ON$: N, 4.0. Found: N, 3.9.

II. 4',4''-Dinitro-*o*-terphenyl, XIV; (a) **From *o*-Terphenyl.**—A solution of 6.9 g. of the hydrocarbon in 50 cc. of 99–100% acetic anhydride was treated, dropwise, with 5 cc. of fuming nitric acid (sp. gr. 1.52) at 10°; after two hours, cooling was discontinued—a solid slowly separated. The mixture was decomposed as usual by iced sodium carbonate, ether extracted, and the solid filtered; the ether contains most of the mononitro compound and any unreacted hydrocarbon. The solid (6.4 g.) was fractionally crystallized from acetic acid, giving about equal amounts of the 4',4''-dinitro-*o*-terphenyl, m. p. 218°, and its 2',4'-isomer, m. p. 169°—this is more soluble.

Anal. Calcd. for $C_{18}H_{12}O_4N_2$: N, 8.8. Found: (4',4''-) N, 8.7; (2', 4'-) N, 8.7.

(b) **From Mononitro Derivative in Ia.**—A solution of 5 g. of XIII in 120 cc. of acetic anhydride was cooled to 10°, and five 2-cc. portions of fuming nitric acid were added. After allowing to stand overnight and working up in the usual way, 6 g. of material was obtained, from which 3.1 g. of 4',4''-dinitro-*o*-terphenyl was isolated after several recrystallizations.

(c) **Oxidation.**—This was carried out by the customary procedure using chromium trioxide in acetic acid overnight. The yield of *p*-nitrobenzoic acid from the 4',4''-dinitro-*o*-terphenyl was 56%; a mixed melting point was not depressed. The 2',4'-isomer gave 2,4-dinitrobenzoic acid, m. p. 181°.[8]

(d) **4',4''-Diamino-*o*-terphenyl, XII,** was secured by reduction of the corresponding nitro compound essentially as described under the monoamine. It crystallizes in hard, waxy rosets from absolute ethanol, m. p. 149°.

Anal. Calcd. for $C_{28}H_{20}O_2N_2$: N, 6.7. Found: N, 6.6.

It is stable in an inert atmosphere, but in the laboratory air soon turns waxy and the melting point falls.

The diamine was tetrazotized in the usual way, except for the replacement by hydrogen reaction, which will be described below. It is essential to work in dilute solutions (1.5 g. per liter) to avoid resin formation. For the Sandmyer reaction, the tetrazotized solution was run into a 48% hydrobromic acid solution containing freshly prepared cuprous bromide. The 4',4''-dibromo-*o*-terphenyl was filtered and recrystallized from acetic acid. It was identical with the product of dibromination.

For the reduction reaction, 0.64 g. of diamine in 50 cc. of cold, absolute ethanol, containing 10 cc. of concentrated sulfuric acid, was tetrazotized at 0°. It was then warmed gently in warm tap water, and finally heated on the steam-bath. After dilution with water, the doughy precipitate was manipulated, and 0.14 g. (22%) of *o*-terphenyl isolated and identified. The remainder had a phenolic odor and failed to crystallize.

A separately prepared tetrazo solution was coupled with alkaline β-naphthol; an immediate scarlet precipitate was formed; it melted, with decomposition, at 209°. Analysis indicated that but one end had coupled, the other, apparently, having been hydrolyzed to a phenolic group.

Anal. Calcd. for $C_{28}H_{20}O_2N_2$: N, 6.7. Found: N, 6.6.

Other, water-soluble dyes will be described in a later paper.

(e) **4',4''-Dinitro-4,5-dibromo-*o*-terphenyl, XI,** was prepared by exposing the dinitro-*o*-terphenyl to bromine vapor for twenty-four hours, as described under bromination. Purification was accomplished through the judicious use of alcohol and acetic acid; there is some insoluble material, presumably the corresponding triphenylene derivative. The dibromodinitro derivative crystallizes in fine rods, m. p. 228°.

Anal. Calcd. for $C_{18}H_{10}O_4N_2Br_2$: N, 5.9. Found: N, 6.2.

Summary

The chemical behavior of *o*-terphenyl has been determined in the Friedel–Crafts reaction, and with the reagents bromine and nitric acid. The structures of the resulting substances have been determined; their reactions and those of related products are described.

ROCHESTER, N. Y. RECEIVED JULY 21, 1942

(8) Claus and Habberstadt, *Ber.*, **13**, 815 (1880).

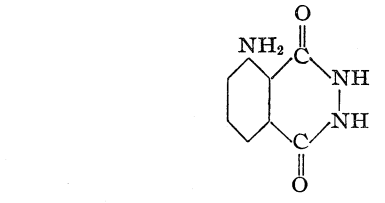
[CONTRIBUTION NO. 272 FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Synthesis of Aminobenzoyleneureas and of Dihydroxyquinoxalines Isomeric with "Luminol"

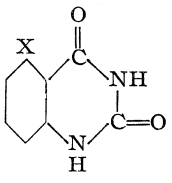
BY ERNEST H. HUNTRESS AND JEANNE V. K. GLADDING[1,2]

The brilliant chemiluminescence produced during alkaline oxidation of 3-aminophthalhydrazide ("Luminol"[3]) has long been the subject of investigation by many workers. Some of these workers have been concerned with the influence of structural changes upon the chemiluminescent properties. With such progress as has been made in this direction this paper cannot in general be concerned in detail. However, Drew[4] has pointed out that since hydrazides in five-membered rings do not show chemiluminescence, a six-membered hetero ring may be essential. It has also been established[4c] that in 3-aminophthalhydrazide both imino hydrogens of the cyclohydrazide ring must be free to enolize. It does not appear, however, that any attempt has been recorded to show that in the heterocyclic portion of 3-aminophthalhydrazide the two imino groups must be adjacent to each other, *i. e.*, that a hydrazine derivative is imperative for the possession of chemiluminescent properties on oxidation.

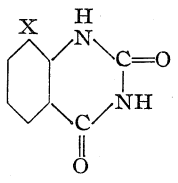
The work reported in this paper is primarily concerned with the preparation of certain hitherto unreported compounds isomeric with 3-aminophthalhydrazide and whose carbocyclic nucleus is precisely the same as in "Luminol," but in which although the heterocyclic ring is varied it still retains the characteristic of being a six-membered ring with two potentially enolizable hydrogen atoms. The particular individual compounds thus constituting the primary interest of this work are the two aminobenzoyleneureas II and IV (X = NH_2) together with the aminodihydroxyquinoxaline VI (X = NH_2). Syntheses of the two other possible aminobenzoyleneureas III and V and the one other possible aminodihydroxyquinoxaline VII (X = NH_2) have been included, although admittedly in them the amino group of the carbocyclic ring is not in the same relationship to the heterocyclic nucleus as in 3-aminophthalhydrazide.



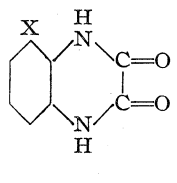
I



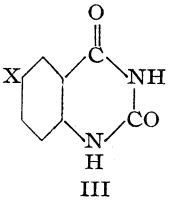
II



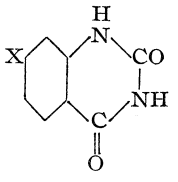
IV



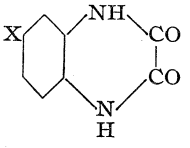
VI



III



V



VII

All six of these new compounds have been prepared and characterized. Each amino compound has been obtained by reduction of the corresponding nitro relative. The three nitro compounds corresponding to structure II, IV and V (X = NO_2) were obtained from the correspondingly substituted nitroanthranilic acids. The first (II, X = NO_2) was prepared by condensation of 6-nitroanthranilic acid with potassium cyanate in acetic acid, the second (IV, X = NO_2) and third (V, X = NO_2) by fusion of 3-nitro- and of 4-nitroanthranilic acids, respectively, with urea. 6-Nitrobenzoyleneurea (III, X = NO_2) was prepared by nitration of benzoyleneurea according to Bogert and Scatchard.[5]

The position of the nitro group in 6-nitrobenzoyleneurea had already been established[5] by its preparation from methyl 2-(ω-nitrocarbamido)-5-nitrobenzoate. The position of the nitro group in the other three isomers is here estab-

(1) This paper is constructed from part of a dissertation submitted in June, 1941, by Miss Jeanne V. Kitenplon (Mrs. E. K. Gladding) to the Faculty of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Present address: Research Associate, Massachusetts Institute of Technology.

(3) Huntress, Stanley and Parker, *J. Chem. Education*, **11**, 142–145 (1934).

(4) (a) Drew, *Sci. J. Roy. Coll. Sci.*, **8**, 33–38 (1938). (b) Drew and Pearman, *J. Chem. Soc.*, 586–592 (1937). (c) Drew and Garwood, *ibid.*, 1841–1846 (1937).

(5) Bogert and Scatchard, THIS JOURNAL, **41**, 2058–2059 (1919).

lished by their mode of preparation from the corresponding anthranilic acids. In the case of 8-nitrobenzoyleneurea (IV, X = NO_2) this evidence is also supported by its further nitration to the same 6,8-dinitrobenzoyleneurea previously obtained by nitration of 6-nitrobenzoyleneurea.

All four mononitrobenzoyleneureas are pale yellow crystalline solids with high melting or decomposition points. They are all phenolic in character and are therefore soluble in dilute aqueous alkalies forming deeply colored solutions from which the parent compounds are reprecipitated by carbon dioxide. They are but sparingly soluble in organic solvents.

The four aminobenzoyleneureas (II, III, IV, V, X = NH_2) have been obtained by stannous chloride reduction of the corresponding nitro compounds. Their hydrochlorides separated from the hot reduction solution in high purity and no complexes with the reagent have been observed. From the salts the amines were released by dilute ammonia. The free amines are white crystalline solids, some melting at high temperatures, others decomposing before true fusion. The free bases are amphoteric and readily dissolved in dilute aqueous alkalies or carbonates. The presence of the amino group was evidenced by the formation of colored coupling products when the diazotized amines were treated with alkaline β-naphthol.

The results of tests for possible chemiluminescence on oxidation, however, were uniformly negative. No significant light evolution occurred. Formation of highly colored red to brown solutions occurred in all cases and suggested that oxidation was taking place. Since no light was observed, however, and since such colored solutions would be poorly adapted for study if there had been, the nature of the reaction products was not further examined.

Experimental Work

All melting points were taken in a Berl and Kullmann copper block on a 360° rod form melting point thermometer set in the block up to its zero point.

The Nitrobenzoyleneureas

5-Nitrobenzoyleneurea (II, X = NO_2).—Potassium cyanate (5.25 g., 0.065 mole) dissolved in water (25 ml.) was added dropwise to a stirred suspension of 6-nitro-2-aminobenzoic acid (9.1 g., 0.05 mole) in water (300 ml.) and glacial acetic acid (4.5 ml., 0.08 mole). After the orange colored solution had been stirred for half an hour, it was treated with flaked sodium hydroxide (80 g., 2 moles) in small portions the temperature being kept below 40° and the alkaline solution allowed to stand overnight in a refrigerator. After removal of any precipitate by filtration the product was precipitated by acidification with sulfuric acid. It separated from these solutions in fine, light yellow crystals or from boiling water in pale tan, thin, regular hexagons. After treatment with decolorizing carbon it was thrice recrystallized from boiling 50% acetic acid; weight, 7.0 g., representing 67% of theoretical; m. p. 339–340° dec. uncor. in sealed tube, 357–358° cor.

Anal. Calcd. for $C_8H_5O_4N_3$: N, 20.3. Found: N, 21.0, 21.1.

5-Nitrobenzoyleneurea is insoluble in ether, benzene, carbon tetrachloride, ligroin, carbon disulfide or toluene; slightly soluble in cold water, ethyl acetate, chloroform or 95% ethanol; moderately soluble in boiling water, boiling 50% acetic acid, methanol, acetone, or pyridine. Its solutions in aqueous sodium hydroxide, sodium carbonate or concentrated ammonium hydroxide are bright yellow, but the compound is precipitated on saturation with carbon dioxide.

5-Nitrobenzoyleneurea N,N'-Dimethyl Ether.—Treatment of 5-nitrobenzoyleneurea (1.03 g., 0.005 mole) dissolved in 5% potassium hydroxide (15 ml.) by shaking with dimethyl sulfate (1.5 g. = 0.010 mole) for half an hour caused evolution of heat and separation of a pale yellow precipitate of the N,N'-dimethyl ether; weight 0.905 g., representing 77% of the theoretical. From boiling 50% ethanol this material separated in fine white needles.

This material was refluxed for twenty minutes with concentrated hydrochloric acid (to hydrolyze any O-ethers) washed with 5% potassium hydroxide, filtered and recrystallized from boiling methanol. Its melting point was 263–265° uncor. (275–277° cor.).

Anal. Calcd. for $C_{10}H_9O_4N_3$: N, 17.9; for $C_{10}H_9O_4N_3 \cdot H_2O$: N, 16.6. Found: N, 16.5, 16.8.

6-Nitrobenzoyleneurea (III, X = NO_2).—This was prepared from benzoyleneurea by nitration with a mixture of concentrated sulfuric acid and fuming nitric acid according to the directions of Bogert and Scatchard.[5] The yield was 86% of theoretical and the product showed a melting point of 315–316° dec. uncor., 331–332° dec. cor. (recorded 330–331° cor.).

6-Nitrobenzoyleneurea-N,N'-dimethyl Ether.—By treatment with dimethyl sulfate exactly as for the 5-nitro isomer, the dimethyl ether was obtained in 85% yield. Although from boiling 50% ethanol this separated in fine white crystals, yet after boiling with concentrated hydrochloric acid (to split any O-ethers) and treatment with potassium hydroxide, recrystallization of the alkali insoluble product from boiling methanol yielded bright yellow needles, melting at 204–205° uncor. (213–214° cor.).

Anal. Calcd. for $C_{10}H_9O_4N_3$: N, 17.9. Found: N, 18.3, 18.5.

7-Nitrobenzoyleneurea (V, X = NO_2).—A mixture of 4-nitro-2-aminobenzoic acid (3.0 g., 0.0165 mole) and urea (3.0 g., 0.05 mole) was heated from room temperature to 200° during thirty minutes and then fused at 200° for one hour. The material was contained in a large Pyrex test-tube suspended within an air-bath, the temperature of the melt being measured by a thermometer inserted directly into the fused material.

During fusion ammonia was evolved and a feathery yellow sublimate formed at the top of the test-tube. After cooling the porous yellow-brown mass was washed with water (50 ml.) to remove ammonium salts. The residual solid was then extracted with warm 5% aqueous sodium bicarbonate (50 ml.) followed by warm 10% aqueous sodium carbonate (50 ml.). This treatment converted the 7-nitrobenzoyleneurea into the sparingly soluble sodium salt and removed unchanged 4-nitro-2-aminobenzoic acid or other acidic material. The solid residue was then treated with dilute sulfuric acid (50 ml.) and small amounts of by-product 4-nitro-2-aminobenzamide extracted with boiling methanol (50 ml.) from the free 7-nitrobenzoyleneurea. Crystallization from boiling 50% acetic acid gave fine cream-colored needles; weight 2.6 g. (76% theoretical); m. p. 323° uncor. or 337° cor. dec. in a sealed capillary tube. Further crystallizations from 50% acetic acid accompanied by the use of decolorizing carbon gave lustrous white plates.

For analyses the potassium salt was recrystallized from very dilute potassium hydroxide solution, followed by acidification with 10% acetic acid and final recrystallization from boiling 50% acetic acid.

Anal. Calcd. for $C_8H_5O_4N_3$: N, 20.3. Found: N, 20.4, 20.5.

7-Nitrobenzoyleneurea is slightly soluble in boiling water, cold 95% ethanol, ether or ethyl acetate. It is moderately soluble in boiling methanol, 95% ethanol or pyridine. Its solutions in aqueous alkali are deep yellow and from them 7-nitrobenzoyleneurea is precipitated by carbon dioxide.

A long series of experiments on the influence of time and temperature on this fusion showed clearly that below 170° both 7-nitrobenzoyleneurea and 4-nitro-2-aminobenzamide were formed as a result of which the yields of former were low. At 170° or above, however, no amide was detectable and the yield of 7-nitrobenzoyleneurea was very satisfactory. The best conditions are given above, but a similar fusion at 170° for seven hours gave 67% yield, showing that the temperature rather than prolonged time is the critical governing factor. This was confirmed by the observation that 4-nitro-2-aminobenzamide (1.0 g., 0.006 mole) fused with urea (1.0 g., 0.017 mole) for two hours at 180–200°, gave 35% yield of purified 7-nitrobenzoyleneurea, m. p. 337° dec. cor.

7-Nitrobenzoyleneurea-N,N'-dimethyl Ether.—This was obtained (85% yield) from its parent with dimethyl sulfate and alkali essentially as for the preceding isomers; from boiling methanol it separates in pale yellow needles, m. p. 229–230° uncor.

8-Nitrobenzoyleneurea (IV, X = NO_2).—The preparation of this compound was effected by fusion of 3-nitro-2-aminobenzoic acid with urea according to the general procedure used for the 7-nitro isomer. Both the desired 8-nitrobenzoyleneurea and the by-product 3-nitro-2-aminobenzamide were always formed, their yields varying considerably with fusion temperature, time and proportion of reactants. Conditions were finally established for obtaining satisfactory yields of the 8-nitrobenzoyleneurea, but (unlike the corresponding 7-nitro isomer) it was always accompanied by at least a small amount of the amide from which it had to be separated.

A mixture of 3-nitro-2-aminobenzoic acid (5.0 g., 0.0274 mole) and urea (10.0 g., 0.167 mole) was heated at 180–190° (thermometer in melt) for five hours. Ammonia was evolved and a yellow sublimate formed at the mouth of the tube. After cooling the yellow-brown solid was extracted with warm 5% aqueous potassium hydroxide and the filtered solution treated with carbon dioxide until precipitation was completed. The resultant small brown crystals were recrystallized from boiling 50% acetic acid; weight 3.9 g. (68% theoretical); m. p. 263–264° uncor. (272–273° cor.) in a sealed capillary tube.

Anal. Calcd. for $C_8H_5O_4N_3$: N, 20.3. Found: N, 20.0, 20.2.

8-Nitrobenzoyleneurea after three crystallizations from boiling 50% acetic acid using decolorizing carbon was obtained in hard yellow-green prisms. It is moderately soluble in methanol, 95% ethanol, acetone, or pyridine; insoluble in ether, benzene, toluene, carbon tetrachloride or carbon disulfide. Its solutions in cold aqueous sodium hydroxide, sodium carbonate or ammonium hydroxide are yellow but from these the original compound is precipitated by carbon dioxide.

6,8-Dinitrobenzoyleneurea.—8-Nitrobenzoyleneurea (0.90 g. = 0.0043 mole) dissolved in concentrated sulfuric acid (10 ml.) was slowly treated with concentrated nitric acid (6 ml., d. 1.42). After heating the solution at 100° for one hour, cooling, and pouring onto ice, the pale yellow solid was filtered, washed with water and dried at 110°. From boiling 50% acetic acid it separated as light yellow prisms; weight 1.10 g. (100% theoretical); m. p. 263–265° uncor.; recorded,[6] 274–275° cor. dec.

Anal. Calcd. for $C_8H_4O_6N_4$: N, 22.2. Found: N, 22.1, 22.3.

The melting point of a 50–50 mixture of this product and authentic 6,8-dinitrobenzoyleneurea was not depressed. The melting point of a 50–50 mixture of 8-nitrobenzoyleneurea and either this product or the authentic sample of 6,8-dinitrobenzoyleneurea was depressed to 219–227° uncor.

8-Nitrobenzoyleneurea-N,N'-dimethyl Ether.—8-Nitrobenzoyleneurea (1.03 g., 0.005 mole) dissolved in 5% aqueous potassium hydroxide (15 ml.) first gave a clear deep red solution which soon solidified to an orange paste. After dilution with water this was shaken for half an hour with dimethyl sulfate (1.5 g., 0.01 mole) at room temperature, then heated at 100° for an hour, cooled and filtered. After washing with water and drying at 100° the crude product weighed 1.035 g. Recrystallization from boiling 50% ethanol gave light tan needles which were refluxed fifteen minutes with concentrated hydrochloric acid (15 ml.), treated with 5% aqueous potassium hydroxide (25 ml.), and finally recrystallized again from boiling methanol; yield, 0.54 g. (45% theoretical); m. p. 217–218° uncor.

Anal. Calcd. for $C_{10}H_9O_4N_3$ (dimethyl ether): N, 17.9. Found: N, 17.8. Calcd. for $C_9H_7O_4N_3$ (monomethyl ether): N, 19.0.

3-Nitro-2-aminobenzamide.—This compound constituted the residue from alkali extraction of the fusion of 3-nitro-2-aminobenzoic acid with urea. From boiling methanol, 95% ethanol or acetone it crystallized in long

(6) Bogert and Scatchard, THIS JOURNAL, **38**, 1612 (1916).

lustrous orange needles, m. p. 226–227°, uncor. (234–235° cor.).

Anal. Calcd. for $C_7H_7O_3N_3$: C, 46.4; H, 3.87. Found: C, 46.3, 46.6; H, 3.70.

Its identity was further supported by hydrolysis on long boiling with either dilute sodium hydroxide or 6 *N* hydrochloric acid which gave 3-nitro-2-aminobenzoic acid and ammonia. Furthermore, on refluxing with acetic anhydride followed by warming of the intermediate 3-nitro-2-acetylaminobenzoic acid with 5% aqueous potassium hydroxide, treatment with carbon dioxide precipitated 8-nitro-2-methyl-4-ketodihydroquinazoline in 36% yield. After recrystallization from boiling 50% acetic acid this separated as hard brown-red crystals; m. p. 260–261° dec. uncor. (267–268° dec. cor.); recorded,[7] m. p. 264° dec. Finally it was observed that 3-nitro-2-aminobenzamide (4.0 g., 0.022 mole) fused with urea (8.0 g., 0.134 mole) for five hours at 200° gave 8-nitrobenzoyleneurea (4.0 g. or 87.0% theoretical), m. p. 262–263° uncor. (271–272° cor.).

3-Nitro-2-aminobenzoic Acid.—This compound was prepared in two ways, *viz.*, by oxidation of 3-nitro-2-aminotoluene and by Hofmann degradation of 3-nitrophthalamic-2-acid-1.

The first sequence started with **3-nitro-*o*-toluidine,** converted[8] it to 3-nitro-2-acetylaminotoluene (91% yield), m. p. 156° uncor. (recorded[8] 156°), oxidized[8] with *neutral* potassium permanganate to 3-nitro-2-acetylaminobenzoic acid (74% yield), and finally by hydrolysis with boiling 50% sulfuric acid gave 3-nitro-2-aminobenzoic acid (87% yield), m. p. 202–203° uncor. (recorded, 205°,[8] 208–9°).[9] The over-all yield by this method was therefore 58.6%.

The alternative procedure started from 3-nitrophthalic acid, converted[10] it to the anhydride (78% yield), ammonolyzed in warm concentrated ammonium hydroxide to 3-nitrophthalamic-2-acid-1 (70% yield), followed by Hofmann degradation[9] to 3-nitro-2-aminobenzoic acid (90% yield), m. p. 201–203° uncor. By this sequence the over-all conversion of 3-nitrophthalic acid to the 3-nitroanthranilic acid was 48%.

6-Nitro-2-aminobenzoic Acid.—This was prepared by starting with 3-nitrophthalic acid, converting it to the acid ammonium salt in 100% yield, fusing this at 235–250°[11] to obtain 94% yield of 3-nitrophthalimide, converting this imide to 6-nitrophthalamic-2-acid-1 by solution in 2 equivalents of 0.5 *N* sodium hydroxide and precipitation at 0° with excess concentrated hydrochloric acid (yield 76%), and finally degrading the amide group to amino (90% yield) via the Hofmann method as employed by Kahn.[12] The over-all yield of this preparation thus represented 64.3% of the theoretical and gave a product melting at 181° dec. uncor.

The Aminobenzoyleneureas

All four isomeric nitrobenzoyleneureas on reduction with stannous chloride in boiling concentrated hydrochloric acid gave the corresponding aminobenzoyleneureas in the form of their hydrochlorides. These were all sparingly soluble in the excess acid and separated during the reduction. No tin double salts were observed. The general method was based upon the procedure reported[13] for the reduction of 6,8-dinitrobenzoyleneurea. It was worked out specifically for the reduction of 6-nitrobenzoyleneurea (see below) and applied without change to the other isomers.

5-Aminobenzoyleneurea (II, X = NH_2).—The hydrochloride separated in very fine white needles from the hot concentrated hydrochloric acid solution. It was also sparingly soluble in cold water. When dissolved in boiling water and treated with ammonium hydroxide, the free base separated in pale green needles which after four recrystallizations from hot water (using decolorizing carbon) became lustrous white needles, m. p. 284° dec. uncor. (295° dec. cor.), in sealed capillary tubes. The yield of amine hydrochloride was 71% theoretical.

Anal. Calcd. for $C_8H_7O_2N_3$: N, 23.7. Found: N, 24.4, 24.6.

The free base was somewhat soluble in hot water, methanol, ethanol or ethyl acetate, the solutions possessing a purple fluorescence. The base is also soluble in dilute sodium hydroxide, dilute sodium carbonate, or concentrated ammonium hydroxide and these solutions were pale yellow. Diazotization of the amine and coupling with alkaline β-naphthol gave a deep brown-red solution.

6-Aminobenzoyleneurea (III, X = NH_2).—6-Nitrobenzoyleneurea (10.5 g., 0.05 mole) was added gradually to a boiling solution of stannous chloride dihydrate (50 g., 0.22 mole) in concentrated hydrochloric acid (160 ml.). After refluxing for four hours the mixture was cooled, the insoluble amine hydrochloride filtered, washed with water, and dried at 110°. To remove any occluded tin salts this material was refluxed with concentrated hydrochloric acid (40 ml.) for fifteen minutes, water (40 ml.) was added, and the mixture boiled five minutes more. The amine hydrochloride separated in fine light tan needles, weight 9.8 g. (91% theoretical).

This salt is only sparingly soluble in cold water, cold dilute acids or hot concentrated hydrochloric acid. When dissolved in a large volume of freshly boiled water (to avoid oxidation) and ammonium hydroxide added to the boiling solution, the free base separated in pinkish-tan needles, which after three recrystallizations from boiling water (using decolorizing carbon) separated as fine lustrous white needles. This base does not show a melting point, but becomes black above 330°.

Anal. Calcd. for $C_8H_7O_2N_3$: N, 23.7. Found: N, 24.0, 24.2.

The free base was only slightly soluble in cold water, but moderately soluble in hot water, in methanol or 95% ethanol. Its alcoholic solutions showed a green fluorescence. Solutions of the amine in dilute aqueous sodium hydroxide, 10% sodium carbonate or in concentrated ammonium hydroxide were light yellow. Diazotization of the amine and coupling with alkaline β-naphthol gave deep red solutions.

7-Aminobenzoyleneurea (V, X = NH_2).—The hydrochloride separated in fine light tan needles from boiling

(7) Zacharias, *J. prakt. Chem.*, [2] **43**, 441 (1891).

(8) James, Kenner and Stubbings, *J. Chem. Soc.*, **117**, 775 (1920).

(9) Chapman and Stephens, *ibid.*, 1795 (1925).

(10) Nicolet and Bender, Organic Syntheses, Coll. Vol. I, (1932), p. 402.

(11) Bogert and Boroschek, THIS JOURNAL, **23**, 747 (1901).

(12) Kahn, *Ber.*, **35**, 3863 (1902); *cf.* Bogert and Chambers, THIS JOURNAL, **27**, 652–653 (1905).

(13) Ref. 5, p. 2060.

concentrated hydrochloric acid. This salt was also sparingly soluble in either cold or hot water. The yield of hydrochloride was 90% theoretical.

The free base was obtained from boiling water as a white flocculent precipitate from hot water. Above 200° it colored yellow, but did not melt up to 350°.

Anal. Calcd. for $C_8H_7O_2N_3$: N, 23.7. Found: N, 24.0, 24.1.

The amine is almost insoluble in cold water, slightly soluble in boiling water, or in methanol, 95% ethanol, acetone or pyridine. Solutions in concentrated sulfuric acid had a purple fluorescence. Diazotization and coupling with alkaline β-naphthol gave a deep red solution.

8-Aminobenzoyleneurea (IV, X = NH_2).—By the stannous chloride method the base hydrochloride separated from the boiling solution in light tan needles (55% yield). This hydrochloride was sparingly soluble in cold water or in either hot or cold concentrated hydrochloric acid; it was moderately soluble in hot water.

When its solution was treated with dilute ammonium hydroxide and saturated with carbon dioxide, the free base was precipitated in light tan needles, purified by recrystallization from boiling water, m. p. 270–272° dec. uncor. (279–281° cor.).

The free base was also obtained by reduction of a glacial acetic acid solution of 8-nitrobenzoyleneurea in the presence of Adams catalyst with hydrogen at atmospheric pressure, yield 40% of the theoretical.

Diazotization of this amine yielded a clear yellow solution which with aqueous alkali turned a yellow-brown and with alkaline β-naphthol gave a heavy yellow-green precipitate.

The Nitro- and Amino-2,3-dihydroxyquinoxalines

5-Nitro-2,3-dihydroxyquinoxaline (VI, X = NO_2).—3-Nitro-*o*-phenylenediamine (2.03 g., 0.0132 mole) was treated with diethyl oxalate (25 ml.). The solid diamine slowly became red-orange and heat was evolved but solution did not occur. The mixture was therefore refluxed until (after about two hours) its color had faded. After heating about five minutes a heavy precipitate of lustrous tan plates separated. After cooling the solid was filtered, washed with alcohol and dried at 100°. After three recrystallizations from boiling 50% acetic acid (using decolorizing carbon) the product was obtained in fine bright yellow plates, m. p. 284° dec. uncor. (295° dec. cor.) in sealed capillary tubes, weight 1.60 g. (60% theoretical).

Anal. Calcd. for $C_8H_5O_4N_3$: N, 20.3. Found: N, 19.8, 19.6.

The compound was only slightly soluble in benzene, toluene, ether, chloroform, carbon tetrachloride or carbon disulfide; was moderately soluble in methanol, 95% ethanol, acetone, ethyl acetate or pyridine. From its deep red solutions in dilute sodium hydroxide, potassium carbonate or concentrated ammonium hydroxide, carbon dioxide precipitated the free base.

6-Nitro-2,3-dihydroxyquinoxaline (VII, X = NO_2).—4-Nitro-*o*-phenylenediamine (7.15 g., 0.0465 mole) mixed with anhydrous oxalic acid (10.7 g., 0.12 mole) was finely powdered, placed in a Pyrex test-tube, the latter arranged for heating in an air-bath. After slowly raising the temperature of the melt to 150°, it was maintained for one hour, then raised to 180–200° for another hour. After cooling the light brown to black product was extracted with warm 5% aqueous sodium hydroxide from which red solution carbon dioxide precipitated small brown crystals. After four recrystallizations from boiling 50% acetic acid (using decolorizing carbon) the product separated in clusters of white needles, m. p. 329–330° dec. uncor. (343–344° dec. cor.) both in sealed capillary tubes. The yield was 7.1 g. (73% theoretical).

Anal. Calcd. for $C_8H_5O_4N_3$: N, 20.3. Found: N, 19.6.

This compound was moderately soluble in methanol, 95% ethanol, ethyl acetate, acetone or pyridine; it was almost insoluble in ether, benzene, toluene, chloroform, carbon tetrachloride or petroleum ether. Its solutions in dilute aqueous sodium hydroxide, potassium carbonate or concentrated ammonium hydroxide were deep orange-red and from these carbonation precipitated the parent compound.

The Amino-2,3-dihydroxyquinoxalines

5-Amino-2,3-dihydroxyquinoxaline (VI, X = NH_2).—5-Nitro-2,3-dihydroxyquinoxaline (1.6 g., 0.008 mole) suspended in a solution of sodium sulfide (nonahydrate) (5 g. = 0.021 mole) in water (25 ml.) was refluxed for one and one half hours. The deep orange suspension gradually dissolved, yielding a clear brown solution. After cooling the solution was strongly acidified, boiled and filtered (to remove free sulfur). Upon neutralization with sodium bicarbonate the flocculent orange precipitate was filtered. After two recrystallizations from boiling water the amine separated in fine light-yellow crystals, blackening at 336° uncor. with decomposition about 344° uncor. in sealed m. p. tubes. The yield was 0.6 g. (44% theoretical). This compound was also prepared by stannous chloride reduction.

Anal. Calcd. for $C_8H_7O_2N_3$: N, 23.7. Found: N, 23.1, 22.9.

Diazotization in hydrochloric acid yielded a clear yellow solution which with alkali turned clear brown and with alkaline β-naphthol gave a yellow-green precipitate.

6-Amino-2,3-dihydroxyquinoxaline (VII, X = NH_2).—6-Nitro-2,3-dihydroxyquinoxaline (5.0 g., 0.024 mole) suspended in a solution of sodium sulfide crystals (20 g., 0.083 mole) in water (100 ml.) was refluxed for two hours, yielding a deep red solution which gradually turned brown. After cooling and diluting with 100 ml. of water, and strongly acidifying with hydrochloric acid, the solution was boiled and filtered from sulfur. Addition of sodium bicarbonate precipitated the free amine as flocks of pale yellow microscopic needles. On heating the compound becomes black at about 330°, but does not melt up to 350°. The yield was 3.22 g. (75% theoretical).

Because the amine is insoluble in almost all ordinary solvents, it cannot be satisfactorily crystallized and analyses are low.

Anal. Calcd. for $C_8H_7O_2N_3$: N, 23.7. Found: N, 23.3, 23.1.

The amine hydrochloride is moderately soluble in either cold or hot water, but the sulfate is sparingly soluble in cold though moderately soluble in hot water. The amine dissolves in aqueous sodium or potassium hydroxides,

sodium carbonate or concentrated ammonium hydroxide to give clear yellow-brown solutions from which the base is reprecipitated by carbon dioxide.

Aqueous solutions of the salts give with ferric chloride a clear blue color. Diazotization and treatment with alkaline β-naphthol gives a deep red solution.

Test for Chemiluminescence.—The four aminobenzoyleneureas and the two amino-2,3-dihydroxyquinoxalines were tested at 28° for possible chemiluminescence on oxidation by visual observation in a dark room. A 10-ml. sample of a 0.04 molar solution of each compound in 0.5 *N* sodium hydroxide was successively treated with 1 ml. of 3% hydrogen peroxide, 1 ml. of 3% potassium ferricyanide. In a second series of tests each 10-ml. sample was treated first with a trace of the catalytic salicylaldehyde ethylenediimine ferric chloride complex,[14] followed by 1 ml. of 3% hydrogen peroxide. In a third series of tests each 10-ml. sample was treated with 10 ml. of 8% sodium hypochlorite solution.

(14) Thielert and Pfeiffer, *Ber.*, **71**, 1401 (1938).

Summary

1. All four isomeric aminobenzoyleneureas and both possible amino-2,3-dihydroxyquinoxalines have been prepared by reduction of the corresponding nitro compounds.

2. None of them shows significant chemiluminescence under conditions which with the isomeric 3-aminophthalhydrazide give intense effects.

3. Previous assumption regarding the indispensability of the hydrazine residue for chemiluminescent power has thus been demonstrated.

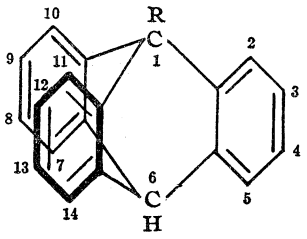
CAMBRIDGE, MASS. RECEIVED MAY 14, 1942

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Triptycene[1] (9,10-*o*-Benzenoanthracene)

BY PAUL D. BARTLETT, M. JOSEPHINE RYAN AND SAUL G. COHEN

Previous publications from this Laboratory have brought out the special properties of substituents located on the bridgehead of a bicyclic ring system.[2] These findings would lead us to

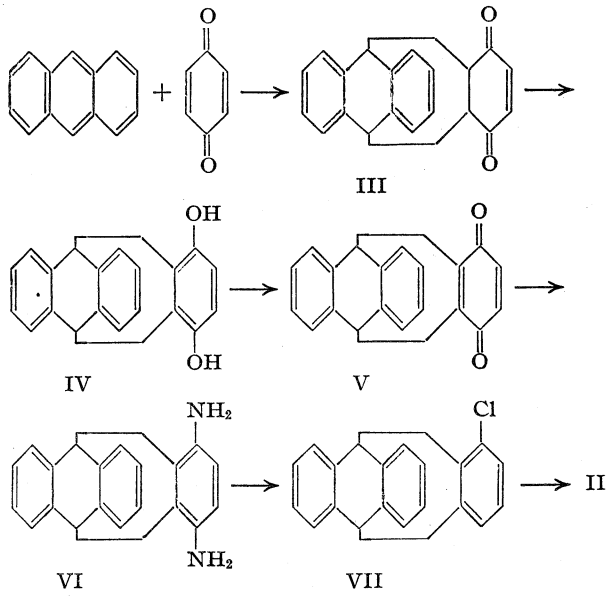


I, R absent

II, R = H

predict that the analog (I) of the triphenylmethyl radical in which the ortho positions of the three phenyl groups are united to a common CH should have much less tendency to exist as a free radical than triphenylmethyl itself, as a result of its inability to assume the coplanar form demanded by the usual resonance structures.[3] With the eventual purpose of testing this prediction we have prepared the parent hydrocarbon II (9,10-*o*-benzenoanthracene, or tribenzobicyclo(2,2,2)octatriene) and studied some of its chemical properties. For convenience, the name "triptycene" is suggested for this symmetrical hydrocarbon.[1]

The steps in the synthesis of triptycene are as follows



The removal of the functional groups was achieved only after very many unsuccessful attempts. We tried to dehydroxylate the hydroquinone IV with zinc dust, to convert it into a dibromide or diiodide with phosphorus halides, to reduce the quinone by hydrogenation, by the

(1) This name is proposed because the shape of this ring system suggests the triptych of antiquity, which was a book with three leaves hinged on a common axis. We are indebted to Professor Mason Hammond of the Harvard Department of Classics for this suggestion.

(2) Bartlett and Knox, THIS JOURNAL, **61**, 3184 (1939); Bartlett and Cohen, *ibid.*, **62**, 1183 (1940); Bartlett and Woods, *ibid.*, **62**, 2933 (1940).

(3) Pauling and Wheland, *J. Chem. Phys.*, **1**, 362 (1933).

Clemmensen and Wolff–Kishner procedures, to gain a start in the reduction by replacing benzoquinone with Δ^2-cyclohexenone in the initial step, as well as several less rational procedures. The hydroxylated ring was successfully reduced, but the hydrogenation product could not be converted to triptycene. Finally, numerous ways were tried for the deamination of the diamine VI, by tetrazotization in dilute and concentrated hydrochloric acid, sirupy phosphoric and concentrated sulfuric acid and mixtures, with nitrous acid and nitrous fumes, followed by attempted reduction with stannous chloride, alkaline formaldehyde, alcohol, and also attempted Sandmeyer reactions. The difficulties appeared to result from the combined facts of the ready nuclear substitution in a diamine and the great tendency of this ring system to yield anthracene under even relatively mild conditions, and especially when the treatment of the substituted ring enabled this to occur irreversibly. Successful deamination of the diamine was accomplished only by tetrazotizing at 10° in a mixture of sulfuric acid, acetic acid and water, destroying the excess nitrous acid, and reducing with hypophosphorous acid.[4] Control of the temperature proved to be of great importance.

The product of the hypophosphorous acid reduction was not triptycene, but monochlorotriptycene accompanied by a little dichlorination product. Apparently the *p*-diazonium substituent, like the *p*-nitro-, activates the N_2-group toward replacement, at the same time deactivating it toward reductive elimination. The replacement of the first N_2-group by chlorine allows the remaining N_2-group to be eliminated, yielding 2-chlorotriptycene as the principal product. The same treatment using the hydrobromide instead of the hydrochloride of the diamine yielded a small amount of dibromotriptycene. Each of these halogenated products was smoothly reduced to triptycene by the method of Busch.[5] In each case the deamination was the weak step in the synthesis giving poor yields.

Triptycene crystallizes in fine white rhomboids melting at 254.8–255.2°, and is advantageously crystallized from methanol–water. It is very soluble in benzene, soluble in ethyl alcohol, ether, acetone, chloroform and slightly soluble in methanol.

To the extent to which the central hydrogen atom of triphenylmethane is activated by the possibility of resonance in the triphenylmethide ion, such activity should be diminished or absent in triptycene. Triptycene in fact yields no exchange with phenylisopropylpotassium under conditions which lead to immediate reaction in the case of triphenylmethane; it is not chlorinated by sulfuryl chloride in the presence of benzoyl peroxide whereas toluene, under identical conditions, gives a high yield of benzyl chloride; and chromic anhydride, under conditions which lead to the formation of triphenylcarbinol from triphenylmethane, gives only anthraquinone and carbon dioxide from triptycene. Moderation of the conditions permitted recovery of only a mixture of unchanged starting material and anthraquinone, showing that if 1-hydroxytriptycene is produced at all under these conditions it is immediately decomposed.

In view of the complete failure of the hydrogen in the 1-position of triptycene to show the reactivity characteristic of the central hydrogen of triphenylmethane, it seems rather likely that the oxidative decomposition of triptycene to anthraquinone is initiated not by attack at the 1-position but by attack upon one of the benzene rings. In seeking a possible reason why these rings should be more susceptible to oxidative attack than normal benzene rings, we observe that the internal bond angles of the bicyclo(2,2,2)octane ring system must always be close to the normal value of 109°28′. This would lead us to expect a Mills–Nixon effect[6] tending to damp the resonance in each benzene ring by giving preference to the bond structures represented in the formula II. Any such effect would render the oxidative disruption of one of the benzene rings more likely, but would disappear upon opening of the bicyclic ring, system and formation of the dihydroanthracene type. In a quantitative oxidation by chromic anhydride in acetic acid slightly more than enough carbon dioxide was produced to account for the missing benzene ring. The Mills–Nixon effect, if present, is not sufficiently extreme to permit reaction of triptycene with maleic anhydride or with triphenylmethyl, since negative results were obtained with both these compounds.

Experimental

Formation of the Adduct III from Anthracene and Quinone.—The route of Clar[7] to the quinone IV was

(4) Adams and Kornblum, THIS JOURNAL, **63**, 188 (1941).

(5) Busch and Stöve, *Ber.*, **49**, 1063 (1916).

(6) See Fieser in Gilman, "Organic Chemistry—An Advanced Treatise," John Wiley & Sons, Inc., New York, N. Y., 1st ed., pp. 71–73.

(7) Clar, *Ber.*, **64**, 1676 (1931).

modified, yielding, under our conditions, an improved product. Anthracene (108 g.) twice recrystallized from xylene, and 73 g. of reagent grade quinone were heated under reflux in 650 cc. of xylene for two hours.[7] The solid was collected on a filter and thoroughly washed with hot water to remove quinone and quinhydrone. It was recrystallized from xylene giving 143 g. (83%) of pale yellow rhomboids. This compound has the characteristic melting behavior observed by Clar, which depends on the rate of heating; it is yellow at 207°, red at 210°, and at higher temperatures it carbonizes.

Rearrangement of the Adduct III to the Hydroquinone IV.—To a solution of 11.5 g. of the adduct III in 150 cc. of glacial acetic acid at the boiling point, four drops of 40% hydrobromic acid were added. A vigorous evolution of heat followed and the solution took on an orange color which gradually faded as a fine white solid precipitated out. After another half hour at the boiling point, the reaction mixture was cooled and filtered; yield 10.3 g. (90%); m. p. 338–340° dec.

Hydrogenation of 2,5-Triptycenediol (IV) with Raney Nickel.—A solution of 2 g. of the hydroquinone IV in 38 cc. of warm dioxane was treated with hydrogen at 1140 lb. pressure in the presence of 1 g. of Raney nickel, and the temperature was gradually raised. At 200° hydrogen absorption took place and had ceased after seventeen hours. The mixture was filtered into water, the resulting solid was washed with petroleum ether and recrystallized from benzene. The product, 0.68 g. of white plates, melted at 220–224°. Its solution in alcoholic alkali turned red on shaking in air and the color was discharged by sodium hydrosulfite. Evidently the triptycenehydroquinone had become hydrogenated in the two unhydroxylated benzene rings.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.20; H, 8.61.

Hydrogenation of the Adduct III with Copper Chromite.—To a solution of 2 g. of the direct addition product III of quinone to anthracene in 35 cc. of dioxane, 0.25 g. of copper chromite was added. The hydrogenation was conducted at 160° under 2200 lb. pressure for ten hours; the solution was filtered in an atmosphere of carbon dioxide and concentrated in a stream of nitrogen. This precaution was found useful in minimizing the dark coloration which always appeared when the hydrogenated solution was exposed to the air. Precipitation with petroleum ether, followed by crystallization from alcohol, yielded 67% of almost colorless crystals melting at 226–228°.

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.15; H, 6.90. Found: C, 82.06; H, 7.10.

This pure product was not oxidized in air in the presence of alkali. It yielded a diacetate, m. p. 177–178°. Apparently the action of copper chromite on the non-aromatic ring of the adduct was to hydrogenate this ring preferentially, whereas the nickel catalyst selected from three aromatic rings the two carrying no oxygenated substituents.

Attempts to Dehydrate the Saturated Diol.—Heating of 0.1 g. of the diol under nitrogen at 300° for thirty minutes, followed by vacuum sublimation, led to the isolation of 0.05 g. of anthracene (mixed melting point).

A mixture of 0.1 g. of the diol and 0.5 g. of anhydrous oxalic acid was heated in an atmosphere of nitrogen. The temperature was slowly raised from 110 to 135° in twenty-five minutes and then to 190° in ten minutes. Anthracene sublimed to the top of the tube.

In the same experiment, but with phosphoric acid instead of oxalic, anthracene appeared somewhat above 100°. The use of *p*-toluenesulfonic acid led to no solid products.

Oxidation of the Hydroquinone IV to the Quinone V.—Nineteeen grams of the hydroquinone IV was dissolved in a minimum amount of hot glacial acetic acid (app. 1100 cc.) and then a solution of 4 g. of potassium bromate in 300 cc. of hot water was added. A deep orange color developed immediately. The solution was boiled for a minute or two and then 200 cc. more of hot water was added and the boiling continued for a few minutes. The solution was cooled and the orange solid collected. The quinone was washed with acetic acid and then with water; yield 17.5 g. (93%); m. p. 292–296°.

The dioxime was prepared by two hours of boiling of a solution of 0.25 g. of V and 1 g. of hydroxylamine hydrochloride in 25 cc. of ethanol. The dioxime was isolated by pouring into water and was crystallized (78% yield of five yellow rosets) from acetic acid. Drying *in vacuo* at 100° for twenty-four hours was necessary to remove acetic acid from the product; m. p. 246° dec.

Anal. Calcd. for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49. Found: C, 76.16; H, 4.67.

Reduction of the Dioxime to the Diamine VI.—Twenty grams of the dioxime was dissolved in 750 cc. of alcohol on the steam-bath. When the alcoholic solution was at about 60°, a solution of 88 g. of stannous chloride in 200 cc. of concentrated hydrochloric acid was added to it with stirring. The mixture was heated for a few minutes more and then cooled and filtered. The solid was washed with alcoholic hydrochloric acid and then with ether. Further purification was effected by dissolving in hot water and precipitating again by the addition of concentrated hydrochloric acid. Each successive reprecipitation makes the salt grayer, probably because of oxidation. The yield was 19.8 g. (86%). The hydrochloride gradually decomposed above 210°.

The free base was prepared by dissolving the diamine hydrochloride in hot water and gradually adding 10% sodium hydroxide. This product turns a grayish-purple in air; m. p. 307° dec. The best analysis obtained was still not good but the compound is extremely difficult to burn.

Anal. Calcd. for $C_{20}H_{16}N_2$: C, 84.50; H, 5.64; N, 9.85. Found: C, 83.06; H, 5.99; N, 9.65.

The diacetyl derivative is obtained as small white crystals from acetic acid, dec. 370°.

Anal. Cacld. for $C_{24}H_{20}N_2O_2$: C, 78.23; H, 5.47. Found: C, 78.05; H, 5.62.

Deamination of the Diamine VI.—A suspension of 5 g. of the amine hydrochloride in 150 cc. of glacial acetic acid was cooled to 10° and to it was added a similarly cooled mixture of 100 cc. of concentrated sulfuric acid, 100 cc. of acetic acid, and 60 cc. of water. The temperature was carefully controlled during the reaction because sulfonation takes place above 15°. Five grams of sodium nitrite was dusted in gradually, turning the solution blood red.

After all the nitrite was added the mixture was stirred in the cold for at least an hour and then urea was added until the solution no longer turned starch–iodide paper blue. The thick solution was added to a filtered solution of 12 g. of sodium hypophosphite in 300 cc. of concentrated hydrochloric acid and allowed to stand overnight. The addition of a quantity of water precipitated 3.8 g. of a flaky tan solid melting at 175° with decomposition. All this material was then subjected to sublimation by heating at 195° at a pressure of 2 mm. The best yield obtained was 1.8 g. of shiny white crystals, m. p. 219–221°. After three recrystallizations from methanol the melting point was 222–223°. A quantitative analysis for chlorine indicated that the product was monochlorotriptycene with a small amount of dichlorotriptycene.

Anal. Calcd. for $C_{20}H_{13}Cl$: C, 83.18; H, 5.17; Cl, 12.30. Found: C, 82.16; H, 4.95; Cl, 13.67.

2,5-Dibromotriptycene.—Reduction of the diazonium compound was attempted in the absence of halogen acid and no reaction whatever took place even over a long period of time. Hydrobromic acid had the same effect as hydrochloric and gave dibromotriptycene, m. p. 227–228°, in very poor yield. Debromination of this compound gave the same product as the dechlorination of chlorotriptycene.

Anal. Calcd. for $C_{20}H_{12}Br_2$: C, 58.43; H, 2.95. Found: C, 58.79; H, 2.73.

Triptycene (II).—This reaction was run by the method of Busch and Stöve;[5] 0.2 g. of the chloro compound was dissolved in 40 cc. of alcohol and 10 cc. of 10% alcoholic potassium hydroxide was added. Four grams of the catalyst, palladium on calcium carbonate, and 12 drops of hydrazine hydrate were added. After refluxing on the steam-bath for one-half hour the mixture was cooled slightly, filtered free of catalyst, and poured into water. There was obtained 0.18 g. of fine white crystals which could be crystallized from methanol–water; m. p. 254.8–255.2°. Like the rest of these compounds the hydrocarbon was hard to burn in a carbon–hydrogen analysis.

Anal. Calcd. for $C_{20}H_{14}$: C, 94.50; H, 5.51. Found: C, **94.13**, 93.25, 93.87, 94.01; H, 5.40, 5.62, 5.32, 5.27.

Triptycene and Phenylisopropylpotassium.—Triptycene (0.1 g.) was placed in a round-bottom, long-necked flask with two side arms. The flask was swept out with nitrogen for a short time and then sealed tightly. Ten cc. of 0.055 *N* phenylisopropylpotassium in dry ether, prepared by Dr. J. E. Jones, was added slowly through one of the side arms. After the solution had stood for twenty-one hours with occasional shaking, no color change could be detected. Dry carbon dioxide was bubbled into the solution and the material removed from the flask. After evaporation of the ether and extraction with alkali, 0.08 g. of triptycene was recovered, m. p. 252–253°, mixed m. p. with known sample 253–254°.

Triptycene and Chlorine.—Triptycene (0.2 g.) was dissolved in 50 cc. of purified carbon tetrachloride. The flask was partially evacuated, and then 25 cc. of the chlorine gas was added from a gas buret. The contents of the flask were thoroughly shaken and left in the sunlight for several days. When the carbon tetrachloride was evaporated, there remained a dirty white solid, m. p. 224°. After sublimation the melting point was 246–248° and a mixed melting point with triptycene was 244–246°. A carbon–hydrogen analysis indicated that a very small amount of chlorine had been taken up.

Anal. Calcd. for $C_{20}H_{14}$: C, 94.50; H, 5.51. Found: C, 91.48; H, 5.10.

In proportions which led to bromination of toluene in good yield[8] without solvent, sulfuryl chloride and benzoyl peroxide had no action on triptycene in carbon tetrachloride, 85% of the hydrocarbon being recovered unchanged.

Oxidation of Triptycene.—Triptycene was oxidized under conditions which oxidize triphenylmethane to triphenylcarbinol. Triptycene (0.2 g.) was dissolved in 50 cc. of purified glacial acetic acid and 0.5 g. of chromic anhydride was added slowly. The flask was heated very gently on the steam-bath overnight. The green solution was poured into water and a yellow solid precipitated which could be crystallized from benzene; m. p. 283–285°; mixed melting point of the sample with anthraquinone 284–285°.

To determine what became of the rest of the molecule during the oxidation, triptycene was oxidized in a stream of dry air. The air was then passed through an absorption tube containing dehydrite and one containing ascarite. A sample of 0.70 g. of triptycene was heated at 55° with 3.5 g. of chromic anhydride, and 0.782 g. of carbon dioxide was absorbed in the ascarite tube. Since the calculated amount would be 0.726 g. if the third benzene ring were completely oxidized, some other formation of carbon dioxide such as further oxidation of anthraquinone or oxidation of acetic acid must be occurring. Anthraquinone was recovered from the reaction flask in 76% yield.

In an attempt to isolate an intermediate in this oxidation 0.2-g. samples of triptycene were put away for a week at room temperature with 0.05 g. of chromic anhydride and 0.12 g. of potassium permanganate, respectively, in acetic acid solution. From the chromic anhydride only triptycene was recovered, but from the reaction with permanganate both anthraquinone and triptycene were recovered, showing that the intermediate products formed are more susceptible to oxidation than triptycene.

Triptycene and Maleic Anhydride.—Triptycene (0.2 g.) and maleic anhydride (1 g.) in 50 cc. of nitrobenzene were refluxed on a hot-plate for four hours. The nitrobenzene was removed *in vacuo* and the black residue was extracted with alcohol. The alcoholic solution was decolorized with charcoal and poured into water. A white solid weighing 0.13 g. was obtained and recrystallized from methanol. It melted at 253–254° alone and at 254° when mixed with triptycene.

Acknowledgment.—We are indebted to the Associates of Physical Sciences of Harvard University for grants in support of this and related work to be published later.

Summary

The symmetrical hydrocarbon, 9,10-*o*-benzenoanthracene or tribenzobicyclo(2,2,2)octatriene (II)

(8) Kharasch and Brown, THIS JOURNAL, **61**, 2142 (1939); Kharasch and Read, *ibid.*, **61**, 3089 (1939).

has been prepared and its properties studied. The name "triptycene" is proposed for this hydrocarbon. Being an analog of triphenylmethane whose symmetrical anion cannot assume the coplanar form demanded by the usual resonance structures, triptycene is entirely lacking in the activity of its aliphatic hydrogen toward potassium exchange, chlorination, and oxidation which characterizes triphenylmethane.

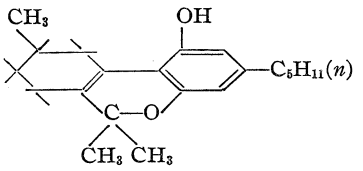
CAMBRIDGE, MASSACHUSETTS RECEIVED JULY 3, 1942

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND FROM THE DEPARTMENT OF PHARMACOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE, IN COLLABORATION WITH THE TREASURY DEPARTMENT, NARCOTICS LABORATORY, WASHINGTON, D. C.]

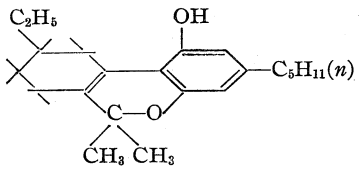
Tetrahydrocannabinol Analogs with Marihuana Activity. XV[1]

BY ROGER ADAMS, S. LOEWE, C. W. THEOBALD AND C. M. SMITH

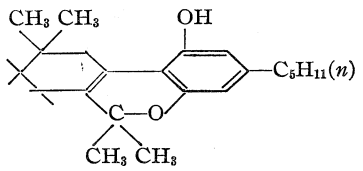
The study of analogs of synthetic tetrahydrocannabinol (I) wherein the left-hand ring was modified has comprised those molecules in which the methyl group was eliminated and those in which the methyl group was shifted to the 8- and 10-positions.[2] This investigation has now been extended, and a variety of products have been synthesized as shown in formulas II–VI.



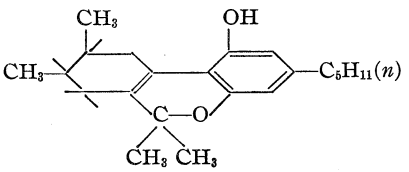
I



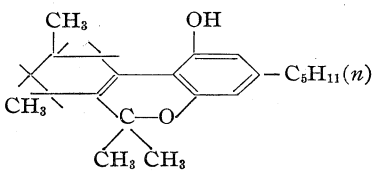
II



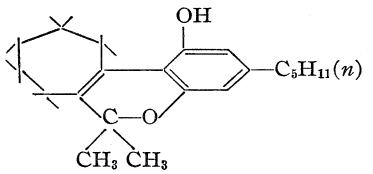
III



IV



V



VI

The pharmacological tests on these molecules by the dog-ataxia method as compared to tetrahydrocannabinol (I) as standard are given in Table I.

TABLE I

PHARMACOLOGICAL ACTIVITY OF TETRAHYDROCANNABINOL ANALOGS

	Expts.	Potency	Mean dev.
1-Hydroxy-3-*n*-amyl-6,6-dimethyl-*9-ethyl*-7,8,9,10-tetrahydro-6-dibenzopyran II	5	0.22	0.02
1-Hydroxy-3-*n*-amyl-*6,6,9,9-tetramethyl*-7,8,9,10-tetrahydro-6-dibenzopyran III	7	.10	.02
1-Hydroxy-3-*n*-amyl-*6,6,8,9-tetramethyl*-7,8,9,10-tetrahydro-6-dibenzopyran IV	10	.11	.03
1-Hydroxy-3-*n*-amyl-*6,6,7,9-tetramethyl*-7,8,9,10-tetrahydro-6-dibenzopyran V	5	.75	.08
2,2-Dimethyl-*3,4-pentamethylene-5-hydroxy-7-n-amyl*-1,2-benzopyran VI	4	.21	.02

These experiments confirm the results from the study of the previously described compounds that relatively minor changes in the left-hand ring structure reduce by 80 to 90% the activity of the

(1) For previous paper see Adams, Smith and Loewe, THIS JOURNAL, **64**, 2087 (1942).

(2) Adams, Smith and Loewe, *ibid.*, **63**, 1973 (1941); see also Russell, Todd, Wilkinson, MacDonald and Woolfe, *J. Chem. Soc.*, 169, 826 (1941).

TABLE II

ETHYL *x*-ALKYLCYCLOHEXANONE-2-CARBOXYLATES

Substituent	B. p. °C.	Mm.	Yield, %	$n^{20}D$	d^{20}_4	*Anal.* Calcd. for $C_{11}H_{18}O_3$: C, 66.65; H, 9.15. Found: C	H	M. p. of 2,4-dinitrophenylhydrazones[a] (cor.), °C.	*Anal.* Calcd. for $C_{17}H_{22}O_6N_4$: C, 53.96; H, 5.86; N, 14.81. Found: C	H	N
5-Ethyl	96–98	2	54	1.4720	1.043	66.84	9.13	122–122.5	54.10	6.02	15.00
5,5-Dimethyl	125–128	14	54	1.4716	1.020	66.85	9.11	89	54.31	6.06	14.82
4,5-Dimethyl	116	10	42	1.4771	1.038	66.68	8.94	146–147	54.16	5.80	15.00
3,5-Dimethyl	103	4	53	1.4560	1.021	66.47	9.16	175	54.09	5.91	14.98

[a] Prepared according to Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1935 (1st ed.), p. 148, and recrystallized from petroleum ether (b. p. 60–110°).

molecules. Compound V, which has a potency not much below that of tetrahydrocannabinol (I), is the only exception; but the normal ataxia action is here accompanied by a convulsant action similar to that observed with tetrahydrocannabidiol.

Experimental

3-Ethylcyclohexanol.—Five hundred grams of *m*-ethylphenol (Eastman Kodak) was reduced with Raney nickel at 136 atm. and 200°. The product was rinsed from the bomb with ethanol, the catalyst removed by filtration, the ethanol removed on the steam-cone, and the residue distilled under reduced pressure. There was obtained 488 g. (89%) of a water-white liquid boiling at 96° (20 mm.) and 192.5–193° (748 mm.); $n^{20}D$ 1.4619; d^{20} 0.9164.

Anal. Calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 75.07; H, 12.67.

The 3,5-dinitrobenzoate of 3-ethylcyclohexanol after crystallization from aqueous ethanol melts at 133–134° (cor.).

Anal. Calcd. for $C_{15}H_{18}O_6N_2$: C, 55.89; H, 5.63; N, 8.69. Found: C, 56.26; H, 5.54; N, 8.67.

The 3,4-dimethylcyclohexanol[3] and the 3,5-dimethylcyclohexanol[4] were prepared in a similar manner. The constants were in agreement with those previously described.

3-Ethylcyclohexanone.—This was prepared by oxidation of 3-ethylcyclohexanol with sodium dichromate and sulfuric acid according to the "Organic Syntheses" procedure for the oxidation of menthol to menthone.[5] A yield of 72% of a liquid boiling at 81° (12 mm.) and at 99–100° (39 mm.) was obtained; $n^{20}D$ 1.4499; d^{20}_4 0.9145.

Anal. Calcd. for $C_8H_{14}O$: C, 76.21; H, 11.19. Found: C, 76.02; H, 11.27.

The semicarbazone of 3-ethylcyclohexanone melted at 166–167° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_9H_{17}ON_3$: C, 58.99; H, 9.36; N, 22.93. Found: C, 59.23; H, 9.57; N, 23.07.

The *p*-nitrophenylhydrazone of 3-ethylcyclohexanone after recrystallization from petroleum ether (b. p. 60–110°) melted at 128–129° (cor.).

These data are not completely in accord with those given by Braun, Mannes and Reuter.[6] They obtained this ketone by dry distillation of the calcium salt of β-ethylpimelic acid and report b. p. 192–194°, $n^{20}D$ 1.4543; semicarbazone, m. p. 184°, *p*-nitrophenylhydrazone, m. p. 130°.

3,4-Dimethylcyclohexanone[7] and 3,5-dimethylcyclohexanone[4] were prepared in 70 and 73% yields, respectively, in the same manner as 3-ethylcyclohexanone.

3,3-Dimethylcyclohexanone was synthesized by the method of Crossley and Renouf[8] and cycloheptanone by ring expansion of cyclohexanone.[9]

All the ketones were readily converted to the keto esters by addition of a mixture of one mole of ketone and one mole of ethyl oxalate to one mole of sodium ethoxide in ethanol to form the glyoxylic esters. These were pyrolyzed, without purification, over powdered soft glass and a trace of iron powder.[1,10] These keto esters, with the exception of ethyl cycloheptanone-2-carboxylate, are new compounds and are listed in Table II.

Ethyl Cycloheptanone-2-carboxylate.—This ester was obtained by the above-mentioned procedure in 14% yield, b. p. 77–79° (0.04 mm.); $n^{20}D$ 1.4700; copper salt, m. p. 193–194° (cor.); the 1-phenyl-3,4-pentamethylene-5-pyrazolone obtained by treatment of the ester with phenylhydrazine melted at 207–210° (cor.) with decomposition. Dieckmann[11] prepared this ester by the cyclization of diethylsuberate and reported b. p. 110–115° (12 mm.); copper salt, m. p. 195°; phenylpyrazolone, m. p. 210°.

1-Hydroxy-3-*n*-amyl-*x*-alkyl-7,8,9,10-tetrahydro-6-dibenzopyrones.—These were prepared from the keto esters

TABLE III

1-HYDROXY-3-*n*-AMYL-?-7,8,9,10-TETRAHYDRO-6-DIBENZOPYRONE

Substituent	Crystallized from methanol, m. p. ° (cor.)	Yield, %	*Anal.* Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C	H
9-Ethyl	167–169	46	77.51	8.64
9,9-Dimethyl	190–190.5	33	76.70	8.75
8,9-Dimethyl	174.5–175.5	61	76.58	8.23
7,9-Dimethyl	151.5–152.5	63	76.55	8.20
			$C_{19}H_{24}O_3$: C, 75.97; H, 8.03. Found:	
3,4-Pentamethylene-5-hydroxy-7-*n*-amylcoumarin	178.5–179.0	45	75.81	8.00

(3) v. Auwers, *Ann.*, **420**, 84 (1920).
(4) v. Braun and Haensel, *Ber.*, **59B**, 1999 (1926).
(5) "Organic Syntheses," Coll. Vol. I (rev. ed.), p. 340.
(6) Braun, Mannes and Reuter, *Ber.*, **66B**, 1499 (1933).
(7) v. Auwers, Hinterseber and Treppmann, *Ann.*, **410**, 257 (1915).
(8) Crossley and Renouf, *J. Chem. Soc.*, **91**, 63 (1907); v. Auwers and Lange, *Ann.*, **401**, 325 (1913).
(9) Kohler, Tishler, Potter and Thompson, THIS JOURNAL, **61**, 1059 (1939).
(10) Shapiro, Thesis, Master of Science, University of Illinois, 1940.
(11) Dieckmann, *Ber.*, **55B**, 2470 (1922).

TABLE IV

1-HYDROXY-3-*n*-AMYL-?-6,6-DIMETHYL-7,8,9,10-TETRAHYDRO-6-DIBENZOPYRANS

Substituent	B. p. °/bath °/mm. °C.	Bath	Mm.	Yield, %	$n^{20}D$	*Anal.* Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C	H
9-Ethyl	172	187	0.1	83	1.5530	80.68	9.68
9,9-Dimethyl	M. p. 89–89.5			78			
8,9-Dimethyl	181–182	210–220	.05	97	1.5512	80.43	9.52
7,9-Dimethyl	186	190	.05	64	1.5473	80.13	9.61
						Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.20; H, 9.62. Found:	
2,2-Dimethyl-3,4-pentamethylene-5-hydroxy-7-*n*-amyl-1,2-benzopyran	180–182	190	.05	71	1.5575	80.23	9.30

by the general procedure previously described.[12] The constants of these molecules are given in Table III.

1-Hydroxy-3-*n*-amyl-?-6,6-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyrans.—The pyrans were formed in the usual way[12]; constants are given in Table IV.

Summary

1. The following pyrans: (1) 1-hydroxy-3-*n*-amyl-6,6-dimethyl-9-ethyl-7,8,9,10-tetrahydro-6-dibenzopyran, (2) 1-hydroxy-3-*n*-amyl-6,6,9,9-tetramethyl-7,8,9,10-tetrahydro-6-dibenzopyran, (3) 1-hydroxy-3-*n*-amyl-6,6,8,9-tetramethyl-7,8,9,10-tetrahydro-6-dibenzopyran, (4) 1-hydroxy-3-*n*-amyl-6,6,7,9-tetramethyl-7,8,9,10-tetrahydro-6-dibenzopyran, and (5) 2,2-dimethyl-3,4-pentamethylene-5-hydroxy-7-*n*-amyl-1,2-benzopyran have been synthesized.

2. The pharmacological potencies of (1), (2), (3), and (5) are only about 10 to 20% that of the synthetic tetrahydrocannabinol standard; the potency of (4) is only slightly less than that of the standard, but the activity of this compound is accompanied by a convulsant action.

(12) Adams and Baker, THIS JOURNAL, **62**, 2405 (1940).

URBANA, ILLINOIS RECEIVED AUGUST 5, 1942

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

The Condensation of Methyl Dipropyl Carbinols with Phenol in the Presence of Aluminum Chloride

BY RALPH C. HUSTON AND CARL R. MELOY[1]

Previous papers from this Laboratory[2,3] have described the condensations of *t*-butyl, *t*-amyl the *t*-hexyl and the *t*-heptyl alcohols with phenol in the presence of aluminum chloride. In a similar manner the dimethylamyl,[4] methylethylbutyl,[5] and diethylpropyl[6] carbinols have been condensed with phenol. In continuation of this investigation the methyldipropyl carbinols have now been prepared.

The 4-methylheptanol-4[7] was prepared by treating two moles of *n*-propylmagnesium bromide with one mole of ethyl acetate, while the 2,3-dimethylhexanol-3[8] resulted from the treatment of one mole of the above Grignard reagent with one mole of 2-methylbutanone-3. Methyl Grignard was used with 2,4-dimethylpentanone-3 in preparing 2,3,4-trimethylpentanol-3.[9]

The alcohols were condensed with phenol in the presence of the anhydrous aluminum salt. Yields of from 47 to 65% of the *p*-*t*-alkylphenols were obtained with no isolation of other isomers or disubstituted products. The α-naphthylurethans and 3,5-dinitrobenzoyl esters of the three *p*-*t*-alkylphenols were prepared.

Huston and Cline[10] isolated and identified from condensations between benzene and methyldipropyl carbinols, 4-methyl-4-phenylheptane, 2,3-dimethyl-3-phenylhexane, and 2,3,4-trimethyl-3-phenylpentane. These alkylbenzenes were nitrated, reduced, diazotized and hydrolyzed to the phenols.[2,3,4] The melting points and mixed melt-

(1) Taken from a thesis presented in partial fulfillment of requirements for the Ph.D. degree.

(2) Huston and Hsieh, THIS JOURNAL, **58**, 439 (1936).

(3) Huston and Hedrick, *ibid.*, **59**, 2001 (1937).

(4) Huston and Guile, *ibid.*, **61**, 69 (1939).

(5) Huston and Snyder, Master's Thesis, Michigan State College, 1938.

(6) Huston and Langdon, Master's Thesis, Michigan State College, 1938.

(7) Gortalow and Saytzeff, *J. prakt. Chem.*, **33**, 203 (1886).

(8) Clarke, THIS JOURNAL, **33**, 528 (1911).

(9) Whitmore and Laughlin, *ibid.*, **54**, 4392 (1932).

(10) Huston and Cline, Master's Thesis, Michigan State College, 1939.

TABLE I

CONDENSATION OF METHYLDIPROPYLCARBINOL WITH PHENOL

Product	4-Methyl-4-*p*-hydroxyphenylheptane	2,3-Dimethyl-3-*p*-hydroxyphenylhexane	2,3,4-Trimethyl-3-*p*-hydroxyphenylpentane
Yield, %	65	47	60
M. p., °C.	63–63.5	72–73	57–58.5
B. p. °C.	282–284	279–281	275–277
B. p. Mm.	738 6	738 2	738 2
Carbon, % (calcd. 81.50)	81.17	80.91	80.96
Hydrogen, % (calcd. 10.75)	10.68	10.77	10.81
3,5-Dinitrobenzoyl esters M. p., °C.	124.5–126.0	97.0–98.0	103.0–103.5
3,5-Dinitrobenzoyl esters N, % (calcd. 7.00)	6.97	7.01	6.98
α-Naphthylurethans M. p., °C.	105.0–106.0	127.5–128.5	106.0–107.0
α-Naphthylurethans N, % (calcd. 3.73)	3.72	3.69	3.70

ing point determinations of the α-naphthylurethans of the phenols thus prepared indicated that they were the same as those prepared in the condensations. The position of the entering group was established through oxidation[11] of the *p*-nitro-*t*-alkylbenzene by heating a portion with 6 *N* nitric acid in a sealed Carius tube at 130°. In each case the product obtained was *p*-nitrobenzoic acid, which was identified by melting point and mixed melting point.

In answer to the suggestion that the alkyl groups might rearrange during condensation and to eliminate any doubt as to the correctness of the formulas assigned the tertiary-octylphenols, attention is called to the following:

(a) The alcohols were prepared by standard methods and checked as to properties with the literature.

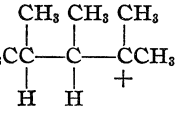
(b) In the rearrangement of alkyl groups during processes of condensation, primary groups may change to secondary or tertiary, and secondary groups may change to tertiary.[12]

We were unable to find instances of the reverse processes in which appreciable yields of primary or secondary groups were formed from groups of higher branching. These generalizations have been recently confirmd by a study of the condensation of secondary alcohols with benzene[13] and with phenol.[14]

(c) Two other possibilities of formation of tertiary octylphenols from 2,3,4-trimethylpentanol-2 might be proposed.

1. One of the tertiary hydrogens might shift to the number three carbon by the intermediate formation of 2,3,4-pentene-2 and the addition of hydrochloric acid. The product of condensation would then be 2,3,4-trimethyl-2-*p*-hydroxyphenylpentane[4] which melts at 74° and gives an α-naphthylurethan which melts at 115°.

2. The formation of the cation



might cause the migration of the methyl group on number three carbon to number two carbon which change might be followed by a migration of the tertiary hydrogen as outlined under (1). Condensation would then give 2,4,4-trimethyl-2-*p*-hydroxyphenylpentane.[4] This phenol melts at 83° and its α-naphthylurethan melts at 102°.

(d) There appears to be only one possibility of rearrangement in the case of 2,3-dimethylhexanol-3. Migration of the tertiary hydrogen would give 2,3-dimethyl-2-*p*-hydroxyphenylhexane[4] as the product of condensation. This compound is a liquid (b. p. 293°) which gives an α-naphthylurethan melting at 105°.

(e) Since 4-methylheptanol-4 contains no tertiary hydrogen, rearrangement without fragmentation does not appear to be possible.

(f) The *seventeen* possible tertiary octyl alcohols have been condensed with phenol yielding *seventeen* different *p*-*t*-octylphenols.[4,5,6]

Experimental

Condensations.—Since all of the condensations were carried out in a similar manner, a typical run is described. Thirty-five grams of phenol was dissolved in 32.5 g. of the octyl alcohol in a 500-ml., three-necked, round-bottomed flask equipped with a short reflux condenser, a

(11) Anschütz and Beckerhoff, *Ann.*, **327**, 219 (1903).

(12) Konowalow, *J. Russ. Phys.-Chem. Soc.*, **27**, 457 (1896); Estreicher, *Ber.*, **33**, 439 (1900); Schramm, *Monatsh.*, **9**, 613, 615 (1888); Grossin, *Bull. soc. chim.*, [2] **41**, 446 (1884); Verley, *ibid.*, [3] **19**, 72 (1898); Meyer and Bernhauer, *Monatsh.*, **53**, 721 (1929); Gilman and Calloway, THIS JOURNAL, **55**, 4197 (1933); Laughlin, Nash and Whitmore, *ibid.*, **56**, 1395 (1934); Ipatieff, Pines and Schmerling, *ibid.*, **60**, 353 (1938), etc.

(13) Huston and Kaye, THIS JOURNAL, **64**, 1576 (1942).

(14) Huston, Guile, Esterdahl and Curtis, "Condensation of Secondary Alcohols with Phenol in the Presence of Aluminum Chloride," in process of publication.

thermometer and a glycerol-sealed stirrer. Seventeen grams of anhydrous aluminum chloride was added in small portions by shaking from a small Erlenmeyer flask equipped with a long neck made of glass tubing. The reaction was carried out at 25–30° and the temperature kept constant by use of a water-bath, when necessary. After standing overnight the mixture was decomposed by pouring on ice and hydrochloric acid. The condensate was extracted from the water solution with ether and the phenols isolated from this ether extract by fractionation.

The 3,5-dinitrobenzoyl esters were prepared by the method of Shriner and Fuson.[15]

The use of pyridine as a catalyst resulted in high yields of the esters which were recrystallized from 60% alcohol.

The method of French and Wirtel[16] was employed in the preparation of α-naphthylurethans. Addition of a few drops of a solution of trimethylamine in ether caused an immediate reaction. Recrystallization was accomplished from warm petroleum ether.

(15) Shriner and Fuson, "Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 138.

(16) French and Wirtel, THIS JOURNAL, **48**, 1736 (1926).

Summary

1. The methyldipropyl carbinols have been condensed with phenol in the presence of aluminum chloride to give good yields of the corresponding *p-t*-octylphenols.

2. The 3,5-dinitrobenzoyl esters and the α-naphthylurethans of these *p-t*-octylphenols have been prepared.

3. The structures have been established by synthesis.

EAST LANSING, MICHIGAN RECEIVED MAY 16, 1942

[CONTRIBUTION FROM THE LEDERLE LABORATORIES]

Water-soluble Compounds with Antihemorrhagic Activity

BY B. R. BAKER AND G. H. CARLSON

In a search for water-soluble compounds with antihemorrhagic activity, a number of derivatives of 2-methyl-1,4-naphthohydroquinone and of the quinone have been prepared and, to minimize duplication of efforts, the experience of this Laboratory is reported at this time.

The highly active sodium salts of 1-acetoxy-2-methyl-4-naphthyl hydrogen succinate[1] (a summary of bioassays is given in Table III) and of the corresponding hydrogen glutarate were sufficiently soluble for parenteral use but were rapidly decomposed in solution even at ordinary temperature.[2] Both the mono- and the disodium salts of the hydroquinone *bis*-hydrogen glutarate were readily hydrolyzed. Likewise the salt of the hydrogen succinate of 3-methyl-1-naphthol,[3] though somewhat more stable than that of 2-methyl-1,4-naphthohydroquinone, gradually decomposed in aqueous solution and further work with partially esterified polycarboxylic acids was discontinued.

Chloroacetyl chloride readily converted 1-acetoxy-2-methyl-4-naphthol to the acetoxy-monochloroacetoxy derivative and the latter, with trimethylamine, yielded the readily soluble quaternary ammonium salt which, like the corresponding diammonium salt prepared from the 1,4-*bis*-chloroacetoxy-2-methylnaphthalene as well as the hydrochloride of 1-acetoxy-4-(β-aminopropionoxy)-2-methylnaphthalene, hydrolyzed in warm, aqueous solution. Accordingly, the purely organic esters proved impractical whether employed in alkaline or acidic media and were not further considered.

Partial esterification of phosphoric, thiophosphoric and sulfuric acids with 1-acetoxy-2-methyl-4-naphthol gave compounds which, as sodium salts, were stable in aqueous solution and could be sterilized by autoclaving. Whereas the phosphate and the sulfate showed antihemorrhagic activity equal to 50 and 35%, respectively, of that of an equimolecular amount of 2-methyl-1,4-naphthoquinone, the thiophosphate was less than

(1) Orientation of the substituents is established by the following reactions. Partial deacetylation of 1,4-diacetoxy-2-methylnaphthalene, prepared by reductive acetylation of 2-methyl-1,4-naphthoquinone [for the method see THIS JOURNAL, **64**, 1096 (1942)], gave an acetoxy-2-methylnaphthol, and its methyl ether, after deacetylation and treatment with ammonium sulfite at 180°, yielded an amine which, as the acetate, was identical with that prepared by reducing the coupling product of 3-methyl-1-naphthol and diazotized sulfanilic acid, acetylating the resulting 2-methyl-aminonaphthol (the hydrochloride of which was readily oxidized to 2-methyl-1,4-naphthoquinone) and converting the acetaminonaphthol to the corresponding methyl ether. By this series of reactions the methoxyl in the acetamino derivative and the acetoxyl group in the acetoxy-2-methylnaphthol are fixed in the 4- and 1-positions, respectively.

(2) The instability of apparently this same hydrogen succinate has been reported also by Buck and Ardis, THIS JOURNAL, **64**, 725 (1942).

(3) The naphthol and 3-methyl-1-tetralone [(a) Bachmann and Struve, THIS JOURNAL, **62**, 1618 (1940); (b) Tishler, Fieser and Wendler, *ibid.*, **62**, 2879 (1940)] were prepared by the improved methods given in the experimental section.

20% as active and was required in too large dosage to be generally applicable in practice. The response with both the phosphate and the sulfate, however, was rapid and these essentially neutral solutions are especially advantageous since administration may be either intravenous or intramuscular.

Whereas the diglucoside of 2-methyl-1,4-naphthohydroquinone is too insoluble for practical use of the aqueous solution,[4] about 3 mg. of the monoglucoside dissolves per milliliter and the solution, like that of the more soluble monomaltoside, showed approximately two-thirds the antihemorrhagic activity of an equimolecular amount of the parent quinone. Aqueous solutions of the glycosides are slowly oxidized by air but are stable in the absence of oxygen and under such conditions, or in the presence of reducing agents such as bisulfite, may be sterilized by autoclaving.

In contrast to the glycosides described above, those of 3-methyl-1-naphthol were less active and showed complete response at a minimum of 10 and 20 micrograms, respectively. Glycoside formation, apparently, had decreased the activity of the naphthol somewhat more than that of 2-methyl-1,4-naphthohydroquinone, but, whereas the naphthol has been reported as active at concentrations of 0.6 microgram,[5] complete response was obtained with no less than 5 micrograms and the relative decrease in the activities appears to be very nearly the same. Comparatively large doses of the naphthol derivatives are required for therapeutic uses, but these compounds have the advantage of being stable in aqueous solution without addition of stabilizers.

Complete response was obtained with 50 and 3 micrograms of the mono- and the dihydrochlorides, respectively, of 1-amino- and 1,4-diamino-2-methylnaphthalene,[6] but, on conversion to the monoacetates, these compounds were inactive at the high concentration. The N-(2-methyl-1-naphthyl)-gluconamide and the N-(1-amino-2-methyl-4-naphthyl)-succinamic acid[7] showed corresponding low activities and were inapplicable. Furthermore, because aqueous solutions of the hydrochlorides of these amines were photosensitive and oxidized very easily, commercial application, even of stabilized solutions, seemed inadvisable.

The decreased activity of 2-methyl-1,4-naphthoquinone-ω-potassium sulfonate,[8] of 2-piperidino-1-naphthol[9] and of 1-amino-2-naphthylacetic acid as compared with the parent compounds substantiates the now widely held opinion that, for high antihemorrhagic activity, the methyl group must remain intact in the 2-methylnaphthalene derivatives and the inactivity of 3-methyl-1,4-dihydroxyisoquinoline[10] indicates that alteration in the nuclear structure similarly results in inactivation.[11]

Experimental

1-Acetamino-2-methyl-4-methoxynaphthalene. (A) From 1,4-Diacetoxy-2-methylnaphthalene.—A mixture of 20 g. of 1-acetoxy-2-methyl-4-naphthol,[1] 20 cc. of dimethyl sulfate, 40 g. of anhydrous potassium carbonate and 200 cc. of acetone was boiled for fourteen hours, the filtered solution, diluted with benzene, was washed with water, cold 2% alkali containing a little sodium dithionite, again with water and solvent was distilled from the benzene solution *in vacuo*. The residue, crystallized from petroleum ether, gave 19 g. of the methyl ether, melting at 67–68° after crystallization from ethanol. *Anal.* Calcd. for $C_{14}H_{14}O_3$: C, 73.0; H, 6.1. Found: C, 72.7; H, 6.5.

Deacetylation of the methyl ether (15 g.) with sodium methylate gave 4-methoxy-2-methyl-1-naphthol (5.5 g.; m. p. 101–103° after crystallization from carbon tetrachloride. *Anal.* Calcd. for $C_{12}H_{12}O_2$: C, 76.7; H, 6.4. Found: C, 76.9; H, 6.6), but a better yield was obtained by adding, during ten minutes, 80 cc. of 10% sodium hydroxide containing 0.5 g. of sodium dithionite to a boiling solution of 19 g. of 1-acetoxy-2-methyl-4-methoxynaphthalene in 80 cc. of methanol and, after forty-five minutes, diluting the cooled solution with water. Extraction of the benzene solution of the product with 5% alkali and acidification of the alkaline extract yielded 13 g. of the methoxynaphthol, m. p. 101–103°.

In the conversion to the 1-amino- derivative, an agitated mixture of 2-methyl-4-methoxy-1-naphthol (15 g.), 25 g. of ammonium sulfite and 75 cc. of 9% ammonia water was heated at 175–180° for thirty hours, the oily product was dissolved in benzene, unchanged naphthol was removed by 10% alkali containing a little sodium dithionite, solvent was evaporated from the washed benzene solution and the residue was distilled at 1 mm. A solution of the crude 1-amino-2-methyl-4-methoxynaphthalene in 10 cc. of benzene was treated with 1 cc. of acetic anhydride and,

(4) Riegel, Smith and Schweitzer, THIS JOURNAL, **63**, 1231 (1941).

(5) Fieser, Tishler and Sampson, *J. Biol. Chem.*, **137**, 685 (1941).

(6) In contrast, 1-amino-3-methylnaphthalene was inactive in concentrations of 25 micrograms.

(7) Identity of the acetate of the succinamic acid prepared from 1,4-diamino-2-methylnaphthalene with that obtained by converting 1-acetamino-2-methyl-4-aminonaphthalene to the succinamic acid established the structure.

(8) Attempts to prepare the ω-sulfonic acid by oxidation of bis-ω-(2-methyl-1,4-dimethoxynaphthalene)-disulfide led to the formation of 2-methyl-3-hydroxy-1,4-naphthoquinone-ω-sulfonic acid. See the experimental section for details.

(9) Prepared according to the method of Auwers, *Ann.*, **344**, 289 (1906).

(10) Prepared according to the method of Gabriel and Colman, *Ber.*, **33**, 989 (1900).

(11) Christiansen and Dolliver [THIS JOURNAL, **63**, 1470 (1941)], report that 6-methyl-5,8-quinolinequinone is inactive.

TABLE I

Expt.	Substance	G.	Anhydride, g.	Pyridine, cc.	Time, hr.	Yield, g.	M. p., °C.	Analyses: Calcd. for	C	H	Found: C	H
I	1-Acetoxy-2-methyl-4-naphthol	4.3	8	30	24	2.2	136–138	$C_{17}H_{16}O_4$	64.6	5.1	65.4 65.3	5.5 5.3
II	1-Acetoxy-2-methyl-4-naphthol	2.5	5	10	43	2.4	109–110	$C_{18}H_{18}O_6$	65.4	5.5	65.7	5.6
III	3-Methyl-1-naphthol	1	2.5	10	50	0.85	109–111	$C_{15}H_{14}O_4$	69.7	5.5	69.4	5.3
IV	2-Methyl-1,4-naphthohydroquinone	1.5	4.0		16	3.0	156–158	$C_{21}H_{22}O_8$	62.7	5.5	62.6	5.1

after two hours at room temperature, the amide (0.5 g.; m. p. 197–199° after crystallization from ethanol) was filtered off. *Anal.* Calcd. for $C_{14}H_{15}O_2N$: C, 73.3; H, 6.6; N, 6.1. Found: C, 73.5; H, 7.0; N, 6.3.

(B) From 3-Methyl-1-naphthol.—The naphthol (4 g.; preparation described below) was treated with a solution prepared by diazotizing 5.3 g. of sulfanilic acid, the azo-derivative was reduced with 16 g. of sodium dithionite and the precipitated aminonaphthol, purified by recrystallization from hydrochloric acid containing stannous chloride, yielded 3.4 g. of pure 1-amino-2-methyl-4-naphthol hydrochloride (charred at 270°). *Anal.* Calcd. for $C_{11}H_{12}NOCl$: C, 63.1; H, 5.8; N, 6.7. Found: C, 63.2; H, 5.7; N, 6.9.

Oxidation of 1 g. of the aminonaphthol with acidified potassium dichromate gave 0.75 g. of 2-methyl-1,4-naphthoquinone (m. p. 103–105°) which did not depress the melting point of an authentic sample.

A solution of 1 g. of the aminonaphthol hydrochloride in 25 cc. of water at 75°, treated with 0.6 cc. of acetic anhydride and 0.5 g. of sodium acetate in 3 cc. of water, gave 0.98 g. of 1-acetamino-2-methyl-4-naphthol, m. p. 206–208° after crystallization from diluted ethanol. *Anal.* Calcd. for $C_{13}H_{13}O_2N$: C, 72.6; H, 6.1; N, 6.5. Found: C, 72.9; H, 6.5; N, 6.5.

The acetaminonaphthol (0.67 g.), methylated in the usual way with dimethyl sulfate and anhydrous potassium carbonate in acetone solution, gave 0.53 g. of the ether which, crystallized from diluted ethanol, melted at 198–200° and did not depress the melting point of the 1-acetamino-2-methyl-4-methoxynaphthalene prepared as previously described. *Anal.* Calcd. for $C_{14}H_{15}O_2N$: C, 73.3; H, 6.6; N, 6.1. Found: C, 73.0; H, 6.9; N, 6.1.

Preparation of the Esters of the Polycarboxylic Acids.—The naphthols were treated at room temperature with succinic anhydride (glutaric anhydride, expt. II) in pyridine solution, ether was added, and the solution was extracted successively with dilute hydrochloric acid and sodium bicarbonate (expt. I); or the reaction product was added to cold hydrochloric acid, the mixture was extracted with ether, and the acidic product, isolated by extraction with sodium bicarbonate, was crystallized from a carbon tetrachloride–chloroform (expts. I and II), or benzene–heptane solution (expt. III). The ether solution of the original reaction mixture (expt. II), after extraction with sodium bicarbonate and concentration, was diluted with carbon tetrachloride and yielded 0.8 g. of *bis*-(1-acetoxy-2-methyl-4-naphthyl) glutarate, m. p. 164–166° after crystallization from an alcohol–benzene solution. *Anal.* Calcd. for $C_{31}H_{28}O_8$: C, 70.3; H, 5.3. Found: C, 70.4; H, 5.4.

In experiment IV the hydroquinone was boiled with glutaric anhydride and 5 cc. of dimethylaniline in 25 cc. of chloroform, the solution was washed successively with dilute hydrochloric acid and sodium bicarbonate, the alkaline extract was acidified and the precipitated product crystallized from ethanol. The results are summarized in Table I.

Preparation of the Esters of the Amino Acids. (A) 1-Acetoxy-2-methyl-4-naphthyl N-Trimethylglycinate Chloride.—The acetoxynaphthol (5 g.) was treated with 4 cc. of chloroacetyl chloride and 10 cc. of dimethylaniline in 50 cc. of chloroform and, after one hour at 25°, the mixture was boiled thirty minutes. After extraction with dilute hydrochloric acid and sodium bicarbonate solution, solvent was distilled *in vacuo* and the residue, crystallized from ethanol, gave 6 g. of the chloroacetate; m. p. 103.5–104° after recrystallization from a chloroform–heptane solution. *Anal.* Calcd. for $C_{15}H_{13}O_4Cl$: C, 61.5; H, 4.5. Found: C, 61.6; H, 4.9.

A solution of 3 g. of the chloroacetate in 30 cc. of acetone containing 1.2 g. of trimethylamine gave, after twenty-four hours at room temperature, 3.3 g. of the glycinate chloride, m. p. 217° after crystallization from an alcohol–acetone solution. *Anal.* Calcd. for $C_{18}H_{22}O_4NCl$: C, 61.4; H, 6.3; N, 4.0. Found: C, 61.2; H, 6.9; N, 3.9.

(B) 2-Methyl-1,4-naphthohydroquinone *bis*-N-Trimethylglycinate Chloride.—The hydroquinone (5 g.), acylated as previously described with 7.5 cc. of chloroacetyl chloride and 13 cc. of dimethylaniline in 50 cc. of chloroform, gave 7 g. of the *bis*-chloroacetate (m. p. 109–110° after recrystallization from heptane. *Anal.* Calcd. for $C_{15}H_{12}O_4Cl_2$: C, 55.1; H, 3.7. Found: C, 54.7; H, 3.9) a portion (3.3 g.) of which, dissolved in 20 cc. of dioxane, was treated with a solution of 1.5 g. of trimethylamine in 15 cc. of acetone and, after twenty-four hours at room temperature, the deposited gummy product, triturated with acetone and crystallized from a methanol–acetone solution, yielded 1.3 g. of the *bis*-glycinate chloride, m. p. 204° after recrystallization. *Anal.* Calcd. for $C_{21}H_{30}O_4N_2Cl\cdot 2H_2O$: C, 52.4; H, 7.1; N, 5.8; Cl, 14.8. Found: C, (1) 52.4, (2) 52.6; H, (1) 6.9, (2) 7.3; N, 6.0; Cl, 14.9.

(C) 1-Acetoxy-2-methyl-4-naphthyl β-Alanate Hydrochloride.—A mixture of carbobenzoxy-β-alanyl chloride (prepared from 10 g. of carbobenzoxy-β-alanine), 7 g. of the acetoxynaphthol and 10 cc. of dimethylaniline in 50 cc. of chloroform was boiled for thirty minutes, the product, purified as previously described, gave 5.5 g. of the carbobenzoxy-β-alanate (m. p. 106.5–108°. *Anal.* calcd. for $C_{24}H_{23}O_6N$: C, 68.5; H, 5.5; N, 3.3. Found: C, 68.2; H, 5.6; N, 3.5), a portion (2 g.) of which, hydrogenated in the usual manner in glacial acetic acid, yielded, after treatment with hydrogen chloride, removal of the

solvent *in vacuo*, trituration with chloroform and crystallization from a methanol–ether solution, 0.65 g. of the β-alanate hydrochloride, m. p. 164–167° after crystallization from a chloroform–acetone solution. *Anal.* Calcd. for $C_{16}H_{18}O_4NCl \cdot H_2O$: C, 56.2; H, 5.9; N, 4.1. Found: C, 55.8; H, 6.1; N, 4.1.

Preparation of the Sodium Salts of the Inorganic Esters of 1-Acetoxy-2-methyl-4-naphthol.—Pyridine solutions of the acid halide and the naphthol (except that the naphthol was boiled ten minutes with a carbon tetrachloride solution of pyridine and chlorosulfonic acid in the preparation of the sulfate) were mixed (at 15–20° and 40°, respectively, in the preparation of the sodium phosphate and the thiophosphate), the product was poured onto ice (except that in the preparation of the sulfate, solvent was decanted and the residue dissolved in 30 cc. of water), the mixture was neutralized with sodium carbonate and the pure sodium salt was isolated as described below.

(A) 1-Acetoxy-2-methyl-4-naphthyl Sodium Sulfate.—The sodium carbonate solution of the product obtained from 3 g. of the naphthol and 1.5 cc. of chlorosulfonic acid was extracted with chloroform and added to an equal volume of saturated sodium chloride solution. The precipitated sulfate (3.6 g.) was recrystallized twice from water. *Anal.* Calcd. for $C_{13}H_{11}SO_6Na$: C, 49.1; H, 3.5; Na, 7.2. Found: C, 48.5; H, 3.6; Na, 7.3.

(B) 1-Acetoxy-2-methyl-4-naphthyl Sodium Phosphate.—The sodium carbonate solution of the phosphate prepared from 20 g. of the naphthol and 13 cc. of phosphoryl chloride was evaporated to dryness *in vacuo*, the residue was extracted with hot butanol, the extract was concentrated to a sirup *in vacuo*, hot isopropyl alcohol was added and the deposited salt (31.5 g.) recrystallized from a butanol–isopropyl alcohol solution, gave 20 g. of the pure phosphate. *Anal.* Calcd. for $C_{13}H_{11}O_6PNa_2 \cdot H_2O$: C, 43.6; H, 3.1. Found: C, 43.1; H, 3.5.

(C) 1-Acetoxy-2-methyl-4-naphthyl Sodium Thiophosphate.—The thiophosphate, prepared from 5 g. of the naphthol and 3.5 g. of thiophosphoryl chloride, was purified as the corresponding phosphate and gave 3 g. of pure compound. *Anal.* Calcd. for $C_{13}H_{11}SPO_3Na_2 \cdot H_2O$: C, 43.3; H, 4.1; S, 8.9. Found: C, 44.2; H, 4.8; S, 8.3.

Preparation of the Glycosides. (A) Glucosides.—Solutions of α-glucose pentaacetate in acetic acid (60 cc. and 15 cc., respectively, in expts. I and III) were saturated with hydrogen bromide. After fifteen hours at room temperature in experiment I, but after two hours in experiment II, chloroform (200 cc. and 50 cc. in the respective experiments) was added, the solutions were washed with ice-water, dried with calcium chloride and stirred twenty-four hours and seventeen hours, respectively, with the naphthol, anhydrous potassium carbonate and reagent acetone. Solvent was distilled *in vacuo* from the filtered solutions, the residue was crystallized from methanol and was recrystallized from an acetone–methanol solution in experiment I.[12] In experiment III the filtered solution of the acetylated glycoside was washed successively with 1% sodium chloride solution, 10% alkali containing a little sodium dithionite and with dilute acetic acid. Solvent was distilled *in vacuo* and the residual acetate was crystallized from ethanol.

(B) Maltosides.—In experiment II the solution of the maltose octaacetate in 260 cc. of acetic acid was added to a solution of 40 g. of hydrogen bromide in 120 cc. of acetic acid at 0° and, after thirty minutes, 200 cc. of chloroform was added, the mixture was extracted twice with ice-water and the dried solution was stirred for twenty-four hours with the naphthol, reagent acetone and anhydrous potassium carbonate. The filtered solution was washed successively with water, 2% alkali, acetic acid and solvent was evaporated *in vacuo*. The residue (m. p. 175–177° with sintering at 140° after crystallization from methanol) was purified by crystallization from a benzene–heptane solution. The acetylated bromomaltose used in experiment IV was prepared as described above from a solution of maltose octaacetate in 60 cc. of acetic acid and 26 cc. of acetic acid saturated with hydrogen bromide at 0° and the acetylated maltoside was purified by crystallization from ethanol.

(C) Deacetylations.—The acetylated glycosides were treated with hot sodium methylate solutions, the solutions were acidified with acetic acid, solvent was distilled *in vacuo* and the residual glycosides were purified in (Ia) by trituration with ethyl acetate followed by crystallization from 75 cc. of water and separation from a methanol solution by dilution with ethyl acetate; (IIa) by trituration with ethyl acetate and crystallization from water; (IIIa) by trituration with chloroform (the insoluble product, 0.63 g., melted at 223–225°) and crystallization from 50% acetic acid; and (IVa) by crystallization from a butanol–ethyl acetate solution. The results are summarized in Table II.

3-Methyl-1-tetralone.—A mixture of diethyl α-phenyl-β-methylglutarate[13] (70 g.), 400 cc. of concentrated sulfuric acid and 80 cc. of water was heated on the steam-bath for three hours, poured into 500 cc. of ice-water, the solidified precipitate was crystallized from a benzene–petroleum ether solution and gave 37.5 g. of 2-methyl-4-keto-1,2,3,4-tetrahydro-1-naphthoic acid, m. p. 107–110° after recrystallization from benzene. *Anal.* Calcd. for $C_{12}H_{12}O_3$: C, 70.7; H, 5.9. Found: C, 70.8; H, 6.1.

A mixture of 46.5 g. of the naphthoic acid, 0.5 g. of cupric oxide and 47 g. of quinoline was heated seventy minutes at 200–215°, the cooled mixture was added to cold, dilute hydrochloric acid, extracted with petroleum ether, the extract was washed successively with dilute hydrochloric acid, alkali, acetic acid and, after removal of solvent, distilled to give 28.5 g. of 3-methyl-1-tetralone, b. p. 142–143° at 16 mm.; oxime, m. p. 121–122.5°.[3]

3-Methyl-1-naphthol. (a) From 2-Methyl-4-keto-1,2,3,4-tetrahydro-1-naphthoic Acid.—The acid (3 g.) and 0.5 g. of sulfur were heated to 255–265° for thirty minutes and, after addition of a small amount of copper oxide, the product was distilled at 1 mm. A benzene solution of the distillate was washed successively with sodium bicarbonate and alkali containing sodium dithionite. Upon acidification, the alkaline extract gave the naphthol which, after two crystallizations from a heptane–petroleum ether solution, melted at 88–90°, resolidified and

(12) The method of preparation of glycosides developed by Montgomery, Richtmyer and Hudson [THIS JOURNAL, **64**, 690 (1942)] also gave the acetate.

(13) Connor and McClellan, *J. Org. Chem.*, **3**, 573 (1939).

TABLE II

Expt.	Aceto-sugar, g.	Naphthol	G.	K_2CO_3, g.	Ace-tone, cc.	Acetate, g.	Meth-anol, cc.	Na, mg.	Glyco-side, g.	M. p., °C.	Analyses, % Calcd. for	C	H	Found C	H
I	46.5	1-Acetoxy-2-methyl-	21	60	180	17.0				180–181	$C_{27}H_{30}O_{12}$	59.4	5.5	59.6	5.8
Ia		4-naphthol				19.0	190	120	9.2	206–208	$C_{17}H_{20}O_7$	60.7	6.0	60.3	5.5
														60.6	6.9
II	76.0	1-Acetoxy-2-methyl-	25	60	200	29.5				183–184	$C_{39}H_{46}O_{20}$	56.2	5.6	56.3	6.1
IIa		4-naphthol				10	100	75	2.7	145–150	$C_{23}H_{30}O_{12}$. H_2O	53.6	6.2	53.0 53.2	6.3 6.1
III	12.0	3-Methyl-1-naphthol	4.2	15	50	1.9				135–137	$C_{25}H_{28}O_{10}$	61.3	5.8	61.0	5.6
IIIa						1.0	10	10	0.3	223–225	$C_{17}H_{20}O_6$	63.7	6.3	63.4	6.1
IV	16.0	3-Methyl-1-naphthol	4.5	13	50	2.9				152.5–154	$C_{37}H_{44}O_{18}$	57.3	5.7	57.2	5.7
IVa						14.3	200	200	2.8	175–178	$C_{23}H_{30}O_{11}$	57.3	6.3	57.2	6.8

In experiment IIa the maltoside at first appeared to be hydrated with no definite melting point and even after twenty-four hours *in vacuo* over potassium hydroxide the compound melted over a range of 5°. Deacetylation of 60.5 g. of 1-acetoxy-2-methyl-4-naphthyl-β-maltoside heptaacetate in an atmosphere of nitrogen, using 600 cc. of methanol and 0.5 g. of sodium, gave 35 g. of crude maltoside, a portion (31.5 g.) of which was recrystallized from water and yielded 29 g. of pure product.

melted at 92.5–93°.[3] *Anal.* Calcd. for $C_{11}H_{10}O$: C, 83.5; H, 6.4. Found: C, 83.2; H, 6.6.

(b) **From 3-Methyl-1-tetralone.**—The tetralone (15 g.) was brominated in the usual manner, boiled with dimethylaniline and gave 10.2 g. of the naphthol, m. p. 87–89°.

2-Methyl-1-naphthylamine.—A suspension of 40 g. of 1-nitro-2-methylnaphthalene[14] in 160 cc. of methanol was reduced with Raney nickel at 1–3 atmospheres pressure, the filtered solutions of three similar preparations were combined, treated with 70 cc. of concentrated hydrochloric acid and yielded, after filtration and concentration, 122 g. of the hydrochloride, m. p. 228–231° with decomposition after crystallization from methanol.[15] *Anal.* Calcd. for $C_{11}H_{12}NCl$: C, 68.2; H, 6.3; N, 7.2; Cl, 18.3. Found: C, (1) 68.0, (2) 67.7; H, (1) 6.6, (2) 6.4; N, (1) 7.7, (2) 8.1; Cl, (1) 20.0, (2) 19.7.

The amine hydrochloride (5 g.), treated with 7 cc. of acetic anhydride and 25 cc. of pyridine gave 3.8 g. of the acetamino derivative (m. p. 191–192° after crystallization from benzene.[15] *Anal.* Calcd. for $C_{13}H_{13}ON$: C, 78.3; H, 6.6; N, 7.0. Found: C, (1) 78.1, (2) 78.2; H, (1) 6.6, (2) 6.1; N, (1) 7.2, (2) 7.2) and the same product was obtained by acetylating the free amine in chloroform solution.

N-(2-Methyl-1-naphthyl)-gluconamide.—A mixture of 3 g. of 1-amino-2-methylnaphthalene, 3.5 g. of δ-gluconolactone, 2 cc. of water and 4 cc. of acetic acid was heated at 100° in an atmosphere of nitrogen for eighteen hours. After dilution with chloroform and water, the precipitated product (3.4 g.) was filtered off and crystallized from 50% acetic acid, m. p. 212–214°. *Anal.* Calcd. for $C_{17}H_{21}O_6N$: C, 60.8; H, 6.3. Found: C, 60.3; H, 6.6.

1-Amino-2-naphthylacetic Acid.—A mixture of 5.5 g. of 1-nitro-2-naphthylacetic acid,[16] 75 cc. of methanol and 10 cc. of 10% sodium hydroxide was hydrogenated in the usual manner with Raney nickel at room temperature. The filtered solution, diluted with 100 cc. of water and acidified with acetic acid, yielded 3.8 g. of the amine, m. p. 238–240° (with decomposition) after crystallization from methanol. *Anal.* Calcd. for $C_{12}H_{11}O_2N$: C, 71.7; H, 5.6; N, 7.0. Found: C, (1) 71.8, (2) 72.0; H, (1) 5.7, (2) 5.6; N, (1) 6.9, (2) 7.0.

3-Methyl-1-naphthylamine Hydrochloride.—An agitated mixture of 5 g. of 3-methyl-1-naphthol, 7.5 g. of ammonium sulfite, 7.5 cc. of 28% ammonia water and 15 cc. of water was heated at 165° for sixteen hours. A benzene solution of the oily product was washed with 10% alkali and water, treated with 50 cc. of 5% hydrochloric acid and yielded 4.7 g. of the amine hydrochloride, m. p. 265–267° after crystallization from 60% hot ethanol by addition of concentrated hydrochloric acid. *Anal.* Calcd. for $C_{11}H_{12}NCl$: C, 68.2; H, 6.3; N, 7.2. Found: C, 68.3; H, 6.7; N, 8.0.

1,4-Diamino-2-methylnaphthalene. (a) **From 2-Methyl-1,4-naphthohydroquinone.**—The hydroquinone (7.8 g.), heated as above with 20 g. of ammonium sulfite, 20 cc. of 28% ammonia water and 40 cc. of water, gave an oily product which, treated as described above, yielded 5.5 g. of the diamine dihydrochloride (m. p. 287–290°; 299–301° after recrystallization from hot water by addition of concentrated hydrochloric acid. *Anal.* Calcd. for $C_{11}H_{14}N_2Cl_2$: C, 54.3; H, 5.8; N, 11.5. Found: C, 54.8; H, 6.3; N, 11.2).

The diacetamino compound (0.8 g., prepared by heating a solution of 1 g. of the dihydrochloride in 10 cc. of water and 25 cc. of acetic acid with 3 cc. of acetic anhydride and 1 g. of sodium acetate) melted at 306–308° and was identical with that prepared from the diamine obtained on reduction of the coupling product of diazotized sulfanilic acid and 1-amino-2-methylnaphthalene as described below.

(b) **From 4-(*p*-Sulfo-phenylazo)-1-amino-2-methylnaphthalene.**—A solution of 2.5 g. of the azo-derivative[15] in 40 cc. of 2.5% sodium hydroxide was reduced at 70° with 3.5 g. of sodium dithionite, 25 cc. of ethylene dichloride was added and concentration of the extract, followed by dilution with petroleum ether, yielded 0.7 g. of the diamine, m. p. 113–114° after crystallization from a benzene–petroleum ether solution.[17] The dihydrochloride was obtained in a similar reduction by treating the ethylene dichloride extract with 5 cc. of concentrated hydrochloric acid, evaporating to dryness and crystallizing the residue from hot water by addition of concentrated hydrochloric

(14) Prepared by the method of Fierz-David and Mannhardt, *Helv. chim. acta*, **20**, 1027 (1937).

(15) Lesser [*Ann.*, **402**, 1 (1913)] gives a value of about 230°, with decomposition, for the hydrochloride and 188° for the acetylated amine.

(16) Mayer and Oppenheimer, *Ber.*, **49**, 2110 (1916).

(17) Vesely and Kapp [*Rec. trav. chim.*, **44**, 360 (1925)] prepared this compound by reduction of 1-amino-2-methyl-4-nitronaphthalene and gave the m. p. as 111–113°.

acid, m. p. 300–301°. *Anal.* Calcd. for $C_{11}H_{14}N_2Cl_2$: C, 54.3; H, 5.8; N, 11.5; Cl, 28.4. Found: C, (1) 54.4, (2) 54.7; H, (1) 5.9, (2) 6.1; N, (1) 11.1, (2) 11.2; Cl, (1) 28.7, (2) 28.9. Similarly, a suspension of the azo-compound (3.5 g.) in 35 cc. of water was reduced with 5 g. of stannous chloride in 15 cc. of hot concentrated hydrochloric acid and gave 1.5 g. of the dihydrochloride, m. p. 297–300° after crystallization from dilute hydrochloric acid.

The diamine (5 g.), treated with 15 cc. of acetic anhydride in 35 cc. of dioxane, deposited 7.2 g. of pure 1,4-diacetamino-2-methylnaphthalene (m. p. 308–309° after crystallization from an acetic acid–benzene solution. *Anal.* Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.2; H, 6.3; N, 11.0. Found: C, (1) 70.2, (2) 70.0; H, (1) 6.4, (2) 6.4; N, (1) 11.0, (2) 10.8).

(c) From 4-(*p*-Carboxyphenylazo)-1-amino-2-methylnaphthalene.—A solution of diazotized *p*-aminobenzoic acid (prepared from 1.4 g. of the acid) was added at 2° to a solution of 1.6 g. of 1-amino-2-methylnaphthalene in 120 cc. of water and 1.5 cc. of concentrated sulfuric acid, the precipitated azo-compound was reduced in the usual manner with palladinized carbon and the filtered solution, after appropriate manipulations, deposited 0.8 g. of the diamine (m. p. 109–111°: 0.3 g. of impure material separated from the filtrate).

1-Acetamino-2-methyl-4-aminonaphthalene.—A mixture of 14.5 g. of 1,4-diacetamino-2-methylnaphthalene, 70 cc. of ethanol and 70 cc. of concentrated hydrochloric acid was boiled for three hours and, after several hours at 5°, the deposited hydrochloride (12.9 g.) was filtered off. A solution of 14.1 g. of the crude product in 350 cc. of hot water, basified with ammonium hydroxide, deposited the free amine which, crystallized from ethylene dichloride, gave 8 g. of 1-acetamino-2-methyl-4-aminonaphthalene (m. p. 190–191°. *Anal.* Calcd. for $C_{13}H_{14}N_2O_4$: C, 72.8; H, 6.6; N, 13.1. Found: C, 73.1; H, 6.7; N, 13.1), identical with the product (0.99 g. *Anal.* Found: C, 72.9; H, 6.8; N, 13.3) obtained by reduction of 1.25 g. of 1-acetamino-2-methyl-4-nitronaphthalene[17] in 25 cc. of ethanol with Raney nickel at room temperature.

N-(1-Acetamino-2-methyl-4-naphthyl)-succinamic Acid. (A) From N-(1-Amino-2-methyl-4-naphthyl)-succinamic Acid.—A hot chloroform solution of 1 g. of 2-methyl-1,4-diaminonaphthalene was treated with 0.7 g. of succinic anhydride, the crude product (1.57 g.) was crystallized from ethanol and gave 1 g. of the pure succinamic acid, m. p. 192° with decomposition. *Anal.* Calcd. for $C_{15}H_{16}O_3N_2$: C, 66.2; H, 5.9; N, 10.3. Found: C, 66.4; H, 6.8; N, 10.6. The acetyl derivative, prepared from 20 mg. of the acid, 1 cc. of acetic acid and 0.1 cc. of acetic anhydride, melted at 250° (with decomposition when fused in a block preheated to 240°), resolidified and then melted at 268–270°. *Anal.* Calcd. for $C_{17}H_{18}O_4N_2 \cdot HOAc$: C, 60.9; H, 5.9; N, 7.5. Found: C, 60.8; H, 5.6; N, 7.8.

(b) From 1-Acetamino-2-methyl-4-naphthylamine.—A hot dioxane solution of 3 g. of the amine and 1.6 g. of succinic anhydride gave 2.7 g. of the succinamic acid, m. p. 245°. After recrystallization from acetic acid the compound melted at 250°, resolidified and melted at 269–271° (the melting point was not depressed by addition of the acetate prepared as above described). *Anal.* Calcd. for $C_{17}H_{18}O_4N_2 \cdot HOAc$: C, 60.9; H, 5.9; N, 7.5. Found: C, 61.2; H, 5.8; N, (1) 7.8, (2) 7.8. When dried at 100° and 1 mm. over potassium hydroxide, the compound lost the acetic acid of crystallization. *Anal.* Calcd. for $C_{17}H_{18}O_4N_2$: C, 65.0; H, 5.8; N, 8.9. Found: C, 64.8; H, 6.2; N, 8.9.

2-Chloromethyl-1,4-dimethoxynaphthalene.—Dimethoxynaphthalene[18] (73 g.) was dissolved in a warm solution of 80 cc. of monochloromethyl ether in 200 cc. of acetic acid and, after fifteen hours at 25°, water was added and the mixture extracted with benzene. The extract was washed with sodium bicarbonate, solvent was distilled from the dried, filtered solution, the residue was extracted with petroleum ether, the solution was treated with active carbon, filtered and solvent was distilled *in vacuo*. The residue was distilled (1 mm.; bath temperature 180–190°) and the crystalline distillate (56.5 g.), crystallized from petroleum ether, gave 50.5 g. of the pure product, m. p. 62–63°. The product from a similar preparation was analyzed. *Anal.* Calcd. for $C_{13}H_{13}O_2Cl$: C, 65.9; H, 5.4. Found: C, 66.2; H, 5.8.

2-Methyl-1,4-naphthoquinone-ω-potassium Sulfonate.—An agitated mixture of 5 g. of 2-chloromethyl-1,4-dimethoxynaphthalene, 15 cc. of methanol and a solution of 3.8 g. of sulfur dioxide in 7 cc. of 28% ammonia water and 15 cc. of water was heated at 135° for sixteen hours. After extraction with chloroform, the aqueous solution was diluted with 10 g. of potassium chloride in 30 cc. of water and the deposited salt, reprecipitated from 20 cc. of warm water by addition of 5 g. of potassium chloride in 15 cc. of water, yielded 1.1 g. of impure potassium sulfonate. *Anal.* Calcd. for $C_{13}H_{13}SO_5K$: K, 12.2. Found: K, 15.4.

A solution of 1 g. of the impure potassium salt in 5 cc. of water, treated with a solution of 2.4 g. of potassium dichromate and 2.4 cc. of concentrated sulfuric acid in 15 cc. of water, gave, after fifteen minutes at 90–100°, a solution which, diluted with 4 g. of potassium chloride in 15 cc. of water and cooled to 5° for four hours, yielded 0.46 g. of the quinone sulfonate. The salt was further purified by recrystallization from acidulated water. *Anal.* Calcd. for $C_{11}H_7SO_5K$: K, 13.5. Found: K, 13.0.

The S-benzylthiuronium salt, crystallized from 50% ethanol, melted at 182–183° with decomposition. *Anal.* Calcd. for $C_{19}H_{18}N_2S_2O_5$: C, 54.5; H, 4.3; N, 6.7. Found: C, 54.4; H, 4.2; N, 7.1.

***ω-bis*-(1,4-Dimethoxy-2-methylnaphthalene)-disulfide.**—A solution of 10 g. of potassium hydroxide in 150 cc. of absolute ethanol was saturated with hydrogen sulfide and boiled for ninety minutes with a suspension of 18.8 g. of 1,4-dimethoxy-2-chloromethylnaphthalene in 100 cc. of absolute ethanol, the diluted mixture was acidified, the separated oil dissolved in ether and the solution was extracted with 10% alkali. The diluted, cold extract was shaken with chloroform containing 25 g.

(18) Prepared in 91% yield by adding (in a nitrogen atmosphere) 40 cc. of dimethyl sulfate to the mixture formed by hydrogenating 16 g. of 1,4-naphthoquinone in 50 cc. of methanol, then adding a solution of 48 g. of potassium hydroxide in 100 cc. of water during thirty minutes and, after forty-five minutes at the temperature of the steam-bath, precipitating the product by addition of water. After recrystallization from ethanol, the ether (17.3 g.) melted at 86–87.5°. Sah [*Rec. trav. chim.*, **59**, 1029 (1941)] reported a yield of 58% and a m. p. of 85°.

of iodine, the chloroform solution was then washed with sodium bisulfite, evaporated to dryness *in vacuo* and the residue, crystallized from heptane–ether solution, yielded 11.2 g. of pure disulfide, m. p. 116–117°. *Anal.* Calcd. for $C_{26}H_{26}O_4S_2$: C, 66.9; H, 5.6. Found: C, 66.5; H, 5.8.

Concentration of the filtrate yielded 0.5 g. more of the disulfide and 0.4 g. was obtained from the original ether solution of the sulfhydryl compound.

In another preparation, a mixture of 48 g. of 2-chloromethyl-1,4-dimethoxynaphthalene, 15.5 g. of thiourea and 150 cc. of ethanol was boiled for two hours, a solution of 12 g. of sodium hydroxide in 120 cc. of water was added and the mixture boiled two hours longer. On acidification, the diluted product yielded the oily sulfhydryl derivative which, dissolved in chloroform, was treated with 20 g. of sodium hydroxide in 200 cc. of water, ice and 40 g. of iodine, unchanged iodine was removed with sodium bisulfite, the chloroform solution was evaporated *in vacuo* and the residue, crystallized from a heptane–ether solution, yielded 35.5 g. of the disulfide, m. p. 115–116°.

TABLE III

Expt.	Compound	Active at micrograms
1	2-Methyl-1,4-naphthoquinone	1
2	2-Methyl-1,4-naphthoquinone-ω-potassium sulfonate	>50
3	2-Methyl-3-hydroxy-1,4-naphthoquinone-ω-potassium sulfonate	>50
4	2-Methyl-1,4-naphthohydroquinone	1
5	2-Methyl-1,4-naphthohydroquinone-*bis*-hydrogen glutarate	10
6	2-Methyl-1,4-naphthohydroquinone-N-trimethylglycinate chloride	12
7	1-Hydroxy-2-methyl-4-naphthyl-β-glucoside	3
8	1-Hydroxy-2-methyl-4-naphthyl-β-maltoside	5
9	1-Acetoxy-2-methyl-4-naphthol	2
10	1-Acetoxy-2-methyl-4-naphthyl-hydrogen succinate	3
11	1-Acetoxy-2-methyl-4-naphthyl-hydrogen glutarate	4
12	1-Acetoxy-2-methyl-4-naphthyl-N-trimethylglycinate chloride	4
13	1-Acetoxy-2-methyl-4-naphthyl-β-alanate hydrochloride	4
14	1-Acetoxy-2-methyl-4-naphthyl-sodium sulfonate	6
15	1-Acetoxy-2-methyl-4-naphthyl-sodium phosphate	4
16	1-Acetoxy-2-methyl-4-naphthyl-sodium thiophosphate	10
17	2-Methyl-1-naphthol	5
18	2-Piperidinomethyl-1-naphthol	>50
19	3-Methyl-1-naphthol	5
20	3-Methyl-1-naphthyl-β-glucoside	10
21	3-Methyl-1-naphthyl-β-maltoside	20
22	3-Methyl-1-naphthyl hydrogensuccinate	10
23	2-Methyl-1-naphthylamine hydrochloride	50
24	1-Acetamino-2-methylnaphthalene	>50
25	N-(2-Methyl-1-naphthyl)-gluconamide	>50
26	1-Amino-2-naphthylacetic acid	>200
27	1-Amino-3-methylnaphthalene hydrochloride	>25
28	2-Methyl-1,4-diaminonaphthalene dihydrochloride	3
29	1-Acetamino-4-aminonaphthalene	>50
30	N-(1-Amino-2-methyl-4-naphthyl)-succinamic acid	>50

2-Methyl-3-hydroxy-1,4-naphthoquinone-ω-potassium Sulfonate.—A suspension of 5 g. of *bis*-ω-(1,4-dimethoxy-2-methylnaphthalene)-disulfide in 25 cc. of 30% hydrogen peroxide and 125 cc. of acetic acid was stirred ten hours at room temperature, the resulting solution was evaporated to dryness *in vacuo*, the residue dissolved in water, the solution washed with chloroform and the product crystallized by adding a solution of 10 g. of potassium chloride in 25 cc. of water. After two similar recrystallizations from acidulated potassium chloride solution, the crude product (2.05 g.) gave the pure salt. *Anal.* Calcd. for $C_{11}H_9SO_6K$: K, 12.8. Found: K, 12.5.

Titration[19] of the potassium salt showed the presence of an acidic group with a pK of 4.65; phthiocol, the corresponding 3-hydroxyquinone, has a value of 4.5.

A solution of 0.48 g. of the potassium salt in 15 cc. of cold water containing a drop of concentrated hydrochloric acid was treated with 0.4 g. of S-benzylthiuronium chloride in 5 cc. of water and the precipitated product, recrystallized from ethanol, gave the pure S-benzylthiuronium salt, m. p. 200–201° with decomposition. *Anal.* Calcd. for $C_{19}H_{18}O_6N_2S_2$: C, 52.5; H, 4.2; N, 6.5. Found: C, 52.4; H, 4.4; N, 6.7.

Bioassays.—Day-old chicks were used for these tests made by Drs. L. W. McElroy and J. J. Oleson as described previously.[1] In experiments 5, 6, 16 and 22 only 30, 36, 73 and 69%, respectively, of the chicks showed a clotting time of less than fifteen minutes. The results are summarized in Table III.

Summary

1. The compounds prepared by partial esterification of polycarboxylic acids with 2-methyl-1,4-naphthohydroquinone and its derivatives, esters of 1-acetoxy-2-methyl-4-naphthol formed with succinic and glutaric acids, the *bis*-hydrogen glutarate of 2-methyl-1,4-naphthohydroquinone, the hydrogen succinate of 3-methyl-1-naphthol, 1-acetoxy-2-methyl-4-naphthyl-β-alanate hydrochloride, the N-trimethylglycinate chloride and the corresponding diammonium salt were all hydrolyzed in warm aqueous solution.

2. Esters of 1-acetoxy-2-methyl-4-naphthol formed with sulfuric, phosphoric and thiophosphoric acids (showing activities of 35, 50 and 20%, respectively, of that of 2-methyl-1,4-naphthoquinone) were stable in hot solution as were the monoglucoside and the maltoside of 2-methyl-1,4-naph-

(19) The determination was made by Dr. T. H. Davies of this Laboratory.

thohydroquinone (activities about 66% of that of 2-methyl-1,4-naphthoquinone) in the absence of oxygen. The corresponding glycosides of 3-methyl-1-naphthol gave complete response in minimum concentrations of 10 and 20 micrograms. The active 1-amino- and 1,4-diamino-derivatives of 2-methylnaphthalene were almost inactivated by conversion to the monoacetyl derivatives and these compounds as well as N-(2-methyl-1-naphthyl)-gluconamide and N-(1-amino-2-methyl-4-naphthyl)-succinamic acid were inapplicable.

3. An improved method for the preparation of 3-methyl-1-naphthol and 3-methyl-1-tetralone is described.

4. The structures of the esters of acetoxy-2-methylnaphthol and of the succinamic acid of 1,4-diamino-2-methylnaphthalene were established. From these orientation determinations structures of the new compounds examined for antihemorrhagic activity were ascertained. Substituents in the methyl of 2-methylnaphthalene lower the activity of the derivatives as compared with the parent quinone; 3-methyl-1,4-dihydroxyisoquinoline was inactive.

PEARL RIVER, N. Y. RECEIVED JULY 8, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Heats of Organic Reactions. XIV. The Digestion of β-Lactoglobulin by Pepsin

BY GOTFRED HAUGAARD AND RICHARD M. ROBERTS

It is the aim of the experiments described here to apply calorimetry to the study of proteolytic processes. During the hydrolysis of a protein peptide bonds adjacent to many different types of side-chains are broken, and the peptides and amino acids formed have widely different ionization properties. The thermochemistry of the process is thus of such complexity that it is scarcely to be hoped that measurement of the net heat evolution would yield results of thermodynamic significance. We proposed, therefore, to use the calorimeter as an indicator, and to supplement the thermal measurements by simultaneous chemical determinations.

Acid or alkali have two drawbacks as hydrolytic catalysts for our purposes. The high temperature required for a reasonable rate of reaction is impractical for calorimetric work. Furthermore, acid and alkali are relatively unspecific in their attack of peptide bonds. Enzymatic catalysis eliminates both of these difficulties. The reaction can be carried out near room temperature. Proteolytic enzymes are specific in their action; each enzyme attacks only a few types of peptide bonds, so that a smaller number of processes is involved in the reaction.

Crystalline β-lactoglobulin was chosen as the substrate for the present work. This protein is easily prepared in a salt-free condition, contains no lipid or carbohydrate, and is homogeneous in the ultracentrifuge and electrophoresis cell.

Experimental Procedure

The enzyme selected was crystalline pepsin, which has a *p*H optimum around 1.5. In this case the buffering power of hydrochloric acid is sufficient to maintain constant *p*H. Complication of the heat evolution in an unknown manner by ionization effects, as would be the case for other enzymes requiring solutions buffered near neutrality, is thus avoided.

Enzyme and substrate solutions were made up in sufficient quantity for two simultaneous digestions to be made, one in the calorimeter, to measure heat evolution, and the other separately in a thermostat at the same temperature, using the same proportions of enzyme and substrate solutions in both digestions. Samples of the latter digest were removed at frequent intervals for determination of the following quantities: amino nitrogen, nitrogen not precipitable by trichloroacetic acid, and nitrogen dialyzable through cellophane.

Lactoglobulin.—Crystalline β-lactoglobulin was prepared from raw, skim milk by a modification of the original procedure suggested to one of the authors by Dr. A. H. Palmer.[1] After removal of the casein by coagulation at *p*H 4.5, the *p*H of the whey was readjusted to 6.0–7.0. The less soluble whey proteins are first precipitated by addition of solid ammonia sulfate to half saturation.[2] Solid ammonium sulfate was added to the filtrate from this first precipitate to 80–85% saturation. This second precipitate was redissolved in a minimum amount of water, adjusted to *p*H 6.0–6.5, and the subsequent dialysis and crystallization were carried out in the manner described in Palmer's article cited above.

The crystalline β-lactoglobulin so obtained was recrystallized as follows. The crystals were suspended in water and dissolved by addition of the minimum amount

(1) Palmer, *J. Biol. Chem.*, **104**, 351 (1934).

(2) See, in this connection, M. and S. P. L. Sörensen, *Compt. rend. trav. lab. Carlsberg. Sér. chim.*, **23**, 61 (1939).

of 0.1 *N* alkali, filtered and readjusted to *p*H 5.2 with 0.1 *N* hydrochloric acid. After seeding, the solution was allowed to stand at room temperature for three to four hours, and then left in the refrigerator for one to two days. The crystals were filtered on a Büchner filter, dried over calcium chloride, and then ground to a powder in a mortar. The powder was dried over phosphorus pentoxide, and was stored in a tightly stoppered bottle in the refrigerator. It is our experience that β-lactoglobulin, treated in this way, can be kept for years without losing its ability to crystallize, and upon dissolving in salt solution leaves behind only a trace of insoluble material.

To make solutions of β-lactoglobulin, the dry powder was dissolved in weak potassium chloride solution. The faintly cloudy solution was clarified by filtration. The filtrate was diluted so as to contain about 3 mg. N/cc. and be 0.15 *N* in electrolyte. Lactoglobulin solutions appear to keep well in the cold for at least two weeks, but in the present work the solutions were always used one to two days after preparation.

Preliminary work showed that β-lactoglobulin is made very much more digestible by pepsin at *p*H 1.5 by previous exposure to *p*H 11. It was found that denaturation of β-lactoglobulin occurs slowly at *p*H 9.5, and that the rate increases with the *p*H. The protein is completely insoluble at *p*H 5.2 after exposure to *p*H 11 for a few minutes. On the other hand, β-lactoglobulin appeared to be stable at fairly low acid *p*H. After exposure to *p*H 1.5 for four hours no precipitate formed upon titration to *p*H 5.2. We therefore assumed that the protein was unaltered by *p*H 1.5. Subsequent work proved that this assumption was false. Samples of the digest of native protein were adjusted to *p*H 6–7 and dialyzed as described below. After the prolonged dialysis the contents of the bags were brought to *p*H 5.2 and seeded with a few crystals of β-lactoglobulin. Some amorphous precipitate settled out on standing, but no sample showed any evidence of formation of new crystals. In order to decide whether the pepsin or the acid was responsible for destroying the ability of the protein to crystallize, a control experiment without the pepsin was carried out. A solution of native protein at *p*H 5.2 was brought to *p*H 1.5 with 0.27 *N* hydrochloric acid. Samples were removed at frequent intervals, starting at five minutes, were adjusted to *p*H 6–7 with 0.28 *N* potassium hydroxide, and dialyzed as before. A sample of the native protein solution at *p*H 5.2 was dialyzed under the same conditions. After dialyzing with frequent changes of water for ten days, all samples were brought to *p*H 5.2 and seeded. Only amorphous material was found in the samples which had been exposed to *p*H 1.5. The sample of native protein solution untreated with acid contained only β-lactoglobulin crystals. That the denaturation was not caused by the alkali during back titration of the acid-treated protein to *p*H 6–7 is proved by the fact that native β-lactoglobulin at *p*H 5.2 can be recrystallized without loss after titration with 0.28 *N* potassium hydroxide to *p*H 9.5.

Exposure to *p*H 1.5 for only five minutes, therefore, destroys the ability of lactoglobulin to crystallize. When the protein has been thus treated with acid, it must be regarded as a different substance, although its complete solubility at *p*H 5.2 makes it appear likely that less alteration of the molecule has occurred than in the case of the protein treated with alkali at *p*H 11.

In order to avoid circumlocution in what follows, "denatured protein" and "native protein" will refer to the previous history of the protein *before* adjusting it to *p*H 1.5 for peptic digestion.

Pepsin.—Crystalline pepsin was prepared from Cudahy Spongy Pepsin 1:10,000 and recrystallized once by the method outlined by Northrop.[3] The pepsin crystals were stored in the cold under saturated magnesium sulfate solution. About one-third of the weight of the crystalline paste was protein.

Pepsin solutions to be used in the digestions were made in the following way. The crystalline paste was suspended in water and dialyzed for two days against water acidified to *p*H 4.5 until most of the sulfate was removed. A measured quantity of potassium chloride solution was then added to the suspension, which was kept at 30–35° for an hour or two to hasten solution. The solution was filtered and diluted so as to be 0.15 *N* in potassium chloride and contain about 0.7 mg. N/cc. Pepsin solutions were stored in the cold under toluene and were always used within one day after preparation.

Determination of Amino Nitrogen.—The increase in amino nitrogen during the digestions was measured by the manometric method of Van Slyke.[4] The saturated solution of sodium nitrite used contained 10 g. of potassium iodide per liter.

Deamination of β-lactoglobulin for five minutes in the Van Slyke apparatus yields 25.5 equivalents of amino nitrogen per mole; in ninety minutes, 36.1 equivalents per mole are produced,[5] part of which is accounted for by the 29 lysine residues found by analysis. This large evolution of non-α-amino nitrogen in the time interval (three to four minutes) required for complete deamination of the α-amino groups leads to a high initial point for the digestion. Thus in order to obtain reproducible and comparable results the time of reaction in the Van Slyke apparatus must always be strictly the same at a given temperature. At the time these experiments were performed the authors were not fully aware of the fact that the lysine content of β-lactoglobulin is so large. It is possible that somewhat greater precision could have been obtained if longer reaction periods had been used, so that slight variations in time interval would give a less variable evolution of non-α-amino nitrogen.

Trichloroacetic Acid.—Of the many reagents used to precipitate proteins, trichloroacetic acid has the reputation of precipitating the least amount of polypeptide from a mixture of protein and its degradation products. We have tried several of the current recipes for using this reagent and found them unsatisfactory. The procedure we have used was finally standardized as follows. A given volume of a protein solution containing enough protein nitrogen to enable one to make a precise Kjeldahl analysis was mixed with an equal volume of a solution containing 20% by weight of trichloroacetic acid, both solutions being at room temperature. The mixture was allowed to stand at

(3) Northrop, "Crystalline Enzymes," Columbia Univ. Press, New York, N. Y., 1939, p. 129.

(4) Peters and Van Slyke, "Quantitative Clinical Chemistry," vol. II, p. 385 (1932).

(5) Cannan, Palmer and Kibrick, *J. Biol. Chem.*, **142**, 803 (1942).

room temperature for twelve to fifteen hours with frequent shaking. The shaking reduces the amount of non-protein nitrogen carried down by the precipitate. At the end of this period, the mixture is filtered and washed three times on the filter with small portions of 10% trichloroacetic acid. After filtration the filter paper containing the precipitate is placed in a Kjeldahl flask for determination of nitrogen. The success of this procedure is to be judged by the fact that both native and alkali-denatured β-lactoglobulin can be precipitated from solutions containing 0–80% of the total nitrogen in the form of peptic digestion products, without carrying down considerable amount of non-protein nitrogen, as shown in the case of denatured β-lactoglobulin in Table I.

TABLE I

DENATURED β-LACTOGLOBULIN

% of digestion products	Protein N per cc. found, mg.	Protein N per cc. calcd., mg.
0	2.46	2.46
18	1.98	1.97
36	1.49	1.48
56	1.03	0.99
77	0.54	.49

Further confirmation of the exactness of the trichloroacetic acid procedure is found in the excellent agreement between the trichloroacetic acid results and those from the dialysis experiments described below.

Dialysis Experiments.—The dialysis experiments made on samples of the digests in Runs A and B were performed in slightly different ways. In the case of Run B we wished to attempt to crystallize the unattacked protein, and for this reason could not use heat-treated protein for the dialysis.

Run A.—Twenty cc. of the heat-treated digest samples was dialyzed in Visking cellophane bags against 200 cc. of distilled water for ten days in the refrigerator. A little toluene was added to the dialyzate.

Run B.—Twenty-five cc. of the digest was brought to *p*H 6–7 with about 15 cc. of potassium hydroxide solution and dialyzed against 200 cc. of water for ten days as above.

At the end of ten days the dialyzates were removed and concentrated to about 50 cc. by vacuum distillation at 40°. Determinations of amino and total nitrogen were made on the concentrated solutions.

In order to measure the extent to which dialyzable nitrogen had been removed from the bags during the ten-day dialysis, and compare the undialyzable nitrogen with that precipitable by trichloroacetic acid, the dialysis was continued in the case of A for thirteen days and in the case of B for seven days longer, this time against frequently changed water. The dialyzates obtained during this period were evaporated on the steam-bath, and the total nitrogen was determined in each.

The Digestions.—A series of digestion experiments with both native and denatured lactoglobulin were carried out, using the same procedure in each case for heat evolution, trichloroacetic acid, and amino nitrogen determinations. The results of these experiments were consistent. All the digestions were carried out at 30 ± 0.1°. For the sake of brevity data from only the last pair, in which dialysis experiments were also performed, will be presented here.

Run A: Denatured Protein.—To 750 g. of β-lactoglobulin solution (*p*H 5.15, approx. 2.9 mg. N/cc.) was added 0.28 *N* potassium hydroxide with stirring until *p*H 11.10 was reached. As judged by completeness of precipitation at *p*H 5.2 upon back titration, denaturation is complete after standing a few minutes at *p*H 11. The solution was allowed to stand for one hour at room temperature. At the end of this time the *p*H was 10.85. 0.27 *N* hydrochloric acid and water were added until the final weight of the solution was 1390 g. and the *p*H was 1.52; 840 g. was placed in the larger compartment of the calorimeter; 500 g. was used for the simultaneous digestion and 50 g. for initial point determinations. This solution was 0.15 *N* in electrolyte.

To 35.0 cc. of pepsin stock solution (0.67 mg. N/cc.) was added 0.27 *N* hydrochloric acid, water, and 2 *N* potassium chloride solution to make a final weight of 134 g., with a *p*H 1.50, 0.15 *N* in electrolyte; 62 g. was placed in the smaller compartment of the calorimeter, 37 g. was used for the simultaneous digestion and 35 g. for initial point determinations.

Run B: Native Lactoglobulin.—To 749 g. of native β-lactoglobulin solution (*p*H 5.13, approx. 3.1 mg. N/cc.) 0.27 *N* hydrochloric acid, water, and 2 *N* potassium chloride solution were added in such quantity that the final weight was 1390 g., electrolyte normality 0.15, and *p*H 1.50. The same quantities as before were used for the calorimeter, concurrent digestion, and initial point.

To 95 g. of pepsin solution (0.784 mg. N/cc.) water and 0.27 *N* hydrochloric acid were added in such quantity that the final weight was 134 g., electrolyte normality 0.15, *p*H 1.48. The enzyme solution was divided into 62-g., 37-g., and 35-g. portions as in A.

Before making the concurrent digestion outside the calorimeter the enzyme and substrate solutions were allowed to come to the proper temperature in a thermostat, and were quickly mixed by pouring back and forth from one vessel to the other, then replaced in the thermostat. Sampling of the digest was done as follows. About 25 cc. was quickly removed, placed in an Erlenmeyer flask, stoppered tightly with a rubber stopper, and swirled in a water-bath at 80° for five minutes. Only a slight cloudiness resulted from this treatment. The sample was stored under toluene in the cold, and the several determinations were made as soon as possible. This method of killing the enzyme appears to cause no further hydrolysis of protein. We found no increase in amino nitrogen when lactoglobulin and pepsin were separately treated in this way.[6]

The Calorimeter.—The calorimeter and its operation have been described previously.[7] The calorimeter is divided into two compartments holding the liquids to be mixed; into one was placed 62 cc. of pepsin solution, and into the other 840 cc. of lactoglobulin solution. The calorimeter was brought to a low thermal head by electrical heating, and after waiting for thermal equilibrium to be reached, the enzyme and substrate were mixed and readings on the main thermel were made at frequent inter-

(6) L. Miller, *J. Biol. Chem.*, **109**, lxvi (1935), has found no further hydrolysis when peptic digests of lactalbumin were inactivated by heating five minutes at 80–85°.

(7) Conn, Kistiakowsky and Roberts, THIS JOURNAL, **62**, 1895 (1940); Conn, Gregg, Kistiakowsky and Roberts, *ibid.*, **63**, 2080 (1941).

vals over a period of three hours. Several non-stirring periods were interspersed through the run to determine the heat of stirring, which we found did not change appreciably during the calorimetric runs.

Blank runs were made in the calorimeter to determine whether native or denatured lactoglobulin or pepsin evolved heat when exposed to *p*H 1.5.

1. Native Lactoglobulin.—Native lactoglobulin was brought to *p*H 1.5, and 900 cc. was placed in the calorimeter; 0.75 mg. N/cc.

2. Denatured Lactoglobulin.—Native lactoglobulin was exposed to *p*H 11.1 for one hour, then brought to *p*H 1.5; 900 cc. was placed in the calorimeter; 0.76 mg. N/cc.

3. Pepsin.—900 cc. of pepsin solution at *p*H 1.5, 0.15 *N* in potassium chloride, was placed in the calorimeter; 0.024 mg. N/cc.

No heat evolution could be detected in any case. There was no increase in amino nitrogen in 1 or 2 after standing for two hours at *p*H 1.5, showing that no hydrolysis by acid occurred.

Heats of dilution of pepsin and lactoglobulin solutions used in the digestions were negligible.

Experimental Results

The experimental results of Runs A and B are compiled in Tables II and III. In Fig. 1 the experimental values for the increase in α-amino nitrogen are plotted against the increase in nitrogen not precipitable by trichloroacetic acid. The points lie on straight lines of different slopes. Thus as the digestion proceeds the increase in amino nitrogen is proportional to the increase in nitrogen not precipitable by trichloroacetic acid. The data of Tables II and III (except the dialysis results) are plotted in Figs. 2 and 3. The curves for amino nitrogen have been smoothed by taking values from the straight lines of Fig. 1.

TABLE II

RUN A: DENATURED β-LACTOGLOBULIN

Time, min.	Amino N, mg./cc.	N precip. by trichlor. acid, mg./cc.	Dialysis: Non-dialyzable N mg./cc.	Dialysis: Dialyzate Amino N / Total N	Dialysis: Inner solution Amino N / Total N	Heat, evolution, cal. per 902 cc. of digest.
0	0.056	1.39				
5.5	.127	0.77	0.84			6.99
15.25	.145	.69	.64	0.146	0.035	9.50
30	.149	.57	.52	.170		11.37
45	.158	.46	.43	.145		12.52
60	.159	.42	.43	.166		13.88
90	.174	.32	.30	.155		16.66
120	.178	.26	.24	.148		19.09
150	.190	.24	.21	.144		21.21
180	.191	.21				23.10
210						24.85
244	.196	.18	.20	.154		
			Average	.153		

TABLE III

RUN B: NATIVE β-LACTOGLOBULIN

Time, min.	Amino N, mg./cc.	N precip. by trichlor. acid, mg./cc.	Dialysis: Non-dialyzable N, mg./cc.	Dialysis: Dialyzate Amino N / Total N	Dialysis: Inner solution Amino N / Total N	Heat evolution cal. per 902 cc. of digest.
0	0.056	1.41				
5.5	.082	1.23				0.48
10						.77
14				0.197	0.0406	
15						1.02
16.75	.081	1.19	1.16			
30	.088	1.16	1.25	.229	.0422	1.73
45						2.52
60	.100	1.10	1.17	.211		3.09
90						4.21
97	.108	1.06	1.05	.212		4.43
120	.116	1.05				5.10
150						5.93
189	.111	0.99	1.06	.218	.0425	
195						7.02
480	.123	.95				
1243	.191	.71	0.75	.212		
2800	.227	.39	.42	.218		
9 days	.329	.086				
			Average	.214	.0418	

The total non-dialyzable nitrogen and the nitrogen precipitated by trichloroacetic acid were found to be identical in amount, as seen from Tables II and III. Further tests showed that the concentrated dialyzates gave no precipitate with trichloroacetic acid, and the amino nitrogen content of the solutions in the dialysis bags after exhaustive dialysis was the same as that of undigested protein.

Referring to Tables II and III one can see that the ratio of amino to total nitrogen in the dialyzates is unchanged as the digestion proceeds. The amino nitrogen content of the dialyzates is easily seen to be in agreement with the slopes of the lines in Fig. 1. Native and denatured lactoglobulin both yield 4.3% of the total nitrogen as amino nitrogen in the standard reaction time for α-amino determination. The amino nitrogen found in the dialyzates will therefore be the sum of the amino nitrogen originally available and the α-amino nitrogen formed by hydrolysis. On the other hand the slopes of the lines of Fig. 1 take into account only the increase in α-amino nitrogen due to hydrolysis. Hence

$$\text{Slope of line} = (\text{amino N/total N})_{\text{dial.}} - 0.04$$

Substituting the experimental values

A. slope = 0.11, (amino N/total N) dial. = 0.15
B. slope = 0.17, (amino N/total N) dial. = 0.21

one finds that this relation is satisfied for both runs.

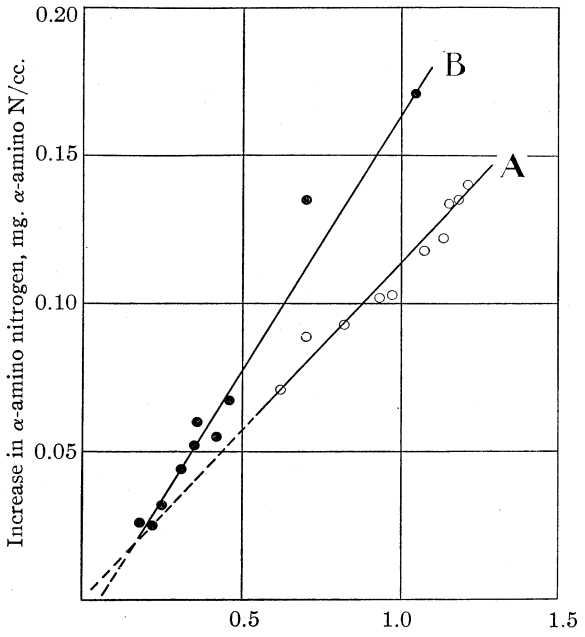


Fig. 1.—Increase in nitrogen not precipitable by trichloroacetic acid, mg. N/cc.

By applying the technique of solubility determinations it will probably be possible to improve the determinations of nitrogen precipitable by trichloroacetic acid, and the amino nitrogen determinations can, as previously mentioned, also be improved by using a longer reaction time. In this case the determinations in question may give figures of constitutional significance, especially when the specificity of the pepsin action is better known.

The amino nitrogen content of the dialyzates and of the inner solutions can be used to analyze the trichloroacetic acid and amino nitrogen data and confirm in a convincing way the existence of two fractions in the digests, whose amino nitrogen contents are independent of time. The trichloroacetic acid and amino nitrogen values in columns A and C of Table IV are taken from the curves of Fig. 1. The values in columns A and B are obtained by multiplying the precipitable nitrogen and the non-precipitable nitrogen present at a given time by the factors 0.04 and 0.153 given above for the amino nitrogen content of the inner solution and that of the dialyzate. The sums of

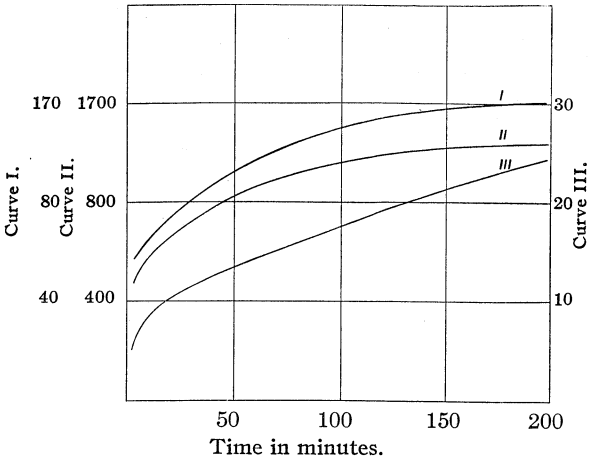


Fig. 2.—Curve I, total increase in α-amino nitrogen; II, total increase in nitrogen not precipitable by trichloroacetic acid; III, heat evolution in calories.

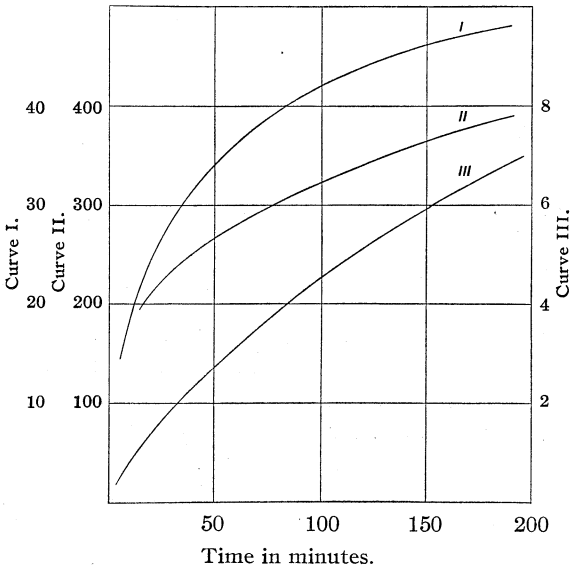


Fig. 3.—Curve I, total increase in α-amino nitrogen; II, total increase in nitrogen not precipitable by trichloroacetic acid; III, heat evolution in calories.

A and B in the next to the last column are to be compared with the experimental values for amino nitrogen in the last column. The excellent agreement is proof of the existence of two fractions in the digest: protein or protein-like material which is non-dialyzable and is precipitated by trichloroacetic acid, and a fraction consisting of much smaller particles which are completely dialyzable and are not precipitated by trichloroacetic acid. A similar analysis for Run B gave equally good results.

The ratio of amino to total nitrogen in the dialyzates is independent of time of digestion; and

TABLE IV

ANALYSIS OF DATA OF RUN A

Amino N/Total N in dialyzate, 0.153; amino N/Total N in lactoglobulin, 0.04.

Time, min.	*a* N precip. by trichlor. acid, mg./cc.	A 0.04 × *a*	*b* N not precip. by trichlor. acid, mg./cc.	B 0.153 × *b*	Calcd. amino N A + B, mg./cc.	C Exptl. amino N, mg./cc.
5	0.77	0.031	0.61	0.093	0.124	0.119
15	.69	28	.69	.106	.134	.134
30	.57	23	.81	.124	.147	.148
45	.46	18	.92	.142	.160	.159
60	.42	17	.96	.147	.164	.164
90	.32	13	1.06	.162	.175	.174
120	.26	10	1.12	.171	.181	.183
150	.24	10	1.14	.175	.185	.186
180	.21	8	1.17	.179	.187	.188
244	.18	7	1.20	.184	.191	.191

increase in amino nitrogen is proportional to increase in non-precipitable nitrogen (or to increase in dialyzable nitrogen). These facts suggest very strongly that when pepsin attacks the lactoglobulin molecule a definite number of fragments is produced at once, and these fragments are not further attacked by the enzyme. A similar conclusion was reached by Tiselius and Eriksson-Quensel after an electrophoretic study of peptic digests of egg albumin at the *p*H optimum.[8]

They found particles of unchanged size in the digest, but there was no evidence of particles intermediate in size between a molecular weight of 1000 and the original protein. That the nature of the digestion products is strongly influenced by the *p*H of digestion is shown by Petermann's ultracentrifugal analysis of the non-dialyzable fractions of peptic digests of beef serum pseudoglobulin between *p*H 2.7 and 4.5.[9] Besides particles unchanged in size, Petermann found particles which sedimented homogeneously which could be interpreted as halves and quarters of the original molecules; the distribution of nitrogen among the various fractions was a function of the *p*H. At *p*H 2.7 most of the nitrogen was in the unchanged and the dialyzable fractions; it thus appears likely that at the optimum *p*H there would be no evidence of products of intermediate size.

If our data are accepted as evidence of "explosion" of the lactoglobulin molecule, the number of bonds per molecule which can be hydrolyzed by pepsin can be determined from the slopes of the lines in Fig. 1. Taking the molecular weight of β-lactoglobulin as 39,000, and the value 0.11 for the slope of A, one finds that 46 peptide bonds per molecule have been broken in the case of denatured lactoglobulin, or 13.5% of the 341 peptide bonds in the molecule.[10] In the case of native lactoglobulin one finds that 71 peptide bonds per molecule, or 20.8% of the peptide bonds were split. It should be pointed out that although the native protein is attacked much more slowly, it is broken into smaller fragments. The average molecular weights of the split products are 870 for the denatured and 560 for the native protein. Particles deviating widely in molecular weight from the average may be present in the degradation products. We attempted to follow the evolution of free amino acids during the digestion by the ninhydrin–carbon dioxide method.[11] We found free amino acids to an extent of 1–2% of the total nitrogen in various digestions. Our results were not sufficiently accurate to detect an increase in the small amount of free amino acid with time of digestion. Blank runs showed that this hydrolytic product did not arise from exposure of pepsin or lactoglobulin to *p*H 1.5.

The calorimetric measurements were more accurate in the digestion of denatured protein. The heat evolution during the period of measurement was more than three times as large as in the digestion of native protein. The heat of stirring of the digests was about 0.04–0.05 cal./min. and could be measured during the reaction with a precision of only about ±5%. In Run A the error of measurement of the total heat evolution was ±2%, but in the digestion of native protein, where the rate of heating due to reaction was of the same order of magnitude as the heat of stirring, the measurement of the total heat evolution due to reaction was subject to very large error, estimated to be about ±13%.

In Fig. 4 the heat evolution is plotted against the increase in amino nitrogen after the same time of digestion. In both Runs A and B the heat evolved per peptide bond split increases markedly with time of digestion. From the slopes of the curves of Fig. 4 at various points one finds the following values:

Denatured protein	Native protein
2000 cal./mole peptide split at start	1300 cal./mole, at 15 min.
4000 cal./mole, at 90 min.	6000 cal./mole, at 190 min.
7000 cal./mole, at 150 min.	

(8) Tiselius and Eriksson-Quensel, *Biochem. J.*, **33**, 1752 (1939).

(9) Petermann, *J. Phys. Chem.*, **46**, 183 (1942).

(10) Hotchkiss, *J. Biol. Chem.*, **131**, 387 (1939).

(11) Van Slyke, Dillon, MacFadyen and Hamilton, *ibid.*, **141**, 627 (1941).

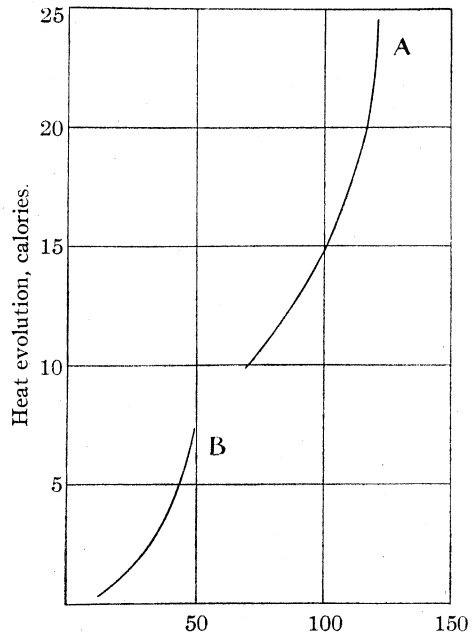


Fig. 4.

In case the degradation products were further hydrolyzed during the treatment with pepsin it could be expected that the heat per peptide linkage split would change as the process proceeded. The change would probably be small and the heat values consequently of the same order of magnitude. This is certainly not the case, and the most probable conclusion, therefore, is that not all the heat is due to the hydrolysis, but to processes we have not followed chemically. As we have shown that the degradation of β-lactoglobulin by pepsin is finished by the first attack, this secondary reaction—of unknown character—must be related to the breakdown products. Logically, of course, pepsin may attack other linkages of the degradation products than peptide bonds, but this is very unlikely. A rearrangement or an oxidation (or both) of some of the degradation products seems more probable.

Assuming that the heat value at the beginning of the experiment, where none or only a very small amount of the degradation products have reacted represents the true value of the heat of hydrolysis, we can use this value combined with the α-amino determinations to construct a heat–time curve which is related only to the degradation by pepsin of the lactoglobulin molecule. The difference between this curve and the actually found heat–time curve will thus represent the heat of the secondary reaction.

We have done this in the case of the run with denatured β-lactoglobulin using the value 2000 calories as representing the heat of hydrolysis. The set of curves are shown on Fig. 5, 1 is the actual heat curve, 2 the calculated heat curve, and 3 represents the heat evolution due to the secondary reaction.

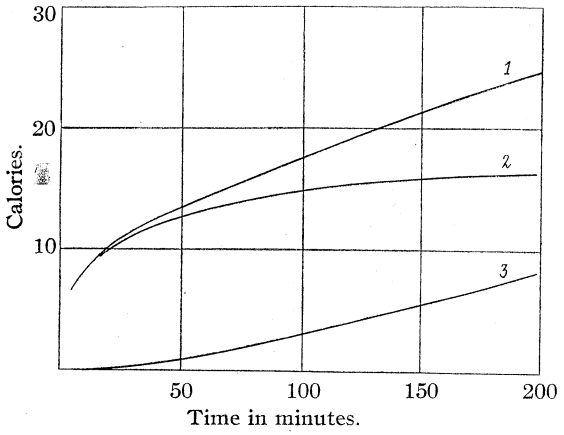


Fig. 5.

After an induction period at the beginning this third curve shows an increasing evolution of heat. The secondary reaction should thus be exothermic.

The lack of proportionality between heat evolution and extent of hydrolysis found in our experiments is reminiscent of dilatometric experiments of Linderström-Lang and Jacobsen on the digestion of native and denatured lactoglobulin and clupein by trypsin and chymotrypsin.[12]

The contraction per mole of peptide bond split was in the case of clupein, a protein considered of simple polypeptide chain structure and of low molecular weight, close to the normal value for peptides and was independent of time of digestion. In the digestion of native β-lactoglobulin, however, the contraction was initially about twice the normal value, and fell off slowly during the digestion. The contraction of heat denatured β-lactoglobulin was initially nearly normal, then rose to maximum almost twice the normal value, and thereafter decreased slowly. Linderström-Lang and Jacobsen believe that the abnormally large contraction may be due to the collapse of a "superstructure" originally present in the protein molecule.

In view of the experiments presented in this paper we should expect that the decreasing volume per peptide bond broken would be independent of

(12) Linderström-Lang and Jacobsen, *Compt. rend. trav. lab. Carlsberg, Sér. chim.*, **24**, 1 (1941).

the time as the degradation products are not further degradated. To prove this we have carried out a few dilatometric measurements using the technique described in detail elsewhere.[13,14]

The dilatometer used had two bulbs, the one (volume 45 cc.) containing at the beginning of the experiment the substrate, the other bulb (volume 8 cc.) containing the enzyme solution. Kerosene was filled in and the capillary tube inserted. The dilatometer was then immersed in water at 27 ± 0.005°. The concentrations of the enzyme and substrate were the same as in the digestion experiments presented on the foregoing pages. The β-lactoglobulin was alkali denatured. After the temperature equilibrium was reached the two solutions were mixed. The reading of the meniscus was continued for two hours. The results are tabulated in Table V.

TABLE V

Time, min.	Number of peptide bonds broken	Change in volume, cc.	Change in volume per peptide bond broken, cc.
5	0.000183	−0.00427	−23.4
10	215	528	24.6
15	241	586	24.4
20	260	630	24.2
30	286	698	24.4
40	305	748	24.6
50	318	783	24.6
75	344	841	24.5
100	360	867	24.1
125	373	877	23.5
		Average	−24.2

The contraction per peptide bond broken was found constant during the time of the experiment, which strongly confirms the results obtained by the trichloroacetic acid precipitations and α-amino nitrogen determinations (Fig. 1).

(13) Linderström-Lang and Lanz, *Compt. rend. trav. lab. Carlsberg, Sér. chim.*, **21**, 315 (1938).

(14) Linderström-Lang in Myrbäck and Baman, "Die Methoden der Fermentforschung," Leipzig, 1940.

In conclusion it may be said that it is difficult to suggest a plausible mechanism for the "explosive" degradation of lactoglobulin and other substrates by pepsin. As Tiselius and Eriksson-Quensel have pointed out, anything less than a simultaneous rupture of a great many peptide bonds would result in an almost continuous spectrum of products, and in our case the linear relationship of Fig. 1 would not hold. However, the notion that the enzyme molecule is able to attack many bonds in the substrate at once is difficult to believe. One is tempted to suggest the following hypothetical process: The splitting of a single peptide bond by the pepsin makes the "superstructure" or the "protein pattern" unstable, whereupon it decomposes.

It is a great pleasure for the authors to thank Professor G. B. Kistiakowsky for his continuous interest and much profitable advice. The work was supported by a grant from the Rockefeller Foundation.

Summary

Native β-lactoglobulin and β-lactoglobulin denatured by alkali were digested by pepsin at *p*H 1.5. Heat evolution, nitrogen precipitable by trichloroacetic acid, increase in amino nitrogen, and dialyzable nitrogen were measured in the same digest as a function of time of digestion.

Precipitation with the trichloroacetic acid and dialysis through cellophane were found to be equivalent methods of fractionation of the total nitrogen in the digest.

Evidence for an "all-or-none" attack of lactoglobulin by pepsin is brought forward.

The heat evolution was not proportional to the extent of hydrolysis. It is suggested that digestion of lactoglobulin by pepsin is accompanied by an exothermic non-hydrolytic process.

CAMBRIDGE, MASS. RECEIVED JULY 31, 1942

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

The Spectrophotometric Determination of the Dissociation Constants of Diphenylselenium Dibromide and Diphenylselenium Diiodide

BY JAMES D. McCULLOUGH

Several properties of the diphenylselenium dihalides indicate a rather loose bonding of the halogen atoms to selenium. Krafft and Lyons[1] found that when heated just above its melting point in a sealed tube, diphenylselenium dibromide undergoes a self bromination in the ring, yielding *p,p'*-dibromodiphenylselenium, diphenylselenium and hydrogen bromide. The analogous reaction with the dichloride was also found to occur. Leicester[2] found that upon dissolving diphenylselenium dibromide in acetone, the solvent was brominated with formation of diphenylselenium. The dichloride did not undergo a similar reaction. X-Ray investigations of the crystal structure of diphenylselenium dibromide[3] and of diphenylselenium dichloride[4] show selenium–halogen bond distances which are somewhat large; the observed distances being 2.52 Å. for Se–Br and 2.30 Å. for Se–Cl. The distances calculated using covalent radii are 2.31 and 2.16 Å., respectively. The melting points,[5] 148° for the dibromide and 183° for the dichloride are somewhat out of line in view of the similarity in molecular and crystal structures for the two dihalides, indicating possible dissociation, at least in the case of the dibromide.

The object of the present work has been to establish the fact that diphenylselenium dibromide does dissociate into diphenylselenium and bromine, to show that diphenylselenium and iodine combine to a limited extent, even though the solid diiodide does not separate at room temperature, and to determine the dissociation constants for the dibromide and the diiodide.

Experimental

Preparation of Materials.—Diphenylselenium dibromide was prepared by adding pure bromine to Eastman Kodak Company diphenylselenium in carbon tetrachloride solution. The resulting solid was recrystallized from carbon tetrachloride three times. The purity of the material was checked by the analysis described later. A solution of pure diphenylselenium in carbon tetrachloride was prepared by adding excess powdered C. P. zinc and a weighed sample of pure diphenylselenium dibromide to the solvent. The mixture was shaken until all of the dibromide was dissolved and the solution became colorless. The solution was then filtered, the solid was washed several times with carbon tetrachloride and the washings were added to the filtrate. The filtrate was then made up to the desired volume. The concentration of diphenylselenium in the solution was based on the weight of the dibromide taken and the final volume of the solution. Bromine, iodine and carbon tetrachloride were purified by the usual methods.

Apparatus and Procedure.—All spectrophotometric measurements were made by means of a Beckman Quartz Photoelectric Spectrophotometer. Carbon tetrachloride was used as the solvent in all cases, and loss of volatile materials from the absorption cells was reduced so as to be inappreciable by capping the cells with cover glass slips held down firmly with cellulose tape. No provision was made for maintenance of constant temperature but in all cases a thermometer was kept near the absorption cells and read from time to time. At the end of each series of measurements, the temperature of the solutions was checked. All temperatures were within one degree of 26°. The transmission of light by a given solution is measured relative to the transmission of the pure solvent which is arbitrarily set at 1.000. The cells used had a depth of 1.30 cm. Corrections were applied for the slight differences in depth from cell to cell, the maximum correction being well under 1%.

Extinction coefficients for diphenylselenium, bromine and iodine were each determined at three different concentrations, and Beer's law was found to hold over the range of concentrations used in the equilibrium measurements. These extinction coefficients, as well as those of the dibromide and diiodide are shown in Table I and in Fig. 1.

TABLE I

MOLAR EXTINCTION COEFFICIENTS OF DIPHENYLSELENIUM DIBROMIDE, DIPHENYLSELENIUM DIIODIDE AND THEIR DISSOCIATION PRODUCTS

λ, mμ	Diphenylselenium dibromide	Diphenylselenium diiodide	Diphenylselenium	Bromine	Iodine
320	8850		35.1		
330	7910		7.8	3.1	28
340	6910	11200	3.5	5.4	22
350	5600	13200	2.1	12.3	16
360	4670	13200	1.3	26	12
370	3530	11600	0.8	53	9
380	2620	9100	.6	87	7
390	1760	6700	.4	129	6
400	1130	4620	.4	166	6
410	745	3240	.4	192	10
420	410		.3	188	23

In order to determine the extinction coefficients for the undissociated diphenylselenium dibromide molecule, meas-

(1) F. Krafft and R. E. Lyons, *Ber.*, **27**, 1761 (1894).
(2) H. M. Leicester, THIS JOURNAL, **57**, 1901 (1935).
(3) McCullough and Hamburger, *ibid.*, **63**, 803 (1941).
(4) McCullough and Hamburger, *ibid.*, **64**, 508 (1942).
(5) Lyons and Bush, *ibid.*, **30**, 835 (1908).

urements were made on solutions in which the dissociation was suppressed by the presence of a large excess of diphenylselenium. The values so obtained were verified over a part of the wave length range by a series of measurements in which the dissociation was suppressed by the presence of a large excess of bromine. The contribution of the excess reagent to the absorption of light was in each case determined by making measurements on solutions containing the excess reagent at the same concentration in the absence of diphenylselenium dibromide. Transmission data and the resulting extinction coefficients are shown in Tables II and III. In making these calculations, allowance was made for the fact that the dissociation was not completely suppressed, the degree of dissociation being calculated by use of the dissociation constant given later.

TABLE II

EXTINCTION COEFFICIENTS FOR DIPHENYLSELENIUM DIBROMIDE (DIPHENYLSELENIUM IN EXCESS)

Solution 1, 2.0×10^{-2} M in diphenylselenium; Solution 2, 2.0×10^{-2} M in diphenylselenium and 7.1×10^{-5} M in diphenylselenium dibromide.

	Transmission		
λ, mμ	(1)	(2)	ε
330	0.625	0.120	7920
340	.810	.192	6920
350	.860	.271	5550
360	.895	.341	4620
370	.936	.447	3530
380	.961	.555	2620
390	.975	.676	1760
400	.978	.770	1130
410	.978	.835	745
420	.980	.896	410

TABLE III

EXTINCTION COEFFICIENTS FOR DIPHENYLSELENIUM DIBROMIDE (BROMINE IN EXCESS)

Solution 1, 1.12×10^{-2} M in bromine; Solution 2, 1.12×10^{-2} M in bromine and 5.1×10^{-5} M in diphenylselenium dibromide.

	Transmission		
λ, mμ	(1)	(2)	ε
320	0.887	0.232	8850
330	.895	.268	7900
340	.834	.292	6900
350	.667	.281	5650
360	.413	.201	4720

The dissociation constant for diphenylselenium dibromide is given by the expression

$$K_1 = \frac{[(C_6H_5)_2Se][Br_2]}{[(C_6H_5)_2SeBr_2]} = \frac{\alpha^2}{1-\alpha} M \qquad (1)$$

where α is the degree of dissociation and M the molarity. If we represent the extinction coefficients of diphenylselenium dibromide; diphenylselenium and bromine by ϵ_1, ϵ_2 and ϵ_3, respectively, then the optical density, d, of a solution of diphenylselenium dibromide is given by the equation

$$d = lM[\epsilon_1(1-\alpha) + \alpha(\epsilon_2 + \epsilon_3)] = \log_{10}(I_0/I) \qquad (2)$$

where l is the distance the light travels through the solution, I_0 the intensity of the incident light and I the intensity of the emergent light. From the measured values of the transmission, I/I_0, and the extinction coefficients, we may calculate α and hence K_1. Absorption data on solutions of diphenylselenium dibromide of various concentrations and values of K_1 derived therefrom are shown in Table IV.

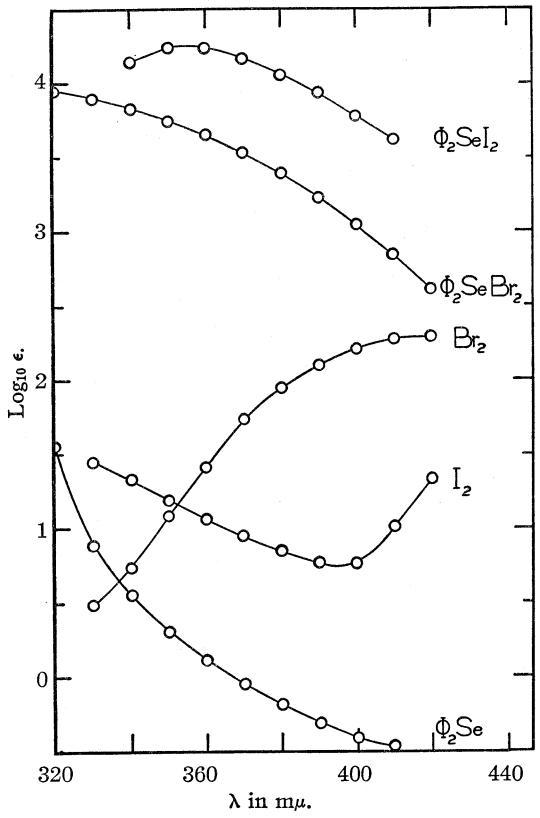


Fig. 1.—Molar extinction coefficients for several substances in carbon tetrachloride solution.

Because of the much larger dissociation constant of diphenylselenium diiodide, it is not practical to attempt complete suppression of the dissociation. The extinction coefficients and dissociation constant for the diiodide are accordingly simultaneously determined by a method different from that just employed for the dibromide.

When using light of such wave length that the undissociated molecule is the only important absorber, the measured optical densities, d_1 and d_2 at the molarities M_1 and M_2 are directly proportional to the concentrations of the undissociated compound. Using C_1 and C_2 to represent the concentrations of diphenylselenium (or of iodine) in the two solutions, we have

$$K_2 = C_1^2/(M_1 - C_1) = C_2^2/(M_2 - C_2) \qquad (3)$$

and

$$d_2/d_1 = (M_2 - C_2)/(M_1 - C_1) \qquad (4)$$

TABLE IV

THE TRANSMISSION, T, AND THE DISSOCIATION CONSTANT, K_1, FOR DIPHENYLSELENIUM DIBROMIDE AT SEVERAL CONCENTRATIONS

The upper figures are the transmissions and the lower figures (in parentheses) are the calculated values of $K_1 \times 10^4$.

	Concentration $\times 10^4$			
λ, mμ	1.62	2.00	2.67	4.00
330	0.448	0.327	0.168	
	(4.9)	(5.0)	(4.9)	
340	0.500	0.386	0.218	
	(4.9)	(5.1)	(5.0)	
350	0.572	0.465	0.292	
	(4.9)	(5.1)	(5.0)	
360	0.632	0.537	0.372	0.140
	(5.0)	(5.3)	(5.4)	(4.9)
370	0.680	0.594	0.442	0.212
	(4.7)	(5.0)	(5.0)	(4.7)
380	0.742	0.680	0.549	0.313
	(4.8)	(5.5)	(5.4)	(4.8)
390	0	0.743	0.640	0.435
		(5.4)	(5.4)	(4.9)
400		0.793	0.713	0.548
		(5.1)	(5.3)	(4.9)

Av. K_1 5.02 $\times 10^{-4}$

For a given pair of solutions, the ratio d_2/d_1, should be constant with varying wave length. After correction is made for absorption due to diphenylselenium and iodine based on the assumption of complete dissociation, this ratio is actually fairly constant as shown in Table V.

TABLE V

TRANSMISSIONS AND OPTICAL DENSITIES OF SOLUTIONS OF DIPHENYLSELENIUM DIIODIDE

Solution 1, 6.0 $\times 10^{-4}$ M in iodine and 6.0 $\times 10^{-4}$ M in diphenylselenium; Solution 2, 12.0 $\times 10^{-4}$ M in iodine and 12.0 $\times 10^{-4}$ M in diphenylselenium.

	Solution 1		Solution 2		Ratio
λ	T	$d_{cor.}$	T	d_{cor}	d_2/d_1
340	0.698	0.139	0.260	0.544	3.91
350	.667	.162	.217	.635	3.92
360	.670	.165	.222	.632	3.83
370	.706	.142	.271	.550	3.87

Av. 3.88

The average value of this ratio, 3.88, when used in equations 3 and 4 leads to a value 0.035 for K_2. Extinction coefficients for diphenylselenium diiodide are now readily calculated from the absorption data in Table V and are given in Table I. In the wave length range λ 380 to λ 410, the extinction coefficients are based on the 0.00120 M solution since the more dilute solution absorbs too little in this region for accurate measurements.

In order to check the value of K_2 obtained by the above method, measurements were made on several solutions containing diphenylselenium in excess of iodine. The concentrations of the various species present at equilibrium were calculated from the transmissions and extinction coefficients by means of the equation

$$d = l[\epsilon_1 C_1 + \epsilon_2(C_2 - C_1) + \epsilon_3(C_3 - C_1)] \qquad (5)$$

where the subscripts 1, 2 and 3 refer to diphenylselenium diiodide, diphenylselenium and iodine, respectively. The concentrations of diphenylselenium and iodine, as represented by C_2 and C_3 are those that would be present if no combination took place. The transmission data and values of K_2 calculated in this way are shown in Table VI. The agreement is excellent considering that the concentration ratio of diphenylselenium to iodine was over 300 in some runs while the data in Table V were obtained from solutions in which the two reactants were present in equimolar quantities.

TABLE VI

TRANSMISSIONS OF SOLUTIONS CONTAINING DIPHENYLSELENIUM AND IODINE, THE DISSOCIATION CONSTANT FOR DIPHENYLSELENIUM DIIODIDE

λ, mμ	Concn. diphenylselenium, $\times 10^3$	Concn. iodine, $\times 10^5$	T	Concn. diphenylselenium diiodide, $\times 10^5$	K_2
390	28.8	17.0	0.209	7.7	0.035
400			.350	7.4	.037
410			.467	7.6	.036
340	6.1	17.0	.397	2.5	.036
350			.356	2.5	.036
360			.367	2.4	.037
370			.420	2.4	.037
380			.503	2.5	.036
390			.612	2.4	.037
400			.718	2.3	.039
410			.780	2.5	.036
400	6.1	102	.118	15	.035
410			.231	15	.035
350	22.3	6.9	.290	2.7	.035
360			.313	2.6	.037
370			.378	2.6	.037
380			.467	2.7	.035
390			.583	2.6	.037
400			.676	2.7	.035
410			.750	2.8	.033

Av. 0.0360

Direct measurement of the dissociation constant for diphenylselenium dichloride was found to be impractical because of the low degree of dissociation even at low concentrations. An attempt was made to determine the value of this

constant by observing the extent of the reaction

$$(C_6H_5)_2SeCl_2 + Br_2 = (C_6H_5)_2SeBr_2 + Cl_2 \quad (6)$$

On adding bromine to diphenylselenium dichloride solution, the transmission is reduced much more than would be expected if no reaction took place, but the problem is complicated by two additional equilibria

$$Br_2 + Cl_2 = 2BrCl \quad (7)$$

$$(C_6H_5)_2SeBr_2 + (C_6H_5)_2SeCl_2 = 2(C_6H_5)_2SeBrCl \quad (8)$$

Reaction (7) is well known and (8) was demonstrated to occur by making absorption measurements on the three solutions (1) 0.0027 *M* in diphenylselenium dichloride, (2) 0.00022 *M* in diphenylselenium dibromide, (3) 0.0027 *M* in diphenylselenium dichloride + 0.00022 *M* in diphenylselenium dibromide.

The transmission of the third solution should be equal to the product of the transmissions of the first two if no reaction takes place. The individual transmissions and the product of the transmissions of solutions 1 and 2 are compared in Table VII.

TABLE VII

EVIDENCE FOR INTERACTION BETWEEN DIPHENYLSELENIUM DIBROMIDE AND DIPHENYLSELENIUM DICHLORIDE

	Transmission				
λ, mμ	(1) Diphenylselenium dichloride	(2) Diphenylselenium dibromide	(3) Mixed solution	(4) Product (1) × (2)	Ratio (3)/(4)
350	0.355	0.415	0.099	0.147	0.67
360	.575	.499	.244	.287	0.85
370	.739	.582	.430	.429	1.09
380	.834	.662	.590	.552	1.07
390	.900	.728	.722	.655	1.09
400	.934	.795	.814	.742	1.10

The dissociation of the diarylselenium dihalides makes possible a rapid and accurate volumetric procedure for their determination. When the dibromides or dichlorides are shaken either in the solid state or the dissolved state with excess aqueous potassium iodide, an equivalent quantity of iodine is liberated. This iodine may then be titrated as usual with sodium thiosulfate solution. The solid material (0.1 to 0.5 g.) is weighed and added to a glass-stoppered flask containing about 25 ml. of approximately 0.3 *N* potassium iodide solution which has been acidified with 1–2 ml. of 6 *N* sulfuric acid. The addition of about 5 ml. of carbon bisulfide just before adding the dihalide speeds up the reaction by dissolving the solid. This mixture is shaken for a few seconds and then titrated at once with standard sodium thiosulfate. Starch solution is added near the end-point. The concentration of a solution of a diarylselenium dihalide may be determined in the same manner. Data in support of the quantitative nature of this procedure are shown in Table VIII.

TABLE VIII

VOLUMETRIC ANALYSIS OF DIARYLSELENIUM DIHALIDES

Compound	Sample, g.	Volume $Na_2S_2O_3$ (0.05132 *N*), ml.	Equiv. wt. Anal.	Equiv. wt. Calcd.
Diphenylselenium dibromide	0.2594	25.76	196.4	196.5
	.2444	24.24	196.8	
Diphenylselenium dichloride	.1545	19.84	151.9	152.1
Di-*p*-tolylselenium dibromide	.3425	31.70	210.5	210.5
	.3567	33.08	210.1	

The dissociation of the diphenylselenium dihalides is, from a structural standpoint, analogous to the dissociation of phosphorus pentachloride and related molecules into the trihalides and free halogen. The similarity of molecular structure between diphenylselenium dihalides and phosphorus pentachloride was predicted by Pauling[6] and verified by crystal structure determinations.[3,4] The molecular structure of phosphorus pentachloride is that of a trigonal bipyramid, the phosphorus atom being at the center of the common base, three chlorine atoms being in the equatorial positions at a distance[6] of 2.04 Å. from the phosphorus atom and the other two chlorine atoms at the apices of the bipyramid at a distance of 2.11 Å. from the phosphorus atom. The last two chlorine atoms are less firmly bonded than the other three as indicated by the dissociation $PCl_5(g) = PCl_3(g) + Cl_2(g)$ which takes place in phosphorus pentachloride vapor and by the lower bond energy[6] (39.4 kcal./mole) for an apical P–Cl bond, as compared to the value 62.8 kcal./mole for a normal P–Cl bond. In the diphenylselenium dihalides, the halogen atoms occupy the apical positions and it is not surprising that the selenium–halogen bond distances are longer than for normal bonds and that the molecules dissociate into diphenylselenium and free halogen.

In a structural investigation of the trimethylantimony dihalides, Wells[7] found similar structures with the halogen atoms in the apical positions at distances somewhat greater than for normal Sb–X bonds. Considering all these facts, one might expect that in molecules of the general types R_3

(6) Pauling, "The Nature of the Chemical Bond," second edition. Cornell University Press, Ithaca, N. Y., pp. 57, 109, 111.

(7) A. F. Wells, *Z. Krist.*, **99**, 367 (1938).

(P, As, Sb, Bi)X_2, R_2 (S, Se, Te)X_2, and RIX_2, the halogen atoms would occupy apical positions in a trigonal bipyramidal structure at distances from the central atom which are greater than for normal M–X bonds. It is also reasonable to expect that all of these molecules show more or less tendency to dissociate in solution, giving the free halogen, X_2, as one product. A number of these dissociation constants are now being determined in this Laboratory.

Summary

1. Spectrophotometric studies of diphenylselenium dibromide and diphenylselenium diiodide indicate that these substances dissociate in carbon tetrachloride solution into diphenylselenium and the free halogen.

2. Dissociation constants for both compounds have been determined at 26° ± 1° at which $K_1 = [(C_6H_5)_2Se][Br_2]/[(C_6H_5)_2SeBr_2] = 5.02 \times 10^{-4}$; and $K_2 = [(C_6H_5)_2Se][I_2]/[(C_6H_5)_2SeI_2] = 3.60 \times 10^{-2}$.

3. Molar extinction coefficients for diphenylselenium, diphenylselenium dibromide and diphenylselenium diiodide are shown in Table I and in Fig. 1.

4. An accurate volumetric procedure for the determination of diarylselenium dihalides is described.

LOS ANGELES, CAL. RECEIVED JUNE 19, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Photochemical Studies. XXXV. The Photochemical Decomposition of *n*-Butyl Methyl Ketone

BY WALLACE DAVIS, JR.,[1] AND W. ALBERT NOYES, JR.

The photochemical decompositions of *n*-butyl methyl ketone and of other ketones containing multi-carbon alkyl groups attached to the carbonyl have been investigated by Norrish and his co-workers.[2] On the basis of their results these authors have suggested that such ketones undergo two types of decomposition, which they designate as I and II

Type I: $R_1CH_2CH_2CH_2COR_2 = CO + (R_1CH_2CH_2CH_2R_2 + R_2R_2 + (R_1CH_2CH_2CH_2)_2)$

Type II: $R_1CH_2CH_2CH_2COR_2 = R_1CH{=}CH_2 + CH_3COR_2$.

Thus for *n*-butyl methyl ketone the reactions would be

Type I: $CH_3CH_2CH_2CH_2COCH_3 = CO +$ hydrocarbons (ethane, pentane, and octane)

Type II: $CH_3CH_2CH_2CH_2COCH_3 = CH_3CH{=}CH_2 + CH_3COCH_3$.

The theoretical discussion of this photochemical reaction will be reserved for a later article in which further data will be presented. It may be pointed out in passing that Norrish and his coworkers have come to the conclusion that the Type I reaction probably proceeds by a free radical mechanism whereas Type II proceeds in a single step leading to the final products. Others have discussed methods by which such a one-step process could occur,[3] and still others are inclined to the belief that Type II can also be explained by a free radical mechanism.[4]

Since acetone, if formed, would decompose photochemically to give carbon monoxide, any photochemical experiment leading to a large percentage decomposition of *n*-butyl methyl ketone would yield carbon monoxide as a secondary product. Furthermore, Norrish found that the yield of carbon monoxide was low. Since the stability of RCO radicals may vary markedly with the temperature, the quantum yields of all the products should be determined over a wide range of conditions.

The objects of the present investigation were as follows: (1) to apply and if necessary devise methods for the micro-analysis of the products formed during the photochemical decomposition of *n*-butyl methyl ketone so that the initial stages of the reaction could be investigated; (2) to determine the quantum yields of the various prod-

(1) Eastman Kodak Company Fellow in Photochemistry at the University of Rochester, 1941–1942. Mr. Davis resigned from this Fellowship in February, 1942, to accept a research position connected with National Defense, and being unable to continue the problem, the preliminary results he obtained are being published at the present time.

(2) C. H. Bamford and R. G. W. Norrish, *J. Chem. Soc.*, 1531 (1938).

(3) F. O. Rice and E. Teller, *J. Chem. Phys.*, **6**, 489 (1938).

(4) G. B. Kistiakowsky; for mention see V. R. Ells and W. Albert Noyes, Jr., THIS JOURNAL, **61**, 2495 (1939); see W. Albert Noyes, Jr., and P. A. Leighton, "The Photochemistry of Gases," Reinhold Publishing Corporation, New York, N. Y., 1941, p. 365.

TABLE I

ANALYSIS OF DECOMPOSITION PRODUCTS OF METHYL *n*-BUTYL KETONE

(Runs without filters on mercury arc)

1 Run	2 Press. of ketone, mm.	3 Exposure time, min.	4 Temp., per *t*, °C.	5 Liquid nitrogen fraction (−195°C.), moles × 10^{-8}	6 *n*-Pentane fraction (−130° or lower), moles × 10^{-8}	CuO combustion tube: *ca* 200° Anal. of liq. N_2 frac. 7[a] C_2H_6–Liq. N_2 frac., moles × 10^{-8}	8 CO_2–*n*-pentane frac., moles × 10^{-8}
1	12	15	24	12.3	...	4.4	5.0
2	10	45	24	58.5	620	5.7	...
3	5	30	24	8.6	97.5	0.9	6.6
4	13	80	24	48.0	...	6.2	41.1
5	7	60	28	17.2	170	1.6	13.1
6	18	30	24	...	151	...	...
7	10	60	28	16.3	227	1.4	13.4
8	12	60	26	45.3	573	...	...
9	11	60	23	43.5	535	...	...
10	12	60	24.5	23.8	397	2.4	19.6
11	12	60	24	27.0	258	2.3	21.3

[a] The copper oxide does not oxidize hydrocarbons, so that this column represents such hydrocarbons (mostly ethane) which can be removed by the Toepler pump when the products are condensed with liquid nitrogen.

Hot Pt wire combustion tube: *ca* >600° Analysis of *n*-pentane Fraction (O_2 combustion) 9 O_2 used in combustion, moles × 10^{-8}	10 CO_2–*n*-pentane fraction, moles × 10^{-8}	11 H_2O-by diff., moles × 10^{-8}	9/6 Moles O_2 used per mole of *n*-pentane fraction of photodecomp. products	10/6 Moles CO_2 formed from comb. of *n*-pentane frac. per mole of *n*-pentane frac.	2 × 11/6 g. atoms H_2 per mole of *n*-pentane fraction	6/5 Ratio of *n*-pentane fraction to liq. N_2 fraction	6/8 Ratio of *n*-pentane fraction to CO_2 in liq. N_2 fraction	8/5 × 100 % CO_2 in liq. N_2 fraction
...	...	...	...	...	...	...	...	40
...	...	...	...	...	...	10.6	...	...
...	...	...	...	...	...	11.3	14.8	77
...	...	...	...	...	...	...	...	86
...	...	...	...	...	...	9.9	13.0	76
685	465	441	4.4	3.08	5.86	...	...	...
1045	690	708	4.6	3.04	6.24	13.9	16.9	82
...	...	...	...	...	...	12.7	...	...
...	...	...	...	...	...	12.3	...	...
...	...	...	...	...	...	16.7	20.2	82
1210	863	695	4.7	3.34	5.4	9.6	12.1	79

ucts under diverse experimental conditions to aid in the elucidation of the mechanism. Much of (2) was not accomplished, and the discussion will be postponed until a later date.

Experimental

Eastman Kodak Company *n*-butyl methyl ketone (b. p. approx. 127°) was converted to the semicarbazone and precipitated from a mixture of distilled water and ethyl alcohol; 250 cc. of water was added to 30 cc. of ketone and ethyl alcohol added until solution was complete. Sodium acetate and semicarbazide hydrochloride were added in slight excess of equivalent amounts and the derivative precipitated, m. p. 123°. The derivative was recrystallized from water and ethyl alcohol, hydrolyzed by refluxing with 15% sulfuric acid, and then distilled. The resulting product was dried with anhydrous magnesium sulfate, $n^{25}D$ 1.4003. The ketone was stored in the dark, under vacuum (usually at −77°).

In the first series of runs unfiltered light from a high pressure mercury arc lamp was used. In the second series the following filter was used to isolate the 3130 Å. line: (1) 5-cm. quartz cell filled with a solution made by adding 14 g. of $CoSO_4 \cdot 7H_2O$, 46 g. of $NiSO_4 \cdot 6H_2O$ to 330 cc. of water; (2) a 0.5-cm. cell filled with solution containing 10 g. of potassium acid phthalate per liter; (3) blue glass to remove the visible mercury lines.

After exposure, the reaction mixture was condensed with liquid nitrogen and the residual gases (CO, H_2, CH_4, part of the C_2H_6) were removed by a Toepler pump. This part was further fractionated and analyzed. It was always small. Next the gases uncondensed by a *n*-pentane mush at temperatures from −130 to −145° were removed and analyzed. As shown in the table this fraction consisted mostly of a compound of empirical formula C_3H_6, presumably propylene. Finally, a fraction removed at −77° gave fair agreement for the empirical formula of acetone. This agreement was obtained by measuring both carbon dioxide produced, water formed, and oxygen consumed during the burning of this fraction. It should be emphasized that the presence of acetone in the quantities indicated has not been definitely established. Difficulty was experienced in removing all of the acetone. The first pump-fulls gave a good analysis, but small amounts of material kept coming over for long periods, and these gave spurious results. If Type II decomposition occurs and the amount of propylene is really equal to

TABLE II

ANALYSIS OF DECOMPOSITION PRODUCTS OF METHYL *n*-BUTYL KETONE

(Runs with filters on mercury arc)

1 Run	2 Press. of ketone, mm.	3 Exposure time, min.	4 Temp., *t*, °C.	5 Liquid nitrogen fraction (−195°) moles × 10^{-8}	6 Fractions taken off after liq. N_2 fraction, moles × 10^{-8}	CuO combustion tube: *ca* 200° Anal. of liq. N_2 frac. 7[b] C_2H_6–Liq. N_2 frac. moles × 10^{-8}	8 CO_2–*n*-pentane frac. moles × 10^{-8}
12	8	220	24	1.24	59.0 (−130°)	...	...
13	12	720	24	4.85	75.0 (−145°)	1.1	3.0
					265.5 (−130°)		
					23.6 (−115°)		
					69.0 (− 80°)		
					111.0 (− 77°)		
					[a]111.0 (− 77°)		
14	12	240	24	1.51	47.0 (−130°)	...	...
15	7	245	26	1.1	38.7 (−130°)	...	...

[a] All this fraction not taken because gas was coming off dry-ice very slowly and evidently very impure. [b] The copper oxide does not oxidize hydrocarbons so that this column represents such hydrocarbons (mostly ethane) which can be removed by the Toepler pump when the products are condensed with liquid nitrogen.

Hot Pt. wire combustion tube: *ca*. >600° near wire Analysis of fractions taken off after removal of liq. N_2 fraction 9 O_2 used in combustion, moles × 10^{-8}	10 CO_2 formed, -*n*-pentane fr., moles × 10^{-8}	11 H_2O formed (by diff.), moles × 10^{-8}	9/6 Moles O_2 used per mole of fraction burned on Pt	10/6 Moles CO_2 formed per mole of fraction burned on Pt	2 × 11/6 g. atoms H_2 per mole of fraction burned on Pt	6/5 Ratio of Σ fraction taken off after liq. N_2 fraction to liq. N_2 fraction	6/8 Ratio of Σ of fractions taken after liq. N_2 fraction to CO_2 in liq. N_2 fraction	8/5 × 100 % CO_2 in liq. N_2 fraction
313	213	200	5.3	3.61	6.78	48	...	...
334	222	224	4.45	2.96	5.98			62
1290	840	900	4.86	3.16	6.73			
111	68.5	85	4.7	2.9	7.2			
279	206	146	4.04	2.99	4.2+2=6.2			
460	348	224	4.14	3.14	4.04+2=6.04			
...	364	...	...	3.28	...			
...	...	...	...	...	...	31	...	...
...	...	...	...	...	...	35	...	...

the amount of acetone, only about 75% of the acetone is recovered from the reaction mixture.

Two attempts were made to estimate the quantum yields, using a galvanometer and photocell circuit calibrated for another research. The values $\Phi_{C_3H_6} = 0.6$ and $\Phi_{CO} = 0.15$ should be given little weight, and further data will be presented in a later article.

Conclusions

The photochemical decomposition of *n*-butyl methyl ketone at room temperature (23–28°) at pressures from 5 to 13 mm. yields mainly compounds having the empirical formula C_3H_6 and C_3H_6O. This is true for unfiltered radiation of the mercury arc and for approximately monochromatic 3130 Å. radiation.

Small amounts of carbon monoxide are produced, the relative amount being greater for the unfiltered radiation than at 3130 Å. However, the amount of decomposition was several fold larger for the unfiltered radiation. In no case was more than a few per cent. of the parent ketone decomposed, and for the unfiltered radiation the amount did not exceed a few tenths of a per cent.

Some doubt may be expressed as to whether any carbon monoxide is formed by the decomposition of *n*-butyl methyl ketone. Carbon monoxide might be formed entirely from the decomposition of acetone formed in the initial reaction.

ROCHESTER, NEW YORK RECEIVED JULY 6, 1942

[COMMUNICATION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MANITOBA]

The Density of Selenium

BY A. N. CAMPBELL AND S. EPSTEIN

The only figures in existence for the density of liquid selenium are those of Dobinski and Wesolowski,[1] who carried their measurements up to 350° and reported a straight-line relationship between density and temperature. They made their determinations by a plummet method and, in view of the high viscosity of liquid selenium, we thought it desirable to repeat their measurements by an independent, pycnometric method. We extended our measurements to certain of the solid forms also.

Experimental

The selenium was of two kinds: (a) pure, from British Drug Houses, (b) crude. The crude material was purified by the method of Hugot,[2] followed by sublimation of the red amorphous selenium under reduced pressure: vitreous selenium was thus obtained. The results obtained with both samples were practically identical.

The method was to melt the selenium under an inert liquid in a calibrated pycnometer which was constructed of combustion tubing, since it was found that anything frailer than this cracked under the expansion of the solidified selenium. The inert liquid was Russian mineral oil (Paraffinol). The density of this oil was determined between 20 and 300° and was found to be represented by the equation

$$D = 0.8823 - 0.000622(t - 20.5)$$

but, of course, the density will vary somewhat for different samples.

Enough selenium (about 80 g.) was introduced to fill about three quarters of the pycnometer, when the selenium was molten. The oil was then added and the pycnometer kept in a bath at 250° until the selenium had melted. While the selenium was liquid, air bubbles were expelled by tapping and suction.

Before using the Paraffinol, experiments were carried out to determine its suitability. Its boiling point was found to be in the neighborhood of 310°. The solubility of selenium in the boiling oil was found to be 0.0013 g. per cc. of oil. The selenium did not react chemically with the oil for, on cooling the hot saturated oil, red selenium precipitated.

Density determinations for liquid selenium were made at temperatures ranging from 227 to 277°. Determinations at higher temperature were unsatisfactory because bubbles of vapor were evolved after prolonged heating. In all determinations the selenium was kept at one temperature for two hours to ensure attainment of a possible internal equilibrium. All determinations were repeated, with very good agreement.

(1) Dobinski and Wesolowski, *Bull. intern. akad. polon. sci., Classe sci. math. nat.*, No. 8–9A, 446 (1936).

(2) *Cf.* Hittorf, *Pogg. Ann.*, **84**, 214 (1851).

The Paraffinol proved to be too viscous for determining the density of solid (metallic) selenium. Benzyl benzoate gave satisfactory results. The density of benzyl benzoate at various temperatures is given in Table I.

TABLE I

Temperature in °C.	d^{t}_{4}
21.8	1.12000
175.0	0.99359
193.0	0.97723
203.0	0.96834

These results can be expressed by the equation

$$D = 1.12001 - 0.000834(t - 22)$$

After the powdered selenium had been introduced into the pycnometer, weighed and covered with benzyl benzoate, it was heated for several hours at 150° to ensure conversion of all the selenium into the metallic state. The results for metallic and for liquid selenium are contained in Table II.

TABLE II

in °C.	Exptl.	d^{t}_{4} Calcd.	Δd	Dobinski and Wesolowski[1]
		Metallic Selenium		
20.4	4.7924	4.7966	+0.0040	4.80 (at 17°,
90.0	4.7641	4.7560	− .0081	"Int. Crit.
159.5	4.7152	4.7165	+ .0013	Tables")[a]
188.5	4.6954	4.6989	+ .0035	
197.5	4.6940	4.6937	− .0003	
205.5	4.6919	4.6891	− .0028	
		Liquid Selenium		
225	3.9705	3.9727	+ .0022	3.976
241	3.9540	3.9479	− .0061	3.955
244.5	3.9394	3.9424	+ .0030	3.947
257	3.9276	3.9236	− .0040	3.929
277	3.8904	3.8925	+ .0024	3.891

[a] The figures of Kruyt [*Z. anorg. Chem.*, **64**, 310 (1909)] for the density of metallic selenium cannot refer to stable states; he gives densities ranging from 4.49 to 4.63. These figures are interpreted along the lines of Smits' theory of pseudo-components. The most recent treatment along these lines is that of Briegleb [*Z. physik. Chem.*, **144**, 321 (1929)].

In Table II, "*t*" represents the temperature, "*d* Exptl." the values of density obtained experimentally, and "*d* Calcd." those obtained from the formulas

$$D = 4.8073 - 0.0005753t \text{ (for metallic selenium)}$$

and

$$D = 3.9851 - 0.001551(t - 217) \text{ (for liquid selenium)}$$

These formulas were computed from the experimental results by the method of least squares: Δd represents the difference between "*d* Calcd." and "*d* Exptl." The figures calculated from Dobinski and Wesolowski's equation are given in the fifth column.

The density of vitreous selenium was also determined. In order to ensure that the sample might consist, as far as possible, entirely of vitreous selenium, liquid selenium was quenched in a steel mold. It was found possible only to determine the density of this form at room temperature because at higher temperatures, *e. g.*, 90°, the velocity of conversion to the stable metallic form was appreciably great. The result obtained was: $d^{21.3}_4 = 4.2524$.

Discussion

The formula obtained by Dobinski and Wesolowski for the density of liquid selenium is

$$D = 3.987 - 0.0016(t - 220)$$

The close agreement of Dobinski and Wesolowski's results with ours shows the suitability of the methods employed by both. The conclusion is that the results of Dobinski and Wesolowski are equally reliable throughout their range of measurement, *i. e.*, up to 345°. The linear relationship between density and temperature indicates that as far as density is concerned the behavior of both solid and liquid selenium is quite regular, *i. e.*, unaccompanied by a shifting internal equilibrium.

From our results, the change in volume on melting results as +0.03737 cc. per gram. Taking the heat of fusion as 13.4 cal. per gram,[3] we obtain for the change in fusion temperature with pressure +0.033° per atmosphere. This seems abnormally large and might make selenium an interesting subject for pressure experiments.

Summary

The densities of selenium (metallic and liquid) have been measured over the range 20–277°. In agreement with the conclusion of Dobinski and Wesolowski[1] these measurements give no indication of a shifting internal equilibrium. The rise of the melting point with pressure has been calculated.

(3) Mondain and Monval, *Bull. soc. chim.*, [4] **39**, 1349 (1926).

WINNIPEG, CANADA RECEIVED MAY 16, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MANITOBA]

The Systems: $LiNO_3$–NH_4NO_3 and $LiNO_3$–NH_4NO_3–H_2O

BY A. N. CAMPBELL

The system $LiNO_3$–NH_4NO_3 is interesting as one of the series of binary systems consisting of NH_4NO_3 and the nitrates of the univalent metals, *viz.*, $TlNO_3$, $AgNO_3$, $LiNO_3$, $NaNO_3$, KNO_3, all which have been studied. In some of these systems, compound formation occurs, in others solid solution, and in others again, the equilibrium diagram is of the simple eutectic form, unaccompanied by solid solution. This appears to be the case with lithium nitrate, according to Perman and Harrison,[1] who investigated the system up to a content of 45% $LiNO_3$.

Certain of the observations of Perman and Harrison are important in the present work and I quote: "On increasing the proportion of lithium salt, the stability was reduced, so that the range of the experiments at higher temperatures was very limited." I have not found this to be the case; on the contrary, measurements were carried as high as 230° (in presence of $LiNO_3$) before decomposition invalidated the results.

"The curve shows the usual two branches, with a eutectic at 97° and 25% $LiNO_3$. There is, however, a marked break in the left branch at 122° indicating a change (on cooling) from the δ to the γ-form of NH_4NO_3.

"A cooling curve was obtained for $LiNO_3$ (in a separate experiment) between 265° (its melting point) and 80°. It showed no breaks, thus proving that this salt exists in but one crystalline form between these limits of temperature."

I have repeated the work of Perman and Harrison, using a refined technique, and have carried the measurements to a higher content of lithium nitrate. The technique used was that of metallurgical practice, and consisted essentially in the use of a neutral body and two thermocouples in opposition: very small thermal changes in the system are thus rendered evident by large displacements of a sensitive galvanometer: the method is due to Roberts-Austen.[2] In the course of this investigation I frequently detected a point of recalescence which led me to suspect either limited solid solubility or the existence of a compound with incongruent melting point. I there-

(1) Perman and Harrison, *J. Chem. Soc.*, **125**, 1709 (1924).

(2) Fifth Report, Alloys Research Committee, Proc. Inst. Mech. Engrs. (London), (1899).

fore investigated the ternary system $LiNO_3$–NH_4NO_3–H_2O at 90, 60, 31 and 25° and have thus shown that neither compound nor solid solutions exist.

Experimental

Two large hard glass test-tubes were placed symmetrically in an electric furnace. One tube contained the $LiNO_3$–NH_4NO_3 mixture, in weighed proportions (from 60 to 100 g.), and the other the neutral body of silica, of such a weight as to have nearly equal thermal capacity. Each test-tube carried an iron–constantan thermocouple, connected in opposition through a delicate reflecting galvanometer. Temperatures were read directly on mercurial thermometers inserted in the system and in the neutral body. The thermometers were calibrated in boiling benzene, water, toluene, *m*-xylene, aniline, nitrobenzene and naphthalene and in freezing lead; an exposed stem correction was also applied. Systems consisting of mixtures of salts are at a disadvantage in comparison with similar systems consisting of metals, because of the low thermal conductivity of the former. It is, therefore, important to make provision for adequate stirring and in the present case this was achieved by means of a fine stream of compressed air passing through a capillary immersed in the melt. Unfortunately, no system of stirring is of any value after solidification, or even partial solidification, has taken place, and the full effect of poor thermal conductivity then comes into play.

In conducting the thermal analysis, the Plato method of graduated cooling[3] was applied; *i. e.*, the temperature of the furnace was reduced by equal decrements per unit of time, by increasing the resistance in the circuit. The lithium nitrate and ammonium nitrate used were British Drug Houses A. R. chemicals. To ensure their dryness, the ammonium nitrate was kept over sulfuric acid, with frequent grinding, and the lithium nitrate was fused just before use; lithium nitrate must not be kept fused for any length of time, or the temperature raised much above the melting point, lest decomposition become appreciable.

To ensure homogeneity of the mixtures, the following procedure was adopted: The ammonium nitrate was first weighed out and brought to the temperature of incipient fusion; the powdered and weighed lithium nitrate was then added, little by little and with constant stirring, until a completely clear and homogeneous melt was obtained. This was then placed in the furnace, which had previously been raised to a temperature above the freezing point of the mixture.

The observation of Lowry[4] that melts rich in ammonium nitrate invariably cracked the test-tube on cooling was confirmed. He attributes this to the transformation NH_4NO_3 II → NH_4NO_3 III at 82°, which occurs with expansion on cooling: the transformation III → IV at 32° is accompanied by a contraction.

Results

The results of the thermal analysis are given in Table I (in duplicate runs, the results were reproducible to ±0.5°). These figures are expressed graphically in Fig. 1.

TABLE I

TEMPERATURE–COMPOSITION DATA FOR THE SYSTEM: $LiNO_3$–NH_4NO_3

% $LiNO_3$	Freezing point, °C.	Peritectic, °C.	Eutectic, °C.
100	270		
75	218		
70	212		
65	205		
60	196	116–113 (indistinct)	
55	182	118	
50	171	120	95
45	151	119	97
40	135	117	96
35	121	...	96
30	110	...	97
25	97	...	97
20	106	...	97
15	119	...	97
10	133	126 (NH_4NO_3 transition)	97
5	153	128	93
0	169	126	

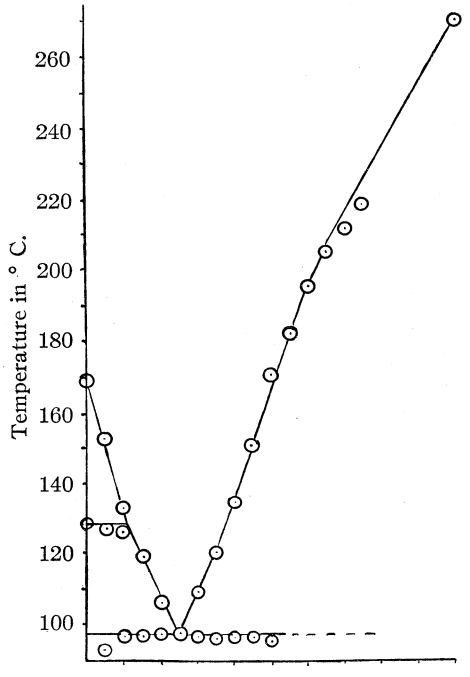


Fig. 1.

Discussion

The figures entirely confirm the results of Perman and Harrison. The only new observation is the so-called "peritectic point." A recalescence on the lithium nitrate curve, for mixtures between 60 and 40% $LiNO_3$, was frequently observed, at a temperature of about 110–120°. No explanation

(3) *Z. physik. Chem.*, **55**, 721 (1906).
(4) Early and Lowry, *J. Chem. Soc.*, **115**, 1387 (1919).

TABLE II

SYSTEM $LiNO_3$–NH_4NO_3–H_2O

Wt. % NH_4NO_3	Wt. % $LiNO_3$
90°	
Solid phase: NH_4NO_3 II	
*88.5	0.0
70.0	10.6
66.7	20.8
66.0	23.3
Invariant Point:	
65.5	29.3
Solid phase: $LiNO_3$ anhyd.	
60.7	32.0
56.3	34.6
52.2	36.9
45.0	41.5
38.5	45.0
38.0	45.5
26.5	52.2
23.2	54.2
17.6	57.8
10.1	61.8
0.0	*68.0

* Literature value: NH_4NO_3 = 89.3 (I. C. T.). $LiNO_3$ = not previously determined.

Wt. % NH_4NO_3	Wt. % $LiNO_3$
60°	
Solid phase: NH_4NO_3 III	
*81.0	0.0
68.5	9.2
63.0	14.9
60.2	18.7
57.0	25.9
57.1	27.4
Invariant Point:	
56.4	31.2
Solid phase: $LiNO_3$ anhyd.	
56.9	31.5
32.2	44.3
30.2	45.5
19.2	51.5
14.4	54.0
9.0	56.6
0.0	*62.2

* Literature Values: NH_4NO_3 = 80.8 (I. C. T.); $LiNO_3$ = 63.6 (Donnan and Burt).

Wt. % NH_4NO_3	Wt. % $LiNO_3$
31°	
Solid phase: NH_4NO_3 IV	
*71.5	0.0
70.0	0.6
68.2	1.6
66.2	2.9
60.5	7.7
56.5	11.4
47.3	22.9
43.8	32.9
42.3	34.5
Invariant Point:	
42.0	38.7
41.9	38.4
Solid phase: $LiNO_3$ anhyd.	
39.9	39.3
39.3	39.9
38.4	40.5
37.7	41.1
32.2	43.0
31.5	43.5
24.0	47.0

Wt. % NH_4NO_3	Wt. % $LiNO_3$
31° (contd.)	
14.8	51.8
9.1	53.9
5.1	56.0
3.1	56.7
1.5	57.7
0.0	*58.5

* Literature Values: NH_4NO_3 = 71.0 (I. C. T.); $LiNO_3$ = 57.8 at 29.6° (Donnan and Burt).

25°	
Solid phase: NH_4NO_3 IV	
*69.2	0.0
55.8	9.9
49.1	17.4
43.6	25.7
40.2	31.5
38.5	35.0
Invariant Point 1:	
37.5	39.0
37.7	38.9

Wt. % NH_4NO_3	Wt. % $LiNO_3$
Solid phase: $LiNO_3$ anhyd.	
36.9	39.5
33.8	41.0
32.2	41.8
29.0	43.3
20.8	47.3
19.6	48.0
14.3	50.5
Invariant Point 2:	
14.0	51.0
Solid phase: $LiNO_3 \cdot 3H_2O$	
12.5	49.0
11.5	47.5
7.0	45.0
3.8	45.0
2.8	45.3
1.0	45.6
0.0	*46.0

* Literature Values: NH_4NO_3 = 68.7 (I. C. T.); $LiNO_3$ = 45.24 (Interpolated from Donnan and Burt).

has been found for this observation. It may be the result of some unknown experimental trouble; or it may indicate a polymorphic transition of lithium nitrate, although this could not be confirmed by the cooling curve of pure lithium nitrate. It does not seem to be the transition temperature of a compound of the two salts, since the ternary system revealed neither compound nor solid solution formation.

$LiNO_3$–NH_4NO_3–H_2O.—This system was investigated at 90, 60, 31 and 25°. Using a small thermostat, a low-lag electrical heating unit, and a sealed mercury arc relay, it was possible to maintain temperature constant to within 0.01° even at 90°. All solutions were stirred for twenty-four hours before analyzing them. In order to obtain a solid phase as free as possible from mother liquor, an all-glass apparatus was designed, incorporating a sintered glass filter and filtration by suction at the temperature of the thermostat. Ammonia was estimated by distillation and lithium by conversion to sulfate in a platinum dish. The accuracy of the ammonia estimation is high, certainly as high as 0.1%; that of the lithium determination not so high, 0.2% at best. The reproducibility was checked by taking solutions close together in composition: the analytical results lie on a smooth curve. Occasional discrepancies were due to insufficient time of stirring: these solutions attain equilibrium very slowly. The results are in Table II, and plotted in Figs. 2, 3, 4 and 5.

Since the hydrate, $LiNO_3 \cdot {}^1/_2H_2O$, described by Donnan and Burt,[5] nowhere occurs as solid phase in any of these systems, a dilatometric investigation of the transition points of hydrated lithium nitrate was carried out. The dilatometer contained anhydrous lithium nitrate to which water was added in amount more than sufficient to convert all the salt to hemihydrate but insufficient to convert it entirely to the trihydrate; the indicator fluid was *m*-xylene. The dilatometer was kept at room temperature overnight to ensure hydration and it was obvious to the eye that this had occurred. According to Donnan and Burt, the bulb should have contained a mixture of tri- and hemihydrates. A marked transition point was found at 28.8°. Donnan and Burt give 29.6° as the temperature of the transition

$$LiNO_3 \cdot 3H_2O \rightleftharpoons LiNO_3 \cdot {}^1/_2H_2O + 2{}^1/_2H_2O$$

(5) Donnan and Burt, *J. Chem. Soc.*, **83**, 335 (1903).

These authors also give 61.1° as the temperature of the transition

$$LiNO_3 \cdot {}^1/_2H_2O \rightleftharpoons LiNO_3 + {}^1/_2H_2O$$

I observed no second transition up to 78.8°.

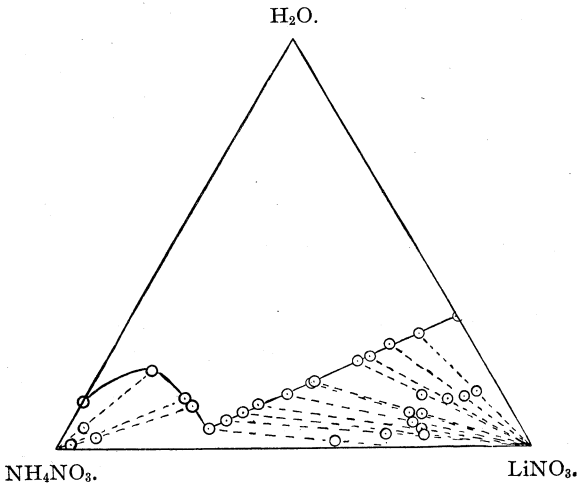


Fig. 2.—90°.

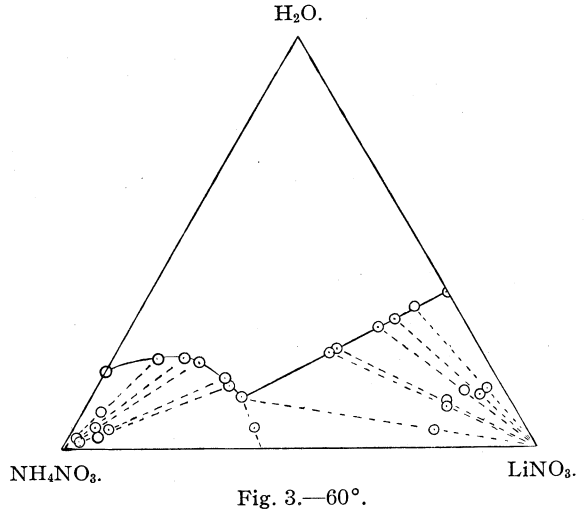


Fig. 3.—60°.

Discussion

It is apparent from the isotherms that no compound is formed between ammonium nitrate and lithium nitrate and that, in the solid state, ammonium nitrate is insoluble in lithium nitrate (up to 90°) and lithium nitrate insoluble in all four crystalline modifications of ammonium nitrate. It is well known that ammonium nitrate forms solid solutions with potassium and cesium nitrates, but not with sodium nitrate. It is pointed out by Tutton[6] that in some cases similarity in crystalline form alone, even when it is

(6) "Crystalline Structure and Chemical Constitution," Macmillan, London, 1910, p. 128.

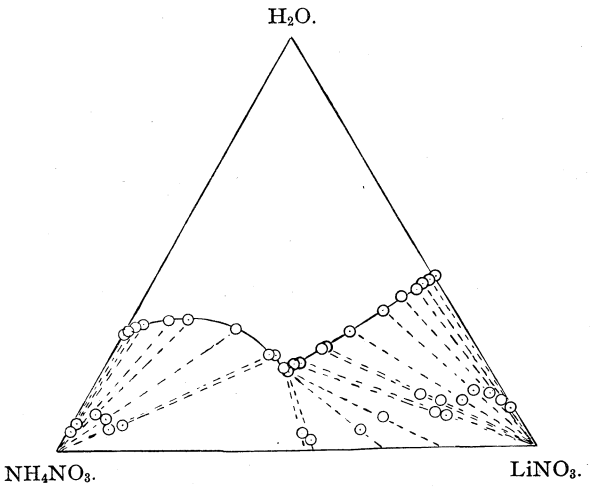


Fig. 4.—31°.

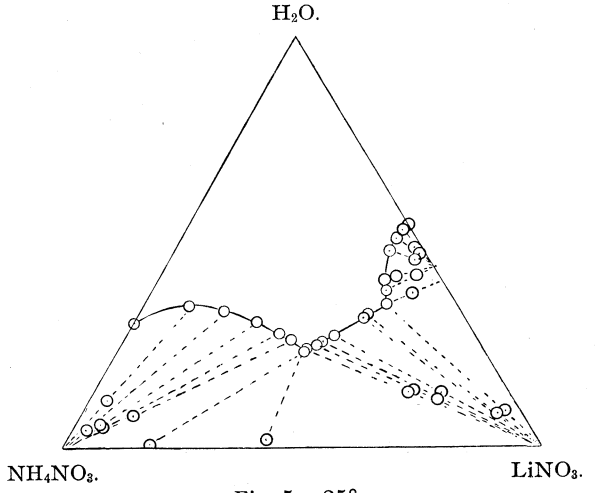


Fig. 5.—25°.

very marked, is not sufficient to cause miscibility in the solid state, but that the molecular volumes of the two substances must also be almost equal. The molecular volumes of the nitrates in cc. are

NH_4NO_3	KNO_3	$CsNO_3$	$LiNO_3$	$NaNO_3$
46.5	48.0	52.8	29.6	35.8

Another striking feature of the isotherms is that the hemihydrate, $LiNO_3 \cdot {}^1/_2H_2O$, nowhere occurs as stable solid phase. A similar observation was made by Massink,[7] working on a system comprising $LiNO_3$, who found that, with the exception of one experiment, anhydrous $LiNO_3$ always occurred as the solid phase, where the results of Donnan and Burt[5] would lead one to expect the hemihydrate. Donnan and Burt base their evidence for the existence of the hemihydrate on a direct determination of transition point in the dilatometer and on the occurrence of a break in

(7) Massink, *Z. physik. Chem.*, **92**, 356 (1916–1918).

their solubility curve for lithium nitrate in water. I have been unable to obtain the transition point dilatometrically and, if the solubility figures of Donnan and Burt are plotted, there seems no reason to give the curve the shape drawn by them; their figures are better represented by a smooth curve: in any case, their determinations are too far apart to settle the matter definitely. I conclude that the existence of the hydrate, $LiNO_3 \cdot {}^1/_2H_2O$, is doubtful.

Summary

1. The system $LiNO_3$–NH_4NO_3 has been investigated by thermal analysis. The results of Perman and Harrison are confirmed and extended.

2. The system $LiNO_3$–NH_4NO_3–H_2O has been investigated at 90, 60, 31 and 25° by the usual solubility technique.

3. No compound occurs, under any of the above conditions; neither is solid ammonium nitrate soluble in solid lithium nitrate (up to 90°), nor lithium nitrate in any of the four crystalline modifications of ammonium nitrate.

4. Lithium nitrate exists in but one crystalline form between room temperature and its melting point, in accordance with Perman and Harrison.

5. The hydrate, $LiNO_3 \cdot {}^1/_2H_2O$, described by Donnan and Burt, nowhere exists as stable solid phase. A direct investigation of transition point with the dilatometer failed to reveal the transition: $LiNO_3 \cdot {}^1/_2H_2O \rightleftarrows LiNO_3 + {}^1/_2H_2O$, which is said to occur at 61.1°. The existence of this hydrate is doubtful.

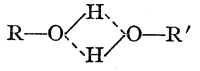
WINNIPEG, CANADA RECEIVED MAY 29, 1942

[CONTRIBUTION FROM THE DEPARTMENTS OF PHYSICS AND CHEMISTRY OF THE UNIVERSITY OF FLORIDA]

Spectroscopic Evidence of Intermolecular Transfer of Protons

BY DUDLEY WILLIAMS[1] AND W. DAVID STALLCUP[2]

The high degree of association exhibited by pure liquids and by liquid mixtures in which the molecules contain hydrogen atoms attached to atoms of the electronegative elements fluorine, oxygen or nitrogen has been explained, qualitatively at least, in terms of proton bonds or hydrogen bridges formed between neighboring molecules. According to the proton-bond theory, protons are "shared" between adjacent molecules in somewhat the following manner



In the case of water and other liquids having especially strong proton bonds, the proton can be transferred from one molecule to another when the molecules are separated. Whether actual intermolecular transfer of protons can occur in all liquid mixtures having association of the type indicated above is not entirely clear. The purpose of the present paper is to report a method for detecting intermolecular transfer and to give the results for a single binary mixture.

The method is rather simple: the hydrogen in one liquid is replaced by deuterium. Then the two liquids are mixed. After mixing, the liquids are separated by distillation and the liquid originally containing no deuterium is tested for the presence of deuterium. The changes in physical constants produced by the presence of deuterium are, in most cases, so slight that it was decided to use the infrared absorption of the liquids as a test for the presence of deuterium. The separation of OH and OD bands in alcohols is approximately 830 cm.$^{-1}$; the OH and OD absorption bands appear at 3.0 μ and 4.0 μ, respectively. The two liquids chosen for study were methanol and heavy butanol.

Experimental Results

Anhydrous methanol was prepared by treating a suspension of magnesium methylate in methanol with freshly distilled methanol and then separating the methanol from this mixture of magnesium oxide and magnesium methylate by distillation. The methanol thus prepared had the following physical constants: b. p. 64.5°, $n^{25}D$ 1.3268, and d^{25}_4 0.7896.

The deuterium butoxide was prepared by adding deuterium oxide to *n*-butyl borate. After standing a few hours, the precipitated boric acid was removed by filtration. The filtrate was then fractionated in order to separate the deuterium

(1) Present address: Radiation Laboratory, Massachusetts Institute of Technology, Cambridge, Mass.

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

butoxide from unreacted butyl borate. The deuterium butoxide fraction was then refractionated through a thirty-plate column and the material distilling at 119.0–119.5° was collected. The physical constants of this material were: $n^{25}D$ 1.3974 and d^{25}_4 0.8131.

The transmission of samples of the methanol and the deuterium butoxide was then measured in the region between 2 and 5 μ. The absorption cells used were approximately 0.03 mm. in thickness. The spectrometer was a Littrow instrument equipped with a rock salt prism. The results obtained are shown in Fig. 1. Curve A is the transmission curve for methanol and exhibits only two absorption bands; the band at 3.0 μ arises from an OH vibration and the band at 3.4μ from a CH vibration. Curve B represents the transmission of the deuterium butoxide prepared in the manner described above. In this curve strong bands are found near 3.4 μ and 4.0 μ, arising from CH and OD vibrations, respectively; a rather weak band is also observed at 3.0 μ, indicating that some OH groups are also present in the heavy butanol.

After the spectra of the original liquids had been studied, equimolecular amounts of the liquids were mixed and heated for two hours. At the end of this time, the methanol and butanol were separated by fractionation through a forty-plate column. The first fraction was collected at the end of ninety minutes and, after discarding intermediate fractions, the final butanol fraction was collected three hours later. The recovered alcohols had the following physical constants

Methanol: b. p. 65.5° $n^{25}D$ 1.3270 d^{25}_4 0.7913
Butanol: b. p. 119° $n^{25}D$ 1.3970 d^{25}_4 0.8103

The spectra obtained for a sample of the recovered methanol is shown in Curve C of Fig. 1. Three absorption bands will be noted; these are produced by OH, CH, and OD vibrations. The OH band is weaker than in the spectrum of the original methanol and an OD band can now be observed near 4.0 μ. Curve D represents the transmission of a sample of the recovered butanol and also indicates absorption arising from OH, CH, and OD groups. The OH band is much stronger than in the original butanol, while the OD band is correspondingly weaker.

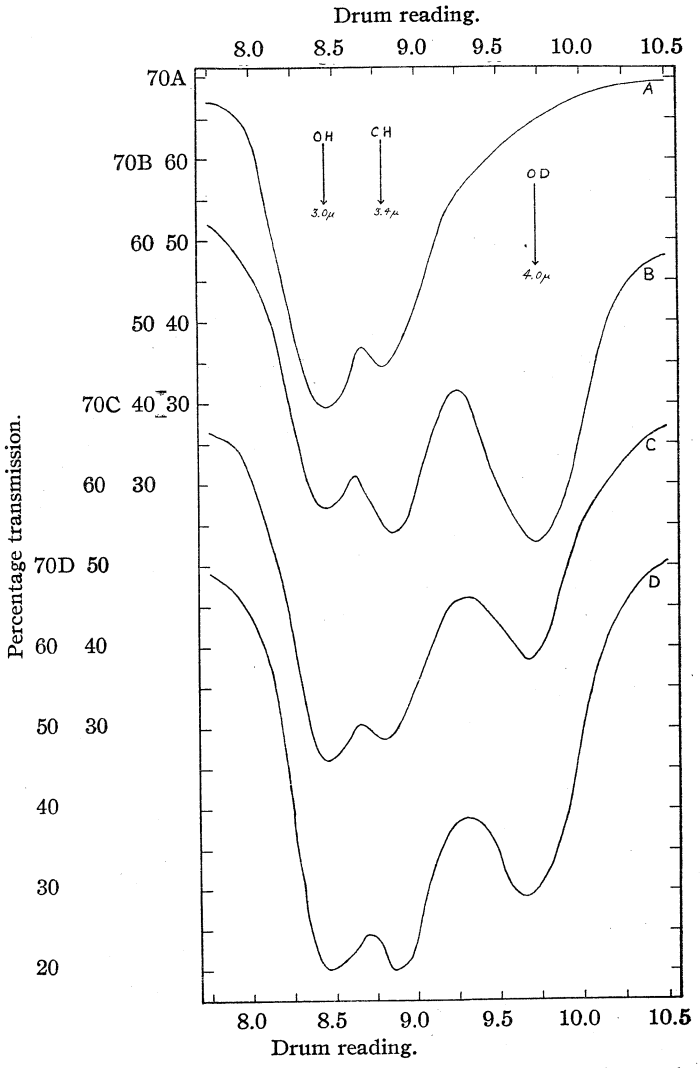


Fig. 1.—The infrared transmission of methanol and butanol: Curve A, original methanol; Curve B, original butanol (containing deuterium); Curve C, recovered methanol; Curve D, recovered butanol.

Discussion

The spectroscopic results indicated in Fig. 1 can be interpreted on the basis of the actual transfer of hydrogen atoms from methanol to butanol and the transfer of deuterium atoms from butanol to methanol. There are obvious extensions of the method developed in the present study to the study of other mixtures whose components can be separated by distillation. It was originally hoped to extend the present investigation to include the study of proton transfers between other alcohol molecules, between amine molecules, and be-

tween alcohols and amines. Numerous other applications of the method suggest themselves, but the pressure of other work will prevent pursuing the problem further at present.

Summary

When a mixture of MeOH and BuOD is fractionated, it is found that MeOH and MeOD are both present in the recovered methanol and that BuOH and BuOD are both present in the recovered butanol. It is concluded that the intermolecular hydrogen bonds involve the actual transfer of protons between molecules. Extension of the present study to include other compounds is suggested.

CAMBRIDGE, MASS. RECEIVED AUGUST 7, 1942

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY OF CORNELL UNIVERSITY]

The Structures of Dimethyl Boron Fluoride and Methyl Boron Difluoride

BY S. H. BAUER AND J. M. HASTINGS

The structures of boron trifluoride and boron trimethyl as determined by Lévy and Brockway[1] were among the first items of information to suggest that rather artificial explanations may be necessary in some cases to make the observed interatomic distances harmonize with the Pauling and Huggins[2] table of covalent radii and with the postulate of the dependence of bond order on the distances between the atoms in a molecule.[3] The suggestion of Schomaker and Stevenson[4] that as a next best approximation the electronegativity difference between the atoms be considered in computing the separation for normal covalent bonding was a welcomed one since it permitted a reasonable interpretation of data otherwise not readily accounted for; it removed the necessity for the artificial postulates applied to various boron compounds.[5] The structures of the methyl boron fluorides discussed in this paper furnish critical tests for the applicability of the table of atomic radii as revised by them and of the use of their equation

$$r_{ab} = r_a + r_b - 0.09|x_a - x_b| \qquad (1)$$

Both the methyl boron difluoride and the dimethyl boron fluoride were furnished by Dr. Anton B. Burg.[6] We wish to acknowledge his coöperation and to thank him sincerely for this and other compounds he gave us.

The Apparatus and Photographs

The present electron diffraction apparatus resembles the latest model constructed by Brockway.[7] A simple but highly effective voltage regulator[8] and voltmeter have been set up so that the net voltage fluctuations have been reduced to a few hundredths of one per cent. The apparatus was designed to be flexible and special provision made for the incorporation of a rotating sector,[9] the assembly of which has now been completed. A more detailed description of this unit will be given in a future paper.

The photographs were taken with electrons having a wave length near 0.06 Å., and with the nozzle–plate distance equal to 13.69 cm. The visual appearance of the photographs is that indicated by curves V, Figs. 2 and 4; the $s_0 = \left[\frac{4\pi}{\lambda} \sin \Theta_0/2\right]$ values for the maxima and minima as determined by the usual visual technique, and their relative intensities above or below the estimated backgrounds (lines through curves V) are given in Tables II and III.

Analysis of the Data

Because of their relative simplicity, considerable information regarding the structures of these molecules can be obtained from their radial distribution curves. These were computed according to the method of Walter and Beach,[10] and are plotted in Fig. 1. The results are summarized in Table I. To facilitate the interpretation of these curves and to show the resolution which might be expected under ideal conditions, "synthetic" radial distribution curves for various

(1) H. A. Lévy and L. O. Brockway, THIS JOURNAL, **59**, 2085 (1937).

(2) L. Pauling and M. L. Huggins, *Z. Krist.*, **A87**, 205 (1934).

(3) For references, L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., Chapter V, 1940.

(4) V. Schomaker and D. P. Stevenson, THIS JOURNAL, **63**, 37 (1941).

(5) S. H. Bauer and J. Y. Beach, *ibid.*, **63**, 1394 (1941).

(6) A. B. Burg, *ibid.*, **62**, 2228 (1940).

(7) E. H. Eyster, R. H. Gillette and L. O. Brockway, *ibid.*, **62**, 3236 (1940), and private communications.

(8) The voltage stabilizer is of the degenerative type and resembles the one described by L. G. Parratt and J. W. Trischka, *Rev. Sci. Instruments*, **13**, 17 (1942).

(9) P. P. Debye, *Physik. Z.*, **40**, 404 (1939).

(10) J. Walter and J. Y. Beach, *J. Chem. Phys.*, **8**, 601 (1940).

models are also included in Fig. 1. The approximate equations given by Debye[11] were used, as was also an average value for the temperature factor, a_{ij} (=0.042). The synthetic D(r)'s thus computed for planar models, boron valence angles equal to 120°, with B–C = 1.56 Å. and B–F = 1.30 Å., agree very well with the experimentally determined R. D. curves. It is clear that only slight distortions of these basic models (Table I) would be needed to obtain the best quantitative check between the calculated and observed patterns.

TABLE I

$B(CH_3)_2F$

Peaks at Å.	Interpreted as	Ratios
0.95	C–H	
1.29	B–F	
1.55	B–C	B–C/B–F = 1.204
2.49	C–F	B–C/C–F = 0.623
		∠CBF = 122° indicated

BCH_3F_2

Peaks at Å.	Interpreted as	Ratios
1.01	C–H	
1.31	B–F	B–F/F–C = 0.512
2.23	F–F	B–F/F–F = 0.586
2.55	C–F	F–F/F–C = 0.874
		∠CBF = 121½° indicated

To begin with, we considered models with 120° valence angles, varying the B–C/F–B ratio. The intensity curves, calculated in the usual manner, are shown in Figs. 2 and 4, with the description of the corresponding models given in the legends. In order to restrict the total number of computations for configurations with unequal boron valence angles, we made use of the following argument. If

$$I(s) = \sum_{ij}{}' Z_i Z_j \frac{\sin l_{ij}s}{l_{ij}s}$$

then

$$\frac{\partial I(s)}{\partial P_n} = \sum_{ij}{}' Z_i Z_j \frac{\partial}{\partial l_{ij}}\left[\frac{\sin l_{ij}s}{l_{ij}s}\right]\frac{\partial l_{ij}}{\partial P_n} \qquad (2)$$

where P_n is a given structure parameter. Furthermore

$$\frac{\partial l_{ij}}{\partial}\left[\frac{\sin l_{ij}s}{l_{ij}s}\right] = \frac{1}{2\epsilon}\left[\frac{\sin s(l_{ij}+\epsilon)}{s(l_{ij}+\epsilon)} - \frac{\sin s(l_{ij}-\epsilon)}{s(l_{ij}-\epsilon)}\right] - \frac{\epsilon^2 s^2}{2l_{ij}}\frac{\sin l_{ij}s}{l_{ij}s} \qquad (3)$$

to the approximation $\sin s\epsilon = s\epsilon$; $\cos \epsilon s = 1 - s^2\epsilon^2/2$; and $\epsilon^2 << l_{ij}^2$. Since with the available $\sin x/x$ strips, ϵ can be made as small as 0.01, equations 2 and 3 are quite accurate. Hence it is a simple matter to estimate the effect an increment in a particular structure parameter will have on the intensity pattern over any given interval of s. Knowing such trends is of considerable aid in deducing a configuration which is satisfactory. However, of greater value is the possibility thus presented of deducing the effects of increments

(11) P. Debye, *J. Chem. Phys.*, **9**, 55 (1941).

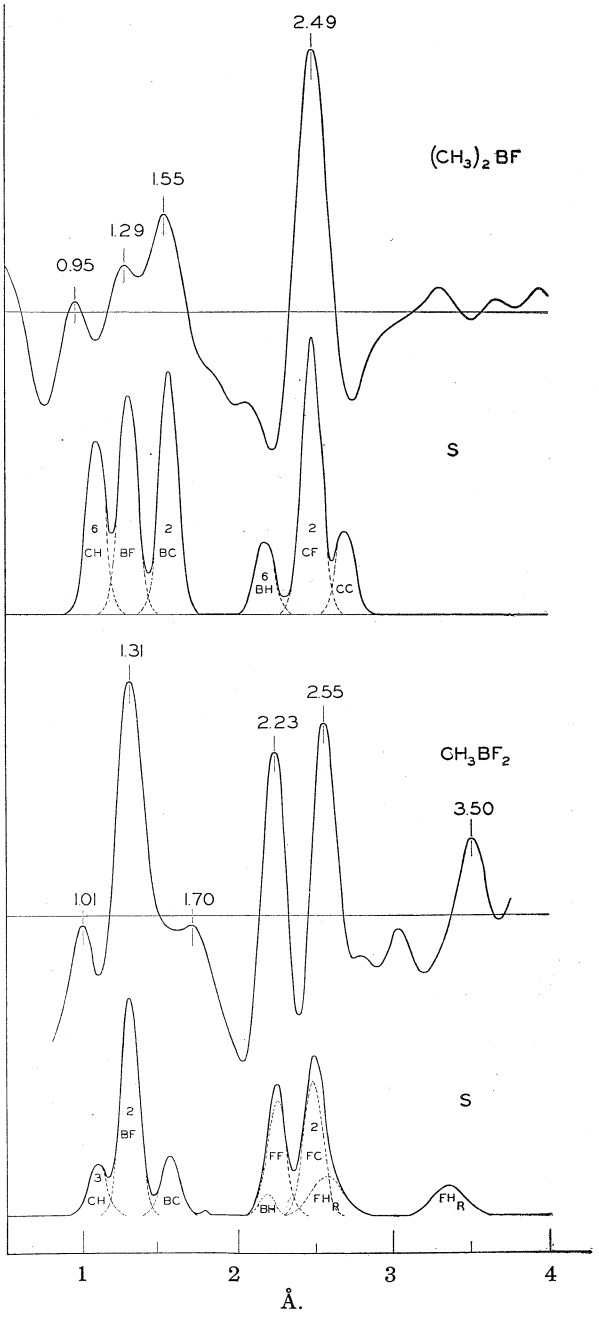


Fig. 1.—Radial distribution curves for methyl boron fluorides. Those marked "S" are synthetic curves for boron valence angles equal to 120°, B–C = 1.56 Å., B–F = 1.30 Å., C–H = 1.09 Å., a_{ij} = 0.042. The other curves were computed from the data quoted in Tables II and III, using the method of Walter and Beach.

in several parameters at once. Were one to start with a satisfactory model and values for $\partial I(s)/\partial P_n$ covering the critical regions, he can quickly estimate the effects of any combination of increments, if these are reasonably small, from

$$I(s)_{\text{new config.}} = I(s)_{\text{original}} + \sum_{P_n} \frac{\partial I(s)}{\partial P_n} \Delta P_n \qquad (4)$$

and thus conclude which combinations will still lead to satisfactory models. Limits on these increments are imposed by the radial distribution curve.

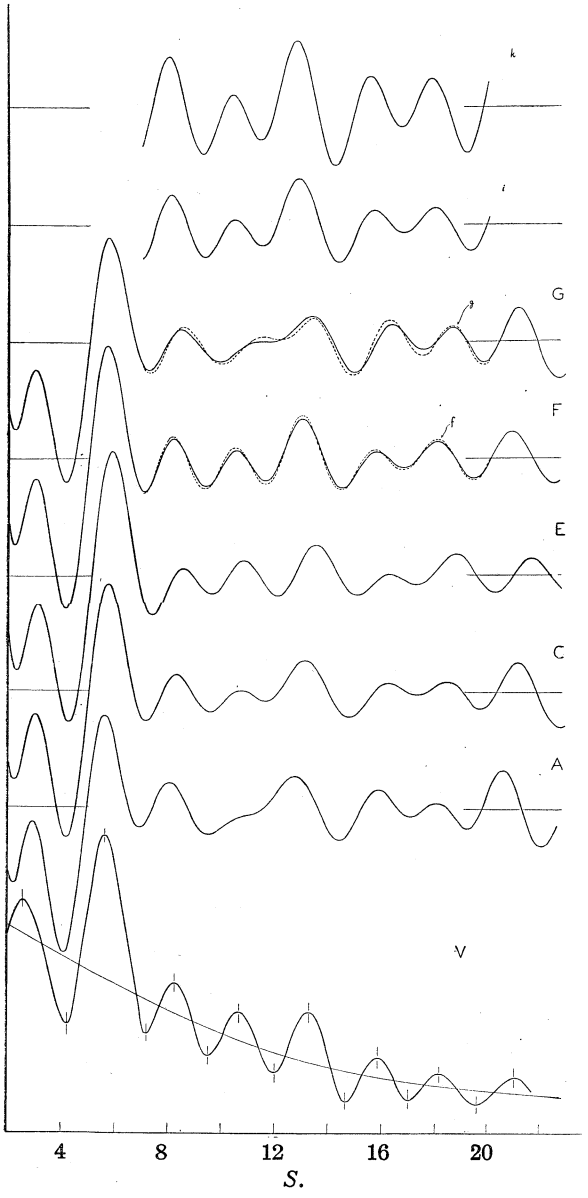


Fig. 2.—Intensity curves for dimethyl boron fluoride. Curve V is a sketch of the visual appearance of the pattern; the dashed curve is the supposed background above and below which our relative intensity estimates were made. For the computed curves, C–H = 1.09 Å., carbon valence angles tetrahedral (assumed); B–F = 1.29 Å., boron valences in a plane, and

B–C = 1.61 Å.,	∠CBF = 120°	Curve A
1.55	120	C
1.49	120	E
1.55	122	F (usual method), f (eq. 4)
1.55	118	G (usual method), g (eq. 4)
1.58	122	i (eq. 4)
1.61	124	k (eq. 4)

Dimethyl boron Fluoride.—The critical points of comparison are the intensities of the fourth and seventh peaks relative to the maxima on either side of these. For configurations with 120° boron valence angles six curves were computed, with the B–C/B–F ratio varying from 1.61/1.29 to 1.49/1.29. Of these, curves A and E, Fig. 2, are the extremes. The curve marked C, for which B–C/B–F = 1.202, and B–C/C–F = 0.630, appears to be quite satisfactory, both qualitatively and quantitatively (Tables I and II). A change of 0.03 Å. in the B–C separation introduces features not experimentally observed in the photographs.

TABLE II

DIMETHYL BORON FLUORIDE

Max.	Min.	$s_{obs.}$	I	C	$s_{calcd.}/s_{obs.}$ i	k
1		2.54	10	(1.181)		
	2	4.20	− 9	0.986		
2		5.59	18	1.020		
	3	7.19	−12	0.992		
3		8.24	10	1.004*	0.982	0.972
	4	9.51	− 5	1.002*	.982	.975
4		10.67	5	1.001*	.978	.975
	5	12.01	− 4	0.965*	.958	.952
5		13.29	5	0.983*	.967	.962
	6	14.65	− 2	1.006*	.978	.969
6		15.85	3	1.022*	.989	.980
	7	16.99	− 1	1.018*	.989	.982
7		18.15	1	1.012*	.986	.982
	8	19.61	− 1	1.003*	.983	.977
8		21.03	1	1.003*		
Average			1.001	1.002	0.979	0.973
Mean deviation			0.011	0.011	0.0072	0.0070
Distances and angle deduced	B–F		1.291	1.293	1.263	1.255
	B–C		1.552	1.553	1.547	1.566
	C–F		2.462	2.465	2.457	2.491
	∠CBF			120° 120°	122°	1.24°

The radial distribution curve suggests a small distortion in the boron valence angles. However, instead of calculating a whole series of curves covering a range in B–C/B–F ratio for various angles in the vicinity 120°, we computed $\partial I(s)/$

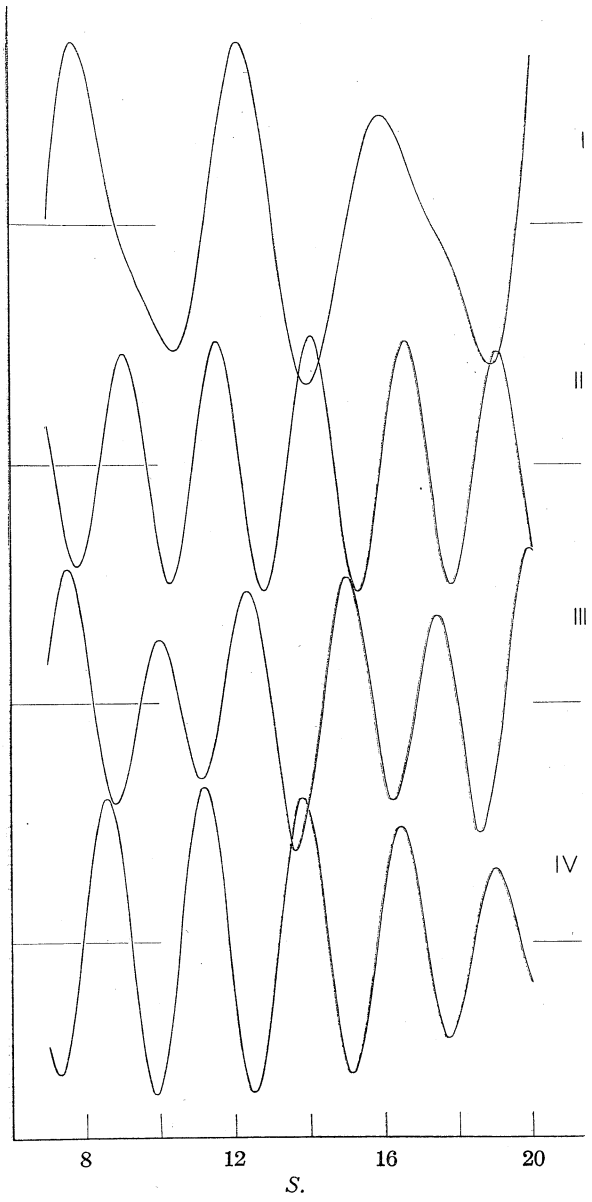


Fig. 3.—The variation of the intensity curves with distance and angle parameters, $(CH_3)_2BF$, curves I and II: $\partial I(s)/\partial$(B–C) and $\partial I(s)/\partial(\angle CBC/2)$, respectively. CH_3BF_2, curves III and IV: same distance parameter, while angle parameter is $\angle FBF/2$.

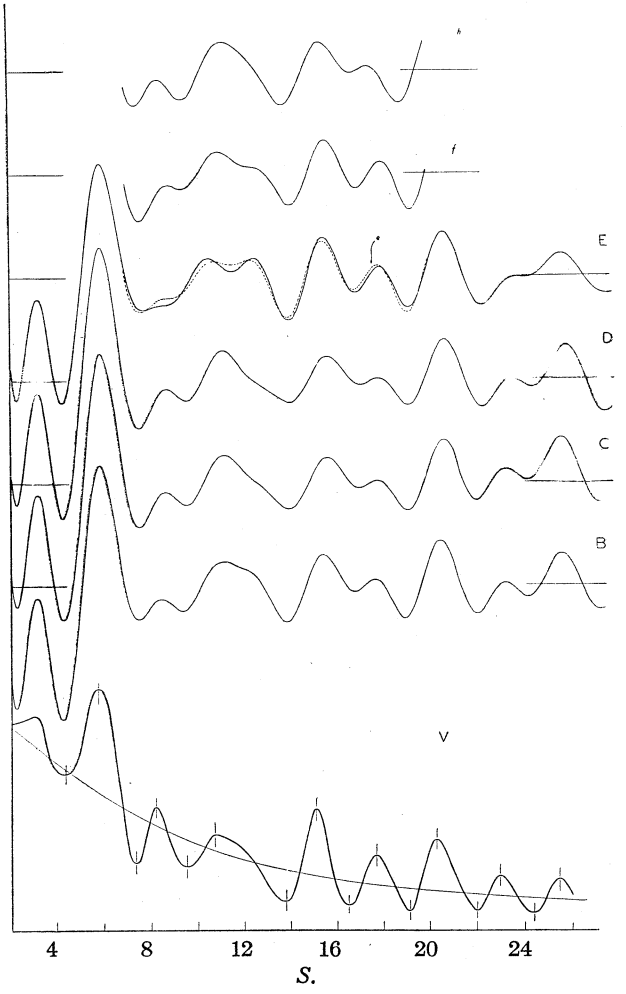


Fig. 4.—Intensity curves for methyl boron difluoride. Curve V is a sketch of the visual appearance of the pattern; the background curve is included. Once more, for the computed curves, C–H = 1.09 Å., carbon valence angles tetrahedral (assumed); B–F = 1.29 Å., boron valences in a plane, and

B–C = 1.61 Å.,	$\angle CBF$ = 120°	Curve B
1.58	120	C
1.56	120	D
1.58	122	E (usual method), *e* (eq. 4)
1.55	122	*f* (eq. 4)
1.625	119	*h* (eq. 4)

∂(B–C) and $\partial I(a)/\partial\alpha$, where $\alpha = \angle$ CBC/2, using curve C as our basic model (Fig. 3, curves I and II, respectively). We then made use of equation 4 to obtain subsequent models, some of which are included in Fig. 2, f–k. The accuracy of the method can be judged from a comparison of curves F and G with *f* and *g*, the former two being computed in the usual manner, with B–C/B–F $\Delta\alpha$ = 1.202 and $\angle$ CBF = 122 and 118°, respectively, while the latter were obtained from eq. 4 (curve II, Fig. 3) with = −2 and +2°, respectively.

It soon became evident that in general increments in either parameter alone lead to unacceptable curves, the fit being least disturbed for $\Delta\alpha$ negative. However, the combination of positive increments in B–C and negative ones in α resulted in a series of curves having the proper form (typical ones are *i*, *k*, Fig. 2); however, due to the good resolution obtained in the R. D. curves,

TABLE III

METHYLBORON DIFLUORIDE

Max.	Min.	$s_{obs.}$	I	$s_{calcd.}/s_{obs.}$ B	C	D	f	h
1		(3.2)	5	(0.991)	(0.997)	(0.997)		
	2	4.35	−14	0.986	0.993	0.991		
2		5.73	20	1.024	1.030	1.033		
	3	7.33	− 1	1.025	1.027	1.027	1.040	1.015
3		(8.16)	1	(1.032)	(1.059)	(1.071)	(1.083)	(1.032)
	4	(9.50)	− 1	(0.981)	(1.007)	(1.007)	(0.993)	(0.994)
4		(10.70)	3	(1.034)	(1.044)	(1.037)	(1.028)	(1.045)
	5	13.79	− 8	1.004	1.012	1.015	1.022	1.001
5		15.06	5	1.024	1.036	1.039	1.039	1.024
	6	16.47	− 2	1.021	1.032	1.036	1.032	1.019
6		17.67	2	1.001	1.005	1.008	1.019	0.990
	7	19.14	− 2	0.990	0.996	1.000	1.008	0.987
7		20.29	3	1.008	1.016	1.020		
	8	22.00	− 1	1.001	1.000	1.012		
8		22.93	1	1.013	1.014	1.026		
	9	24.39	− 1	0.991	0.990	1.000		
9		25.44	1	1.006	1.006	1.015		
	Average			1.007	1.012	1.017	1.027	1.006
	Mean deviation			0.011	0.013	0.012	0.010	0.013
Distances and angles deduced	B–F			1.299	1.305	1.312	1.325	1.298
	B–C			1.621	1.599	1.587	1.592	1.635
	C–F			2.538	2.520	2.512	2.557	2.535
	F–F			2.256	2.267	2.278	2.249	2.223
	∠CBF			120°	120°	120°	122°	119°

not all of these are acceptable. On weighing the various data, we concluded that dimethyl boron fluoride is a planar molecule, B–F = 1.29 ± 0.02 Å.; B–C = 1.55 ± 0.02 Å.; C–F = 2.48 ± 0.03 Å.; C–H = 1.09 Å. and tetrahedral carbon valence angles were assumed. The above combination of distances leads to ∠CBF = 121½°.

Methylboron Difluoride.—The critical region extends from $s = 7$ to 19. Due to the steeply decreasing background and the presence of a broad fourth maximum, the exact shape of the pattern in the interval $s = 8$ to 13 could not be clearly determined. Again, using 120° valence angles for boron, four curves were computed for the B–C/B–F ratio ranging from 1.66/1.29 to 1.56/1.29, with the best qualitative and quantitative fit being somewhere between curves B and C (Fig. 4 and Table III) B–C/B–F = 1.61/1.29 and 1.58/1.29, respectively.

With model B as a base, $\partial I(s)/\partial$(B–C) and $\partial I(s)/\partial\beta$ where β = ∠ FBF/2 (Fig. 3, III and IV, respectively) were obtained. It is clear that positive or negative increments in the two parameters would cancel each other except in the range $s = 8$ to 11. Thus, although the R. D. curve suggests that ∠ CBF is greater than 120°, a negative increment in β leads to unacceptable curves (E and e, Fig. 4), as do increments in either parameter alone. However, small positive increments both in B–C and in β lead to several acceptable curves (*h*, Fig. 4 is typical), as do small negative increments in both (*f* of Fig. 4). One may conclude that methyl boron difluoride is a planar molecule, B–F = 1.30 ± 0.02 Å.; B–C 1.60 ± 0.03 Å.; C–F = 2.53 ± 0.03 Å.; C–H = 1.09 Å. and tetrahedral carbon valence angles assumed. The above combination of distances leads to ∠ CBF = 121°.

Discussion

The electron diffraction results of Lévy and Brockway[1] coupled with the data obtained in this investigation show that the molecules comprising the series $B(CH_3)_3$, $B(CH_3)_2F$, BCH_3F_2, and BF_3 have the same configuration, and essentially the same interatomic distances. For quantitative comparison we have compiled Table IV. All but one of the reported B–C separations are equal to that expected for normal covalent bonding; at present writing we are unable to propose a theory which would account for the small increase in the B–C distance in BCH_3F_2 and which would not introduce difficulties for the remaining data. Empirically, the difference between the B–F separations observed in the methyl boron fluorides and those in $(CH_3)_2O:BF_3$, etc., may be

TABLE IV

Compound	B–C distance, Å.	B–F distance, Å.	Reference
H_3BCO	1.57 ± 0.03		12
$(CH_3BO)_3$	1.57 ± .03		5
$B(CH_3)_3$	1.56 ± .02		1
$B(CH_3)_2F$	1.55 ± .02	1.29 ± 0.02	B and H
BCH_3F_2	1.60 ± .03	1.30 ± .02	B and H
BF_3		1.30 ± .02	1
		1.29	13
$(CH_3)_2O:BF_3$		1.41 ± .02	14
Alkali fluoborates		1.43	15
Expected, for bonds of unit order: S and S	1.57	1.39	4, 5

ascribed to the transition in the coördination of boron from three to four, although reasoning on the basis of this postulate would lead one to expect a somewhat larger B–C distance in H_3BCO, wherein the boron atom is tetrahedrally bonded, than in the other compounds.

Introduction of the assumption of the dependence of bond distance on bond type always raises the question as to the interatomic distance one should select for a unit bond. Assuming that no distinction need be made between sp^2 and sp^3 type bonds (Table IV), it follows that the B–C linkages are all of unit order, whereas the B–F bonds in boron trifluoride are of an order higher than unity; *i. e.*, that the three excited structures $F_2B^-::F^+::$ contribute appreciably to the ground state. This is borne out by a rough comparison of the bond strengths in BF_3 and BF_4^- as deduced from their heats of formation,[16] and is further supported by the low parachor value which must be assigned to boron in BF_3 (8 as compared with about 15 in the other trihalides).[17]

If the postulate of sp^2 plus graphite type resonance presented above for boron trifluoride is extended to the methylboron fluorides, the fact that the B–F separation is the same for the three compounds appears to be fortuitous. Thus one has to assume that a bond order of about 1.2 may result either from the normal $(CH_3)_2B:F:::$ plus the single excited structure $(CH_3)_2B^-::F^+::$, or from the normal $F_2B:F:::$ plus the three excited structures $F_2B^-::F^+::$, in which each $B^-::F^+$ link is on the average only one-third double bond. Clearly, resonance among the latter three equivalent structures lowers some of the levels and raises others, so that the consequent resonance with the ground state is not strictly parallel to the case for dimethyl boron fluoride.

Finally one might point out the difference between the effects of successive substitutions of fluorine atoms on carbon and on boron. In CH_2F_2 the C–F separation is around 0.05 Å. less than in the monosubstituted methane,[18] whereas all the observed B–F distances are equal in the series BF_3, BF_2CH_3, $BF(CH_3)_2$.

Summary

An electron diffraction study of dimethyl boron fluoride and methyl boron difluoride leads to the following: the molecules are planar, $B(CH_3)_2F$: B–F = 1.29 ± 0.02 Å.; B–C = 1.55 ± 0.02 Å.; C–F = 2.48 ± 0.03 Å. BCH_3F_2: B–F = 1.30 ± 0.02 Å.; B–C = 1.60 ± 0.03 Å.; C–F = 2.53 ± 0.03 Å.

ITHACA, NEW YORK RECEIVED AUGUST 12, 1942

(12) S. H. Bauer, THIS JOURNAL, **59**, 1804 (1937).

(13) D. M. Gage and E. F. Barker, *J. Chem. Phys.*, **7**, 455 (1939).

(14) S. H. Bauer and G. Finlay, unpublished electron diffraction results, to be submitted for publication in THIS JOURNAL.

(15) C. Finbak and O. Hassel, *Z. physik. Chem.*, **B32**, 433 (1936); J. L. Hoard and V. Blair, THIS JOURNAL, **57**, 1985 (1935).

(16) In BF_4^- the average bond strength is estimated to be 144 kcal./mole bond, whereas in BF_3 it is 169 kcal./bond mole. Roth and Erika Borger, *Ber.*, **70B**, 48 (1937); de Boer and van Liempt, *Rec. trav. chim.*, **46**, 124 (1927).

(17) A. W. Laubengayer, R. P. Ferguson and A. E. Newkirk, THIS JOURNAL, **63**, 559 (1941).

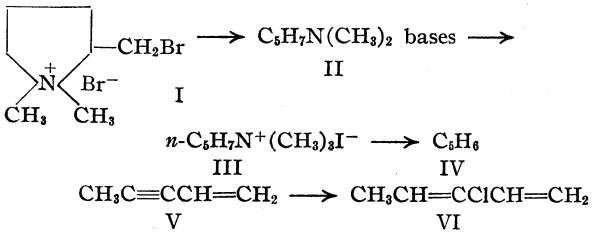
(18) L. O. Brockway, *J. Phys. Chem.*, **41**, 747 (1937).

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 903]

The Constitution of Pirylene: Chemical Evidence

BY HERBERT SARGENT, EDWIN R. BUCHMAN AND JOHN P. FARQUHAR

The C_5H_6 hydrocarbon pirylene (IV) was first prepared by Ladenburg[1] starting from piperidine and following essentially the path here indicated over the intermediates (I) to (III). The structure of these intermediates was but imperfectly known in Ladenburg's time,[2] so that a correct formulation of the pirylene molecule was out of the question. In 1928, von Braun and Teuffert[3] reinvesti-



gated the subject, and concluded that pirylene must possess a doubly unsaturated ring structure. A number of possibilities were cited; that of methylenecyclobutene[4] seemed most in accord with their observations. Because of our interest in cyclobutane derivatives the present study was undertaken.

It was found that degradation of (I) led to a mixture of bases (II), a fact which had been overlooked by previous investigators,[1,3,5] who had assumed the homogeneity of their $C_5H_7N(CH_3)_2$ base. From (II), a methiodide (III) was obtained which is without doubt the parent substance from which pirylene was formed. The straight-chain nature of the C_5H_7 radical in this quaternary salt was demonstrated by catalytic reduction of the corresponding chloride to *n*-amyltrimethylammonium chloride. From (III) pirylene (IV) was made in the usual way[1,3]; its properties, which agreed with the previous descriptions, were those of a pure substance.

A sample of this hydrocarbon has been submitted to Dr. V. Schomaker and Dr. R. Spurr of these Laboratories who have been able to work out its structure from the electron diffraction pattern.[6] Their investigation indicates that (IV) is not a ring compound, but possesses the structure (V) of 1-methyl-2-vinylacetylene, a known substance,[7] the physical properties of which agree well with those of pirylene.

The results of our chemical investigation are in full conformity with this conclusion. On catalytic reduction pirylene readily took up three moles of hydrogen; the reduced product was shown to be *n*-pentane. It also added one mole of hydrogen chloride, as has been demonstrated[8] for (V), giving 3-chloro-1,3-pentadiene (methylchloroprene) (VI).

Experimental

$C_5H_7N(CH_3)_2$ Bases (II).—The pyrrolidinium bromide (I)[5c] was degraded according to directions in the literature.[1b,3] From 136.5 g. (0.5 mole) of (I), 39 g. (70%) of mixed bases (II) was obtained, b. p. *ca.* 56–70° at 50 mm.; the exact composition of this mixture[9] was not determined due to its unstable nature. Fractionation through a precision column at 50 mm. gave 7.5 g. (13%) of material boiling constantly at 66.5°; examination of this fraction disclosed that it represented a substantially pure substance. It was used directly for conversion to the quaternary salt (III).

A portion of this base was further purified over the diliturate[10] which crystallized from alcohol in well-formed narrow rectangular crystals; m. p. 161–162°. The regenerated base, b. p. 65° at 49 mm., d^{25}_4 0.800, $n^{25}D$ 1.4430, entirely stable for months in an atmosphere free from carbon dioxide, was obtained by distilling the diliturate with excess aqueous alkali.

Anal. Calcd. for $C_7H_{13}N$: C, 75.60; H, 11.79. Found: C, 75.89; H, 12.10.

The picrate was prepared from the components in ether, cube-like crystals from ethanol–isopropyl ether, m. p. 100.5–101.0°.

Anal. Calcd. for $C_{13}H_{16}N_4O_7$: N, 16.47. Found: N, 16.25.

With methyl iodide the methiodide (III) described below was obtained.

***n*-$C_5H_7N(CH_3)_3I$ (III).**—To 54.3 g. of base (from fractionation of (II), b. p. *ca.* 66.5° at 50 mm.), in 250 cc. of ethanol, 76.4 g. of methyl iodide (10% excess) was added slowly, keeping the temperature at below 35° by cooling in an ice-bath. The crystalline product started to separate

(1) Ladenburg, (a) *Ber.*, **15**, 1024 (1882); (b) *Ann.*, **247**, 56 (1888).

(2) It was not until 1900 that Willstätter, *Ber.*, **33**, 365 (1900), elucidated the structure of the N,N-dimethyl-α-(bromomethyl-)-pyrrolidiniumbromide (I).

(3) von Braun and Teuffert, *ibid.*, **61**, 1092 (1928).

(4) Stevens and Richmond, THIS JOURNAL, **63**, 3133, Footnote 14 (1941), have pointed out that it is difficult to explain the formation of this hydrocarbon.

(5) See also (a) Ladenburg, *Ber.*, **14**, 1347 (1881); (b) Merling, *ibid.*, **17**, 2139 (1884); (c) Willstätter, ref. 2.

(6) Spurr and Schomaker, THIS JOURNAL, **64**, 2693 (1942).

(7) Jacobson and Carothers, *ibid.*, **55**, 1622 (1933).

(8) Jacobson and Carothers, *ibid.*, **55**, 1624 (1933).

(9) A fuller account of the constituents will be published in another connection.

(10) Compare Redemann and Niemann, *ibid.*, **62**, 590 (1940).

almost immediately; after recrystallization from aqueous alcohol, the yield of (III) was 104 g. (84%), m. p. 259° d. (lit.[3] m. p. 257°), entirely stable when heated with water at 100° (compare ref. 3).

Anal. Calcd. for $C_8H_{16}IN$: C, 37.96; H, 6.36; N, 5.53. Found: C, 38.33; H, 6.60; N, 5.57.

The same methiodide (III) was obtained when the mixed bases (II) were methylated according to directions[1] in the literature. As a characteristic derivative, the picrate was prepared from concentrated aqueous solutions of (III) and of sodium picrate, needles from ethanol, m. p. 112.5–113.0°.

(III) was not amenable to catalytic reduction; it was converted to the corresponding chloride[3] which was hydrogenated in aqueous solution under two atmospheres pressure using a palladium–charcoal catalyst. Two moles of hydrogen was taken up; the product was characterized by conversion to the picrate, prisms, m. p. 93.2–94.0°, from ethanol–isopropyl ether, and to the bromide, needles, m. p. 181.0–181.5°,[11] from ethanol. These derivatives gave no depression when mixed with authentic samples of the corresponding *n*-amyltrimethylammonium salts made from *n*-amyl bromide and trimethylamine.

Pirylene (IV)[1].—Quaternary iodide (III) (57.5 g.) was introduced together with 27 g. of potassium hydroxide and 70 cc. of water into a flask, and the mixture distilled from an oil-bath into a receiver immersed in a bath at −15°. A smooth decomposition took place (bath temperature 120–135°); the distillate was acidified with 6 *N* hydrochloric acid, and the hydrocarbon separated and dried over potassium carbonate, and over sodium. After distillation through a precision column, 8.9 g. (59%) of (IV) was obtained which boiled constantly; in a second similar experiment the yield was 11.0 g. (73%) of material having a 0.3° range. The constants observed were: b. p. 59.4° at 744 mm., d^{25}_4 0.7339, $n^{25}D$ 1.4467 (lit. pirylene[3]: b. p. 60°, d^{19}_4 0.7443, $n^{19}D$ 1.4505; methylvinylacetylene (V)[7]: b. p. 59.2° at 760 mm., d^{20}_4 0.7401, $n^{20}D$ 1.4496); the material polymerized slowly (much less rapidly than (VI)) on standing (compare refs. 3, 7).

The hydrocarbon (IV) (2.140 g.) was hydrogenated in ethanol solution using a palladium–charcoal catalyst. The hydrogen adsorbed (2.415 l. at 23° and 745 mm.) corresponded to 3 double bonds. The reduced hydrocarbon was distilled from the reduction mixture, treated with concentrated sulfuric acid and redistilled through a precision column; the sole product detected was *n*-pentane, yield 1.0 g., b. p. 36.3–36.5° (lit.[12] 36.1°).

Methylchloroprene (VI) was prepared from 3.7 g. of (IV) according to directions in the literature.[8] Two and two-tenths grams of (VI) b. p. 98.5–101°, $n^{25}D$ 1.4745 (lit.[8] b. p. 99.5–101.5°, $n^{20}D$ 1.4785) was obtained, and 1.5 g. of hydrocarbon was recovered. (VI) was identified by condensing with α-naphthoquinone; the derivative[8] melted at 180.7–181.0° cor. (lit.[8] 181°). When excess of (IV) and α-naphthoquinone were heated for two hours in a sealed tube at 100° no reaction[13] was observed.

Summary

The conclusion, first arrived at as a result of the electron diffraction investigation,[6] that pirylene and 1-methyl-2-vinylacetylene are identical, is supported by the chemical evidence.

(11) von Braun and Murjahn, *Ber.*, **59**, 1205 (1926), reported the m. p. 175–176°.

(12) Egloff, "Physical Constants of Hydrocarbons," Vol. I, Reinhold Publishing Corp., New York, N. Y., 1939, p. 33.

(13) Compare Butz and Joshel, THIS JOURNAL, **63**, 3344 (1941). Under the same conditions, piperylene gave an adduct which was oxidized to 1-methylanthraquinone, m. p. 170–171°.

PASADENA, CALIF. RECEIVED JULY 7, 1942

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 902]

The Constitution of Pirylene: Electron Diffraction Investigation

BY ROBERT SPURR AND VERNER SCHOMAKER

In connection with the studies described in the foregoing article[1] we have carried out an electron diffraction investigation of the C_5H_6 hydrocarbon pirylene with the object of determining its structural formula. Our results show that pirylene does not contain a three or four-membered ring as suggested by von Braun and Teuffert[2] but that it is methylvinylacetylene, $CH_3—C{\equiv}C—CH{=}CH_2$. This identification is substantiated by the agreement[1] of the physical properties of pirylene with those reported for methylvinylacetylene and by chemical evidence.[1] We wish to express our thanks to Dr. E. R. Buchman for suggesting the problem and to him and his collaborators for providing the sample of pirylene used in the investigation.

Experimental

The preparation of the pirylene has been described.[1] The apparatus and technique used have been reviewed by Brockway.[3] Twenty photographs were taken of the scattering from the vapor. The camera distance was about eleven or about twenty centimeters, and the wave length of the electrons was about 0.06 Å. (based on a_0 = 4.070 Å. for Au). The diffraction pattern showed fine structure indicative of long inter-

(1) Herbert Sargent, Edwin R. Buchman and John P. Farquhar, THIS JOURNAL, **64**, 2692 (1942).

(2) von Braun and Teuffert, *Ber.*, **61**, 1092 (1928).

(3) L. O. Brockway, *Rev. Modern Phys.*, **8**, 231 (1936).

atomic distances of the order of 5 Å. Thirty-one features were measured; the q values are represented by the arrows drawn through curves E′ and E $q = \frac{40}{\lambda} \sin \frac{\psi}{2} = \frac{10}{\pi} s$, where λ is the electron wave length and ψ is the scattering angle). The intensity pattern is well represented by curve E′ in the figure for $q < 40$ and by curve E for $q > 40$.

Discussion

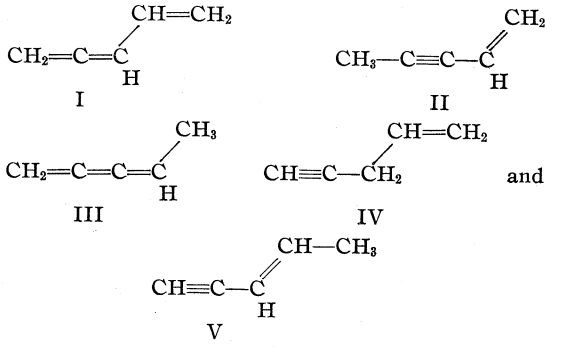
In most electron diffraction investigations the structural formula of the compound is known and the task is to find certain interatomic distances and bond angles. In the case of pirylene, however, only the molecular formula was known, and it was desired to find the correct structural formula (there are about 30 possibilities) even though a precise determination of the various important parameters seemed not to be feasible. To do this the expected molecular structures corresponding to the various structural formulas were compared with the information obtainable from the electron diffraction photographs with the aim of finding the satisfactory formula and eliminating all the others.[4] The procedure followed involved mainly the use of the radial distribution function[3] together with only a few theoretical intensity curves, as described below.

The radial distribution curve R is a plot of

$$rD(r) = \sum_{n=0}^{88} I_n e^{-an^2} \sin \frac{\pi}{10} rn \qquad (e^{-a(88)^2} = 0.1)$$

where the I_n are the ordinates at unit intervals of q of a curve drawn to represent the appearance of diffraction pattern, the measured positions of the rings, and the general characteristics of the simplified theoretical intensity function as defined below. With this interval of q, this radial distribution summation is still an entirely satisfactory approximation to the corresponding Fourier integral for $r = 5$ Å., and no false peaks of significant size are to be expected (except from possible errors in the I_n) for values of r less than about 10 Å. We have found that radial distribution summations of this kind are superior to the ordinary summations especially at large values of r, where the heights of the peaks of the ordinary summations are difficult to interpret and false peaks often appear. With these exceptions, the ordinary summations made for pirylene agreed well with R.

Since the radial distribution curve shows that there are important interatomic distances in the molecule up to about 5 Å., and none greater (the longest carbon–carbon distances expected for structures containing a ring or a branched chain is about 4.2 Å.), and since no branched chain or ring structures giving good general agreement with the radial distribution function could be found, an extended structure is indicated. Of the extended structures, only I and II will be



given detailed consideration here. It was found that the interatomic distances expected for structures III, IV, and V are in disagreement with the radial distribution curve, and that theoretical intensity curves (not shown here) drawn for models representing these structures bear little resemblance to the observed diffraction pattern; moreover, these structures are unlikely for chemical reasons.[5]

The intensity curves of Fig. 1 were drawn[6] for

(4) Since the present knowledge of the bond distances and bond angles in the lower hydrocarbons is very extensive (see L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, New York, N. Y.; L. Pauling, H. Springall, and K. Palmer, THIS JOURNAL, **61**, 927 (1939)), the predictions made for pirylene are almost certainly sufficiently accurate for this choice of the structural formula, and the reliability of the choice will depend only on the accuracy and completeness of the electron diffraction data.

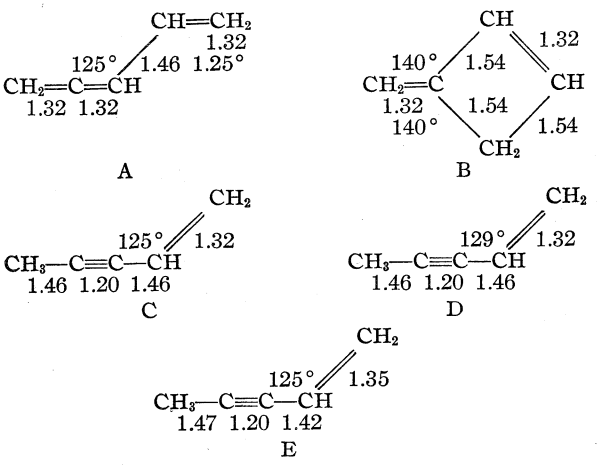
(5) Structures IV and V may be definitely excluded because pirylene does not undergo the typical reactions of substances which contain an acetylenic hydrogen atom. See Ladenburg, *Ber.*, **15**, 1024 (1882); *Ann.*, **247**, 56 (1888), and the procedure for the preparation of pirylene, ref. 1.

(6) The intensity functions were calculated according to the formula

$$I = \sum_{ij}{}' \frac{Z_i Z_j}{r_{ij}} e^{-a_{ij} q^2} \sin \frac{(\pi q r_{ij})}{10}$$

with the use of International Business Machines. In the temperature factor the coefficients a_{ij} were taken as zero for all except the C—H bonded interactions, for which the value 0.00022 was used. The non-bonded C...H terms, which require a more severe temperature factor, were omitted except for the best model, E. For it the intensity function E was calculated with the omission of these terms, and the function E′ with their inclusion with a_{ij} equal to zero. The probable effect of these terms was estimated for the other models by a comparison of E and E′. In the correlation of Model E with the measured q values a transition from curve E′ to curve E was made in the region where a_{ij} values of 0.00044 would reduce the non-bonded C...H terms to approximately one-half their initial amplitude. In the figure the arrows representing the measurements change from E′ to E at this point. The C—H distance was taken

the models shown below with the indicated distances and angles. All of the models are coplanar with respect to the carbon atoms; it is to be noted that A has the *trans* or extended configuration.



These models represent the remaining possible structures, I (model A) and II (C, D, and E; the parameters of C and D include small variations from the expected values used in E), and the ring structure most favored by von Braun and Teuffert.[2,7]

TABLE I

Max.	Min.	$q_{calcd.}$[a]	$q_{obsd.}$	$q_{calcd.}/q_{obsd.}$
	2		3.18	
2			4.70	
	3		6.56	
3			8.73	
	4		11.05	
4			12.52	
	5	13.5	13.98	0.966
5		18.4	17.91	1.027
	6		19.06	
6			20.27	
	7		21.67	
7			23.76	
	8	27.2	27.27	0.997
8		32.0	31.40	1.019
	9		32.95	
9			35.42	
	10	37.5	36.78	1.020
10		40.5	40.07	1.011
	11	43.0	42.69	1.007
11		45.7	45.93	0.995
	12		47.23	
12			48.39	
	13		52.71	
13			57.5	56.46	1.018
	14		59.0	58.10	1.015
14			60.5	60.31	1.005
	15			64.72	
15			69.8	68.72	1.016
	16		71.5	71.41	1.001
16			74.5	74.18	1.002
	17			78.51	
17			85.0	85.31	0.996
		Average			1.006
		Average deviation			0.011

[a] Only the more easily measurable features are chosen for comparison with calculated q values.

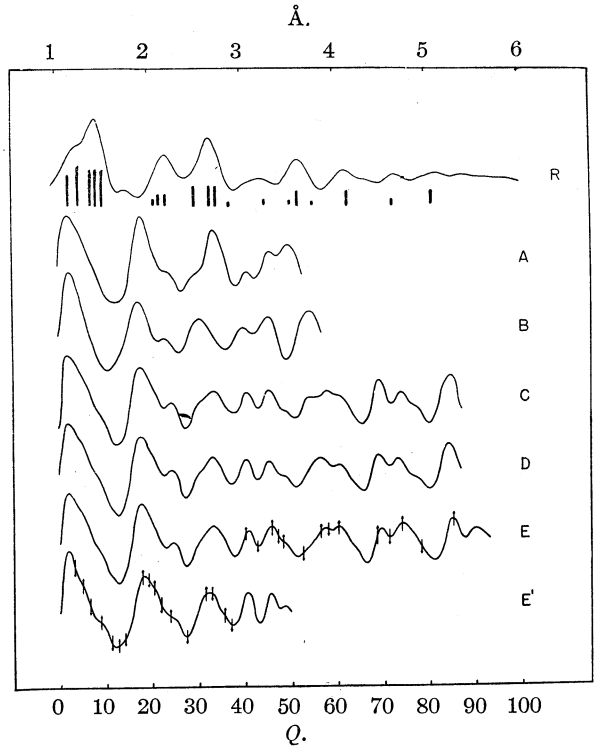


Fig. 1.

The appearance of the pictures is well represented only by curves E′ and E, although for $q < 50$ C and D are not significantly less satisfactory than E. The numerical comparison for E′-E,[6] given in the table, possesses satisfactory internal consistency and indicates that the over-all size of the model is essentially correct. The agreement between the radial distribution function and the interatomic distances of model E is

as 1.09 Å., the bond angles involving hydrogen were based on ethylene and methane, and for hydrogen Z was replaced by the value 1.25.

The use of the intensity function here described, which differs from the one usually used[3] by the factor q, will be discussed in detail at a later time; it offers advantages of convenience both in the construction of the radial distribution function and in the correlation procedure. Only at small values of q does the difference in behavior of the two functions become great. There, however, the measured ring diameters are not sufficiently reliable for use in the quantitative comparison anyway, and neither function faithfully represents the appearance of the photographs although either can be used to the extent that experience and comparison with molecules of known structure can be used as guides.

(7) The bond angles involving the side chain in this model were given a value (140°) larger than expected in an effort to obtain better agreement with the radial distribution function.

very satisfactory as shown by the vertical lines under the peaks in the figure.

The other intensity curves are quite unsatisfactory. Curve B is of some interest because it lacks the fine structure on the inside of the first minimum which appears on the other curves, apparently as a result of the terms above 4 Å. The possibility of obtaining a satisfactory curve with any reasonable variation of Model A seems remote. One cause of the disagreement with Curve A is revealed by the width and position (1.42 Å.) of the first peak of the radial distribution function. For Model A one would expect instead a rather sharp peak at about 1.34 Å. with weak shoulders or satellites at 1.46 Å. and 1.09 Å. Another factor is the absence of any distance which would correspond to the radial distribution peak at 4.12 Å.

Our electron diffraction investigation thus leads to the conclusion that pirylene is 1-methyl-2-vinylacetylene (Structure II) with the bond distances and bond angles which were assumed for Model E from the existing information regarding similar molecules. Because the agreement of the photographs and the radial distribution function with Model E is so detailed that it could hardly be fortuitous, we should have confidence in this conclusion even if no effort to eliminate other possible formulas had been made.

Summary

The electron diffraction investigation of pirylene shows it to be 1-methyl-2-vinylacetylene. The structural parameters found were those anticipated from a knowledge of the structures of similar molecules.

An approximation to the radial distribution integral which is more accurate than the usual summation is briefly described.

PASADENA, CALIFORNIA RECEIVED JULY 7, 1942

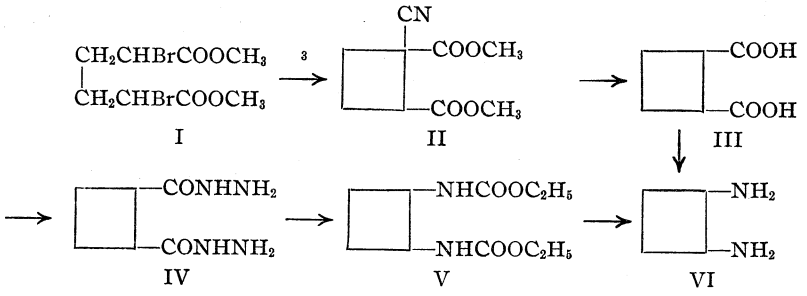
[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 894]

Cyclobutane Derivatives. I.[1] The Degradation of *cis*- and *trans*-1,2-Cyclobutanedicarboxylic Acids to the Corresponding Diamines

BY EDWIN R. BUCHMAN, ALF O. REIMS, THURSTON SKEI AND MAURICE J. SCHLATTER

According to scattered references in the literature,[2] the Curtius degradation of cyclic dicarboxylic acids proceeds in the normal fashion without change in configuration. In the present work it was found that the *cis*- and *trans*-isomers (III) could be converted, over the intermediates (IV) and (V), into the corresponding diaminocyclobutanes (VI). The diamine obtained from the *cis*-acid was shown to possess the *cis*-structure by the preparation from it of cyclic derivatives; under the same conditions cyclic products were not obtained from *trans*-(VI).

The K. F. Schmidt degradation[4] had not previously been applied to cyclic dicarboxylic acids. When *cis*- and *trans*-(III) were treated with hydrazoic acid according to this method they were transformed directly, with retention of configuration, to *cis*- and *trans*-(VI); thus the method affords an alternative preparative route to these substances.



(1) The results contained in this and the two following papers were presented before the Pacific Division of the American Association for the Advancement of Science at the Pasadena Meeting, June, 1941.

(2) (a) Curtius, *J. prakt. Chem.*, [2] **91**, 23 (1915); (b) Diels, Blom and Koll, *Ann.*, **443**, 242 (1925); (c) Alder and Stein, *ibid.*, **514**, 211 (1934). However, in the case of the 1,3-cyclohexanedicarboxylic acids, Skita and Rössler [*Ber.*, **72**, 461 (1939)] claim that the same diurethan results both from the *cis*- and from the *trans*-diazide.

(3) Fuson and Kao, THIS JOURNAL, **51**, 1536 (1929); Ellingboe and Fuson, *ibid.*, **56**, 1774 (1934).

(4) Hurd in Gilman's "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, p. 698. From succinic acid a small yield of ethylenediamine has been obtained (Oesterlin, *Angew. Chem.*, **45**, 536 (1932)).

Experimental[5]

The cyclobutanedicarboxylic acids (III) were made by the method[3] of Fuson employing both the methyl and the ethyl esters of the intermediates. The use of the methyl esters is to be recommended as pure crystalline meso (I) can more conveniently be prepared than the corresponding diethyl ester. It is possible to utilize the crude liquid racemic dibromoadipic esters for ring closure or for conversion to the crystalline isomers but, since the crude esters contain[6] some α,α-dibromo isomer, additional purification steps are necessary.

α,α'-Dibromoadipic Dimethyl Ester (I).[7]—Adipic acid (1460 g. = 10 moles) was treated in all glass apparatus with thionyl chloride[7b,8] (2380 g. = 3% excess); the latter was added at two to three hour intervals in portions of about 750 g. while heating at 70–80°. When reaction was complete, 3520 g. of bromine (10% excess) was added dropwise (eighteen hours) with continued heating and the product finally heated for eight hours at 100°. The crude acid halide was added with stirring to 2000 cc. of methyl alcohol in a flask surrounded by an ice-bath; meso (I) crystallized on seeding and cooling. After filtering and washing with methanol the yield was about 50%. Crude (I) was recovered from the filtrate by distillation,[7b] b. p. *ca.* 163° at 3 mm., average[9] total yield 93%. Additional meso (I) was obtained from the distillate, needles, m. p. 73.5–74.0° from methanol, average total yield 2329 g. = 70% (corresponding yield in case of the diethyl ester, 46%).

The non-crystalline distillate consisted largely of the unstable racemic modification, which crystallized out slowly at about −10°. It was obtained pure by recrystallization from methanol at −78°, m. p. +11–12°.

Anal. Calcd. for $C_8H_{12}Br_2O_4$: C, 28.94; H, 3.64. Found: C, 29.07; H, 3.86.

1-Cyano-1,2-cyclobutanedicarboxylic Acid Dimethyl Ester (II).—Two moles[10] of meso[11] (I) (664 g.), 368 g. (5.5 moles) of potassium cyanide (Merck reagent[12]) and 360 cc. of methanol were refluxed for fifty-six hours from an oil-bath maintained at about 75°; occasional stirring was necessary to break up the solid cake which formed. The product was taken up in anhydrous ether and fractionated *in vacuo;* the average yield, b. p. *ca.* 128° at 3 mm. was 284 g. = 72% (82% in the ethyl ester series). The distillate crystallized in part; the resulting crystals (26% of the weight of the distillate) were recrystallized from methanol, colorless needles m. p. 89.5–90.0°. The non-crystalline part[13] was refractionated and the portion boiling at 119–120° at 2 mm. subjected to analysis; this material did not crystallize at 0°.

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found (solid): C, 55.15; H, 5.62; N, 7.15. Found (liquid): C, 54.49; H, 5.62; N, 6.85.

1,1,2-Cyclobutanetricarboxylic Acid.—This acid was prepared from crystalline (II) following essentially the procedure of Fuson.[3] The colorless barium salt was decomposed with the requisite amount of sulfuric acid and the filtrate evaporated *in vacuo.* The crystalline residue consisted of hydrated tricarboxylic acid, m. p. 135° dec. from dioxane on addition of benzene. The water of crystallization was not lost on drying *in vacuo* under the usual conditions; in one experiment which we have not since been able to reproduce, water was apparently removed during recrystallization. The anhydrous acid, colorless massive prisms from anhydrous ether in which it is soluble without difficulty at room temperature, melted at 91–92° and began to lose carbon dioxide at about 130°.

Anal. Calcd. for $C_7H_8O_6$: C, 44.69; H, 4.29. Found: C, 44.90; H, 5.12.

On treatment with water, the acid was reconverted to the stable hydrate.

***cis*- and *trans*-1,2-Cyclobutanedicarboxylic Acids (III).**—The crude liquid isomer (II) (789 g.) was refluxed with 2000 cc. of 6 *N* hydrochloric acid for twenty-four hours, the hydrolyzate evaporated on the steam-bath and the residue extracted with anhydrous ether (acetone may also be used). After removal of solvent, the crude acid was decarboxylated by heating at 170–180° at 20 mm. for three hours and the mixture refluxed[14] for an additional three hours with 2000 g. of acetyl chloride. Acetyl chloride and acetic acid were distilled off; the material remaining was heated from an oil-bath at 150–160° at 20 mm. for several hours and finally distilled at 2 mm. An 81% yield of *cis*-anhydride was obtained boiling at 127–130°; a portion was recrystallized from benzene, blades, m. p. 76.5–77.0°. Distillation residues from several runs were combined and subjected to a second treatment with acetyl chloride; a small additional amount of anhydride was recovered.

cis-Anhydride was heated to boiling with 0.8 its weight of water; *cis*-acid crystallized from the resulting solution on cooling. Saturation of the filtrate with dry hydrogen chloride yielded additional amounts of less pure material. The yield of *cis*-(III) was 85%; from benzene–dioxane it crystallized in rectangular prisms exhibiting extensive twinning, m. p. 139.5–140.0°. From the residual mother liquors, recovery was best effected via the anhydride.

trans-(III) has been prepared from the *cis*-isomer by treatment with hydrochloric acid[15]; in the present investi-

(5) All melting points are corrected. The authors are indebted to Dr. G. Oppenheimer and Mr. G. A. Swinehart for microanalyses reported in this and the two following papers.

(6) Ingold, *J. Chem. Soc.*, **119**, 956 (1921).

(7) (a) Le Sueur, *ibid.*, **95**, 275 (1909); (b) Stephen and Weizmann, *ibid.*, **103**, 271 (1913); (c) Bernton, Ing and Perkin, *ibid.*, **125**, 1492 (1924).

(8) Fuson, Kreimeier and Nimmo, THIS JOURNAL, **52**, 4074 (1930).

(9) Average yields reported in this paper are based on the results of six or more identical experiments.

(10) A ten-mole batch gave only a 40% yield due to decomposition during distillation of the crude product.

(11) The racemic form of (I) behaved in the same way, giving a comparable yield of crystalline and liquid (II) with the latter predominating.

(12) A commercial grade of sodium cyanide proved satisfactory[8] for effecting ring closure of the meso diethyl ester in ethanol but its use in the present instance led to extensive tar formation.

(13) A portion which had stood in a loosely stoppered bottle for a year had deposited a small amount of crystals, colorless rectangular prisms from methanol, m. p. 172.5–173.5° dec., easily soluble in water and hot methanol, difficultly soluble in ether. Analyses point to the formula $C_{10}H_{12}N_2O_5$: Calcd.: C, 50.00; H, 5.04; N, 11.66. Found: (average) C, 50.23; H, 5.43; N, 11.36. The substance may be related to α,α'-dicyanoadipic ester.

(14) *trans*-(III) is converted by this treatment to a mixed anhydride with acetic acid which on stronger heating decomposes into *cis*-anhydride; compare however reference 15.

(15) Perkin, *J. Chem. Soc.*, **65**, 572 (1894).

gation two further methods for effecting the isomerization were found. *trans*-(III) may also conveniently be prepared, although the method is expensive, from the readily obtainable *trans*-dihydrazide (IV) by hydrolyzing with boiling 6 *N* hydrochloric acid and isolating by continuous extraction with ether.

cis-(III) (50 g.), heated[16] under reflux from a bath at 200° for five hours was partially isomerized. Recrystallization of the product from water yielded 25.5 g. of *trans*-(III), clusters of blades from benzene–dioxane, m. p. 130.5–131.0°.

Twenty grams of *cis*-(III) dimethyl ester was heated under reflux from a water-bath for two and one-half hours with 0.3 g. of sodium dissolved in 5 cc. of methyl alcohol.[17] The product was washed with water, dried and distilled, giving 16.3 g. of ester, b. p. 118–119° at 24 mm. A portion of this ester, hydrolyzed by heating with dilute hydrochloric acid, yielded 76% of *trans*-(III). From another portion the *trans*-dihydrazide (IV) was obtained in 86% yield; the amount of *cis*-ester present in the equilibrium mixture[18] must, therefore, be small.

cis- and trans-(III) Esters.—Pure *cis*-(III) dimethyl ester was prepared in 94% yield from the acid with diazomethane, b. p. 85° at 3 mm. On a preparative scale the diethyl ester was made by heating under reflux 500 g. of *cis*-(III) (anhydride could be used directly) for four hours with 2000 cc. of absolute alcohol while passing in a slow stream of dry hydrogen chloride. The reaction mixture was then poured into water and worked up in the usual manner. The yield was 493 g. (71%), b. p. 99–100° at 2 mm., 123° at 24 mm.; this ester contained at most only small amounts of *trans*-isomer (best detected by the reaction with hydrazine hydrate). Incompletely esterified acid in the water and carbonate washings was recovered by evaporation and conversion to anhydride.

A suitable source material for the preparation of large amounts of *trans*-(IV) was made directly from crude (III), resulting from saponification of crude liquid (II) and subsequent decarboxylation. This was esterified by heating with alcohol, carbon tetrachloride[19] and aqueous hydrochloric acid; an average yield of 82% of a mixture consisting of about equal amounts of each isomer was obtained (in the case of the cyano diethyl ester intermediate, the average yield was 71% of a similar product).

cis- and trans-1,2-Cyclobutanedicarboxdihydrazides (IV).—These compounds were prepared by adding *cis*- and *trans*-(III) esters dropwise to 10% excess of hydrazine hydrate (85%) which was heated under reflux from an oil-bath at 130° (lower temperatures gave incomplete reaction) and continuing the heating at this temperature for five hours. Under these conditions a practically quantitative yield of crude (IV) resulted. No changes in configuration took place; *cis*- and *trans*-(IV) on acid hydrolysis gave, respectively, *cis*- and *trans*-(III).

From *cis*-(III) dimethyl ester an 80% yield of *cis*-(IV) was obtained. On a preparative scale, 246 g. of *cis*-(III) diethyl ester was treated with 160 g. of 85% hydrazine hydrate. The product was allowed to crystallize in the ice-chest, was filtered off and washed with alcohol; the filtrates were evaporated and the residue pressed on tile. The combined crude material was refluxed for a short while with 500 cc. of absolute alcohol (not sufficient to effect complete solution); after cooling and filtering, 160 g. (75%) of substantially pure *cis*-(IV) was obtained. The mother liquors did not usually afford crystalline material and were hydrolyzed for recovery of (III). In a few cases the m. p. of the crude indicated an admixture of *trans*-isomer arising probably from impurity in the *cis*-(III) ester used; separation was effected by digesting the crude (IV) with an amount of 85–90% ethanol sufficient to dissolve the *cis*-isomer and filtering hot. The greater part of *cis*-(IV) could be recovered from the filtrate.

cis-(IV) crystallized from absolute alcohol in massive prisms which exhibit extensive twinning, m. p. 140.0–140.5°. Occasionally when recrystallized from this solvent a second metastable form was encountered which was separated mechanically, clusters of fine needles, m. p. 134.5–135.0°, mixed m. p. with the stable form 135–140°; on standing it is transformed to the stable variety. *cis*-(IV), over a period of months, was largely converted into material of different composition difficultly soluble in water and the common organic solvents.

It was found convenient to prepare the *trans*-isomer from *cis*-, *trans*-(III) diethyl ester mixtures (see above); *trans*-(IV) crystallized from the reaction mixture and *cis*-isomer could be isolated from the mother liquors (better to hydrolyze for recovery of (III)). *trans*-(IV) was purified by recrystallization from 50% aqueous alcohol, clusters of colorless needles, m. p. 223.0–223.5°. The (III) ester mixture from crude liquid (II) gave an average yield of 54% while the ester mixture from cyano diethyl ester gave a 48% yield.

Anal. Calcd. for $C_6H_{12}N_4O_2$: C, 41.85; H, 7.02; N, 32.54. Found (*cis*-needles): C, 42.03; H, 6.92; N, 32.74. Found (*cis*-prisms): C, 41.71; H, 7.01; N, 32.70. Found (*trans*): C, 42.18; H, 7.01; N, 32.89.

cis- and trans-(IV) Dihydrochlorides.—To 100 g. of *cis*-(IV) suspended in an equal weight of water and surrounded by an ice-bath, 98 cc. of concentrated C. P. hydrochloric acid was added dropwise with stirring during twenty minutes. A further addition of 100 cc. excess of hydrochloric acid caused the precipitation of the dihydrochloride which was filtered off on a sintered glass filter, washed with cold absolute alcohol and dry ether and dried in a desiccator over sodium hydroxide, yield 78.5 g. (55%). The material is easily altered; it was analyzed without further purification. Additional amounts contaminated with hydrazine hydrochloride were obtained from the mother liquors by saturating with hydrogen chloride gas at 0°; such material could also be used for the preparation of *cis*-(V).

trans-(IV) (250 g.) was suspended in 300 cc. of water and the theoretical amount of concentrated hydrochloric acid (242 cc.) added during twenty minutes as above. Excess acid (500 cc.) was added and the precipitate isolated as before, yield 342.5 g. (96%). A portion was recrystallized by dissolving in methanol at 25° and cooling to 0°, compact rosets of fine needles, m. p. about 200° dec.

(16) Compare Liebermann, *Ber.*, **22**, 2245 (1889); Stoermer and Bachér, *ibid.*, **55**, 1865 (1922); Skita and Rössler, *ibid.*, **72**, 271 (1939).

(17) Compare Hückel and Goth, *ibid.*, **58**, 447 (1925).

(18) Compare ref. 2c.

(19) Hultman, Davis and Clarke, THIS JOURNAL, **43**, 366 (1921).

Anal. Calcd. for $C_6H_{14}Cl_2N_4O_2$: C, 29.40; H, 5.76; N, 22.86. Found (*cis*): C, 29.67; H, 6.06; N, 23.19. Found (*trans*): C, 29.73; H, 6.02; N, 22.76.

***cis-* and *trans*-N,N'-Dicarbethoxy-1,2-diaminocyclobutanes (V).**[20]—*cis*-(IV) dihydrochloride (100 g.) was dissolved in 100 cc. of water, the solution layered with 700 cc. of anhydrous ether and a solution of 56.2 g. of sodium nitrite in 120 cc. of water was added over a period of fifteen minutes with continuous stirring, maintaining the temperature at 13–16°[21] (cooling bath at −15°). Stirring with cooling was continued for an additional five minutes; the ether layer was then separated and dried by shaking in the cooling bath for five minutes with 40 g. of reagent grade calcium chloride. The aqueous layer was twice extracted with 100-cc. portions of ether, the extracts dried and combined with the above. After the addition of 440 cc. of absolute alcohol, the ether solution was distilled from a water-bath at about 60°; nitrogen was evolved. The resulting alcoholic solution was refluxed from an oil-bath for one hour, the solvent removed *in vacuo* and the residue treated at room temperature with absolute alcohol. The portion difficultly soluble (1.0 g.) was recrystallized from 80% alcohol, colorless hexagonal plates, m. p. 258.5–259.0°; this substance is possibly 4,5-dimethylenedihydrouracil.

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.63; H, 5.88; N, 19.89.

The portion readily soluble in alcohol gave on evaporation 52 g. (55%) of crude crystalline *cis*-diurethan (V) which was suitable for conversion to *cis*-(VI). A sample was recrystallized from ethyl acetate, colorless needles, m. p. 101.5–102.0°.

The preparation of *trans*-(V) was carried out in a similar fashion except that the *trans*-(IV) dihydrochloride (100 g.) was dissolved in 200 cc. of water and the sodium nitrite solution was added maintaining the temperature of the reaction mixture at 18–20° (this slightly higher temperature was found, as the result of a series of experiments, to afford optimum yields). The reaction between the diazide and alcohol gave 2.2 g. of amorphous material difficultly soluble in absolute alcohol; this material, m. p. *ca.* 210°, could not be crystallized; on hydrolysis with alkali it yielded substantial amounts of *trans*-(VI). The average yield of alcohol soluble material was 57 g. (60%); it was used for conversion to *trans*-(VI). Pure *trans*-(V) was obtained by crystallization from aqueous alcohol, from which solvent it came out in both needles and cube-like crystals, m. p. 129.5–130.0°.

Anal. Calcd. for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found (*cis*): C, 52.24; H, 7.52; N, 12.05. Found (*trans*): C, 51.89; H, 7.51; N, 12.22.

***cis-* and *trans*-1,2-Diaminocyclobutanes (VI) from the Diurethans (V).**—A solution of 250 g. of C. P. potassium hydroxide in 680 cc. of methanol was refluxed with 62 g. of crude *cis*-diurethan for one hour from a bath at 100°. The solvent was distilled off and the residue steam distilled from a bath at 170° until the distillate was neutral to litmus. The aqueous and methanolic distillates were combined, acidified with C. P. concentrated hydrochloric acid and evaporated to dryness on the steam-bath, yield of crude hydrochloride nearly theoretical. The salt was dissolved in the minimum amount of water and the solution added dropwise to 100 g. of potassium hydroxide. The free base was isolated by continuous ether extraction; the ether extract after drying and distilling over sodium yielded 17.2 g. (77%) of diamine, b. p. 147°, b. p. 75° at 50 mm., $n^{20}D$ 1.4881, d^{20}_4 0.9652.

The *trans*-diamine was prepared from crude *trans*-(V) in exactly the same manner; yield of crude hydrochloride theoretical. The continuous ether extraction required a longer time for completion than was necessary in the case of the *cis*-compound. From 62 g. of crude *trans*-(V), 14.4 g. (63%) of base was obtained, b. p. 151°, b. p. 74° at 50 mm., $n^{20}D$ 1.4837, d^{20}_4 0.9490.

Anal. Calcd. for $C_4H_{10}N_2$: C, 55.77; H, 11.70; N, 32.53. Found (*cis*): C, 55.77; H, 11.90; N, 32.00. Found (*trans*): C, 55.59; H, 11.62; N, 31.77.

The diamines react readily with carbon dioxide[22]; the resulting ether insoluble addition compounds sublimed with decomposition, *cis-* at *ca.* 150°, *trans-* at *ca.* 110°. The following derivatives of *cis-* and *trans*-(VI) were made in the usual manner; the empirical formulas given were confirmed by analysis. Dibenzenesulfonamides, $C_{16}H_{18}N_2O_4S_2$: *cis-* m. p. 145.5–146.5° from alcohol, *trans-* m. p. 153.5–154.0° from alcohol. Dibenzamides from benzoyl chloride, base and aqueous alkali, $C_{18}H_{18}N_2O_2$: *cis-* m. p. 204.5–205.0° from absolute alcohol, *trans-* m. p. 245.5–246.0° from dioxane. Dipicrates from base with ethereal picric acid, $C_{16}H_{16}N_8O_{14}$: *cis-* insoluble in the usual solvents, crystallized by dissolving in pyridine and adding absolute alcohol, m. p. 255° dec.,[23] *trans-* m. p. 254° dec.,[23] from aqueous alcohol. Derivative from *trans*-diamine with phenyl isocyanate, $C_{18}H_{20}N_4O_2$: fine needles, m. p. 279–280° from dioxane-water; *trans*-oxalate, $C_6H_{12}N_2O_4$: prisms from aqueous alcohol, m. p. 268° dec.

***cis-* and *trans*-(VI) from the Dicarboxylic Acids (III).**—In a 1-liter three-neck flask equipped with dropping funnel, mechanical stirrer, gas evolution indicator, and thermometer dipping into the liquid was placed 46 cc. of concentrated C. P. sulfuric acid. First, 20 g. (0.139 mole) of *cis*-(III) was added and then a solution of hydrazoic acid[24] in chloroform (from 32 g. of sodium azide and found by titration to contain 14.8 g. (0.335 mole) of hydrazoic acid) was added over a period of twenty-five minutes maintaining the temperature at about 40°. Heating was continued at this temperature for twelve hours; the reaction mixture was poured on ice, separated from chloroform and distilled to remove traces of this solvent. A solution of 180 g. of potassium hydroxide in water was added slowly with cooling and the mixture steam distilled at a bath temperature of about 160° (compare preceding section). The crude dihydrochloride, 16.5 g. (75%), was contaminated with a small amount of ammonium chloride. The free base was isolated as before, yield 4.2 g. (35%).

trans-Diamine was made by essentially the same procedure; a theoretical yield of crude dihydrochloride re-

(20) Procedure based on that used by Curtius [*J. prakt. Chem.*, [2] **52**, 221 (1895)] in the case of succindihydrazide.

(21) Higher temperatures gave poorer yields.

(22) Compare *Chem. Zentr.*, **72**, II, 519 (1901).

(23) Minimum temperature at which a fresh sample will decompose when placed for twenty seconds in a bath at this temperature.

(24) von Braun, *Ann.*, **490**, 125 (1931).

sulted. The yield of *trans*-(VI) was 7.3 g. (55%) from 22 g. of *trans*-(III).

These amines made directly from the dicarboxylic acids had the same physical constants and gave the same characteristic derivatives as the amines prepared by the Curtius degradation.

Preparation of Cyclic Derivatives from *cis*-(VI).—Although benzil reacted vigorously with *cis*-(VI), the reaction did not afford the expected derivative[25]; the only product isolated was tetraphenylpyrazine, needles from alcohol, m. p. 252.0–252.5° (analysis). Even when equivalent amounts of the reactants were brought together in ether solution at room temperature, under which conditions they react slowly, only tetraphenylpyrazine was isolated in pure form from the complex mixture of reaction products. The same substance was also formed by heating benzil together with *trans*-(VI).

Gaseous phosgene in excess was passed into an ethereal solution of *cis*-(VI) at 0°; the reaction proceeded rapidly with separation of solid. After evaporation of solvent the residue was dissolved in water, made alkaline and continuously extracted with ether. From the extract the cyclic urea derivative[26] was recovered as a crystalline solid together with unchanged *cis* diamine. The former was purified by sublimation at 100° at 2 mm. and recrystallization from a mixture of isopropyl ether and a small amount of absolute alcohol, colorless octahedra, m. p. 147.0–147.5°, difficultly soluble in ether, easily in alcohol or water.

Anal. Calcd. for $C_5H_8N_2O$: C, 53.55; H, 7.19; N, 24.99. Found: C, 53.63; H, 7.32; N, 25.10.

When *trans*-(VI) was treated in the same manner with phosgene, in addition to unchanged amine, only an amorphous insoluble product was isolated.

When excess of carbon disulfide was added to an alcoholic solution of *cis*-(VI), a white crystalline precipitate separated immediately. This salt[27] crystallized from aqueous alcohol, colorless plates, sintering with loss of hydrogen sulfide at about 152° and then melting at the melting point of the 2-thiol-4,5-dimethyleneimidazoline. The latter was prepared by evaporating an aqueous solution of the dithiocarbamate on the water-bath, colorless plates from water, m. p. 168.5–169.0°.

Anal. Calcd. for $C_5H_8N_2S$: C, 46.84; H, 6.29. Found: C, 46.80; H, 6.16.

When the *trans*-diamine was treated with carbon disulfide in the same manner, a similar precipitate of a dithiocarbamic acid internal salt formed, stable granular white crystals from hot water, sintering at 263°,[23] difficultly soluble in cold water or hot alcohol.

Anal. Calcd. for $C_5H_{10}N_2S_2$: C, 37.01; H, 6.21; N, 17.27. Found: C, 36.77; H, 6.18; N, 16.81.

cis-Diamine (0.86 g. = 0.01 mole) and thioacetamide (0.75 g. = 0.01 mole) when stirred together at room temperature reacted exothermally with vigorous evolution of ammonia and hydrogen sulfide.[28] After the reaction had subsided, the mixture was heated for one-half hour at 80°. The product was taken up in 20 cc. of 12 *N* hydrochloric acid, the solution evaporated to dryness on a steam-bath, and the residue made alkaline and continuously extracted with ether. The pale yellow mass of needles thus obtained was sublimed at 90° and 2 mm. giving 0.82 g. of 2-methyl-4,5-dimethyleneimidazoline, colorless needles, m. p. 89.0–90.0° from benzene.

Anal. Calcd. for $C_6H_{10}N_2$: C, 65.42; H, 9.15; N, 25.43. Found: C, 65.51; H, 9.03; N, 25.66.

The picrate crystallized from aqueous alcohol in yellow plates, m. p. 150.0–150.5°.

The reaction was carried out with *trans*-(VI) in the same manner; it was necessary to heat the mixture before gases were evolved. The product[29] was easily hydrolyzed with regeneration of *trans*-(VI) and was not investigated further.

Summary

cis- and *trans*-1,2-cyclobutanedicarboxylic acids have been degraded by the Curtius and by the K. F. Schmidt method. These methods were shown to involve no change in configuration and to provide preparative routes to the diaminocyclobutanes.

PASADENA, CALIFORNIA RECEIVED JULY 22, 1942

(25) Compare Mason, *Ber.*, **20**, 268 (1887).

(26) Compare Einhorn and Bull, *Ann.*, **295**, 216 (1897).

(27) Compare Hofmann, *Ber.*, **5**, 240 (1872).

(28) The preparation of imidazolines by the interaction of a thioamide with a diamine has been limited to a few instances (Forssel, *Ber.*, **25**, 2132 (1892); McClelland and Warren, *J. Chem. Soc.*, 2621 (1929); see also U. S. Patent 2,252,721, *Chem. Abs.*, **35**, 7658 (1941)). In view of the current interest in imidazoline chemistry, it may be pointed out that the reaction is quite generally applicable, proceeds readily under mild conditions (advantage over usually employed methods) and affords good yields of the desired products which may in many instances be isolated directly from the reaction mixture by sublimation. Caution! Many imidazolines readily undergo hydrolytic fission, Aspinall, *J. Org. Chem.*, **6**, 895 (1941).

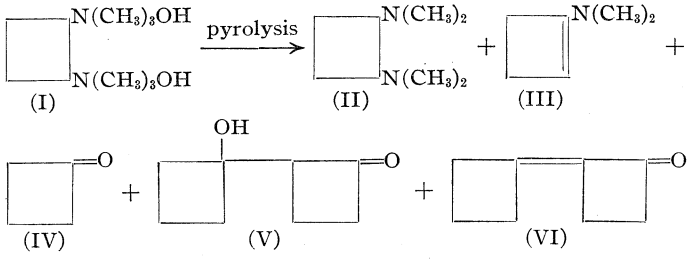
(29) Compare Schlatter, THIS JOURNAL, **64**, 2722 (1942).

[Contribution from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, No. 895]

Cyclobutane Derivatives. II. The Thermal Decomposition of *trans*-1,2-Cyclobutane-*bis*-(trimethylammonium) Hydroxide

By Edwin R. Buchman, Maurice J. Schlatter and Alf O. Reims

The investigation of the thermal decomposition of *trans*-1,2-cyclobutane-*bis*-(trimethylammonium) hydroxide (I) was carried out as part of a research program directed toward the synthesis of cyclobutadiene. The diquaternary base was made by stepwise methylation (see Experimental) of *trans*-1,2-diaminocyclobutane.[1] Although its decomposition was studied carefully under a variety of conditions, no indication for the formation of the desired hydrocarbon[2] was obtained. The nature of the products may be seen from the accompanying chart.



Because of its unstable nature[3] (III) was not isolated. It is undoubtedly the parent compound from which (IV), (V) and (VI) are derived and must be considered the principal primary product of the reaction.

Experimental[4]

trans-**Tetramethyldiamino-1,2-cyclobutane (II).**[5]—Crude *trans*-1,2-diaminocyclobutane hydrochloride obtained[1] either by the action of hydrazoic acid on *trans*-1,2-cyclobutanedicarboxylic acid or from crude *trans*-1,2-cyclobutanediurethan was methylated. The hydrochloride from 20 g. of *trans*-acid was refluxed for four hours with 200 g. of aqueous 36% formaldehyde[6] and 100 g. of 90% formic acid. During the first half hour a rapid gas evolution took place; after the reaction subsided small additional amounts of formaldehyde and formic acid were added to insure complete methylation. The resulting solution was concentrated to a small volume on the steam-bath and the base liberated by treating with excess of strong sodium hydroxide solution and taken up in ether. The ether solution was dried and distilled over sodium; yield 10 g. (50% from *trans* acid) of product boiling chiefly at 164°. From 50 g. of crude urethan a 71% yield of methylated base was obtained; the methylation reaction proceeds therefore with at least this efficiency. On refractionation the base distilled with practically no range, b. p. 83° at 50 mm., b. p. 101° at 100 mm., d^{20}_4 0.8455, $n^{20}D$ 1.4472.

Anal. Calcd. for $C_8H_{18}N_2$: C, 67.55; H, 12.76; N, 19.70. Found: C, 67.54; H, 13.17; N, 19.63.

The dipicrate $C_{20}H_{24}N_8O_{14}$ (analysis) precipitated when ethereal solutions of the components were mixed, yellow needles, m. p. 244° dec.,[7] from aqueous alcohol.

Preparation of *trans*-1,2-Cyclobutane-*bis*-(trimethylammonium) Hydroxide (I).—The diquaternary iodide was conveniently prepared by adding slowly 67 g. of methyl iodide (40% excess) to a solution of 23.8 g. of (II) in 67 cc. of methanol while cooling in an ice-bath. After a few minutes, crystals started to come out. When the precipitation was complete, the product[8] was filtered off and washed with methanol, yield 65.9 g. (92%); additional amounts could be recovered from the mother liquors. A portion of the salt was recrystallized from aqueous ethanol, colorless plates, m. p. 251° dec.[7]

Anal. Calcd. for $C_{10}H_{24}I_2N_2$: C, 28.18; H, 5.68; N, 6.57. Found: C, 28.08; H, 5.87; N, 6.80.

The salt is difficultly soluble in solvents except water; it was found possible to recover it by continuous extraction with chloroform. When its aqueous solution was treated with aqueous sodium picrate, a precipitate was obtained, orange-yellow needles from water, m. p. 288° dec.,[7] analysis indicates the expected formula $C_{22}H_{28}N_8O_{14}$.

The direct methylation of *trans*-diaminocyclobutane with methyl iodide in the presence of alkali did not yield

(1) Buchman, Reims, Skei and Schlatter, This Journal, **64**, 2696 (1942).

(2) For examples of hydrocarbon formation from the pyrolysis of 1,2-diquaternary bases see Hurd and Drake, *ibid.*, **61**, 1943 (1939).

(3) Compare other molecules containing the C=C—NR_2 grouping; Merling, *Ber.*, **24**, 3108 (1891); Willstätter, *Ann.*, **317**, 267 (1901); Ciamician and Silber, *Ber.*, **26**, 2738 (1893); Willstätter and Waser, *ibid.*, **44**, 3423 (1911); von Braun and Kirschbaum, *ibid.*, **52**, 2261 (1919); K. H. Meyer and Hopff, *ibid.*, **54**, 2274 (1921); von Braun and Ritter, *ibid.*, **55**, 3798 (1922). (The picrate mentioned here, m. p. 157° is in all probability dimethylamine picrate); Fuson, This Journal, **50**, 1446 (1928); Ti, *Chem. Abst.*, **30**, 4463 (1936); see also Mannich and co-workers, *Ber.*, **69**, 2106, 2112 (1936).

(4) All melting points are corrected.

(5) When *cis*-1,2-diaminocyclobutane[1] was refluxed with excess of aqueous formaldehyde and formic acid, approximately the theoretical amount of carbon dioxide was evolved. However, after evaporating the resulting solution and making basic, only an insoluble, non-distillable tar was obtained.

(6) Regarding methylation by this method see Clarke, Gillespie and Weisshaus, This Journal, **55**, 4571 (1933).

(7) Minimum temperature at which a fresh sample will decompose when introduced into a bath at this temperature for twenty seconds.

(8) This product consisted solely of diiodide; cases have been reported [Rupe and Bohny, *Helv. Chim. Acta*, **19**, 1305 (1936)] of tetramethyldiamino ring bases (apparently *trans*-configuration) reacting with only one mole of methyl iodide.

the expected product.[9] A solution of 12.6 g. of crude diamine hydrochloride (from urethan) in 90 cc. of methanol was mixed with 136 g. of methyl iodide (100% excess), and a solution of 53.6 g. of potassium hydroxide (100% excess) in 170 cc. of methanol was added slowly with stirring while refluxing gently over a period of one and one-half hours. The refluxing was continued for an additional two hours and the mixture evaporated to dryness *in vacuo* at about 40°. Exhaustive extraction of the residue with chloroform gave no hexamethylated salt. The product, after several recrystallizations from absolute alcohol, was homogeneous and consisted of colorless feather-like crystals decomposing sharply at 218.0–218.5°.

Anal. Calcd. for $C_9H_{21}IN_2$: C, 38.04; H, 7.45; N, 9.86. Found: C, 37.94; H, 7.17; N, 9.66.

The formulation of this compound as (1-dimethylaminocyclobutyl-2)-trimethylammonium iodide was confirmed by its conversion to the diquaternary iodide by heating for fifteen hours at 100° in a sealed tube with excess methyl iodide in ethanol.

The free base (I) was prepared from the diiodide by shaking it in aqueous solution with an excess of freshly prepared silver oxide (washed free of alkali by decanting several times with distilled water) until the colloidal particles in the supernatant liquid had coagulated. The mixture was then filtered rapidly with suction and the filter cake washed with distilled water. The filtrate and washings were concentrated *in vacuo* at 40° to a small volume and the resulting gray to brownish, cloudy solution used for pyrolysis. In order to avoid carbonate formation all operations involving the free base were carried out in an atmosphere of nitrogen.

Thermal Decomposition of (I).[10]—The decomposition was carried out by heating at approximately 250° in a glass vessel without a catalyst and was extensively studied in the range 350–420° in the presence of platinized asbestos. No essential differences in the course of the reaction under these varied conditions could be detected. In the following a typical pyrolysis carried out at 350–360° is described.

The apparatus has been previously described.[11] The spiral gas wash bottle contained 100 cc. of 3 *N* hydrochloric acid. The air was displaced from the apparatus with carbon dioxide and the concentrated solution of the base (from 42.6 g. = 0.1 mole of diiodide) dropped on platinized asbestos at 350–360° over a period of fifteen minutes. No gas collected in the gasometer[12] and very little went into the hydrochloric acid wash bottle.

The pyrolysis distillate was made acid with a small excess of 6*N* hydrochloric acid and the neutral products removed by several extractions with ether. The basic material was recovered from the aqueous phase by making alkaline with 6*N* sodium hydroxide solution and continuously extracting with ether. The contents of the hydrochloric acid wash bottle were investigated separately.

Investigation of Neutral Products.—The ether solution containing this fraction was dried with anhydrous sodium sulfate and the ether removed by distillation through an efficient total reflux column. The residue was fractionated carefully in specially designed equipment, which treatment gave 1.8 g. of material boiling from 80–100°, smaller amounts of an intermediate fraction and 1.3 g. of material boiling at 5 mm. over a 10° range at approximately 85°.

The lower boiling (80–100°) liquid was shown to contain cyclobutanone (b. p. 98.5–99°[13]) as its chief constituent. Its odor was similar to that of cyclopentanone; it formed a bisulfite addition compound[13] somewhat less readily[14] than the five ring ketone. The ketone derivatives, with one exception, checked the literature description for the corresponding cyclobutanone derivatives; semicarbazone (analysis) rosets of white needles from water, m. p. 212.0–212.5° (lit. m. p. 211–212° dec.[15]), phenylhydrazone pale yellow needles from aqueous alcohol m. p. 98.0–98.5° (lit. m. p. 95–96°[15a]) decomposed after a few days' standing, 2,4-dinitrophenylhydrazone, orange-red needles, m. p. 147.0–147.2°[16] from absolute alcohol.

Anal. Calcd. for $C_{10}H_{10}N_4O_4$: C, 48.00; H, 4.03; N, 22.39. Found: C, 48.27; H, 4.07; N, 22.53.

The higher boiling fraction (1.3 g.) consisted of 1-(1'-hydroxycyclobutyl-1'-)-cyclobutanone-2 (V) mixed with smaller amounts of 1-cyclobutylidenecyclobutanone-2 (VI). From the mixture, with phenylhydrazine, with semicarbazide and with sodium bisulfite, derivatives were obtained which however were not suitable for characterization. The 2,4-dinitrophenylhydrazones were prepared from approximately 0.1 g. of ketone mixture by adding to a hot suspension of 0.2 g. of 2,4-dinitrophenylhydrazine in 3 cc. of glacial acetic acid, heating for twenty minutes at 80°, evaporating to dryness in a stream of nitrogen and removing the last of the volatile material at 1 mm. and 80°. The residue was taken up in benzene and chromatographed[17] on alumina. Three zones appeared on the column, a thin dark brown very strongly adsorbed layer on the top of the column (due to impurities), a moderately strongly adsorbed yellow zone (derivative of (V)) and a very weakly adsorbed orange zone (derivative of (VI)) which was washed completely into the filtrate.

The yellow zone was eluted with 2% acetic acid in benzene, the eluate filtered and evaporated to dryness in an inert atmosphere. The residue (230 mg.) was crystallized from benzene yielding clusters of orange needles, m. p. 186–187°.[7]

Anal. Calcd. for $C_{14}H_{16}N_4O_5$: C, 52.49; H, 5.04; N, 17.49. Found: C, 52.96; H, 5.30; N, 17.20.

(9) Compare von Braun, Kruber and Danziger, *Ber.*, **49**, 2642 (1916); von Braun and Neumann, *ibid.*, **53**, 109 (1920).

(10) See Schlatter, Thesis, California Institute of Technology, 1941.

(11) Schlatter, THIS JOURNAL, **63**, 1733 (1941).

(12) In an exactly similar pyrolysis but carried out at 410–420°, about 300 cc. of gas was collected. A sample of this condensed at −70° giving a mobile liquid with a pleasant unsaturated odor. The analysis carried out in a semimicro combustion apparatus indicated an H/C ratio of 1.94; calcd. for cyclobutadiene, C_4H_4, 1.0.

(13) Kishner, *J. Russ. Phys.-Chem. Soc.*, **39**, 923 (1907) [*Chem. Zentr.*, **79**, I, 123 (1908)].

(14) Compare Petrenko-Kritschenko and Kantscheff, *Ber.*, **39**, 1456 (1906).

(15) (a) Curtius, *J. prakt. Chem.*, [2] **94**, 362 (1916); (b) Demjanow and Dojarenko, *Ber.*, **55**, 2740 (1922); (c) Lipp and Köster, *ibid.*, **64**, 2824 (1931).

(16) Lipp, Buchkremer and Seeles, *Ann.*, **499**, 20 (1932), report the m. p. of this compound as 132–133°.

(17) See Zechmeister and Cholnoky, "Principles and Practice of Chromatography" (translation by Bacharach and Robinson), John Wiley and Sons, Inc., New York, N. Y., 1941. The chromatographic separation of 2,4-dinitrophenylhydrazones has been described by Strain, THIS JOURNAL, **57**, 758 (1935).

The column filtrate containing the material which had given rise to the orange zone was also evaporated to dryness in an inert atmosphere and the residue (40 mg.) crystallized from benzene and isopropyl ether. Clusters of scarlet blades were obtained sintering at 184°[7]; the color[18] agrees well with the formulation of this substance as a derivative of an α,β unsaturated ketone (VI).

Anal. Calcd. for $C_{14}H_{14}N_4O_4$: C, 55.62; H, 4.67; N, 18.54. Found: C, 55.67; H, 4.97; N, 18.93.

Investigation of Basic Products.[19]—The ether solution obtained by continuous extraction of the liberated bases from the pyrolysis distillate was carefully distilled to remove solvent and the residue fractionated in special equipment. Because of the small amounts of material available (0.4 cc.) accurate separations were not achieved. The unsaturated base, 1-dimethylaminocyclobutene-1 (III) was not isolated nor could any characteristic derivative be obtained. However, cyclobutanone (identified as semicarbazone) was recovered from the fraction boiling at 90–110°. 1,2-*bis*-(Dimethylamino)-cyclobutane (II) was shown to be present in the appropriate fraction (*ca.* 0.25 cc.) by conversion to its characteristic dipicrate, dimethiodide and (from this latter) dimethopicrate. The properties of these derivatives agreed with those found above.

The contents of the hydrochloric acid wash bottle were evaporated to dryness *in vacuo* at 100°, giving 12.4 g. of a mixture of the hydrochlorides of dimethylamine and of trimethylamine. The former was identified by its benzenesulfonyl derivative, m. p. 47°[20] from isopropyl ether, and the latter by its picrate, yellow needles from aqueous alcohol, m. p. 224–225°.[21] A comparison of the amount of benzenesulfonyl derivative obtained, with that formed under identical conditions in control experiments from mixtures of dimethylamine and trimethylamine of known composition indicated that these had been formed during the pyrolysis in the ratio of approximately 1 to 5.

(18) According to a generalization formulated by Dr. C. E. Redemann (based on unpublished observations made in this Laboratory), when the parent carbonyl compound has a double bond conjugated with the carbonyl group, the 2,4-dinitrophenylhydrazone is colored red; a few exceptions are known. The method used above to prepare the dinitrophenylhydrazones of (V) and (VI) is based on a procedure recommended by Redemann.

(19) In one pyrolysis carried out at 350–400°, the contents of the hydrochloric acid wash bottle were combined with the pyrolysis distillate and the neutral material removed with ether. The acid solution was then evaporated to dryness *in vacuo*, taken up in a small amount of water and slowly added to potassium hydroxide pellets in an apparatus arranged for distillation. Volatile amines were removed at a bath temperature of 60° and the oily top layer remaining allowed to stand for 24 hours in contact with the concentrated base. During this time the oily layer had been transformed to an amorphous non-volatile solid, difficultly soluble in water and ether, soluble in alcohol and pyridine; it was easily soluble in dilute hydrochloric acid and from the resulting solution was reprecipitated by addition of alkali. Evidently dimethylamine had added to condensation products of cyclobutanone to give high molecular weight bases.

Summary

Cyclobutadiene was not detected among the products of thermal decomposition of *trans*-1,2-cyclobutane-*bis*-(trimethylammonium) hydroxide. Dimethylamine, trimethylamine, *trans*-1,2-*bis*-(dimethylamino)-cyclobutane, cyclobutanone and condensation products of the latter were identified as products of the pyrolysis. 1-Dimethylaminocyclobutene-1 is postulated as an unstable intermediate in the reaction.

(20) Beilstein, "Handbuch der organischen Chemie," 4th ed., 1928, Vol. XI, p. 40.

(21) Beilstein, "Handbuch der organischen Chemie," 4th ed., 1923, Vol. VI, p. 280.

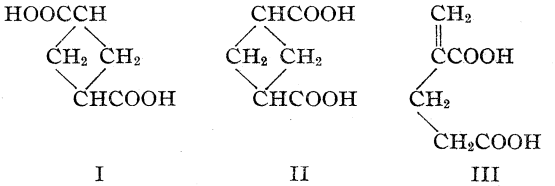
PASADENA, CALIF. RECEIVED JULY 22, 1942

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 896]

Cyclobutane Derivatives. III. *cis*-1,3-Cyclobutanedicarboxylic Acid

BY EDWIN R. BUCHMAN, ALF O. REIMS AND MAURICE J. SCHLATTER

In 1890 Markownikoff[1] converted *trans*-1,3-cyclobutanedicarboxylic acid (I) into an isomeric acid to which the *cis*-structure (II) was later assigned by E. Haworth and Perkin, Jr.[2] These latter authors also reported[2] that they were able to isolate (II) from the mother liquors resulting from the preparation[3] of (I) and from the product of the action of alkali on polymeric methylenemalonic ester. The preparation of (II) by related reactions (from formaldehyde and malonic ester or their equivalents) was claimed in further studies[4] by Perkin, Jr., and co-workers. Although the acid obtained in this way yielded,[4c] under relatively mild conditions, products having an open



I II III

(1) Markownikoff, *J. Russ. Phys.-Chem. Soc.*, **22**, 279 (1890) [*Ber.*, **23R**, 432 (1890)].

(2) Haworth and Perkin, *J. Chem. Soc.*, **73**, 330 (1898).

(3) From the action of sodium ethylate on ethyl α-chloropropionate, Markownikoff and Krestownikoff, *Ann.*, **208**, 333 (1881).

(4) (a) Bottomley and Perkin, *J. Chem. Soc.*, **77**, 294 (1900); (b) Simonsen, *ibid.*, **93**, 1777 (1908); (c) Perkin and Simonsen, *ibid.*, **95**, 1166 (1909).

chain, the assigned structure has not previously been questioned.[5]

In connection with researches involving the preparation of considerable amounts of cyclobutanedicarboxylic acids, the above syntheses were reëxamined. It was found that (II) may be obtained both from the *trans*-isomer (I) as had been demonstrated by Markownikoff[1] and as a by-product in the preparation of (I) as shown by Haworth and Perkin.[2] Its structure was substantiated by the fact that it was found possible (see Experimental) to reconvert it to (I).

However the acid obtained by a variety of methods[2,4] from formaldehyde and malonic ester does not possess the cyclic structure and is, in fact, identical with the well characterized[6] α-methyleneglutaric acid (III). Its properties when made by the English investigators' methods[2,4] coincided with the literature data[6] on this substance; the constitution was confirmed by direct comparison with (III) of known structure made from methyl acrylate.[6b]

There is a fortuitous physical resemblance between (II) and (III) and between some of their derivatives which accounts for the mistake in identity. Chemically the two acids can easily be distinguished; (II) has saturated properties consistent with its formula while (III) reacts instantaneously with alkaline permanganate,[6b,c] adds hydrobromic acid[4c,6b,c,7] and with diazomethane readily gives a pyrazoline derivative.

Experimental[8]

***cis*-1,3-Cyclobutanedicarboxylic Acid (II).**—Following the procedure of Markownikoff,[1] the silver salt of the *trans*-acid (I) was treated with acetyl chloride to give the mixed anhydride, distillation of which at 2 mm. yielded the anhydride of (II), rosets of colorless blades from absolute ether, m. p. 47.5–48.0°.

Anal. Calcd. for $C_6H_6O_3$: C, 57.14; H, 4.80. Found: C, 56.89; H, 4.97.

The mixed anhydride was more conveniently prepared by refluxing (I) with ten molecular proportions of acetyl chloride[9] for five hours. After removal of solvent by distillation, the residue was treated as above to give the anhydride of (II).

The *cis*-acid (II) was obtained from its anhydride by evaporating a solution in five times its weight of 6 *N* hydrochloric acid to dryness on a steam-bath and recrystallizing the residue from hydrochloric acid and finally from water, m. p. 143.0–143.5°.

Anal. Calcd. for $C_6H_8O_4$: C, 50.00; H, 5.60. Found: C, 50.20; H, 5.85.

Crude diethyl ester[3] b. p. 123–130° at 28 mm. was refluxed for twenty-four hours with 6.5 times its weight of 6 *N* hydrochloric acid and the resulting solution evaporated on a steam-bath. The residue, consisting of crude crystalline *trans*-acid (I) and a dark oil was pressed on porous tile and the tile extracted with ether. After removal of solvent, seeding and allowing to stand at about 0°, a small amount of crude crystalline (II) was obtained which, after two recrystallizations from hydrochloric acid, melted at 143° and gave no depression when mixed with (II) made from the anhydride. Further larger amounts of (II) were obtained from the mother liquors; treatment of these with acetyl chloride, distillation and refractionation of the distillate gave a portion boiling at about 104° at 4 mm. which crystallized on cooling and was hydrolyzed to (II) as above.

Alkaline permanganate was not decolorized by (II) at room temperature. The dimethyl ester was prepared by refluxing (II) with methyl alcohol and a small amount of sulfuric acid, b. p. 110–111° at 20 mm.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.94; H, 7.09.

The dihydrazide was formed by heating the dimethyl ester for five hours at 130° with the theoretical amount of 85% hydrazine hydrate, clusters of colorless prisms or plates from alcohol–water, m. p. 172–174°.

Anal. Calcd. for $C_6H_{12}N_4O_2$: C, 41.85; H, 7.02; N, 32.54. Found: C, 41.98; H, 6.85; N, 32.37.

The *p*-bromophenacyl ester was made from the disodium salt of (II) in the usual manner, colorless needles from absolute alcohol, m. p. 121.2–121.7°.

Anal. Calcd. for $C_{22}H_{18}Br_2O_6$: C, 49.09; H, 3.37. Found: C, 49.24; H, 3.33.

Reconversion of *cis*-Acid (II) to *trans*-Acid (I).[10]—Attempts to effect this change by heating (II) for five to six hours at 180° with concentrated hydrochloric acid in a sealed tube were unsuccessful. Extensive destruction[11] of (II) took place with formation of carbonized material and sirups; no (I) could be detected among the reaction products.

The effect of heat on (II) was also studied. When heated for five hours from a bath at 200°, complete conversion to its anhydride was observed. Heating at higher temperatures also gave no (I).

To a solution of sodium methylate prepared from 0.25 g. of sodium in 50 cc. of methanol, 5 g. of the dimethyl ester of (II) was added and the mixture refluxed for one hour. After distilling off the solvent, the product was washed with water and hydrolyzed by evaporating to dryness on the steam-bath with 10 volumes of 6 *N* hydrochloric

(5) Compare Wassermann, *Helv. Chim. Acta*, **13**, 223 (1930); see also Clemo and Welch, *J. Chem. Soc.*, 2621 (1928).

(6) (a) Weidel, *Monatsh.*, **11**, 513 (1890); [*Ber.*, **24R**, 148 (1891)]; (b) von Pechmann and Röhm, *ibid.*, **34**, 428 (1901); (c) Fichter and Beisswenger, *ibid.*, **36**, 1202 (1903).

(7) The product obtained by Perkin and Simonsen[4c] must be formulated as α-(bromomethyl)-glutaric acid. The other supposed products of ring splitting retain their previously assigned formulas.

(8) All melting points are corrected.

(9) Haworth and Perkin[2] employed acetic anhydride.

(10) Compare conversion of *cis*-1,2-cyclobutanedicarboxylic acid to the *trans*-isomer, Buchman, Reims, Skei and Schlatter, THIS JOURNAL, **64**, 2696 (1942).

(11) The instability of (II) toward hydrochloric acid was apparently first noted[2] by Haworth and Perkin.

acid. The residue was recrystallized from water, m. p. and mixed m. p. with an authentic sample of (I) 172.0–173.0°.

α-Methyleneglutaric Acid (III).—Samples of (III) made by various methods were shown to be identical by mixed melting point determinations; all samples reacted instantaneously at room temperature with alkaline permanganate. Substantial depressions of the melting point were observed when (III) and (II) or corresponding derivatives (anhydride, *p*-bromophenacyl ester) were mixed.

(III) was prepared in small yield from polymerized methyl acrylate,[6b] from methoxymethylmalonic ester,[4b,5] from crude 1-methoxy-2,2,4,4-tetracarbethoxybutane[4c] (b. p. 180–185° at 3 mm.), from diethyl methylenemalonate,[4a,12] and in somewhat better yield (21%) from "ethylparamethylenemalonate."[2,4a]

A superior method for preparation of (III) was developed starting from formaldehyde and malonic ester. To 192 g.[13] (1.2 moles) of the latter in a flask surrounded by an ice-bath was added 100 g.[13] (1.33 moles) of 40% formaldehyde and 3.4 g. of piperidine. After two hours the mixture was removed from the ice-bath and allowed to stand at room temperature for twelve hours. The heavier organic layer (220 g.) was separated and added to 100 g. (2.5 moles) of sodium hydroxide[14] in one liter of methanol in a flask surrounded by an ice-bath. The mixture slowly turned to a white pasty mass, was then removed from the ice-bath and permitted to stand at room temperature overnight; it was again cooled to 0° and 2 liters (6 moles) of 3 *N* hydrochloric acid added. After standing for two hours the methanol was distilled off, 500 cc. (6 moles) of concentrated hydrochloric acid added and the mixture refluxed for twelve hours. The residue obtained on evaporating the mixture to dryness on a steam-bath was extracted with absolute alcohol, the solvent removed and the material again evaporated with 500 cc. of water to hydrolyze any ester which might have formed. The oil remaining was allowed to crystallize for several days in the ice-box and the crude crystals recrystallized from water, yield 17.9 g. (20% yield from malonic ester) of (III), m. p. 131.0–132.0°, b. p. 175° at 3.5 mm.

Anal. Calcd. for $C_6H_8O_4$: C, 50.00; H, 5.60. Found: C, 50.07; H, 5.71.

The mother liquors from several preparations of (III) by essentially the above method were combined and esterified with ethanol in the presence of hydrochloric acid and the esters carefully fractionated.[15] The ethyl esters of glutaric acid (a major product), b. p. 104–105° at 8 mm., of α-methyleneglutaric acid (III), b. p. 111–113° at 8 mm. and of 1,3,5-pentanetricarboxylic acid, b. p. approx. 128–132° at 2 mm.[16] were isolated and identified by conversion to the corresponding acids.[17] From a fraction present in small amount, boiling at about 103° at 2 mm., on hydrolysis with 6 *N* hydrochloric acid, a new acid, α,α′-dimethyleneglutaric acid,[18] was obtained which after recrystallization from water melted at 152.0–153.0°.

Anal. Calcd. for $C_7H_8O_4$: C, 53.84; H, 5.16. Found: C, 53.90; H, 5.23.

When the acid (III) was esterified with ethanol in the presence of hydrochloric acid there was a substantial loss due to polymerization. The diethyl ester, obtained in 43% yield, b. p. 132–133° at 23 mm., on treatment with hydrazine hydrate gave no crystalline dihydrazide. The anhydride was prepared in the usual fashion,[2,4c] b. p. 112–115° at 2 mm., large colorless prisms from anhydrous ether, m. p. 51.0–51.5° (analysis).

On treatment with 10% excess of thionyl chloride and distillation at reduced pressure, (III) gave the acid chloride, b. p. 82–83° at 5 mm., and smaller amounts of the anhydride. A portion of the acid chloride dissolved in ether was saturated with excess of dry ammonia, the ether evaporated and the residue extracted with chloroform. The diamide was obtained from the chloroform extract, m. p. 164.0–165.0° from absolute alcohol.

Anal. Calcd. for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.63; H, 7.38; N, 19.82.

The *p*-bromophenacyl ester crystallized in colorless needles from 96% alcohol, m. p. 121.6–121.7°.

Anal. Calcd. for $C_{22}H_{18}Br_2O_6$: C, 49.09; H, 3.37. Found: C, 49.11; H, 3.33.

An excess of diazomethane in ether was added to 1 g. of (III), the ether removed and the residual oil heated in a sealed tube at 100° for twenty hours with 20 cc. of an alcoholic ammonia solution (saturated at 0°). After evaporation of the solvent on a steam-bath the remaining oil crystallized, m. p. 145.0–145.5° from absolute alcohol. The analysis indicates that this substance is the diamide of the pyrazoline[19] resulting from the addition of diazomethane to the double bond in (III).

Anal. Calcd. for $C_7H_{12}N_4O_2$: C, 45.64; H, 6.57; N, 30.42. Found: C, 45.92; H, 6.67; N, 30.42.

Summary

In accord with literature claims, *cis*-1,3-cyclobutanedicarboxylic acid may be obtained from the *trans*-isomer or as a by-product in the preparation of the latter. It has properties consistent with its structure.

The compound obtained from formaldehyde and malonic ester or their equivalents and reported as *cis*-1,3-cyclobutanedicarboxylic acid is α-methyleneglutaric acid.

PASADENA, CALIF. RECEIVED JULY 22, 1942

(12) Made in poor yield both by distillation of the polymer and also by the method of Bachman and Tanner, *J. Org. Chem.*, **4**, 493 (1939).

(13) These relative amounts appeared to give optimum yields of (III).

(14) It was not found possible to work out as convenient a method employing potassium hydroxide.

(15) From the forerun (up to 80° at 2 mm.) a small amount of a crystalline material containing ionic halogen separated on standing, m. p. 220.0–220.5° from alcohol, easily soluble in water, quite insoluble in ether, acid to litmus. The analysis (Found: C, 49.79; H, 8.36; N, 7.77; Cl^-, 18.43) points to the formula $C_8H_{16}ClNO_2$ (Calcd.: C, 49.61; H, 8.33; N, 7.23; Cl^-, 18.31); the substance is obviously derived from the piperidine used as catalyst.

(16) Kay and Perkin, *J. Chem. Soc.*, **89**, 1647 (1906).

(17) 1,3,5-Pentanetricarboxylic acid, m. p. 112.5–113.0° (analysis); compare ref. 4a.

(18) This structure is in accord with the method of formation from malonic ester and formaldehyde. All of the products isolated could be formed from a common intermediate, methylenedimalonic ester; compare Welch, *J. Chem. Soc.*, 257 (1930).

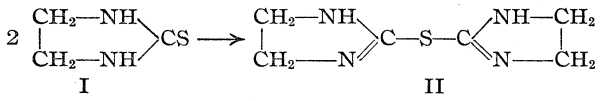
(19) Regarding its probable structure see von Auwers and Cauer, *Ann.*, **470**, 284 (1929); von Auwers and König, *ibid.*, **496**, 27 (1932).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Complex Formations between Iodine and μ-Mercapto-dihydroglyoxalines[1]

BY TREAT B. JOHNSON AND C. O. EDENS[2]

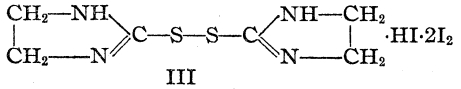
In a recent paper from this Laboratory the authors[3] reported on the characteristic behavior of ethylene-thiourea I when oxidized by 5,5-dibromoxyhydrouracil. They found that this cyclic ureide is transformed into a representative of a new class of glyoxaline sulfides, namely, dihydroglyoxaline sulfide II, which proved to be identical with a sulfur compound of unknown constitution,



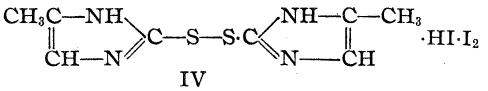
I II

obtained by Jaffe, in 1894, by interaction of ethylenediamine with thiophosgene. Since this change is brought about through the agency of hypobromous acid (HOBr) resulting from the dissociation of the pyrimidine, 5,5-dibromoxyhydrouracil, it was of interest to the authors to examine the behavior of ethylenethiourea I toward iodine solution. Practically no attention has hitherto been paid to the action of iodine on cyclic ureides of the thiodihydroglyoxaline type I. The experimentation has led to results of immediate interest, and opened a gate to a new field of heterocyclic sulfur compounds of biochemical significance.

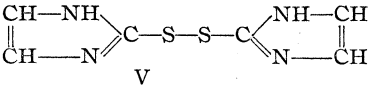
Ethylene-thiourea I does not react with iodine in aqueous solution to form Jaffe's dihydroglyoxaline sulfide II. On the other hand, it undergoes the normal change of oxidation of a true thiol compound and is converted into a disulfide which combines at once with iodine to form the characteristic periodide III. Propylene-thiourea (2-thio-5-methyl-dihydroglyoxaline) interacts with iodine solution to yield a corresponding periodide derivative, while the unsaturated 2-thio-5-methyl-glyoxaline[5] reacts under similar conditions to form periodide containing one molecule only of iodine IV. The simplest glyoxaline disulfate V or its periodide have not been described in the literature.



III



IV

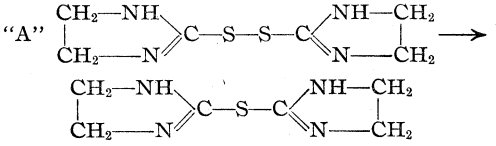


V

Especially interesting is the behavior of the periodide III on hydrolysis. Boiling with water leads to decomposition of the molecule with evolution of iodine vapors and formation of the hydriodide of Jaffe's sulfur base—dihydroglyoxaline sulfide II. Free sulfur and sulfuric acid are also products of this change. The periodide III is also destroyed by treatment with aqueous ammonia. This leads to reduction of the disulfide grouping with regeneration of ethylene-thiourea I and formation of ammonium iodide.

Dihydroglyoxaline sulfide II likewise combines with iodine in aqueous solution to give a periodide conforming in constitution to the formula $C_6H_{10}N_4C\cdot HI\cdot I_3$. This dissociates quantitatively at 125° into iodine and the hydriodide of dihydroglyoxaline sulfide II.

Previously, the irreversible change expressed by equation "A" has not been emphasized.



It is very possible that this interesting change of the sulfur linkage may be the cause of some of the irregularities in analytical results from the titration of certain 2-thioglyoxalines with iodine solutions. Further attention will be given to this problem as our work progresses, and when we have an opportunity to apply our technique to other representatives of the thiodihydroglyoxaline series.

Experimental Part

Periodide of 4,5-Dihydroglyoxaline-2-disulfide, $C_6H_{10}N_4S_2\cdot HI\cdot 2I_2$, III.—A solution of five grams of ethylenethiourea I dissolved in 200 ml. of water was cooled to room temperature and a solution of 0.4 *N* iodine, in aqueous potassium iodide, was added from a buret during vigorous stirring. The first few drops produced a yellowish-brown precipitate which redissolved immediately; further addition of iodine produced a permanent turbidity, which

(1) A grant for partial support of this work made by the Rockefeller Foundation of New York City, is gratefully acknowledged by the authors.

(2) Sterling Professorship of Chemistry Research Assistant, 1940–1941.

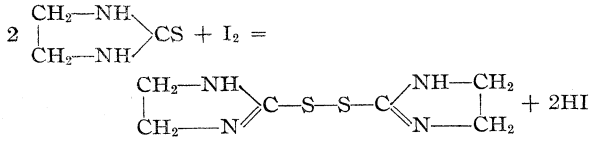
(3) Johnson and Edens, THIS JOURNAL, **63**, 1058 (1941).

(4) Jaffe and Kuhn, *Ber.*, **27**, 1664 (1894).

(5) Gabriel and Pinkus, *ibid.*, **26**, 2203 (1893).

gradually turned to a reddish-brown appearance. At this point, a dark red powder began to take form and settled to the bottom of the beaker. Iodine solution was added until there was no further precipitation, the volume consumed being 185 ml. or practically the equivalent of about 3 moles of iodine per mole of ethylene-thiourea I. A further addition of 25 ml. was added to assure an excess. This product was separated by filtration and washed with cold water and finally with carbon tetrachloride. The yield was 20.5 g. or 87.3% of the theoretical.

The equation leading to the formation of the unknown disulfide may be expressed as



This disulfide then adds iodine immediately, giving the above periodide derivative.

The periodide is a dark red substance of crystalline character. It melts at 119° and is extremely soluble in acetone, diethyl ether, ethanol, methanol, ethyl acetate and warm glycerol. It is moderately soluble in benzene and insoluble in carbon tetrachloride, petroleum ether and water. It can be recrystallized from dilute alcohol.

Anal. Calcd. for $C_6H_{11}N_4S_2I_5$: C, 8.60; H, 1.31; I, 75.85; S, 7.63. Found: C, 8.55; H, 1.28; I, 76.00; S, 7.55.

Behavior of the Periodide III on Heating with Water.—Two grams of the above periodide of dihydroglyoxaline disulfide was digested with 75 ml. of boiling water for about forty-five minutes. Iodine vapors were evolved copiously, and the compound gradually changed to a dark oil, which finally dissolved yielding a pale-yellow aqueous solution. This was then concentrated to about 10 ml. *in vacuo* and cooled, when glistening needles crystallized from the solution. These melted at 284° and a mixed melt with the hydriodide of dihydroglyoxaline sulfide II ($C_6H_{10}N_4S\cdot HI$) gave no depression in melting point. The free base and picrate were likewise prepared and checked with mixed melts. Sulfuric acid was identified in the aqueous filtrate, and free sulfur also was present.

Anal. Calcd. for $C_6H_{10}N_4S\cdot HI$: N, 18.79; I, 42.6. Found: N, 18.63; I, 42.75.

Action of Ammonia on the Periodide $C_6H_{11}N_4S_2I_5$ (Ammonolysis).—The periodide interacts with aqueous ammonia with evolution of heat, and is decolorized almost immediately. The disulfide linkage is destroyed by this treatment with formation of ethylene-thiourea I and ammonium iodide. Other products are undoubtedly formed here, but after two applications to ammonolysis the only pure sulfur compound isolated was the cyclic ureide I. This reaction is under investigation in this Laboratory and the results of our experimentation will be reported in a subsequent paper.

Synthesis of Ethylene-thiourea (2-Thiol-dihydroglyoxaline I) and Propylene-thiourea (2-Thiol-4-methyl-dihydroglyoxaline).—These cyclic ureides are easily prepared from ethylenediamine and propylenediamine, respectively, according to the following procedure:

One hundred grams of carbon disulfide is placed in a 500-ml. flask attached to a reflux condenser. Then 75 g. of the respective commercial diamine (80%) is added dropwise with frequent shaking. The reaction is vigorous. After final addition of the amine, the mixture is then carefully refluxed for one-half hour and cooled. The excess of carbon disulfide is now poured off and the viscous reaction product dissolved by warming in 200 ml. of water. Ring closure of the respective dithiocarbamate intermediate is easily accomplished by adding 15 ml. of concentrated hydrochloric acid and finally refluxing the solution at 100° for one hour. On cooling, the dihydroglyoxaline separates in crystalline condition. Further material is obtained by concentration of the aqueous mother liquors. The ethylene-thiourea is obtained in a yield of 64.5 g. and melting at 198°, or 63%.[6]

Propylene-thiourea is easily purified by crystallization from benzene, and the yield was 64.5 g., melting at 100°. This ureide is much more soluble than ethylene-thiourea I.

Anal. Calcd. for $C_4H_8N_2S$: C, 41.33; H, 6.94; N, 24.11. Found: C, 41.41, 41.42; H, 6.62, 6.76; N, 24.38, 24.28.

Periodide of 5-Methyl-4,5-dihydroglyoxaline-2-disulfide, $C_8H_{14}N_4S_2\cdot HI\cdot 2I_2$.—To a solution of 5 g. of propylene-thiourea in 100 ml. of water was added dropwise with stirring the calculated volume of 163 ml. of 0.4 *N* iodine solution. The first addition produced an immediate turbidity and finally a compound separated in the form of a glistening viscous oil adhering to the sides and bottom of the beaker. After the addition of five atoms of iodine per mole of the propylene-thiourea, a further addition of 25 ml. of the standard iodine solution was made, the total volume added being 187 ml. On standing, the viscous oil finally solidified to a brittle solid which was washed with water and dried. After grinding it formed a heavy dark red powder melting at 67°. This periodide is very soluble in acetone, ether and ethanol; insoluble in water and carbon tetrachloride.

Anal. Calcd. for $C_8H_{15}N_4S_2I_5$: C, 11.09; H, 1.73; I, 73.31; S, 7.39. Found: C, 11.23; H, 1.79; I, 73.52; S, 7.28.

When this periodide was heated with boiling water iodine vapors were evolved and the compound completely dissolved. After concentrating the solution to 10 ml. and cooling no crystals separated as did in the case of the ethylene-thiourea experiment. Instead, a dark red oil separated that failed to crystallize on long standing. The solution gave a strong test for sulfuric acid.

4,5-Dihydroglyoxaline-2-thioglycolic Acid, $C_5H_8O_2N_2S$.—An aqueous solution (50 ml.) of 5 g. of ethylenethiourea I and 9.4 g. of chloroacetic acid was heated at its boiling point for three hours. It was then concentrated to a thick sirup and 50 ml. of ethanol added when the hydrochloride of this acid separated in crystalline form. The yield was 8 g. or 81%. The hydrochloride was purified by crystallization from hot ethanol, and melted at 223° with decomposition. Qualitative tests showed the presence of sulfur, nitrogen and chlorine. The cyclic ureide derivative is very resistant to hydrolysis.

(6) Hoffmann, *Ber.*, **5**, 242 (1872); Schacht, *Arch. Pharm.*, **235**, 442 (1897); Ruiz and Libenson, *Anales asoc. quím. Argentina*, **18**, 37 (1930); *C. A.*, **24**, 5726 (1930).

Anal. Calcd. for $C_6H_9O_2N_2SCl$: C, 30.53; H, 4.58; N, 18.05. Found: C, 30.59, 30.85; H, 4.54, 4.36; N, 18.00, 17.81.

5-Methyl-4,5-dihydroglyoxaline-2-thioglycolic Acid, $C_6H_{11}O_2N_2S$.—This was obtained in the form of its hydrochloride by digesting a solution of 5 g. of propylene-thiourea and 8.2 g. of chloroacetic acid in 50 ml. of water for three hours. The yield was 8 g. and the salt melted at 215° after crystallization from ethanol. This compound was recovered unaltered after digestion for two hours with 20% hydrochloric acid.

Anal. Calcd. for $C_6H_{11}O_2N_2SCl$: Cl, 16.86. Found: Cl, 16.85, 16.83.

Periodide of 4,5-Dihydroglyoxaline Sulfide, $C_6H_{10}N_4S \cdot HI \cdot I_3$.—This is easily prepared by dissolving the hydriodide of dihydroglyoxaline sulfide $C_6H_{10}N_4S \cdot HI$ (0.4 g.) II in 100 ml. of water at room temperature, and then adding dropwise 5 ml. of standard iodine solution (0.4 *N*). At this point no further precipitation was observed. The precipitate was filtered off and after washing it with cold water and carbon tetrachloride it was dried in a vacuum desiccator over sulfuric acid. This periodide crystallizes as a dark red powder melting at 170–175°. It is quite soluble in ether and acetone.

Anal. Calcd. for $C_6H_{11}N_4SI_4$: C, 10.83; H, 1.62; I, 74.81. Found: C, 10.61; H, 1.62; I, 74.55.

Dissociation of the above Periodide $C_6H_{11}N_4SI_4$ **by Heating.**—A small amount of the periodide was spread on a porous plate and exposed to the temperature of a drying oven at 125°. In fifteen minutes the three atoms of iodine had volatilized completely and a colorless powder remained behind. This was identified as the hydriodide of 4,5-dihydroglyoxaline sulfide and melted at 284°. No change in the linkage of sulfur had taken place.

Action of Chloroacetic Acid on Jaffe's Base—Dihydroglyoxaline Sulfide, II.—One gram of the glyoxaline derivative, $C_6H_{10}N_4S$, and 1.19 g. of chloroacetic acid were dissolved in 50 ml. of water and the solution boiled for three hours. The solution was then concentrated to 5 ml. and diluted with ethanol. The hydrochloride of Jaffe's sulfur base separated immediately. No other product was identified, and there was no evidence of desulfurization by this treatment or formation of a thioglycolic acid derivative.

Anal. Calcd. for $C_6H_{10}N_4S \cdot HCl$: Cl, 17.20. Found: Cl. 17.45.

Periodide of 5-Methylglyoxaline Disulfide, $C_8H_{10}N_4S_2 \cdot HI \cdot I_2$.—2-Thio-5-methylimidazole[7] (0.5 g.) was dissolved in 100 ml. of cold water and a 0.4 *N* solution of iodine in aqueous potassium iodide added slowly with vigorous stirring. Addition of 5 ml. produced a deep yellow solution; 13.4 ml. led to the formation of a precipitate which was complete after adding 28.5 ml. The periodide separated as dark red crystals. After washing with cold water and chloroform it was dried in a vacuum over sulfuric acid. The compound decomposed on heating.

Anal. Calcd. for $C_8H_{11}N_4S_2I_3$: C, 15.75; H, 1.80; I, 62.44; S, 10.52. Found: C, 15.93, 15.77; H, 1.66, 1.64; I, 62.47; S, 10.41.

Summary

1. Ethylene-thiourea and propylene-thiourea interact with iodine in aqueous potassium iodide solution to form the periodides $C_6H_{10}N_4S_2 \cdot HI \cdot 2I_2$ and $C_8H_{14}N_4S_2 \cdot HI \cdot 2I_2$, respectively.

2. The periodide resulting from ethylene-thiourea is converted by hydrolysis into dihydroglyoxaline sulfide $C_6H_{10}N_4S$. Interaction with ammonia (ammonolysis) leads to the regeneration of ethylene-thiourea.

3. Dihydroglyoxaline sulfide reacts with iodine to give the periodide $C_6H_{10}N_4S \cdot HI \cdot I_3$ which dissociates at 125° yielding the hydriodic salt of dihydroglyoxaline sulfide.

4. Dihydroglyoxaline sulfide $C_6H_{10}N_4S$ is not desulfurized by digestion with chloroacetic acid.

5. Ethylene-thiourea and propylene-thiourea interact with chloroacetic acid to form the representative 2-thioglycolic acid derivatives without desulfurization.

6. 2-Thio-5-methylimidazole interacts with iodine in aqueous solution to give a periodide of formula $C_8H_{10}N_4S_2 \cdot HI \cdot I_2$.

NEW HAVEN, CONNECTICUT RECEIVED JUNE 27, 1942

(7) Gabriel and Pinkus, *Ber.*, **26**, 2197 (1893).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

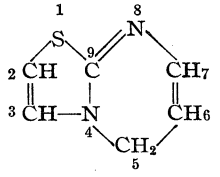
Researches on Thiazoles. XXV. Some New Thiazolidinopyrimidines of Barbituric Acid Type

BY EDWARD J. MASTERS AND MARSTON TAYLOR BOGERT

Since the proof of the structure of vitamin B_1,[1] great interest has been shown in compounds containing the thiazole or thiazoline ring. A miscellany of such compounds having therapeutic value appears in the patent and regular literature. These compounds are characterized by relatively low toxicity when introduced into the body.

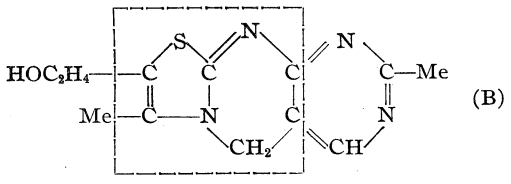
Thus, sulfathiazole[2] is an example of this type of compound and is useful in the treatment of certain types of bacterial infection. More recently, its thiazoline analog, sulfathiazoline,[3] has been synthesized. A variety of compounds containing the thiazole or thiazoline ring and possessing local anesthetic activity has been prepared.[4-9]

The immediate object of this investigation was the synthesis of compounds related to the structure (A)



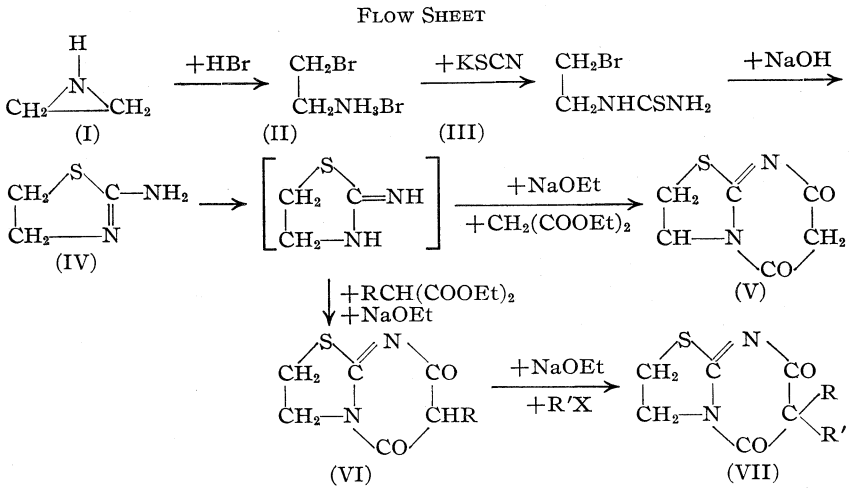
(A)

Compounds containing this skeletal structure are as yet unknown in the literature. The nearest approach to it is found in the thiochrome molecule[10] (B), the thiazolopyrimidine portion of which is enclosed in broken lines.



(B)

FLOW SHEET



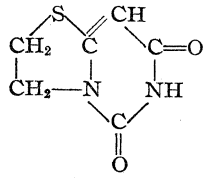
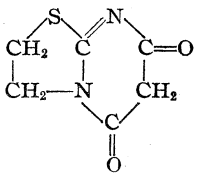
R = Me, Et, *i*-Pr, Ph, and $PhCH_2$
R′ = Et, *i*-Pr, *n*-Bu, Ph, and $PhCH_2$

The 5,7-dioxo derivatives of constitution (A) present an interesting variation in the barbituric acid structure, and the analogs of the more important barbituric acids might be expected to possess hypnotic or anesthetic activity. The flow sheet for the reactions involved includes standard methods for the synthesis of barbituric acids.

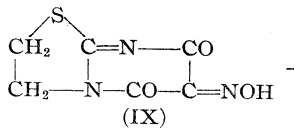
As will be noted in this flow sheet, 2-aminothiazoline (IV) is assumed to react in its tautomeric 2-iminothiazolidine form under the conditions employed.

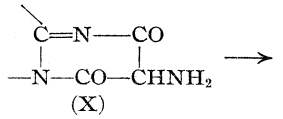
Bogert and Mills[11] in laying the groundwork for the synthesis of compounds of type (A) synthesized β,β′-di-(1-barbituryl)-ethyl disulfide, using β-mercaptoethylamine as the starting material. Bogert and Nathan[12] continued this work and by reduction of β,β′-di-(1-barbituryl)-ethyl disulfide, using zinc and hydrochloric acid, obtained a compound of the empirical formula $C_6H_6N_2O_2S$. Since condensation at two different positions was possible, it was not clear whether the structure of this compound was

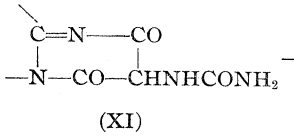
(1) Cline, Williams and Finkelstein, THIS JOURNAL, **59**, 1052 (1937).
(2) Lott and Bergeim, *ibid.*, **61**, 3593 (1939).
(3) Raiziss and Clemence, *ibid.*, **63**, 3124–3126 (1941).
(4) Johnson, *ibid.*, **52**, 4141 (1930).
(5) U. S. Patent 1,970,656 (1931).
(6) Ballowitz, *Arch. Exptl. Path. Pharm.*, **163**, 687 (1932).
(7) Niederl, Hart and Scudi, THIS JOURNAL, **58**, 707 (1936).
(8) Hart and Niederl, *ibid.*, **61**, 1145 (1939).
(9) Adams, *ibid.*, **59**, 2264 (1937).
(10) Bergel and Todd, *J. Chem. Soc.*, 1601 (1936).
(11) Bogert and Mills, THIS JOURNAL, **62**, 1173–1180 (1940).
(12) Bogert and Nathan, *ibid.*, **63**, 2361–2366 (1941).

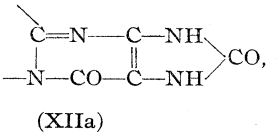
(VIII)  or  (V)

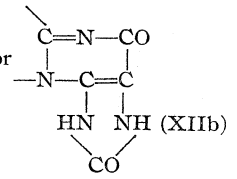
In the present work, it was thought that a more direct and unequivocal synthesis of (V) could be effected by condensation of 2-aminothiazoline (IV) with malonic ester, analogous to that used by Chichibabin[13] in which 2-aminopyridine was condensed with malonic ester to yield the bicyclic pyridinopyrimidine.


(IX)


(X)


(XI)


(XIIa)


(XIIb)

In the attempts to condense 2-aminothiazoline with malonic ester to form the desired pyrimidine (V), the conditions of Chichibabin's experiment were followed, *i. e.*, the slow heating of the reactants to 195°. Extensive decomposition occurred with the formation of a hard red resin. Lower temperatures were used without success. The condensation was finally effected in high yield using sodium ethylate with absolute ethyl alcohol as solvent. This synthesis of compound (V) proves that the compound synthesized from β,β′-di-(1-barbituryl)-ethyl disulfide by Bogert and Nathan[12] was (VIII), since the two products were not identical.

When mono-substituted alkyl or aryl malonic esters were used in the condensation with 2-aminothiazoline in the presence of sodium ethylate, the reaction proceeded readily with formation of the mono-substituted thiazolidinopyrimidines listed in Table I. The synthesis of the disubstituted pyrimidines was effected by alkylation of the appropriate monosubstituted pyrimidine containing the more sterically hindered group. The alkylations were conducted in absolute ethyl alcohol in the presence of sodium ethylate. The disubstituted pyrimidines synthesized in this series (Table II) are the analogs of the barbituric acids: Veronal, Neonal, Ipral and Phenobarbital.

Of the compounds described in Tables I and II, nos. 1, 2 and 6 formed white dendritic crystals; no. 3, white needles; nos. 4, 8, 10 and 11 colorless plates; nos. 5, 7 and 9, colorless needles.

Solubilities.—No. 1, 1% in hot absolute alcohol, 2% in hot water; no. 2, 1 g. in 150 cc. of hot water; no. 3, 1% in hot water, more soluble in alcohol; no. 4, 1 g. in 9 cc. of hot alcohol; no. 7, 0.25% in hot water.

From the thiazolidinobarbituric acid (V), the corresponding uric acid (XII) was synthesized via the usual oximino (IX), uramil (X), and pseudouric acid (XI) derivatives

The results of the pharmacological tests upon the compounds described in this paper will be reported later.

Acknowledgments.—We are greatly indebted to the Carbide & Carbon Chemicals Corp. of New York for their courtesy in supplying us with ethyleneimine and β-aminoethyl sulfate required for this investigation. We are also under obligations to Mr. Saul Gottlieb for the analysis of our products.

Experimental

All melting points recorded are corrected for stem exposure.

β-Bromoethylamine hydrobromide (II) was prepared most satisfactorily as follows: 174 g. (4 mols) of 99% ethyleneimine was added dropwise to 1250 cc. (11.1 mols) of 48% HBr. The temperature of the reaction mixture was maintained at 0–5°, and the solution was stirred vigorously during the addition. It was then concentrated to a thick sirup under vacuum, allowed to cool, the crystalline mass filtered off and washed with a little absolute alcohol. The filtrate and washings were concentrated further to yield more of the product. The product after drying weighed 660 g. or a yield of 80%. After recrystallization from absolute alcohol, the compound melted at 173.3–174.3° (lit.,[14] m. p. 172–173°).

Anal. Calcd. for $C_2H_7Br_2N$: C, 11.7; H, 3.4. Found: C, 11.7; H, 3.3.

It is stated by Gabriel,[15] and in "Organic Syntheses,"[16] that the above compound can be prepared "by the addition of hydrogen bromide to ethyleneimine," but if the reaction is carried out in that way the compound sought will not be obtained.

β-Bromoethylthiourea (III) was prepared from β-bromoethylamine hydrobromide and potassium thiocyanate by

(13) Chichibabin, *Ber.*, **57**, 1168 (1924).

(14) Leffler and Adams, THIS JOURNAL, **59**, 2255 (1937).

(15) Gabriel, *Ber.*, **21**, 1054 (1888).

(16) "Organic Syntheses," XVIII, 14 (1938).

TABLE I

6-MONOSUBSTITUTED 2,3,6,7-TETRAHYDRO-5,7-DIOXO-5-THIAZOLO[3,2-a]PYRIMIDINES

No.	Formula	Group at 6	Yield, %	M. p. (cor.), °C.	Calcd. C	Calcd. H	Found C	Found H
1	$C_6H_6O_2N_2S$	H	88	244.5–245.5	42.5	3.6	42.6	3.8
2	$C_7H_8O_2N_2S$	Me	72	272–276	45.7	4.4	45.9	4.5
3	$C_8H_{10}O_2N_2S$	Et	70	224.4–224.7	48.5	5.1	48.7	5.2
4	$C_9H_{12}O_2N_2S$	*i*-Pr	76	262.3–262.8	51.1	5.7	51.5	6.0
5	$C_{12}H_{10}O_2N_2S$	Ph	45	247.2–247.7	58.5	4.1	58.5	4.1
6	$C_{13}H_{12}O_2N_2S$	$PhCH_2$	82	241.9–242.3	60.0	4.7	60.0	4.8

TABLE II

6,6-DISUBSTITUTED 2,3,6,7-TETRAHYDRO-5,7-DIOXO-5-THIAZOLO[3,2-a]PYRIMIDINES

No.	Formula	Groups at 6	Yield, %	M. p. (cor.), °C.	Calcd. C	Calcd. H	Found C	Found H
7	$C_{10}H_{14}O_2N_2S$	Et, Et	29	138.2–138.7	53.1	6.2	53.4	6.4
8	$C_{11}H_{16}O_2N_2S$	Et, *i*-Pr	33	92.6–93.1	55.0	6.7	55.3	6.8
9	$C_{12}H_{18}O_2N_2S$	Et, *n*-Bu	31	89.7–90.3	56.7	7.1	56.8	7.1
10	$C_{14}H_{14}O_2N_2S$	Et, Ph	36	120.3–121.3	61.3	5.2	61.4	5.2
11	$C_{15}H_{16}O_2N_2S$	Et, $PhCH_2$	30	136.0–136.4	62.5	5.6	62.7	5.7

the method of Gabriel,[17] and melted at 173.6–174.2° (lit.,[17] m. p. 172.5–173.5°); yield, 60%.

The 2-aminothiazoline (IV) used was obtained by treating (III) with caustic soda solution.[17] The m. p. was 84–85° (lit.,[17] m. p. 84–85°); yield, 86%; over-all yield from ethyleneimine was 41%.

2,3,6,7-Tetrahydro-5,7-dioxo-5-thiazolo[3,2-a]pyrimidine (V).—2.3 g. (0.10 mole) of clean metallic sodium was dissolved in 50 cc. of absolute ethyl alcohol. This solution was cooled to 50° and 8 g. (0.05 mol) of ethyl malonate was added, followed by a solution of 5 g. (0.05 mol) of 2-aminothiazoline in 20 cc. of absolute ethyl alcohol. The reaction mixture was refluxed for three hours, during which period a white solid separated rapidly.

The mixture was cooled, brought to acidity by the addition of 11 cc. of concentrated hydrochloric acid, the precipitate filtered off and washed with a few cc. of alcohol. It was then slurried with about 30 cc. of water, to remove any sodium chloride, filtered, dried at 105° for an hour, and then weighed. The yield was 6.8 g. From the original filtrate, 0.7 g. more was obtained, making a total yield of 7.5 g. or 88%. Recrystallized from alcohol, it formed small dendritic crystals, which melted with decomposition at 244.5–245.5°.

Anal. Calcd. for $C_6H_6O_2N_2S$: C, 42.5; H, 3.6. Found: C, 42.6; H, 3.8.

The mono-R derivatives of (V) were synthesized in a manner analogous to the above, using the appropriate mono-substituted malonic ester in the place of malonic ester. Data concerning them appear in Tables I and II. The phenyl malonic ester employed was prepared from phenyloxaloacetic ester.[18]

6,6-Diethyl-2,3,6,7-tetrahydro-5,7-dioxo-5-thiazolo[3,2-a] pyrimidine (VII).—4 g. (0.020 mole) of the monoethyl derivative (VI) was added to an alcoholic solution of sodium ethylate prepared by dissolving 0.50 g. (0.022 mole) of clean metallic sodium in 50 cc. of absolute ethyl alcohol, and the temperature was kept at 50°.

3.9 g. (0.025 mole) of ethyl iodide was added, and the solution refluxed until neutral. The time of refluxing was about two hours. It was then concentrated to about 15 cc., 100 cc. of water added slowly with shaking, and small white feathery crystals precipitated. The crystals were collected on a Büchner funnel, washed with a few cc. of dilute bicarbonate solution, to dissolve any unreacted (VI), then with a few cc. of alcohol, and finally with water. Dried at 105°, the yield was 1.3 g., or 29%.

Recrystallization of the product from a large volume of hot water resulted in the formation of beautiful long needles, m. p. 138.2–138.7°.

Anal. Calcd. for $C_{10}H_{14}O_2N_2S$: C, 53.1; H, 6.2. Found: C, 53.4; H, 6.4.

The other 6,6-disubstituted products were prepared similarly, using the appropriate halide. Analyses and other data are given in Tables II and III. These compounds were quite soluble in various organic solvents, but dissolved only slightly in water. A convenient method of isolating them consisted in removing all of the alcohol from the reaction mixture, when the residual oil congealed on standing and cooling. Unaltered initial mono-substituted esters were then easily removed by washing with a potassium carbonate solution.

6-Isonitroso-2,3,6,7-tetrahydro-5,7-dioxo-5-thiazolo[3,2-a] pyrimidine (IX).—A suspension of 7 g. (0.041 mol) of (V) in 100 cc. of 30% alcohol was stirred vigorously and 6.3 g. (0.054 mol) of isoamyl nitrite added dropwise over a period of a half hour. After further vigorous stirring for an hour, the temperature was slowly raised to 50° and the stirring continued for another hour. The white suspension slowly changed into the purple of the nitroso compound. The mixture was chilled, the nitroso compound removed, washed with alcohol and air dried; yield, 5 g., or 61%; m. p. 175–178°. As some difficulty was experienced in purifying this compound, it was used without further purification in the subsequent reactions. It dissolved readily in alkali to a deep purple solution.

6-Amino-2,3,6,7-tetrahydro-5,7-dioxo-5-thiazolo[3,2-a] pyrimidine (X).—To a solution of 4 g. (0.02 mol) of (IX) in 10 cc. of concentrated ammonium hydroxide diluted with 10 cc. of water, 7 g. of sodium hydrosulfite, dissolved in 15 cc. of water containing a few drops of ammonia, was added slowly until the purple color disappeared. The

(17) Gabriel, *Ber.* **22**, 1141 (1889).

(18) "Organic Syntheses," XVI, 33 (1936).

solution was chilled and neutralized with dilute hydrochloric acid. The precipitate was filtered off, washed with water and crystallized from hot water. The yield was 2 g. or 54%. The compound turned red at 174° and decomposed at 194°. Not unlike other uramils, this compound was very troublesome to purify, changed color rapidly in the air or on drying *in vacuo*, and burned with difficulty in the microanalytical apparatus, so that it was felt that not much reliance could be placed upon the analytical results, although these indicated that the substance was the impure monohydrate.

Anal. Calcd. for $C_6H_9O_3N_3S$: C, 35.5; H, 4.5. Found: C, 36.4; H, 4.5.

6-Ureido-2,3,6,7-tetrahydro-5,7-dioxo-5-thiazolo[3,2-a]pyrimidine (XI).—To a solution of 0.5 g. of (X) (0.0027 mol) in 30 cc. of hot water, there was added a solution of 0.32 g. (0.0040 mol) of potassium cyanate in 10 cc. of water, and the solution was warmed to the disappearance of its purple color. It was then chilled, acidified with dilute hydrochloric acid, the yellow precipitate collected and dried; yield, 0.5 g., or 80%. Recrystallized from hot water containing a little Norit, a white crystalline product resulted, m. p. 261–263°.

Anal. Calcd. for $C_7H_8O_3N_4S$: C, 36.9; H, 3.5. Found: C, 37.2; H, 3.5.

The thiazolidinouric acid (XIIa or XIIb) was obtained from the corresponding pseudouric acid (XI) by an adaptation of the classic method of Fischer and Ach.[19]

A mixture of 46 mg. of the pseudouric acid (XI) with 1 g. of anhydrous oxalic acid was placed in a test-tube and heated in an oil-bath, the temperature of which was brought to 185° in the course of ten minutes. Most of the oxalic acid volatilized, and some of the pseudouric acid was decomposed with liberation of hydrogen sulfide. The residue when cold was extracted with alcohol, to remove any oxalic acid still present, and the undissolved material was dissolved in dilute sodium hydroxide solution, boiled with activated carbon, the filtrate acidified with dilute hydrochloric acid and chilled. The precipitate, removed and dried, weighed 15 mg., *i. e.*, a yield of 36%. Recrystallized from a large volume of water, it separated in glistening white microscopic crystals, which remained unmelted at 300°.

Anal. (on 1 mg. of product). Calcd. for $C_7H_6O_2N_4S$: C, 40.0; H, 2.9. Found: C, 39.7; H, 2.7.

Not enough material was available to determine whether the constitution of this product should be represented by formula XIIa or XIIb, either one of which could be formed by the elimination of water from the initial pseudouric acid.

(19) Fischer and Ach, *Ber.*, **28**, 2473 (1895).

Summary

1. Thiazolidinopyrimidines of barbituric acid type are easily prepared pure and in satisfactory yields from 2-aminothiazoline as initial material by familiar reactions.

2. Among the compounds so prepared are analogs of Veronal, Neonal, Ipral and Phenobarbital.

3. From the thiazolidinobarbituric acid, the corresponding thiazolidinouric acid has been synthesized via the oximino, uramil and pseudouric acid derivatives.

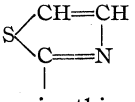
4. The physiological effects of these compounds are now being studied, to ascertain to what extent, if at all, their properties resemble those of the corresponding barbituric acids.

NEW YORK, N. Y. RECEIVED JULY 18, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

Researches on Thiazoles. XXVI. Some Acyl Derivatives of 2-Aminothiazole

BY EDWARD J. MASTERS AND MARSTON TAYLOR BOGERT

The behavior of 2-aminothiazole (I) when digested with ethyl malonate and sodium ethylate, in alcoholic solution, is quite different from that of 2-aminothiazoline under similar conditions,[1] as can be seen from the following flow sheet, in which R represents the thiazole residue, 

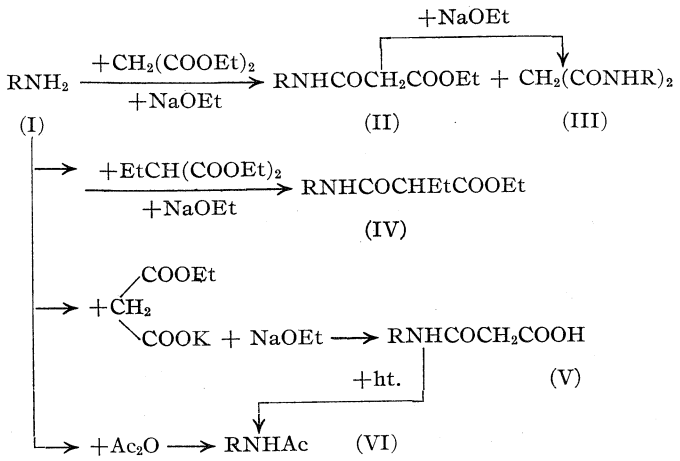
This difference in the behavior of 2-aminothiazole as compared with 2-aminothiazoline is probably due, as pointed out in our previous article,[1] to the fact that the thiazoline can react in its tautomeric iminothiazolidine form, a rearrangement which is less likely to occur with the more stable conjugated system of the thiazole.

Refluxing of the thiazole, in alcoholic solution, with sodium ethylate and ethyl malonate, resulted in the formation of both the thiazolylmalonamic ester (II), and the *sym*-dithiazolylmalonamide (III).

Some years ago, the I. G. Farbenind. A.-G.[2] took out patents for the manufacture of acetoacetyl derivatives of 2-aminothiazole by heating together the aminothiazole and acetoacetic ester (and analogous esters) without any solvent. In

(1) Masters and Bogert, THIS JOURNAL, **64**, 2709 (1942).

(2) I. G. Farbenind. A.-G., German Patent 603,623, Oct. 8, 1934; *C. A.*, **29**, 814 (1935); and addition thereto, Jan. 3, 1935; *C. A.*, **29**, 4024 (1935).



our own experiments, when the aminothiazole and malonic ester were heated together directly, a great deal of decomposition ensued, but both (II) and (III) were isolated from the crude product.

When the malonamate (II) was heated above its m. p., or was refluxed in absolute ethanol solution with sodium ethylate, the diamide (III) was formed.

By the use of a substituted ethyl malonate, instead of ethyl malonate itself, in the condensation with the aminothiazole, the corresponding substituted malonamate (IV) was obtained.

From the potassium salt of the malonic ester acid, 2-aminothiazole, and sodium ethylate, in absolute ethanol solution, the malonamic acid (V) was prepared. This acid when heated lost carbon dioxide, with formation of the same 2-acetaminothiazole as resulted from direct acetylation of the aminothiazole.

All attempts to cyclize the malonamic acid (V) to a thiazolopyrimidine have so far proved fruitless.

Acknowledgments.—Our thanks are due to the Monsanto Chemical Co., of St. Louis, Missouri, and to the Calco Chemical Division of the American Cyanamid Company, Bound Brook, New Jersey, for supplies of 2-aminothiazole; and to Mr. Saul Gottlieb for the analysis of our products.

Experimental

All melting points are corrected for exposed stem.

2-Aminothiazole (I) can be prepared readily from thiourea and dichloroethyl ether, by the method of Traumann,[3] if necessary, but it is also available commercially.

(3) Traumann, *Ann.*, **249**, 35 (1888).

Ethyl N-(2-Thiazolyl)-malonamate (II).—To a solution of 11.5 g. (0.5 mole) of clean sodium in 500 cc. of absolute ethanol, cooled to 50°, there was added 80 g. (0.5 mole) of ethyl malonate, followed by 50 g. (0.5 mole) of 2-aminothiazole. After refluxing the mixture for five hours, it was cooled, and acidified by the addition of 42 cc. of concentrated hydrochloric acid. The precipitate contained two products, the more soluble of which was extracted by leaching with large volumes of hot water. The total yield of this product, including some recovered from the original filtrate, was 34.5 g. Recrystallized from water, it formed white crystals, m. p. 149–149.5°, soluble in alcohol or benzene.

Anal. Calcd. for $C_8H_{10}O_3N_2S$: C, 44.8; H, 4.7; N, 13.1. Found: C, 45.0; H, 4.6; N, 13.1.

sym-**N-(2-Thiazolyl)-malonamide** (III), which was the less soluble product in the above reaction, was isolated in a yield of 34 g. The combined yield of (II) and (III) accounted for about 80% of the aminothiazole used.

The amide (III) was purified by precipitating its bicarbonate solution by dilute acid. It began to change color at about 258° and decomposed sharply at 271°.

Anal. Calcd. for $C_9H_8O_2N_4S_2$: C, 40.3; H, 3.0; N, 20.8. Found: C, 40.2; H, 3.0; N, 20.6.

N-(2-Thiazolyl)-malonamic acid (V) was prepared as described for (II), using the potassium salt of malonic ethyl ester acid in place of ethyl malonate. By acidification with dilute mineral acid, the free malonamic acid was obtained as white dendritic crystals, in a yield of 54%. At 185.8–186.8°, it melted with decomposition, losing carbon dioxide and forming the 2-acetaminothiazole (VI), m. p. 206.5–207° (lit.,[3] m. p. 203°), long needles, whose identity was checked by preparation of the same compound from the aminothiazole (I) and acetic anhydride.[3]

Anal. Calcd. for $C_6H_6O_3N_2S$: C, 38.8; H, 3.3; acid equivalent, 186. Found: C, 39.1; H, 3.6; acid equivalent, 186.

Ethyl N-(2-thiazolyl)-ethylmalonamate (IV), prepared by the same method as (II), using ethyl ethylmalonate in place of ethylmalonate, was obtained in a yield of 46%, m. p. 117.8–118.8°, as white dendritic crystals.

Anal. Calcd. for $C_{10}H_{14}O_3N_2S$: C, 49.6; H, 5.8. Found: C, 49.8; H, 5.8.

In this case, no diamide analogous to (III) was isolated.

Summary

1. The behavior of 2-aminothiazole when digested, in alcoholic solution, with ethyl malonate and sodium ethylate, is quite different from that of 2-aminothiazoline, in that there results a mixture of the thiazolylmalonamic ester and the *sym*-dithiazolylmalonamide, but no thiazolopyrimidine, nor could the latter be obtained by cyclization of the thiazolylmalonamic acid.

NEW YORK, N. Y. RECEIVED JULY 18, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Condensations. XVIII. The Acylation of the Anions of Certain Esters with Ethyl Carbonate

BY CHARLES R. HAUSER, B. ABRAMOVITCH AND JOE T. ADAMS

The acylation of organic esters having two α-hydrogens with alkyl carbonates in the presence of sodium or potassium alkoxides has been developed by Wallingford and co-workers[1] for the convenient production of malonic esters. Esters having only one α-hydrogen failed to be acylated, and even with ethyl *t*-butyl acetate the yield was not reported. Moreover, the method does not appear to be applicable to the preparation of malonic esters with two different ester groups, that is, "mixed" malonic esters.

Although these acylations fail in the presence of metal alkoxides, they may be effected by means of the stronger base, sodium triphenylmethyl, which converts esters largely into their anions.[2] The acylation of the anions of esters with only one α-hydrogen, for example, ethyl isobutyrate, is probably best effected with ethyl chlorocarbonate, diethyl α,α-dimethylmalonate being obtained in this manner in 75% yield.[2] The anion of ethyl isovalerate (which has two α-hydrogens) with ethyl chlorocarbonate, however, gives only a low yield of the malonic ester, forming mainly the diacylated ester.[2] It is shown in the present investigation that the anions of certain esters having two or three α-hydrogens may be acylated satisfactorily with ethyl carbonate to produce malonic esters. With this acylating reagent, the anion of ethyl *t*-butylacetate gives diethyl *t*-butylmalonate in 47% yield, while the anions of *t*-butyl acetate and *t*-butyl propionate give the "mixed" malonic esters, *t*-butyl ethylmalonate and *t*-butyl ethyl-α-methylmalonate in yields of 54 and 72%, respectively. These acylations may be represented as follows.

$$C_2H_5OCO_2C_2H_5 + [(CH_3)_3CCHCO_2C_2H_5]^- \longrightarrow (CH_3)_3CCH(CO_2C_2H_5)_2 + {}^-OC_2H_5$$

$$C_2H_5OCO_2C_2H_5 + [CH_2CO_2C(CH_3)_3]^- \longrightarrow C_2H_5O_2CCH_2CO_2C(CH_3)_3 + {}^-OC_2H_5$$

$$C_2H_5OCO_2C_2H_5 + [CH(CH_3)CO_2C(CH_3)_3]^- \longrightarrow C_2H_5O_2CCH(CH_3)CO_2C(CH_3)_3 + {}^-OC_2H_5$$

In each of these reactions equivalent amounts of the ester having α-hydrogen, sodium triphenylmethyl and ethyl carbonate were used. The malonic ester formed was probably converted into its anion by means of the ester anion first prepared, and the corresponding amount of the ester was regenerated. The amount of ethyl carbonate used was twice that theoretically required but the excess seemed desirable in order to minimize the self-condensation of the ester having α-hydrogen. The yields of malonic esters reported above are based on the sodium triphenylmethyl used.

This method should be applicable to the acylation with ethyl carbonate of other esters that undergo self-condensation relatively slowly[3] (compared to ethyl acetate) to produce malonic esters in which the ester groups are the same or different.

Experimental

Ethyl *t*-Butyl Malonate.—Sodium triphenylmethyl[2] (1700 cc., 0.730 mole) was prepared in a 2-liter "Pyrex" bottle. The stopper was removed and the bottle quickly fitted with an efficient mechanical stirrer, dropping funnel, and bent tube delivering a slow stream of dry nitrogen. *t*-Butyl acetate (94.5 cc., 84.7 g., 0.73 mole) was added rapidly to the vigorously stirred solution (the red color being discharged immediately) and after one minute 88 cc. (86.1 g., 0.73 mole) of ethyl carbonate (b. p. 125.5–126.0°) was added during seven minutes, the bottle being cooled if the ether began to boil. Stirring was continued for two hours longer. Glacial acetic acid (60 cc.) dissolved in 300 cc. of ice-water was then added and the mixture transferred to a 2.5-liter separatory funnel. The mercury, aqueous solution, and sludge were then separated, the latter being washed with ether. The combined ether solutions were extracted with 10% sodium carbonate solution, and dried over anhydrous sodium sulfate followed by Drierite, and the solvent distilled. Distillation of the residue from a 1-liter Claisen flask yielded 41.0 g. of recovered esters (b. p. 45° at 60 mm. to 70° at 35 mm.) and 69.5 g., of material (b. p. 70° at 35 mm. to 150° at 18 mm.) which on fractionation through a twelve-inch Vigreux column at 17 mm., yielded 27.0 g. of a fore-fraction (b. p. 40–93°) and 36.0 g. (54% yield based on the sodium triphenylmethyl) of ethyl *t*-butyl malonate, b. p. 93–95°.

Anal.[4] Calcd. for $C_9H_{16}O_4$: C, 57.4; H, 8.57. Found: C, 57.4; H, 8.56.

Ethyl *t*-Butyl-α-methylmalonate.—*t*-Butyl propionate (b. p. 118.0–118.5°) was prepared in 63% yield from *t*-butyl

(1) Wallingford, Homeyer and Jones, THIS JOURNAL, **63**, 2056 (1941).

(2) See Hudson and Hauser, *ibid.*, **63**, 3156 (1941).

(3) Results on the relative ease of self-condensations of esters in the presence of sodium triphenylmethyl will be published shortly.

(4) Analysis by Saul Gottlieb, Columbia University, New York, N. Y.

alcohol and propionyl chloride in the presence of dimethylaniline, essentially according to the procedure of Norris and Rigby[5] for the preparation of *t*-butyl acetate.

Anal.[4] Calcd. for $C_7H_{14}O_2$: C, 64.6; H, 10.84. Found: C, 65.1; H, 11.20.

t-Butyl propionate (107 cc., 92 g., 0.708 mole) was added to sodium triphenylmethyl[2] (1700 cc., 0.708 mole), the color being discharged within thirty seconds, and after two minutes 86 cc. (83.5 g., 0.708 mole) of ethyl carbonate was added. Stirring was continued for one and one-half hours longer. Glacial acetic acid (60 cc.) was added and the mixture worked up. After distilling off the solvent the residue gave 55.2 g. of a mixture (b. p. 35–77° at 40 mm.) of *t*-butyl propionate and ethyl carbonate, and 66.2 g. of material (b. p. 77° at 40 mm. to 150° at 12 mm.). Redistillation of the latter fraction through a twelve-inch Vigreux column at 14 mm., yielded 13.0 g. of a fore-fraction (b. p. 49–94°) and 48.7 g. (72% yield based on the sodium triphenylmethyl) of ethyl *t*-butyl-α-methylmalonate (b. p. 94–95°).

Anal.[4] Calcd. for $C_{10}H_{18}O_4$: C, 59.4; H, 8.97. Found: C, 60.0; H, 9.10.

Diethyl *t*-Butylmalonate.—Ethyl *t*-butyl acetate (38.2 g., 0.266 mole) prepared by the method of Homeyer, Whitmore and Wallingford,[6] was added with shaking to an ether solution of 0.266 mole of sodium triphenylmethyl and, after standing for ten minutes, 31.4 g. (0.266 mole) of ethyl carbonate was added. After twenty-four hours the reaction mixture was acidified with dilute acetic acid, the ether solution dried and the solvent distilled. The residue yielded 30 g. of recovered esters (b. p. 67–78° at 100 mm.) and 13.3 g. (47%) of diethyl *t*-butylmalonate (b. p. 102–104° at 11 mm.).

Anal.[7] Calcd. for $C_{11}H_{20}O_4$: C, 61.10; H, 9.32. Found: C, 61.24; H, 9.20.

(5) Norris and Rigby, THIS JOURNAL, **54**, 2097 (1932).

(6) Homeyer, Whitmore, and Wallingford, *ibid.*, **55**, 4209 (1933).

(7) Analysis by William Saschek, 630 W. 168 St., New York, N. Y.

Summary

The anions of ethyl *t*-butyl acetate, *t*-butyl acetate and *t*-butyl propionate (prepared by means of sodium triphenylmethyl) have been acylated with ethyl carbonate to form, respectively, diethyl *t*-butylmalonate and the "mixed" malonic esters, ethyl *t*-butylmalonate and ethyl *t*-butyl-α-methylmalonate.

DURHAM, N. C. RECEIVED AUGUST 12, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

A Study of the Products Obtained by the Reducing Action of Metals upon Salts in Liquid Ammonia Solution. VIII. The Reduction of Complex Cyanides

BY JOHN W. EASTES AND WAYLAND M. BURGESS[1]

Introduction

The unusual result obtained by the action of alkali metals on the complex cyanides of nickel in liquid ammonia solution,[2] as contrasted to that obtained through the use of simple nickel salts,[3] prompted the examination of the behavior of the complex cyanides of other metals, some of whose simple salts are also known to give the free metal when reduced by alkali metals in liquid ammonia solution. For this purpose the complex cyanides of cadmium, copper, silver and zinc were chosen. Also the action of calcium on potassium cyanonickelate was investigated. The reactions were carried out as described in previous articles.[2]

Preparation of Complex Cyanides

The complex potassium cyanides of silver, copper and zinc were prepared in the way previously described for the nickel compound.[2] All were markedly more soluble in hot than cold water. Inasmuch as cadmium cyanide is soluble in water, the complex cyanide was prepared by crystallization from a solution containing the stoichiometric quantities of cadmium sulfate and potassium cyanide. The product was recrystallized until free of sulfate ion and then dried at 110°.

All of these complex cyanides were very soluble in liquid ammonia, giving clear colorless solutions.

Potassium Cyanocadmiumate, $K_2Cd(CN)_4$, and Potassium.—Pieces of potassium, when added to a liquid ammonia solution of potassium cyanocadmiumate (in excess), slowly react in such a way that each piece is replaced by a clump of metallic cadmium. No hydrogen gas is given off during the reaction. The black metallic cadmium is not reactive with water, but is highly pyrophoric.

Potassium Cyanocopperate, $K_3Cu(CN)_4$, and Potassium.—Potassium, when added to a solution of potassium cyanocopperate in liquid ammonia, reacts to give a finely divided black precipitate of pyrophoric copper. At the instant the solution turns blue, due to reaction of all of the complex cyanide and solution of the excess potassium, a beautiful copper mirror forms on the surface of the reaction tube in contact with the solution.

Potassium Cyanosilverate, $KAg(CN)_2$, and Potassium.—When pieces of potassium are added to a liquid ammonia

(1) This article is based upon the thesis presented to the Faculty of the Graduate School, University of Cincinnati, by John W. Eastes in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1936.

(2) Eastes and Burgess, THIS JOURNAL, **64**, 1187 (1942).

(3) Burgess and Eastes, *ibid.*, **63**, 2674 (1941).

solution of potassium cyanosilverate, each piece reacts slowly to be replaced by a clump of black pyrophoric silver. Only a trace of hydrogen gas is given off before the solution becomes blue with excess potassium after reaction of all the complex cyanide. Thereafter hydrogen is very, very slowly given off until the blue color of the dissolved potassium disappears. Thus the clumps of silver are very poor catalysts for the formation of potassium amide and hydrogen. The silver was not reactive with water.

Potassium Cyanozincate, $K_2Zn(CN_4)$, and Sodium.—Sodium reacts rapidly with a liquid ammonia solution of potassium cyanozincate to give a finely divided precipitate of metallic zinc. This precipitate is not reactive with water nor is it pyrophoric. No hydrogen gas is given off during its formation nor after the solution has become blue with excess sodium. Thus the precipitate is not a catalyst for the amide formation. At the instant the solution becomes blue with excess sodium, a beautiful silvery mirror is formed on the walls of the reaction tube exposed to the solution. This mirror was not reactive with water.

The formation of zinc instead of $NaZn_4$ is comparable to the case wherein Burgess and Rose[4] observed the formation of metallic zinc by reaction of sodium with a 20% excess of zinc cyanide.

Potassium Cyanonickelate, $K_2Ni(CN)_4$, and Calcium.—Calcium, when added to a solution of potassium cyanonickelate in liquid ammonia, gives the same type of reaction as does sodium and potassium,[2] but with the difference that hydrogen gas is given off throughout the course of the reaction. The insoluble reaction products are soluble in water to give the characteristic red solutions.

(4) Burgess and Rose, THIS JOURNAL, **51**, 2127 (1929).

Summary

Unlike that of nickel, the complex cyanides of cadmium, copper, silver and zinc are reduced to the free metal by alkali metals in liquid ammonia solutions. Under the conditions used all of the precipitated metals but zinc were pyrophoric.

Calcium, in liquid ammonia solution, reduces alkali metal cyanonickelates to give the same type of products as obtained by reduction with alkali metals

RECEIVED JUNE 15, 1942

[COMMUNICATION NO. 871 FROM THE KODAK RESEARCH LABORATORIES]

The Viscosity of Dilute Solutions of Long-Chain Molecules. IV. Dependence on Concentration[1]

BY MAURICE L. HUGGINS

In the first[2] and second[3] papers of this series an equation was derived for the specific viscosity (η_{sp}) of dilute solutions of randomly-kinked chain compounds. At the limit of infinite dilution this equation reduces to

$$\left(\frac{\eta_{sp}}{c}\right)_{c=0} = \frac{\eta-\eta_0}{\eta_0} = K_0 + K_n n = K_0 + K_M M \quad (1)$$

where η and η_0 are the viscosities of the solution and of the pure solvent, c is the concentration in submoles per liter (or any units proportional to these), n is the number of submolecules per molecule, M is the molecular weight, and K_0, K_n and K_M are constants.

In deriving this expression, Stokes' law

$$\text{Force} = 6\pi\eta a u \quad (2)$$

was assumed in computing the frictional force acting on each submolecule as a result of its velocity (u) relative to the liquid immediately surrounding it. The insertion of η_0 for η in (2) leads to the limiting Equation (1) just given. If, instead, one inserts into (2) the value of the viscosity of the *solution*

$$\eta = \eta_0(1 + \eta_{sp}) \quad (3)$$

the expression

$$\frac{\eta_{sp}}{c} = \left(\frac{\eta_{sp}}{c}\right)_{c=0}(1 + \eta_{sp}) \quad (4)$$

is obtained.[4]

For small concentrations, (4) is equivalent to

$$\frac{\eta_{sp}}{c} = \left(\frac{\eta_{sp}}{c}\right)_{c=0} + \left(\frac{\eta_{sp}}{c}\right)^2_{c=0} c \quad (5)$$

At first sight, it might seem that this should give the initial variation of η_{sp}/c with concentration. The application of Equation (2) to the solutions under discussion is, however, very questionable. Strictly speaking, this equation would be applicable only if each submolecule were isolated from all others, so that the liquid streaming past one

(1) Presented before the Division of Colloid Chemistry at the Buffalo Meeting of the American Chemical Society, Sept. 9, 1942. Some of the material contained herein was previously presented at the Symposium on "Viscosity, Molecular Size and Molecular Shape," held under the sponsorship of the Society of Rheology at the Polytechnic Institute of Brooklyn on Feb. 20, 1942.

(2) M. L. Huggins, *J. Phys. Chem.*, **42**, 911 (1938).

(3) M. L. Huggins, *ibid.*, **43**, 439 (1939).

(4) This is equivalent to Eq. (25) of ref. 2 and, except for the Einstein term in the numerator, to Eqs. (123) and (126) of ref. 3. If Einstein's derivation (which also depends on (2)) is similarly modified, to make it applicable to solutions of finite concentration, by the use of η instead of η_0 for the frictional coefficient in Stokes' law, Eqs. (123) and (126) of ref. 3 also become equivalent (as regards the concentration dependence) to (4) above.

would not be affected by the disturbances of the streaming around other submolecules. Moreover, the use of this equation involves the assumptions that the submolecules are spherical and are large relative to the solvent molecules, also that there is no sliding friction, as the solvent molecules move around the submolecules. It certainly does not seem proper, in calculating the dissipation of energy when a *solute* submolecule interacts with the surrounding (chiefly *solvent*) molecules, to use a value of η which is related primarily to the mutual interaction between *solvent* molecules.

It seems reasonable to assume that these objections to the use of Equation (2) can all be met, approximately, by the introduction in it of another factor, k', having a magnitude characteristic of the system under consideration—depending on the sizes, shapes and cohesional properties of both solvent molecules and solute submolecules, but not on the number of submolecules (*i. e.*, the length) of the solute molecule chain. In place of (2), we thus put

$$\text{Force} = 6\pi k'\eta a u \qquad (6)$$

This leads to

$$\frac{\eta_{sp}}{c} = \left(\frac{\eta_{sp}}{c}\right)_{c=0}(1 + k'\eta_{sp}) \qquad (7)$$

which is identical with an empirical equation recently published by Schulz and Blaschke[5] and tested by them on solutions in chloroform of methyl methacrylate polymers. The same value of k' (0.30) was found satisfactory for unfractionated polymers of various average sizes and for their fractions (see Fig. 1).

Equation (7) can readily be put into the form

$$\frac{\eta_{sp}}{c} = \left(\frac{\eta_{sp}}{c}\right)_{c=0} + k'\left(\frac{\eta_{sp}}{c}\right)^2_{c=0} c + \text{terms in higher powers of } c \qquad (8)$$

the higher terms being negligible for dilute solutions. This form is especially well suited for comparison with the many other equations which have been proposed to represent the variation with concentration of the viscosity of solutions. Nearly all of them can be expanded into an expression of this sort; they differ only with respect to the value and interpretation of k' and with respect to the higher terms. Although we shall not here enter into an exhaustive comparison of these various equations, a few will be mentioned.

Martin,[6] considering data for solutions of a variety of high-molecular weight solutes in various solvents, has concluded that the relation

$$\frac{\eta_{sp}}{c} = \left(\frac{\eta_{sp}}{c}\right)_{c=0} \exp\left[k_M \left(\frac{\eta_{sp}}{c}\right)_{c=0} c\right] \qquad (9)$$

accurately represents the viscosity–concentration relationships up to concentrations of 5%, the constant k_M varying with solvent and with solute, but being constant for members of a given polyhomologous series dissolved in a given solvent. Neglecting the higher terms in the expansion of the exponential, this equation reduces to Equation (8), with k' equal to 2.3 k_M, thus confirming the theoretical argument just outlined.

The equations

$$\frac{\eta}{\eta_0} = (1 + k_B c)^{k'_B} \qquad (10)$$

$$\eta_{sp} = \frac{k_F k'_F c}{1 - k'_F c} \qquad (11)$$

and

$$\eta_{sp} = k_J c e^{k'_J c} \qquad (12)$$

have been proposed by Baker,[7] by Fikentscher

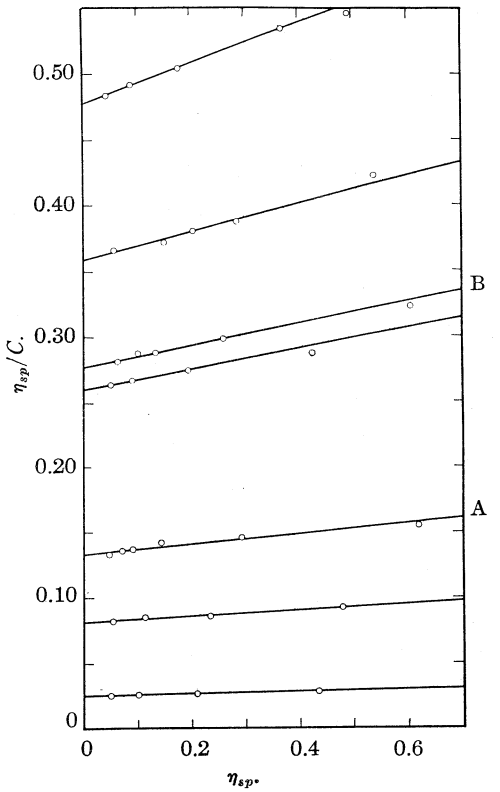


Fig. 1.—Illustrating the agreement with Eq. (4) for solutions in chloroform of methyl methacrylate polymers: concentrations in g./l.; data by Schulz and Blaschke.[5] The samples giving the curves labelled A and B were obtained by fractionation; the other samples were unfractionated.

(5) G. W. Schulz and F. Blaschke, *J. prakt. Chem.*, **158**, 130 (1941).

(6) A. F. Martin, paper presented at the Memphis Meeting of the American Chemical Society, April, 1942.

(7) F. Baker, *J. Chem. Soc.*, **103**, 1653 (1913).

and Mark,[8] and by de Jong, Kruyt and Lens,[9] respectively. Here k_B, k_B', k_F, etc., are empirically determined constants. These equations all reduce to Equation (8), with k' equal to $^1/_2 - {}^1/_2 k'_B$, $1/k_F$, and k'_J/k_J, respectively.

Arrhenius,[10] Hess and Philippoff[11] and Bredée and de Booys[12] have proposed the following equations, respectively

$$\ln\left(\frac{\eta}{\eta_0}\right) = k_A c \qquad (13)$$

$$\frac{\eta}{\eta_0} = \left(1 + \frac{k_H c}{8}\right)^8 \qquad (14)$$

$$\frac{\eta}{\eta^0} = \left(1 + \frac{5k_{BB}c}{12}\right)^6 \qquad (15)$$

The last two are special cases of Baker's equation, (10). All three reduce to Equation (8), with k' equal to $^1/_2$, $^7/_{16}$ and $^5/_{12}$, respectively,—constants independent of the solvent–solute system. As would be expected, these inflexible equations do not give as good general agreement as do (7) and (9)–(12), which contain an additional adjustable constant.

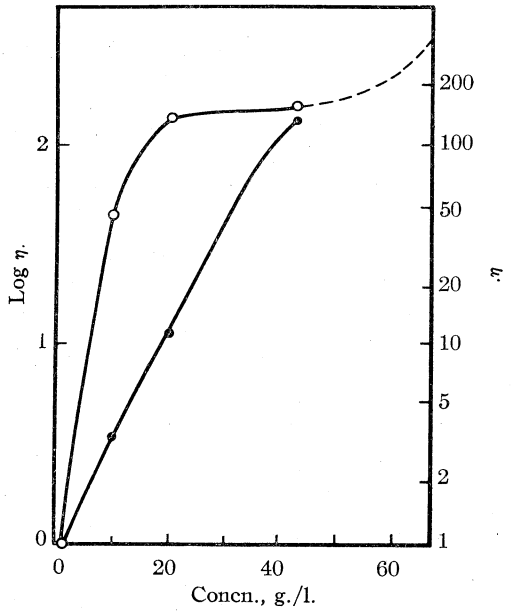


Fig. 2.—Dependence of viscosity on concentration, for polyisobutylene (polybutene) solutions in *n*-butyl ether: O, 20°; ●, 37.78°; data by Evans and Young.[14]

It should be noted that our comparison of these various equations for the concentration dependence of viscosity has concerned only the initial slope of the η_{sp}/c *vs.* c curve and so applies only to quite dilute solutions. We shall not here enter into a discussion of the theoretical or empirical treatment of this dependence at higher concentrations, except to make one remark:

If the attractions between *like* molecules in the solution are considerably more potent than those between *unlike* molecules—as indicated[13] by a large value of μ_1 and by a separation into two phases at sufficiently high concentrations—the solute molecules tend to form aggregates at concentrations somewhat below that at which the second phase becomes evident. This results in a viscosity–concentration curve with a slope which decreases (or even becomes negative) at the higher concentrations. Solutions of polyisobutylene in *n*-butyl ether at 20°, for example, show this effect[14] (see Fig. 2). As would be expected, the anomalous behavior disappears as the temperature is raised; μ_1 is decreased and the aggregates are dissociated. The viscosity behavior of solutions of polyisobutylene in benzene is likewise anomalous,[15] apparently for the same reason.

Summary

1. It has been shown that a simple, reasonable modification of the author's previous theoretical treatment of the viscosity of dilute solutions of long-chain molecules leads to the equation

$$\frac{\eta_{sp}}{c} = \left(\frac{\eta_{sp}}{c}\right)_{c=0}(1 + k'\eta_{sp})$$

for the initial concentration dependence of the viscosity. This is identical with an equation arrived at empirically by Schulz and Blaschke.

2. The constant k' is characteristic of a given solute-solvent system; it is the same for solutions, in a given solvent, of different members of a polymer-homologous series, however.

3. At low concentrations (such as assumed in the theoretical derivation), this relationship is equivalent to

$$\frac{\eta_{sp}}{c} = \left(\frac{\eta_{sp}}{c}\right)_{c=0} + k'\left(\frac{\eta_{sp}}{c}\right)^2_{c=0} c$$

Equations proposed by Baker, by Fikentscher and Mark, by de Jong, Kruyt and Lens, and by Martin all reduce to this same limiting equation, with k' different for different systems. Equations proposed by Arrhenius, by Hess and Philippoff, and by Bredée and de Booys likewise reduce to this form, but with k' having the same value for all systems.

ROCHESTER, NEW YORK RECEIVED AUGUST 28, 1942

(8) H. Fikentscher and H. Mark, *Kolloid-Z.*, **49**, 135 (1930).
(9) H. G. de Jong, H. R. Kruyt and W. Lens, *Kolloid Beihefte*, **36**, 429 (1932).
(10) S. Arrhenius, *Medd. Vetenskapakad., Nobel-inst.*, **4**, 13 (1916).
(11) K. Hess and W. Philippoff, *Ber.*, **70B**, 639 (1937).
(12) H. L. Bredée and J. de Booys, *Kolloid-Z.*, **79**, 31 (1937).
(13) M. L. Huggins, THIS JOURNAL, **64**, 1712 (1942).
(14) H. C. Evans and D. W. Young, *Ind. Eng. Chem.*, **34**, 461 (1942).
(15) A. R. Kemp and H. Peters, *Ind. Eng. Chem.*, **34**, 1192 (1942).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

The Halogenation of Certain Esters in the Biphenyl Series. II. The Chlorination of 4-Phenylphenyl Benzoate and 4-Phenylphenyl Benzenesulfonate[1]

BY CORA MAY SEGURA SAVOY AND JOHN LEO ABERNETHY

Prior to the chlorination of 4-phenylphenyl acetate, recently reported,[2] work was begun on the chlorination of 4-phenylphenyl benzoate and 4-phenylphenyl benzenesulfonate in an endeavor to find a more direct route to 4-(4-chlorophenyl)-phenol than had been used previously.[3] In view of the unanticipated mode of entry of chlorine into the biphenyl nucleus in the case of 4-phenylphenyl acetate and the ease of hydrolysis of the resultant chlorinated ester to 4-(4-chlorophenyl)-phenol, it seemed of value to continue the present problem. The present paper shows that chlorination of 4-phenylphenyl benzoate and 4-phenylphenyl benzenesulfonate results in substitution in the same position of the biphenyl nucleus as does 4-phenylphenyl acetate.

Chlorination of 4-phenylphenyl benzoate in the presence of iodine catalyst, using carbon tetrachloride as the solvent, gave rise to 4-(4-chlorophenyl)-phenyl benzoate. That chlorine had entered the 4′-position of the biphenyl nucleus was proved by hydrolysis of the chlorinated ester to the known 4-(4-chlorophenyl)-phenol and benzoic acid. Benzoylation of 4-(4-chlorophenyl)-phenol, prepared by a different method, yielded the same chlorinated ester.

When 4-phenylphenyl benzenesulfonate was chlorinated, using similar conditions, 4-(4-chlorophenyl)-phenyl benzenesulfonate resulted. The position of entry of chlorine was proved by hydrolysis.

Although 2-chloro-4-phenylphenyl benzoate and 2-chloro-4-phenylphenyl benzenesulfonate were sought for in the above chlorination processes, neither was found.

During the progress of this investigation it was found desirable to prepare the benzenesulfonates of the known chlorophenylphenols. Accordingly, 4-(4-chlorophenyl)-phenyl benzenesulfonate, 2-chloro-4-phenylphenyl benzenesulfonate, 2,6-dichloro-4-phenylphenyl benzenesulfonate and 2,6-dichloro-4-(4-chlorophenyl)-phenyl benzenesulfonate were synthesized by the interaction of benzenesulfonyl chloride with the corresponding phenols.

A comparison of the yields of 4-(4-chlorophenyl)-phenol by chlorination of the various esters of 4-phenylphenol shows that the route through the acetate gives the best yield. The extreme ease of hydrolysis of the acetate is indeed worthy of mention.

Acknowledgment.—The writers are indebted to Professor H. R. Henze of the University of Texas and Professor E. G. Feusse of Southwestern Louisiana Institute for their valuable assistance during the progress of this investigation, and to the Research Institute of the University of Texas for a grant permitting the continuance of this work.

Experimental

4-(4-Chlorophenyl)-phenyl Benzoate.—A trace of iodine was added to 13.7 g. of 4-phenylphenyl benzoate suspended in 125 cc. of carbon tetrachloride. A solution of 3.9 g. (10% excess) of chlorine in 75 cc. of carbon tetrachloride was introduced dropwise over a period of two hours. When the reaction mixture had been allowed to stand overnight, the white solid was filtered, washed with cold ethanol, and twice digested with ethanol. The purified 4-(4-chlorophenyl)-phenyl benzoate, which melted at 182° weighed 8.5 g. (55% yield). An additional 0.5 g. was obtained upon distillation of the filtrate from the reaction mixture.

This same ester was prepared by benzoylation of 4-(4-chlorophenyl)-phenol. A mixed melting point caused no depression.

Anal. Calcd. for $C_{19}H_{13}O_2Cl$: Cl, 11.49. Found: Cl, 11.52.

Hydrolysis of 4-(4-Chlorophenyl)-phenyl Benzoate.—A mixture of 5 g. of 4-(4-chlorophenyl)-phenyl benzoate and 10 g. of potassium hydroxide in 100 cc. of 50% ethanol was refluxed for three hours, cooled and poured into 100 cc. of water. After the ethanol had been removed by distillation, the alkaline solution was extracted with ether and the ether extract dried with anhydrous sodium sulfate. Evaporation of the ether and digestion of the remaining solid with ethanol yielded 0.4 g. of unhydrolyzed 4-(4-chlorophenyl)-phenyl benzoate.

Saturation of the aqueous solution with carbon dioxide resulted in the formation of a white precipitate which was extracted with ether and dried over anhydrous sodium sulfate. When the solvent was evaporated, 3.0 g. of solid resulted. Purification of this product by crystallization from chloroform and petroleum ether (b. p. 35–55°) gave rise to a white solid which melted at 145.5–146°, and did not

(1) From a portion of a thesis submitted by Mrs. Savoy to the Graduate Faculty of the University of Texas in partial fulfillment of the requirements for the degree of Master of Arts, August, 1942.

(2) Savoy and Abernethy, THIS JOURNAL, **64**, 2219 (1942).

(3) Angelleti and Gatti, *Gazz. chim. ital.*, **58**, 633 (1928).

depress the melting point of 4-(4-chlorophenyl)-phenol, prepared by the hydrolysis of 4-(4-chlorophenyl)-phenyl acetate. The yield was 2.2 g. (67%).

The aqueous solution previously saturated with carbon dioxide was acidified with hydrochloric acid and again extracted with ether. After drying with anhydrous sodium sulfate and removing the ether, 1.4 g. of benzoic acid was obtained.

Benzoylation of 4-(4-chlorophenyl)-phenol gave rise to 4-(4-chlorophenyl)-phenyl benzoate, which did not depress the melting point of the ester prepared by the chlorination of 4-phenylphenyl benzoate.

4-(4-Chlorophenyl)-phenyl Benzenesulfonate.—A solution of 5 g. (10% excess) of chlorine in 100 cc. of carbon tetrachloride was introduced, drop by drop, into a solution of 20 g. of 4-phenylphenyl benzenesulfonate,[4] a trace of iodine, and 100 cc. of carbon tetrachloride. After the reaction mixture had been allowed to stand overnight, the solvent was removed by distillation under reduced pressure. The viscous, amber colored liquid which resulted was dried with anhydrous sodium sulfate and distilled at 8 mm. pressure. The portion which distilled between 220 and 300°, when purified with methanol, yielded 15.1 g. of crystals. After five recrystallizations from methanol, the product, m. p. 74–75°, weighed 4.7 g. (21% yield).

Anal. Calcd. for $C_{18}H_{13}O_3ClS$: S, 9.303. Found: S, 9.309.

Reaction of benzenesulfonyl chloride with 4-(4-chlorophenyl)-phenol in pyridine yielded this same ester.

Hydrolysis of 4-(4-Chlorophenyl)-phenyl Benzenesulfonate.—A mixture of 3 g. of 4-(4-chlorophenyl)-phenyl benzenesulfonate and 10 g. of potassium hydroxide in 100 cc. of 50% ethanol was refluxed for ten hours, cooled and poured into 100 cc. of water. After the ethanol had been removed by distillation, the alkaline solution was extracted with ether. The ether extract was dried with anhydrous sodium sulfate and the solvent was removed by distillation under reduced pressure. No residue was left after all the ether had been removed. The aqueous solution was acidified with hydrochloric acid and extracted with ether. After drying with anhydrous sodium sulfate and removal of the ether, 1.6 g. of light yellow solid was obtained. Three recrystallizations from chloroform and petroleum ether reduced the yield to 0.7 g. (39% yield) of a pure white solid, m. p. 145–146°. A mixed melting point with known 4-(4-chlorohenyl)-phenol caused no depression.

(4) Hazlet, THIS JOURNAL, **59**, 1087 (1937).

Benzenesulfonylation of Certain of the Chlorinated Phenylphenols.—A mixture of 2 g. of the phenol, 20 cc. of 10% aqueous sodium hydroxide, and 2 cc. of benzenesulfonyl chloride was refluxed for ten minutes, poured into 100 cc. of water and allowed to stand for one hour. Filtration of the product and recrystallization from ethanol yielded the ester. The results are recorded in Table I.

TABLE I

BENZENESULFONATES FROM CERTAIN CHLORINATED PHENYLPHENOLS

Benzenesulfonate	M. p., °C.	Sulfur, % Calcd.	Found
4-(4-Chlorophenyl)-phenyl	74– 75	9.303	9.309
2-Chloro-4-phenylphenyl	59– 60	9.303	9.287
2,6-Dichloro-4-phenyl-phenyl	128–129	8.457	8.372
2,6-Dichloro-4-(4-chloro-phenyl)-phenyl	125–126	7.753	7.738

Summary

It has been shown that chlorination of 4-phenylphenyl benzoate and 4-phenylphenyl benzenesulfonate introduces chlorine in the 4′-position of the biphenyl nucleus. Hydrolysis of the resultant chlorinated esters gave rise to 4-(4-chlorophenyl)-phenol.

The benzenesulfonates of 2-chloro-4-phenylphenol, 2,6-dichloro-4-phenylphenol and 2,6-dichloro-4-(4-chlorophenyl)-phenol were prepared for the first time.

AUSTIN, TEXAS RECEIVED AUGUST 24, 1942

NOTES

The Acylation of Acetonitrile with Ethyl *n*-Butyrate and the Alcoholysis of the Resulting Ketonitrile to Ethyl *n*-Butyrylacetate

BY B. ABRAMOVITCH AND CHARLES R. HAUSER

McElvain and co-workers[1] have shown that, in the presence of sodium ethoxide, acetonitrile (and also certain other nitriles) may be acylated satisfactorily with ethyl benzoate or ethyl isobutyrate to form β-ketonitriles, which may be alcoholyzed to form β-keto esters. Apparently, the acylation of acetonitrile with esters capable of undergoing self-condensation in the presence of sodium ethoxide, for example, ethyl *n*-butyrate, was not attempted. The acylation of the relatively reactive nitrile, phenylacetonitrile, with ethyl acetate, however, may be effected satisfactorily.[2]

(1) (a) Dorsch and McElvain, THIS JOURNAL, **54**, 2960 (1932); (b) Cox, Kroeker and McElvain, *ibid.*, **56**, 1172 (1934).

(2) "Organic Syntheses," 1925, Vol XVIII, p. 36.

In the present investigation it is shown that acetonitrile may be acylated with ethyl *n*-butyrate by first converting the nitrile into its anion by means of sodium triphenylmethyl[3] and then treating the anion with the ester; in this manner *n*-butyryl acetonitrile was obtained in 52% yield (based on the sodium triphenylmethyl). Alcoholysis of the β-ketonitrile gave a 64% yield of ethyl *n*-butyrylacetate, the over-all yield being 33%. The reactions may be represented as

$$CH_3CN + (C_6H_5)_3C^- \longrightarrow (CH_2CN)^- + (C_6H_5)_3CH$$

$$CH_3(CH_2)_2CO_2C_2H_5 + (CH_2CN)^- \longrightarrow CH_3(CH_2)_2COCH_2CN + {}^-OC_2H_5$$

$$CH_3(CH_2)_2COCH_2CN + C_2H_5OH \xrightarrow{HCl} CH_3(CH_2)_2COCH_2CO_2C_2H_5$$

To a stirred solution (1300 cc.) of 0.19 mole of sodium triphenylmethyl[3] at 0° was added 7.8 g. (0.19 mole) of acetonitrile (b. p. 81.5–82.0°) dissolved in 25 cc. of dry ether. The red color of the sodium triphenylmethyl was discharged immediately yielding a light orange solution with a white precipitate. To this stirred mixture was added during five minutes 22 g. (0.19 mole) of cold ethyl *n*-butyrate (b. p. 121.0–121.5°) dissolved in 25 cc. of dry ether. The mixture was stirred for five minutes longer, removed from the ice-bath, and shaken vigorously for two minutes. Ice water (500 cc.) was then added with shaking to the mixture, the alkaline layer separated and the ether layer washed with sodium hydroxide solution followed by water. From the dried ether solution were recovered 2.5 g. of acetonitrile and 12.0 g. of ethyl *n*-butyrate. Acidification (with cold 10% sulfuric acid) of the combined alkaline solution and washings yielded an oil. The mixture was extracted three times with ether and the combined ether solutions washed with 10% sodium bicarbonate solution, dried, and the solvent distilled. On distilling the residue *in vacuo* there was obtained 5.5 g. (52% based on the sodium triphenylmethyl) of *n*-butyryl acetonitrile boiling at 104–105° at 11 mm.

Anal.[4] Calcd. for C_6H_9ON: C, 64.8; H, 8.17. Found: C, 65.3; H, 8.21.

By allowing the reaction mixture to stand at room temperature (25°) for two days, the same yield (52%) of product was obtained, there being also formed more alkali-soluble by-product.

Treatment of the *n*-butyryl acetonitrile with dry halogen chloride in absolute alcohol[1a] gave a 64% yield of ethyl *n*-butyrylacetate (b. p. 94–95° at 15 mm.; copper compound, m. p. 124–125°).[5]

DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
DURHAM, NORTH CAROLINA RECEIVED AUGUST 15, 1942

(3) See especially Hudson and Hauser, THIS JOURNAL, **63**, 3156 (1941).

(4) Analysis by S. Gottlieb, Columbia University, New York, N. Y.

(5) Moureu and Delange, *Compt. rend.*, **136**, 753 (1903); *Bull. soc. chim.*, [3] **29**, 668 (1903).

Catalytic Hydrogenation of Cystine

BY KEVIN E. KAVANAGH

The applicability and high efficiency of the recently developed palladium and platinum synthetic high polymer catalysts were described in previous papers.[1,2,3] In an effort to determine whether these polymers are able to protect against the well-known poisoning of noble metals by sulfur, an attempt was made to hydrogenate cystine using a PVA–Pd catalyst. Bergmann and Michalis[4] reduced cystine to cysteine using palladium black: for the almost complete reduction of 4.8 g., 2 g. of palladium black and six hours of shaking were required. Applying the Pd–PVA catalyst, partial reduction of cystine was slowly obtained using only 10 mg. of Pd. Therefore, the amount of Pd was increased to 100 mg., whereupon almost complete hydrogenation resulted.

Procedure

A catalyst containing 500 mg. of PVA, 100 mg. of Pd and 50 cc. of water was prepared. Two grams of cystine dissolved in 50 cc. of 2 *N* hydrochloric acid was introduced into the vessel and the whole shaken for forty-five hours at room temperature and ordinary pressure. At the end of this time 176 cc. of a theoretical 199 cc. of hydrogen had been absorbed. Thereupon, the still colloidal catalyst was made strongly acid with 5 cc. of 12 *N* hydrochloric acid and then flocculated by the addition of excess alcohol. The cysteine hydrochloride hydrate was isolated and air-dried. The melting point of the hydrochloride, after the molecule of water of crystallization had been removed by drying in a vacuum desiccator, was 184° decomp. The absence of cystine was ascertained by the iodometric titration of the cysteine to cystine.[5,6] 0.4389 g. of cysteine hydrochloric acid hydrate required 25.05 cc. of 0.1004 *N* iodine. Calcd. 24.91 I_2.

Anal. Calcd. for the cysteine hydrochloric acid hydrate: N, 7.97; H_2O, 10.25. Found: N, 7.79; H_2O, 10.49.

The repeatedly emphasized[4,7] sensitivity of Pd catalysts to sulfur-containing proteins was smoothly overcome by using a Pd–PVA catalyst.

Acknowledgment.—This investigation was partly supported by grants of the American Philosophical Society and the Bache Fund of the National Academy of Sciences.

DEPARTMENT OF ORGANIC CHEMISTRY
FORDHAM UNIVERSITY
BRONX, NEW YORK, N. Y. RECEIVED JULY 30, 1942

(1) H. S. Taylor and W. J. Shenk, THIS JOURNAL, **63**, 2756 (1941).

(2) Louis D. Rampino and F. F. Nord, *ibid.*, **63**, 3268 (1941); and forthcoming article.

(3) T. H. James, *ibid.*, **64**, 732 (1942).

(4) M. Bergmann and G. Michalis, *Ber.*, **63**, 987 (1930).

(5) Th. F. Lavine, *J. Biol. Chem.*, **109**, 141 (1935).

(6) G. Toennies and M. A. Bennett, *ibid.*, **112**, 497 (1935–1936).

(7) H. Wieland, *Ber.*, **45**, 2617 (1912); E. B. Maxted and H. C. Evans, *J. Chem. Soc.*, 603 (1937).

The Reaction between Thioamides and Primary Amines

BY MAURICE J. SCHLATTER[1]

The older literature[2] implies that the reaction between thioamides and primary amines proceeds solely with elimination of hydrogen sulfide and resultant formation of amidine. The present studies show that under certain conditions ammonia may be split out between the reacting molecules giving an N-substituted thioamide.[3] The interaction may also result in the simultaneous elimination[4] of hydrogen sulfide and ammonia.

Experimental

Thioacetamide and *n*-Butylamine.—Five grams of thioacetamide (0.077 mole) was mixed with 16.8 g. of *n*-butylamine (0.23 mole) and heated under reflux until the initially brisk gas evolution had almost ceased (about three hours). Fractionation of the product *in vacuo* gave 5.3 g. of light yellow oil,[5] the major portion of which boiled at 131.5° (5 mm.) and gave analytical figures for N-butylthioacetamide.

Anal. Calcd. for $C_6H_{13}NS$: C, 54.91; H, 9.99; N, 10.67. Found: C, 54.91; H, 10.06; N, 10.73.

Thioacetamide and Benzylamine.—Benzylamine (2.14 g. = 0.020 mole) was mixed with thioacetamide (1.43 g. = 0.022 mole) and heated in a bath at 80° for one and one-quarter hours. The initially vigorous gas evolution almost stopped after forty-five minutes. On fractionation, the reaction mixture distilled almost completely at 158–162° at 2 mm. The distillate (2.28 g.) solidified on cooling and on recrystallization from anhydrous ether gave colorless needles, insoluble in water, soluble in alcohol, m. p. 65.1–65.3°[6] (cor.).

Anal. Calcd. for $C_9H_{11}NS$: C, 65.41; H, 6.71; N, 8.48. Found: C, 65.60; H, 6.68; N, 8.27.

Thioacetamide and Ethanolamine.—Ethanolamine (15.3 g. = 0.25 mole) and thioacetamide (18.0 g. = 0.276 mole) were mixed in a flask equipped with stirrer and immersed in a bath. On heating at 60–75° an active gas evolution took place which lasted about one-half hour. The stirrer was then replaced by a distilling head and the temperature of the bath raised slowly to 215° while volatile material was removed *in vacuo* (30 mm.). The residue (17.9 g.) solidified on cooling and was recrystallized from absolute alcohol; colorless rectangular prisms, m. p. 101.0–101.5° (cor.). The analysis indicates that two molecules of each of the reactants have combined with loss of two molecules of ammonia and one of hydrogen sulfide; a possible formula is $[HOCH_2CH_2N{=}C(CH_3)-]_2S$.

Anal. Calcd. for $C_8H_{16}N_2O_2S$: C, 47.03; H, 7.90; N, 13.71; S, 15.69. Found: C, 47.09; H, 7.79; N, 13.64; S, 15.82.

A derivative crystallized from the reaction mixture when equal volumes of saturated solutions of the substance and of picric acid in ethyl acetate were mixed, heated to boiling and then cooled to 0°. The crystals were washed with ether and dried, m. p. 95.0–95.5° (cor.).

CONTRIBUTION NO. 897 FROM THE
GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIFORNIA RECEIVED JULY 22, 1942

(1) Present address, Chemistry Department, University of California at Los Angeles.

(2) Bernthsen, *Ann.*, **184**, 290 (1877).

(3) Compare Westphal and Andersag, *Chem. Abstr.*, **35**, 1413 (1941); **36**, 1950 (1942); see also Gatewood and Johnson, THIS JOURNAL, **50**, 1423 (1928).

(4) Compare Buchman, Reims, Skei and Schlatter, *ibid.*, **64**, 2696 (1942).

(5) Compare Sakurada, *Chem. Zentr.*, **99**, I, 683 (1928).

(6) Worrall, THIS JOURNAL, **50**, 1459 (1928), gives m. p. 62–63° for N-benzylthioacetamide.

Preparation of *d*-Fructose-1,6-diphosphate by Means of Baker's Yeasts

BY C. NEUBERG AND H. LUSTIG

The preparation of the phosphoric esters of carbohydrates has not been achieved up to now with fresh baker's yeast, as phosphorylation with top yeast was only possible by addition of co-ferment to acetone yeast or alcohol–ether dried yeast (phosphorylation to 100%), or, with the same type of yeast, if dried before in the usual manner (phosphorylation to 20%).[1] By means of the procedure described below, *d*-fructose-1,6-diphosphate is readily obtained by the use of commercial bakers' yeasts without the necessity of treating brewers' yeast by washing, pressing, etc. Nearly equally satisfactory results have been obtained with various brands of fresh bakers' yeast (Atlantic, Federal, Blue Ribbon and National Grain), but not with fresh Fleischmann's yeast.

Procedure

To a solution of 200 g. of sucrose, 42 g. of monosodium phosphate ($NaH_2PO_4{\cdot}2H_2O$) and 11 g. of sodium bicarbonate in 1000 cc. of tap water contained in a 5-l. bottle add 450 g. of fresh bakers' yeast (Atlantic) and 150 cc. of ether.[2] Shake the mixture until homogeneous, stopper the bottle in a manner which will allow the escape of gases, and place in an incubator at 37° until phosphorylation is complete[3] (four and one half hours). The completeness of this process may be judged by adding 3 cc. of 2.5% ammonia and 1 cc. of 10% ammonium chloride to 2 cc. of the filtered fermentation mixture and then adding magnesia mixture. An immediate precipitation does not occur when phosphorylation is complete.

When phosphorylation is complete, add a few cc. of a

(1) C. Neuberg and A. Gottschalk, *Biochem. Z.*, **154**, 492 (1924).

(2) Carbon tetrachloride is an equally satisfactory plasmolytic agent, also for the phosphorylation with brewers' yeast, as our experiments with yeasts obtained from the Piel and Schaefer breweries (bottom yeasts) demonstrate.

(3) The time required for complete phosphorylation varies with different brands of yeast and with the temperature. Similar experiments made with Atlantic and Federal yeasts at room temperature (20–24°) required twenty and seventy-two hours, respectively.

10% solution of octyl alcohol in ethanol to the fermentation mixture and immerse the container in an actively boiling water-bath until the proteins are coagulated. Separate the coagulum by centrifugation or filtration (in a refrigerator), neutralize the clear filtrate to phenolphthalein by the addition of 4 *N* sodium hydroxide and immediately precipitate by the addition of a solution of 55 g. of calcium chloride in 100 cc. of water; *i. e.*, slightly more than one mol of this reagent is required for each mol of monosodium phosphate present in the initial mixture. Complete the precipitation by heating at a boiling water-bath for a short time, and filter the warm mixture with suction. Wash the precipitated calcium *d*-fructose-1,6-diphosphate with warm water; yield, 22 g.

An alternative procedure is the following: When phosphorylation is complete add to the fermentation mixture a solution of 40 g. of picric acid in 200 cc. of hot ethanol. Allow the mixture to stand in a refrigerator for two hours and filter. Add 4 *N* sodium hydroxide to the filtrate until neutral to phenolphthalein, then add calcium chloride as previously described. The precipitated calcium salt contains some picrate but this is removed by washing with hot water and subsequently with alcohol. An experiment conducted in this fashion with the quantities of material stated above yielded 24 g. of crude calcium *d*-fructose-1,6-diphosphate.

To purify the crude calcium salt obtained by either of these procedures, dissolve the moist crude product in 250 cc. of 2 *N* acetic acid, add 125 cc. of water, filter if necessary, and to the clear solution add 2 *N* sodium hydroxide until neutral to phenolphthalein. Heat the resulting mixture in a boiling water-bath for a short time, filter and wash the precipitated salt with warm water; yield about 80% of the crude product.

In analogous manner the barium salt can be prepared, but in this case the use of picric acid for the deproteinization is not advisable because of the difficult solubility of barium picrate.

As mentioned in the introduction, fresh Fleischmann's yeast is not satisfactory for the preparation of *d*-fructose-1,6-diphosphate in the manner described. If, however, this brand of yeast is well dried at room temperature in the usual manner, it may be employed, for with such dried yeast phosphorylation takes place rapidly. When a mixture of 30 g. of dried Fleischmann's yeast, 15 cc. of carbon tetrachloride and 100 cc. of the sugar–phosphate solution of the composition mentioned earlier was incubated at 37°, phosphorylation was found to be complete within one and one-half hours. Similar results were obtained with dried preparations of National Grain and Federal yeasts. The product of phosphorylation contains, as well as in the other cases described, in addition to hexose-diphosphate also sugar-monophosphates.

A purity test can be made using an observation published many years ago.[4] Calcium and barium hexose–diphosphate dissolve readily in solutions of ammonium tri-salts, such as acetate, chloride, nitrate, rhodanide, while calcium and barium phosphate are practically insoluble. Consequently the pure salts of hexose–diphosphate are completely dissolved in the ammonium salt solutions and added magnesia mixture does not cause a precipitate.

(4) C. Neuberg and S. Sabetay, *Biochem. Z.*, **161**, 240 (1925).

We are indebted to the manufacturers of the various brands of yeast mentioned for generous supplies of their respective products.

DEPARTMENT OF CHEMISTRY
NEW YORK UNIVERSITY
NEW YORK, N. Y. RECEIVED MAY 28, 1942

The Catalytic Reduction of Cholesterol α-Oxide

BY HOMER E. STAVELY

The catalytic reduction of oxides of the ethylene oxide type has been suggested as a possible approach to certain synthetic problems in the steroid hormone field. Only a few such examples can be found in the literature. Triphenylethylene oxide,[1] ethylene oxide[2] and ethyl stearate oxide[3] have been catalytically reduced to alcohols. Fernholz[4] hydrogenated stigmasterol α-oxide-(5,6) acetate using platinum and acetic acid, and obtained stigmastanediol-3,5 monoacetate in 20% yield. According to a patent[5] 3-acetoxy-pregnadiene-5:6,20:21 can be converted into a dioxide, which can then be reduced in acetic acid with palladium and hydrogen to 3-acetoxypregnanediol-5,20.

Similar treatment of cholesterol α-oxide[6] should yield either 3,5- or 3,6-cholestanediol. The 3,5-diol was obtained by Chinaeva and Ushakov[7] when they treated cholesterol α-oxide with phenyllithium.

Cholesterol α-oxide was hydrogenated in acetic acid with palladium catalyst. The hydrogen uptake was slow, and was therefore allowed to proceed over a period of several days with intermittent shaking. The reaction products were acetylated and chromatographed on alumina. Three substances were isolated in pure form, cholestanediol-3,5 monoacetate,[8] cholestanol-3 acetate, and α-cholestanetriol-3,5,6 diacetate. The latter compound obviously is not a reduction product; it can be prepared by heating the oxide acetate with acetic acid. It is evident that the major part of the oxide is reduced to the 3,5-diol, from

(1) Weill and Kayser, *Bull. soc. chim.*, [5] **3**, 841 (1936).

(2) Ushakov and Mikhaĭlov, *J. Gen. Chem.* (U. S. S. R.), **7**, 249 (1937); *C. A.*, **31**, 4645 (1937).

(3) Pigulevskiĭ and Rubashko, *J. Gen. Chem.* (U. S. S. R.), **9**, 829 (1939); *C. A.*, **34**, 378 (1940).

(4) Fernholz, *Ann.*, **508**, 215 (1934).

(5) Swiss Patent 214,540.

(6) Windaus and Westphalen, *Ber.*, **48**, 1064 (1915).

(7) Chinaeva and Ushakov, *J. Gen. Chem.* (U. S. S. R.), **11**, 335 (1941); *C. A.*, **35**, 5903 (1941).

(8) The melting points of the free diol and the diol acetate are somewhat higher than the figures given by Chinaeva and Ushakov. The two diols may be isomeric at C_5.

which the tertiary hydroxyl is then partially eliminated with the production of cholestanol-3. It is probable that the formation of the primary reduction product would have taken precedence over the side reactions if the experimental conditions had permitted a shortening of the reduction period.

The several examples now at hand permit the generalization that when an ethylene oxide ring is opened by hydrogenation the hydroxyl group formed will be attached to the carbon atom carrying the smaller number of hydrogen atoms,[9] as one would expect on theoretical grounds.

Experimental

Two hundred mg. of palladium catalyst in acetic acid was saturated with hydrogen, and a solution of 300 mg. of cholesterol α-oxide, m. p. 141°, in acetic acid was added. After three hours of shaking only two-thirds mole (10 cc.) of hydrogen had been absorbed. Intermittent shaking was continued for two days, and the total hydrogen uptake was 18 cc. (1.2 moles). After removal of the catalyst the acetic acid was removed by vacuum distillation and the residue acetylated at room temperature overnight with pyridine–acetic anhydride. The total acetylated reaction product was dissolved in hexane and chromatographed on a column of alumina 1 × 15 cm. Elution was carried out with hexane, then with hexane–benzene mixtures, and finally with benzene. The hexane fractions yielded 85 mg. After two recrystallizations from methanol the m. p. was 109–110°. The m. p. of a mixture with cholestanol-3 acetate was not depressed.

Anal. Calcd. for $C_{29}H_{50}O_2$: C, 80.86; H, 11.70. Found: C, 80.80; H, 11.77.

The combined residues from the hexane–benzene (2/1) mixtures weighed 120 mg. After several recrystallizations the m. p. was constant at 181°.

Anal. Calcd. for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 77.81; H, 11.08.

Twenty-five mg. of the diol acetate was hydrolyzed with methanolic potassium hydroxide. The diol had a m. p. of 216–217°. Chinaeva and Ushakov[7] give a m. p. of 201° for the diol and 177° for the acetate.

The residue from the benzene fractions weighed 75 mg. After several recrystallizations from methanol the m. p. was 165–167°. The m. p. of a mixture with authentic α-cholestanetriol-3,5,6 diacetate was not depressed.

Anal. Calcd. for $C_{31}H_{52}O_5$: C, 73.77; H, 10.39. Found: C, 73.67; H, 10.63.

The triol was prepared by hydrolysis of the diacetate, m. p. 227–230°. The m. p. of a mixture with an authentic sample was not depressed.

THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH
DIVISION OF ORGANIC CHEMISTRY
NEW BRUNSWICK, N. J. RECEIVED AUGUST 10, 1942

(9) Krassusky, *Chem. Ztg.*, **31**, 704 (1907), found that a similar rule applies when the alkene oxide ring is opened with ammonia to form α-amino alcohols.

Revised Constants for the Debye–Hückel Theory

BY H. I. STONEHILL AND M. A. BERRY

Using the newer values of certain fundamental constants, *viz.*, e (electronic charge) = 4.803×10^{-10} e. s. u., $k = 1.379 \times 10^{-16}$ erg/°C., $N = 6.028 \times 10^{23}$, T_0 (ice point) = 273.18°K.,[1] D (dielectric constant of water at 25°) = 78.54,[2] it may be calculated that the values of h and g in the first term of the Debye–Hückel expression for the log of the activity coefficient of a $z_1:z_2$ valent electrolyte in aqueous solution at 25°

$$\log \gamma = \frac{-hz_1z_2\sqrt{I}}{1 + ga\sqrt{I}} - \log (1 + 0.018\Sigma m_i)$$

are $h = 0.5103$ and $g = 0.3290 \times 10^8$.

The older values, $e = 4.774 \times 10^{-10}$, $k = 1.372 \times 10^{-16}$, $N = 6.061 \times 10^{23}$, $T_0 = 273.1$°K.,[3] lead to $h = 0.5065$, $g = 0.3287 \times 10^8$. Harned and Robinson in two recent publications[4,5] employed the values $h = 0.5065$, $g = 0.3288 \times 10^8$ and $h = 0.5056$, $g = 0.3288 \times 10^8$. While the value of g is practically unchanged, there are discrepancies of 1.0 and 0.8% between 0.5103 and the two values of h used by Harned and Robinson, leading to corresponding discrepancies in the first term of the Debye–Hückel equation. This term is the most important one even in extended forms of the equation containing arbitrary linear, quadratic or other additional functions of concentration, at least up to about $I = 1.0$. Thus a 0.9% error in h corresponds to an approximately equal error in log γ. A 0.9% error in log γ corresponds to % errors in γ of 0.1, 0.2, 0.3, 0.5, 0.7, 0.8, 1.1, 1.5, 2.1 when γ is, respectively, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2 and 0.1. Hence any equation purporting to give activity coefficients with an error not exceeding these limits should use the newer value of h. This will not affect the work of Harned and Robinson[5] since they only claimed an accuracy of 0.3% in γ where γ was always greater than 0.8; but there are many other calculations which will need revision, *e. g.*, the linear relation between log a and log B discovered by Harned and Robinson[4] for the alkali halides may not exist if values of a and B are recalculated with the newer value of h.

The authors on February 26, 1942, furnished the following supporting information: "Take the case of a 1:1 valent

(1) Childs, "Physical Constants," London, 1939.
(2) Wyman, *Phys. Rev.*, **35**, 623 (1930).
(3) "International Critical Tables."
(4) Harned and Robinson, *Chem. Rev.*, **28**, 419 (1941).
(5) Harned and Robinson, *Trans. Faraday Soc.*, **37**, 302 (1941).

electrolyte at concentration c (equal to the ionic strength). Then

$$\log f = \frac{-h\sqrt{c}}{1 + ga\sqrt{c}} + Bc$$

Assume a fixed value for c and thus for $\log f$. To find how a slight change in the value of h will affect a and B, we differentiate, treating g as a constant, since its value has been shown to remain practically unchanged when new fundamental constants are used. Thus

$$0 = -\mathrm{d}h \frac{\sqrt{c}}{1 + ga\sqrt{c}} + \frac{h\sqrt{c}}{1 + ga\sqrt{c}} \cdot \frac{g\sqrt{c}}{1 + ga\sqrt{c}} \mathrm{d}a + c\mathrm{d}B$$

Hence

$$\mathrm{d}h = \frac{hg\sqrt{c}}{1 + ga\sqrt{c}} \mathrm{d}a + \sqrt{c}(1 + ga\sqrt{c})\mathrm{d}B \qquad (1)$$

Robinson and Harned's proposed logarithmic relation between a and B is

$$\log B = 14 \log a - 9.75$$

which gives upon differentiation

$$\mathrm{d}B/B = 14\mathrm{d}a/a \qquad (2)$$

Now take a definite though hypothetical example chosen for simplicity, namely, an electrolyte for which $ga = 1$, or $a = 1/g = (1/0.3289) \times 10^{-8} = 3.04 \times 10^{-8}$. Put $h = 0.5065$ (the value at 25° used by Robinson and Harned), and $\mathrm{d}h = 0.0038$ (the difference between 0.5065 and the newer value 0.5103). Applying equation (1) to a convenient pair of arbitrarily chosen concentrations, $(0.1)^2$ and $(0.3)^2$, which are low enough for the theory to apply, we obtain

$$0.0038 = \left[\mathrm{d}a \times \frac{0.5065 \times 0.1 \times 0.3289 \times 10^8}{1.1}\right] + [\mathrm{d}B \times 0.1 \times 1.1]$$

and

$$0.0038 = \left[\mathrm{d}a \times \frac{0.5065 \times 0.3 \times 0.3289 \times 10^8}{1.3}\right] + [\mathrm{d}B \times 0.3 \times 1.3]$$

whence

$$\mathrm{d}a = 0.634 \times 10^{-8}$$
$$\mathrm{d}B = -0.0528$$

Results such as these would, of course, have to be obtained for various pairs of concentrations and then averaged by the method of least squares. The preservation of the logarithmic relation between a and B requires, as shown by equation (2), that any increase in a should be accompanied by an increase in B, whereas we have just shown that an increase in a due to a change in the value of h is accompanied by a very great *decrease* in B (for alkali and hydrogen halides B is of the order 0.01 to 0.2, so $\mathrm{d}B$ is relatively important)."—THE EDITOR.

CHEMISTRY DEPARTMENT
TECHNICAL COLLEGE
BRADFORD, YORKSHIRE, ENGLAND

RECEIVED DECEMBER 11, 1941

Crude Boron. Analysis and Composition

BY EARL H. WINSLOW AND HERMAN A. LIEBHAFSKY

When "pure" boron bought commercially began to vary widely from one lot to the next, we planned analyses to discover why. The chemical literature was not very helpful, and we have consequently explored several ways in which such analyses can be done. The results for three commercial borons will be given below; but the experimental methods will be outlined only, and detailed literature references will be omitted. This procedure is justified because our results are not exact, because the methods may need modification to fit the particular boron being examined, and because much of the literature on elementary boron is unsatisfactory. In judging this literature, however—and in judging our work—the complexity of the boron problem should not be forgotten.

Total Boron by Fusion.—The *sodium peroxide* fusion was done in a Parr bomb with 12 g. of sodium peroxide and 1 g. of sucrose. For the *carbonate–nitrate* fusion, the sample was mixed in a platinum crucible with 12 g. of the fusion mixture (by weight, 2 parts sodium carbonate, 1 part potassium nitrate) and covered with 6 g. of the mixture. The crucible was heated for two hours on a hotplate near 700°, then by a free flame until appreciable melting had occurred. Attack of the platinum was slight.

The fusion mixtures were dissolved and neutralized; the solutions were titrated for boron by the usual method except that a glass electrode—which is very convenient for the purpose—was used. The maximum value of $\Delta\ p\mathrm{H}/\Delta$ cc. was taken as the end-point. Any precipitate was dissolved and reprecipitated; the resulting solution was titrated for boron also. Table I shows that fine, black powders sold commercially as pure boron may contain less than 80% of that element. We have found chlorination to be an effective tool for studying the impurities present.

TABLE I

PER CENT. TOTAL BORON BY FUSION OF DRIED SAMPLES

Sample	Boron I	"Pure" Boron	"99%" Boron
Sodium Peroxide Fusion	70	77[a] 76	71 72
Carbonate–Nitrate Fusion	65	71	75

[a] Result from 100-mg. sample; all other samples near 25 mg.

Rapid Chlorination.—Very dry chlorine was passed into a vertical quartz test-tube on the bottom of which rested a quartz bucket containing the boron. A snugly fitting glass seal, through which the chlorine tube passed, prevented air or water from entering the test-tube against the issuing stream of chlorine and (later) of boron trichloride. The temperature of the sample was raised whenever glowing and fuming at a lower temperature had ceased. When no further reaction could be observed, the residues (sometimes white, sometimes gray) were weighed and examined; iron and aluminum were determined in the sublimate on the walls of the test-tube. The quartz buckets changed neither in weight nor appearance. Experiments with boric oxide showed that appreciable volatilization of this substance was not to be expected at 725°, the maximum temperature for these chlorinations.

TABLE II

RESULTS FROM THE RAPID CHLORINATION OF DRIED SAMPLES

Sample		Boron I	"Pure" Boron	"99%" Boron
No. of determinations		4	3	7
Average residue, %		14.3	60.1	23.1
Upper and lower limits, %		15.4–13.4	60.9–59.0	24.4–22.1
Sublimed chlorides	Ferric, % Fe	0.6	1.8	0.15
	Aluminum, % Al	8.6	Trace	.06
Composition of residue	Chloride, % Cl	Trace	19.8	14.9
	Magnesium,[a] % Mg	...	6.8	5.1
	Boric oxide,[b] % B_2O_3	None	8.5	3.0
Spectrographic report on residue	Appreciable	B, Na, Al, Si	B, Mg, Si	B, Mg, Si
	Traces	Ca, Mg	Mn, Cu, Ca	Mn, Cu, Ca

[a] Calculated from results of chloride determination. Qualitative tests showed magnesium present in approximately the expected amounts. [b] Boric oxide reported here is that extracted by hot water.

Slow chlorination.—Additional information was sought by chlorinating more slowly 100-mg. samples of boron in a horizontal reaction train. The less volatile reaction products, such as ferric and aluminum chlorides, condensed in the train before they reached two gas washing bottles, which contained water initially. Boron trichloride was absorbed and hydrolyzed in these washing bottles, the solutions in which were eventually titrated for hydrochloric and boric acids; the glass electrode was used here also.

Despite space limitations, it seems well to point out that chlorine can complicate these acid determinations in several ways. These complications were finally minimized by wrapping the washing bottles with black cloth (to prevent photochemical reactions during the chlorination); by shaking the solution from a washing bottle with excess mercury (to extract the residual chlorine), mercury and mercurous chloride being removed and washed before the solution and washings were titrated; and by carrying out the chlorine extraction immediately a run was finished. Runs made without boron showed blank corrections to be small.

The results of this work are given in Table III. The residues were usually light gray.

TABLE III

SLOW CHLORINATION DATA FOR DRIED 100-MG. SAMPLES

	Boron I			"Pure" Boron		"99%" Boron	
BCl_3 liberated, as % B	59.0	56.7	55.8	60.5	65.5	59.7	62.3
% Residue[a]	..	20.8	22.5	59.2	56.8	23.1	21.9
Moles HCl/moles H_3BO_3	3.16	3.05	3.17[b]	2.95	3.01[b]	2.83	3.00[b]

[a] Residues should have compositions corresponding to those of Table II. [b] Obtained by final, improved method.

Boron trichloride seems to be the only boron compound and the only acid-producing substance reaching the washing bottles in appreciable amount. (In all our chlorination work, the sublimed reaction products could have included small amounts of volatile boron compounds.) We believe that Table III truly gives the percentage of the sample converted to boron trichloride; this percentage is in every case appreciably smaller than the per cent. total boron in Table I; it probably includes all the boron present as the element and as metallic borides.

According to Table II, the percentage of the samples volatilized out of the test-tube during rapid chlorination is 100 − (14.3 + 0.6 + 8.6) = 76.5 for Boron I; (100 + 19.8) − (60.1 + 1.8) = 57.9 for "Pure" Boron; and 91.6 for "99%" Boron. For "Pure" Boron, this percentage agrees with the % B in Table III; but in the other cases it is appreciably greater.

Spectrographic examination of our samples showed carbon to be absent. The analytical results (Tables I and II) show that some element (presumably oxygen) not listed in Table II must be present in appreciable amount. The data of the preceding paragraph point to a possible volatilization of lower boron oxides or oxychlorides during the chlorination of Boron I and of "99%" Boron; that this could have escaped observation has been mentioned.

As a matter of historical interest, we examined the small quantity available of a pinkish beige powder[1] labeled "Weintraub B_6O 1908." Fusion gave 76.3% total boron. Rapid chlorination gave 3.4% residue, 0.06% iron. Spectrographic report on the residue: B, high; Si, present; Mg, trace. We do not consider that the existence of B_6O has been established.

We wish to emphasize finally that materials sold commercially as pure boron may contain less than 80% total boron, much of which is not present as the element. The most likely impurities are oxygen and whatever reducing agent (in our cases, magnesium, aluminum) was used in the preparation. We hope that the methods outlined here will prove useful in further work on the problems of crude boron.

(1) *Cf.* Weintraub, *Trans. Electrochem. Soc.*, **16**, 165 (1909).

RESEARCH LABORATORY
GENERAL ELECTRIC COMPANY
SCHENECTADY, N. Y.

RECEIVED JULY 1, 1942

NEW COMPOUNDS

sym-*p*,*p*′-Dichlorotetraphenylethylene

Treatment of 100 g. of *p*-chlorobenzophenone with 100 g. of phosphorus pentachloride at 150° according to Overton[1] yielded 110 g. (90%) of *p*-chlorobenzophenone chloride;

(1) Overton, *Ber.*, **26**, 28 (1893).

b. p. 189–194°[2] (12 mm.); d^{20}_4 1.302; $n^{20}D$ 1.6110. Attempts to convert this chloride to the desired ethylene by treatment with sodium iodide in dry acetone yielded a mixture of crystalline compounds which could not be separated by repeated recrystallizations. Analysis indicated the product to be a mixture of the two pinacolones, $C_6H_5C(=O)C(C_6H_4Cl)_2$ and $ClC_6H_4C(=O)C(C_6H_5)_2$, in spite of precautions to exclude moisture. From 63 g. of *p*-chlorobenzophenone chloride and 70 g. of sodium iodide boiled under reflux in 500 cc. of dry acetone for twelve hours, 45 g. of the mixture was obtained, m. p. 126–145°. After repeated recrystallization a sample melted at 130–142°.

Anal. Calcd. for $C_{26}H_{18}Cl_2O$: C, 74.82; H, 4.35. Found: C, 75.09; H, 4.39.

The desired ethylene was obtained by boiling 5 g. of *p*-chlorobenzophenone chloride in 50 cc. of dry ether with 10 g. of pure zinc dust for one hour. The mixture was filtered, washed with dilute hydrochloric acid, alkali and water and dried over calcium chloride. The ether was evaporated and the solid residue was extracted twice with 20-cc. portions of boiling alcohol. The residue was then crystallized several times from 50 cc. of alcohol to yield 0.5 g. (12%) of *sym-p,p'-dichlorotetraphenylethylene*, m. p. 202–203°.

Anal. Calcd. for $C_{26}H_{18}Cl_2$: C, 77.81; H, 4.52. Found: C, 77.85; H, 4.56.

When 0.25 g. of the ethylene in 10 cc. of benzene and 10 cc. of absolute alcohol was treated with 1 g. of sodium, a quantitative yield of fine white needles of tetraphenylethane was obtained, m. p. 209°.[3]

Anal. Calcd. for $C_{26}H_{22}$: C, 93.37; H, 6.63. Found: C, 92.89; H, 6.80.

Reduction of 1.1 g. of the ethylene in 15 cc. of methylcyclohexane with hydrogen at 110 atm. and 100° using 2 g. of Raney nickel as a catalyst yielded a mixture of products from which 0.3 g. of fine white needles of *p*-chlorotetraphenylethylene was isolated by recrystallization from aqueous acetic acid. The product melted sharply at 168°; Bergmann and Christiani[4] report 165–166° and Norris and Tibbetts,[5] 162°.

Anal. Calcd. for $C_{26}H_{19}Cl$: C, 85.11; H, 5.22. Found: C, 85.28; H, 5.43.

(2) Overton[1] reports the boiling point as 192° (12 mm.); Morgan (THIS JOURNAL, **38**, 2100 (1916)) reports 190° (10–12 mm.); and Ingold and Wilson (*J. Chem. Soc.*, 1493 (1933)) report 191–193° (13 mm.).

(3) Sagumenny, *Ann.*, **184**, 177 (1877).

(4) Bergmann and Christiani, *J. Chem. Soc.*, 412 (1936).

(5) Norris and Tibbetts, THIS JOURNAL, **42**, 2085 (1920).

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS
CHARLES C. PRICE
PAUL E. FANTA

RECEIVED JULY 30, 1942

dl- and *meso-*γ,γ'-Diphenyl-γ,γ'-suberodilactone

The reduction of β-benzoylpropionic acid with zinc dust in boiling 80–90% acetic acid has been found to yield γ-phenyl-γ-butyrolactone, m. p. 35–36°, in 30–40% yield accompanied by the corresponding bimolecular reduction products, the two stereoisomeric γ,γ'-diphenyl-γ,γ'-suberodilactones, in 12–17% yields. For example, 16 g. of β-benzoylpropionic acid in 75 cc. of 80% acetic acid was boiled for three and one-half hours while 25 g. of zinc dust was added in portions. The hot mixture was filtered and the cake of zinc dust was extracted with several portions of hot acetic acid to remove the high-melting dilactone. After several recrystallizations from glacial acetic acid, 1.5 g. (9%) of high melting dilactone was obtained, m. p. 267°.[1]

On cooling the filtered reaction mixture, zinc acetate crystallized. This was removed by filtration and water was added. Crystalline dilactone and oily lactone separated from solution. Filtration yielded 1 g. (6%) of low-melting dilactone. After repeated recrystallization from alcohol, various samples showed a characteristic behavior in that they melted sharply at 165° to a cloudy semi-liquid which changed to a clear liquid sharply at 175.5°.

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.57; H, 5.63; sapn. eq., 161. Found (267°): C, 74.55; H, 5.58; sapn. eq.,[2] 162. Found (165°): C, 74.34; H, 5.65; sapn. eq.,[2] 164.

(1) Fieser ("Organic Syntheses," Vol. XV, John Wiley and Sons, Inc., New York, N. Y., 1935, p. 65) has reported the isolation of γ,γ'-diphenyl-γ,γ'-suberodilactone, m. p. 254°, as a by-product of the Clemmensen reduction of β-benzoylpropionic acid.

(2) Redemann and Lucas, *Ind. Eng. Chem., Anal. Ed.*, **9**, 521 (1937).

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS
CHARLES C. PRICE
ARTHUR J. TOMISEK

RECEIVED JULY 30, 1942

A Dioxanate of Iodine Pentafluoride

Iodine pentafluoride is partially soluble in dry 1,4-dioxane, addition of an excess causing colorless crystals of a dioxanate of formula $IF_5 \cdot C_4H_8O_2$ to precipitate. The crystals start to hydrolyze immediately upon contact with the atmosphere, yielding iodic acid as the only solid residue after complete hydrolysis. They are likewise hydrolyzed over sulfuric acid in a desiccator.

When placed upon a melting point block, the dioxanate melts after an interval of time as low as 84°, but on immediate contact with the block only at 112° or above. In all cases melting is accompanied by decomposition and the evolution of hydrogen fluoride and purple iodine fumes.

Analysis was conducted by a modification of the method of Prideaux[1] (samples being weighed by shaking from a weighing bottle). Calculated for $IF_5 \cdot C_4H_8O_2$: IF_5, 71.6. Found: IF_5, 69.9.

THE CHEMICAL LABORATORY
REED COLLEGE
PORTLAND, OREGON
ARTHUR F. SCOTT
JOSEF F. BUNNETT[2]

RECEIVED AUGUST 25, 1942

(1) E. B. R. Prideaux, *J. Chem. Soc.*, **89**, 316 (1906).

(2) Present address: University of Rochester, Rochester, New York.

NEW BOOKS

Electrochemistry and Electrochemical Analysis. By HENRY J. S. SAND, D.Sc., Ph.D., F.I.C. Volume III, Electrical Methods Applied to Titration, Moisture Determination and *p*H Measurement. Chemical Publishing Company, Inc., 234 King Street, Brooklyn, New York, 1942. ix + 118 pp. Illustrated. 12.5 × 19 cm. Price, $2.25.

This volume is devoted primarily to potentiometric and conductometric methods. Probably a statement could have been added that activities of other radicals could have been determined by applying the same principles as in the electrometric and *p*H determinations. If the "Determination of Moisture" is to be available to chemists, it is buried in a book with this general title. Volume III seems to be written from the same point of view as Volume II and to be equally meritorious. It seems to include all workable methods up to date written in a readily understandable style.

D. J. BROWN

Polarography. Polarographic Analysis and Voltammetry. Amperometric Titrations. By I. M. KOLTHOFF, Professor and Head of the Division of Analytical Chemistry, University of Minnesota, Minneapolis, Minn., and J. J. LINGANE, Dept. of Chemistry, Harvard University. Interscience Publishers, Inc., 215 Fourth Avenue, New York, N. Y., 1941. xvi + 510 pp. 141 figs. 15.5 × 23.5 cm. Price, $6.00.

This book is an excellent, timely and comprehensive treatise that covers the essentials of the theory and practice of the polarographic method of investigation that was originated by J. Heyrovsky and his associates. This text is the most complete and systematic treatise in the field that has thus far appeared. Both authors have made numerous and significant original communications to the development of the science and art of polarography and for this reason the text has a masterful and purposeful style that could only come from long and substantial work with the subject.

The book is divided into eight parts. *Part one* is a brief and simple introduction. *Part two* contains twelve chapters which expound fully the fundamental theory of the diffusion current along the lines established by Ilkovic and amplified by MacGillavry and Rideal. The diffusion coefficient and the other factors that enter into the magnitude of the diffusion current are thoroughly and critically discussed. Many of the illustrative data are taken from the careful and exhaustive researches of the authors and their associates. Separate chapters deal with the migration current, the electrocapillary curve of mercury, the residual current and with maxima in current–voltage curves and with the inadequacy of our present knowledge of the causes of these maxima. The detailed theory of the reduction of simple metallic ions, complex ions and of organic substances is treated in the three following chapters. The authors properly lay much stress upon half-wave potentials, accurate measurement of capillary constants, and the analysis of waves by plotting log $i/i_d - i$ *versus* potential (i being the diffusion current at any point in the wave and i_d the limiting diffusion current). A very generous number of formulations of simple and complicated cases of current–voltage relations is given to aid the unfamiliar worker to set up equations for use in connection with a particular problem. The rather involved question of hydrogen discharge in various media is well reviewed. The concept of mixed potentials is introduced and briefly discussed in a short chapter.

Part three deals with technique and equipment. A list of typical equipment is given with photographs of some commercially available instruments. The section on technique, though brief, is adequate and contains some very useful ideas not available in other books on the subject.

Part four attempts to summarize in rather brief space the fundamental facts about the polarographic behavior of the various inorganic ions. This section gives a very good summary of the facts that were known at the time the manuscript was prepared. There still remains a great need for systematic practical measurements in many instances. A few actual polarograms giving unusual forms of waves might be of some service to the worker. A final chapter in this part gives a few practical applications to the analysis of alloys and other substances.

Part five deals with the polarographic estimation of organic substances. This is a rapidly expanding field of work and the authors have made a careful study and summary of the published data. The information is well classified and systematically treated.

Part six is a very brief survey of the biological applications of the method. Here again the book gives a rather brief introduction to a rapidly growing body of literature.

Part seven treats briefly the measurement of current–voltage curves with micro-platinum electrodes. A large proportion of this work has come from the researches of the senior author and his associates. This line of study is still fragmentary but the results thus far obtained suggest that such electrodes may extend the application of the method to certain cases where the use of the dropping mercury electrode is impractical.

Part eight deals with polarometric or amperometric titrations. A beginning of the application of the polarized mercury electrode system to titrations was made by various associates of Heyrovsky, notably V. Majer, Strubl and others. The senior author and his collaborators have systematized and extended this field of work and have introduced improved techniques. The essentials of the theory and practice are briefly and clearly given.

The appendix gives tables of the potentials of reference electrodes and of the half-wave values for inorganic ions, and a chart for the latter in various media. The indices appear to be adequate and accurate.

The book as a whole is attractively arranged and reflects well the skill and care that have been used by both authors and publishers in its composition and production. Anyone

who has worked even briefly in this interesting field can appreciate the meticulous care that the authors have used in the preparation of the manuscript and the proper emphasis that they have placed upon the fundamentals of theory and practice. The book can be recommended without reservation to anyone who is interested in the theory or the practical application of the methods.

N. HOWELL FURMAN

Principles and Practice of Chromatography. By L. ZECHMEISTER, California Institute of Technology, and L. CHOLNOKY, University of Pecs. Translated from the second and enlarged German edition by A. L. Bacharach and F. A. Robinson. Foreword by I. M. Heilbron. John Wiley and Sons, Inc., 440 Fourth Ave., New York, N. Y., 1941. xviii + 362 pp. 74 figs. 14 × 22 cm. Price, $5.00.

The second edition of this invaluable pioneering book appeared only a year and a half after the first. The revision has kept pace with the rapid progress in the field and results in a larger volume of wider scope, with many new illustrations and 200 new references to the literature.

Chromatographic analysis (use of Tswett adsorption columns) is offered as a means of testing for homogeneity, establishing the possible identity of two substances, of concentration from great dilution, separating mixtures, and of purification. Some isomers have been separated by this method.

Since the book is both text and laboratory manual (in a general rather than detailed way) there is much helpful discussion of adsorption powders, solvents, eluents, development and extrusion. Micro-chromatography is included. The original technique of Tswett was applied to plant pigments and other colored substances, but Zechmeister and Cholnoky review the modern applications to separation of colorless substances, as by the use of ultraviolet light, indicators, color reactions, etc. The important triumphs of chromatographic separations in the fields of chlorophylls, porphyrins, bile pigments, carotenoids, flavins, anthocyanins, pigments, dyestuffs, alkaloids, vitamins, sterols, hormones, enzymes and even with inorganic cations and anions are well presented.

This book is most stimulating to biochemists, organic chemists and botanists, but many other scientists will find it extremely useful.

HARRY N. HOLMES

An Outline of Organic Nitrogen Compounds. By ED. F. DEGERING, CARL BORDENCA and B. H. GWYNN and collaborators. John S. Swift Co., 5 E. Third St., Cincinnati, Ohio, 1942. Prev. editions 1938, 1940. 381 pp. 16 × 23.5 cm. Price, $2.00 and $3.00.

This is a planographed edition of extensive chemistry notes accumulated by the senior author during his teaching career in dealing with a special Course on Organic Nitrogen Compounds offered for graduate students in Purdue University during the past twelve years. Acknowledgment is made of abstraction of much of the material presented in the book from several standard texts on organic chemistry including "Recent Advances in Organic Chemistry" by Stewart; "Organic Chemistry" by Gilman; Sidgwick's "Organic Chemistry of Nitrogen" by Taylor and Baker; and "Syntheses of Nitrogen Ring Compounds" by Hollins.

The edition is devoted chiefly to a concise and intelligible presentation of the chemistry of the ammonia system of organic compounds. Fundamental reactions illustrating the transformations of type compounds in both the aliphatic and aromatic series are reviewed.

The general concepts of organic structure and reaction mechanisms are explained according to the modern electronic theory of chemical change, but the authors have restricted the use of electronic formulas in the major text for the following reasons: "It must be apparent that the continuous use of electronic formulas and equations throughout the book would make its price prohibitive."

A short chapter is devoted to a condensed review of the chemical nature of alkaloidal substances, and one to the review of nitrogen heterocyclic chemistry. The latter is practically limited, however, to the chemistry and review of nitrogen ring compounds containing only one nitrogen atom as—dimethyleneimines, trimethyleneimines, pyrrols, pyrrolines, pyrrolidines, pyrrolidones, indols, pyridine, quinoline, isoquinoline and related condensed nitrogen ring compounds.

Cyclic ureide chemistry is illustrated briefly by reference to barbituric acid and its relationship to uric acid, and the naturally occurring purines—theobromine, theophylline and caffeine.

Comprehensive references to the original literature enhance the practical value of the book.

TREAT B. JOHNSON

Micromethods of Quantitative Organic Analysis. By JOSEPH B. NIEDERL, PH.D., Associate Professor of Chemistry, and VICTOR NIEDERL, Teaching Fellow, New York University, Washington Square College. Second edition. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1942. xiii + 347 pp. 62 figs. 15.5 × 23.5 cm. Price, $3.50.

The following statements, taken from the Introduction, indicate the scope of changes introduced into the second edition of this successful text. "In the present edition the chapters on balances and weighing have been enlarged to include the use of ordinary analytical balances of proper sensitivity and precision. Additional paragraphs treating the calibration of weights, the determination of the zero reading and the determination of the sensitivity and precision of microanalytical as well as the ordinary analytical balance have also been included." "To the changes in the carbon and hydrogen determination as given in the first edition, . . ., have been added several types of combustion-tube fillings," and the manometric method of D. D. Van Slyke and J. Folch has been described. "The determinations of halogen and sulfur have been improved" and "the standard solutions have been unified in a single chapter." "To the ebullioscopic, cryoscopic and vaporimetric molecular-weight has been added an iso-thermic method." "Liberal time estimates have been given for all the more important determinations in order to facilitate the planning of a day's working or teaching schedule."

A valuable feature of this edition, as well as the earlier one, is the literature survey, which has been brought up to 1941. The citations number well above a thousand references.

The present edition maintains the same high standard set by its predecessor.

W. M. LAUER

Volumetric Analysis. By I. M. KOLTHOFF, Professor and Head of Division of Analytical Chemistry, University of Minnesota, and V. A. STENGER, Analytical Research Chemist, The Dow Chemical Company. Second Revised Edition, 1942. Vol. I. Theoretical Fundamentals. Interscience Publishers, Inc. 215 Fourth Ave., New York, N. Y. xv + 309 pp. 31 illus. 23.5 × 15.5 cm. Price, $4.50.

The reviewer believes that the first edition of this book has become so well known that a detailed enumeration of the contents of this revision is not necessary. Such an omission seems further justified because, although this edition appears to have been quite completely rewritten, there has been no radical change in either contents or arrangement.

The number of chapters remains the same. An introductory chapter has been added and the chapter on the "Stability of Solutions" has been eliminated and is to be included in the second volume; with these exceptions the chapter headings and order are essentially as before. A much more liberal use of references to the original literature adds substantially to the value of the book. The chapters on "Reaction Velocity" and on "Adsorption and Coprecipitation Phenomena" have been extensively revised and there has been added to Chapter X a discussion of amperometric titrations.

The present first chapter, which contains considerable material previously found in Chapter X, affords a more logical introduction to the book. It contains various definitions, a classification of volumetric methods, and a general introductory discussion of ionization and oxidation–reduction principles. The Brönsted definition of acids and bases is presented briefly but thereafter the treatment of neutralization methods and hydrolysis effects is along conventional lines.

The reviewer obtained the impression that the present edition has been held to a slightly more elementary level than the former one: this may account for the change on the title page from "Theoretical Principles" to "Theoretical Fundamentals." Also, there seems in some cases a lack of consistency in the extent to which certain topics are treated. Hydrogen ion indicators are presented as organic compounds behaving as weak acids or bases with no discussion of their structures or of the theory of their color change, while thirty pages are given to potential indicators with fifty or more detailed structural formulas being shown.

In some few cases it seems unfortunate that topics should be discussed without reference to more recent work. Thus in the discussion of the permanganate–oxalate reaction the only reference is to the work of Skrabal (1904). Also in the very interesting chapter on "Volumetric Methods of Organic Chemistry" it would seem that the behavior of the double bond could have been more explicitly discussed in the terms of modern organic theory rather than by resorting to the "partial valence" and "complete affinity quantity" of Thiele (1899, 1901).

The above are minor criticisms of a very valuable book which should be available to everyone seriously interested in the theory and development of volumetric methods of analytical chemistry.

E. H. SWIFT

BOOKS RECEIVED

September 10, 1942–October 10, 1942

F. RUSSELL BICHOWSKY. "Industrial Research." Chemical Publishing Company, Inc., 234 King Street, Brooklyn, New York. 126 pp. $2.50.

H. C. DAKE AND JACK DE MENT. "Ultra-Violet Light and its Applications." Chemical Publishing Company, Inc., 234 King Street, Brooklyn, New York. 209 pp. $3.25.

ED. F. DEGERING and One Hundred Six Collaborators. "Fundamental Organic Chemistry." Reproduced by Photo-Offset and Planographed by John S. Swift Co., Inc., Cincinnati, Ohio. 485 pp. Paper binding, $2.00; cloth binding, $3.00.

CARL J. ENGELDER. "Calculation of Qualitative Analysis." Second edition. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y. 174 pp. $2.00.

NORMAN KHARASCH AND HELEN S. MACKENZIE. "Essentials of College Chemistry." D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N. Y. 513 pp. $3.50.

C. B. NEBLETTE. "Photography, its Principles and Practice." Fourth edition. D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N. Y. 865 pp. $7.50.

M. CANNON SNEED AND J. LEWIS MAYNARD. "General Inorganic Chemistry." D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N. Y. 1166 pp. $4.50.

HUGH S. TAYLOR AND H. AUSTIN TAYLOR. "Elementary Physical Chemistry." Third edition. D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N. Y. 551 pp. $3.75.

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

VOLUME 64 DECEMBER 23, 1942 NUMBER 12

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Synthesis of 5-D-Glucosido-D-arabinose

BY NORMAN S. MAC DONALD AND WM. LLOYD EVANS[1]

The disaccharide, 5-D-glucosido-D-arabinose, is of much scientific interest. In the first place, this compound is a possible intermediate in the alkaline degradation of the 6-hexosido-hexose type[2] of carbohydrate. Furthermore, the acetylated 5-D-glucosido-D-arabinose would possess both the pyranoid ring in the hexose section of the molecule and the furanoid ring in the pentose section. So far as the authors are aware, a carbohydrate of this type has not been synthesized hitherto.

The purpose of the present work was to prepare this disaccharide and characterize it. After trying to obtain the compound by several of the well known degradative and synthetic procedures, its preparation was finally achieved by the Wohl technique for the degradation of sugar oximes, as modified by Zemplén.[3]

The 5-D-glucosido-D-arabinose heptaacetate was characterized by an elementary analysis, determination of acetyl number, and by an estimation of the pentose content.

Deacetylation of the acetate gave a white amorphous hygroscopic powder whose aqueous solution exhibited mutarotatory power. The deacetylated sugar failed to give an aldehyde reaction with Schiff reagent, a fact which when coupled with that of mutarotation indicates the presence of a ring in the reducing section of this new disaccharide. Since the point of biosidic linkage of the reducing section is carbon atom five, it therefore follows that the lactal ring of the arabinose section is of the furanoid type. Treatment of this water solution with phenylhydrazine led to a phenylosazone.

The acetylation of the free sugar was carried out with hot acetic anhydride–sodium acetate and, therefore, it seems likely that the crystalline material is the β-isomer.

Upon working up the mother liquors of the degradation, a small amount of a different crystalline substance was isolated. An insufficient quantity of this compound prevented complete characterization. It is suggested, however, that this lower melting, higher rotating compound is the α-isomer.

Experimental Part

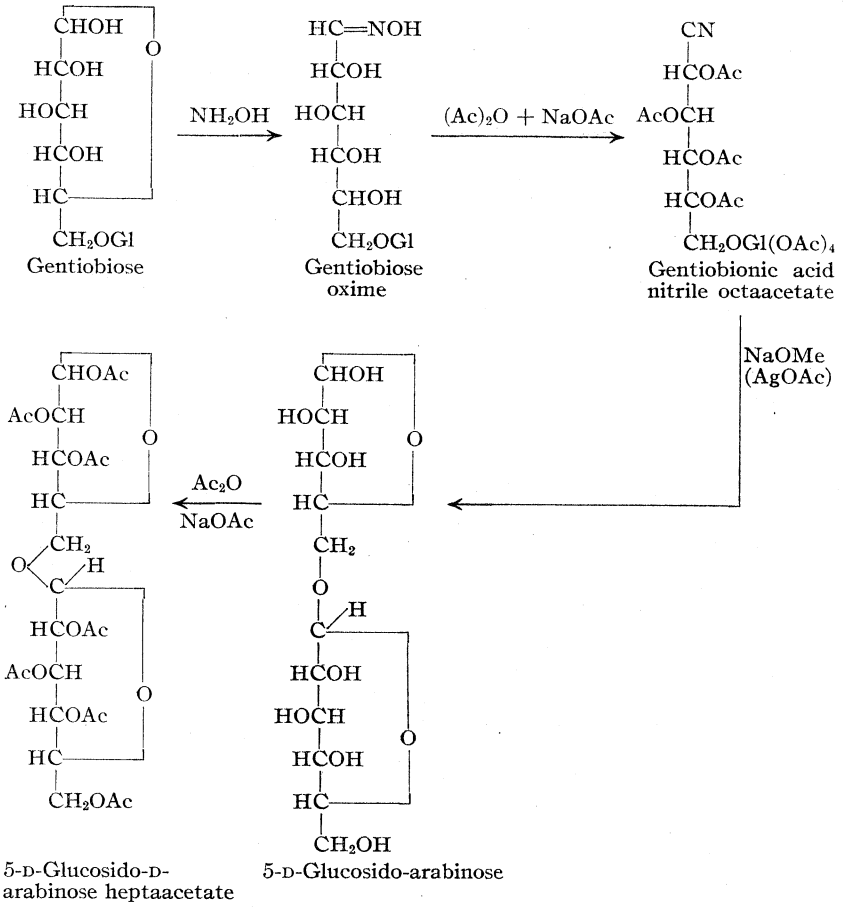
Preparation of Gentiobiose Oxime.—To a solution of 17.5 g. of gentiobiose, obtained by the deacetylation of β-gentiobiose octaacetate[4] with NaOMe, was added an alcoholic solution of hydroxylamine. The latter was made by adding 2.6 g. sodium in 65 cc. of absolute ethanol to 8.9 g. of hydroxylamine hydrochloride (98% pure) in 6 cc. of hot water, cooling, and filtering the precipitated sodium chloride. The hydroxylamine hydrochloride used is 150% in excess while the sodium is 90% of the amount required to neutralize the hydrochloric acid completely. After the dropwise addition of the hydroxylamine to the sugar solution, 10 g. of powdered calcium carbonate was added to neutralize any possible acidity which might hydrolyze the biosidic link. The temperature was then raised to 55° and kept at that point for two hours. Without removing the calcium carbonate, the solution was

(1) Abstracted from a Thesis presented by N. S. MacDonald to the Graduate School of The Ohio State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) (a) W. L. Evans and R. C. Hockett, THIS JOURNAL, **53**, 4384 (1931); (b) W. L. Evans, *Chem. Revs.*, **6**, 281 (1929).

(3) G. Zemplén, *Ber.*, **59**, 1254 (1926).

(4) D. D. Reynolds and Wm. Lloyd Evans, THIS JOURNAL, **60**, 2559 (1938).



concentrated to dryness *in vacuo*. Twenty-five cc. of absolute ethanol was then added, and the solution again evaporated to dryness. The residue was dissolved in 20 cc. of water, decolorized with carboraffin, and evaporated several times with absolute alcohol in order to dry it completely. The powder so obtained could not be crystallized and hence it was used directly in the next step.

Preparation of Gentiobionic Acid Nitrile Octaacetate.—Twenty grams of freshly fused sodium acetate was added to 145 cc. of acetic anhydride in a 250-cc. Erlenmeyer flask and the mixture heated to 110° in an oil-bath. To this was added 17.9 g. of dry, powdered gentiobiose oxime in such small portions that the temperature neither rose above 120° nor fell below 105°. This operation required about one-half hour. After the temperature was kept at 110–115° for an hour longer the deep brown solution was allowed to cool to 80°. It was then poured into 750 cc. of cold water and stirred for one hour. The crumbly material which appeared was stirred with fresh water, filtered, dissolved in ethanol and decolorized with carboraffin. Dilution of the resulting solution with water led to the separation of sirups. These sirups were each subjected to fractional precipitation from ethanol–water and, after some time, nuclei were obtained. Upon inoculating the sirups with these nuclei, crystals became readily available. The long needles are very soluble in chloroform and ethyl acetate, moderately soluble in methanol and ethanol, very slightly soluble in ligroin and water; m. p. 108–109° (cor.); yield 14.5 g. (35%); $[\alpha]^{25}D$ +8.60°, ($CHCl_3$, c = 2.5). It may be noted here that the sign of the optical rotation is in accord with that predicted by the Hudson–Levene hydrazide rule, as extended to sugar acid nitriles.[5] This empirical generalization states that if the hydroxyl group on carbon two lies on the right side in the straight chain structural formula, the acetylated nitrile of the sugar acid will be dextrorotatory.

Anal. Calcd. for $C_{27}H_{37}O_{18}CN$: C, 49.78; H, 5.48; N, 2.07. Found: C, 49.73, 49.77; H, 5.51, 5.57; N, 2.38, 2.57.

The compound gives a positive qualitative test for —CN (addition of sodium hydroxide and ferrous sulfate followed by acidification gives the characteristic prussian blue precipitate).

Quantitative Determination of —CN Group.—The weighed sample (0.1156 g.) was dissolved in 25 cc. of absolute methanol and a solution of 0.3 g. of silver nitrate in 4 cc. of water added. After adding 10 cc. of methanol saturated with ammonia, the flask was stoppered and allowed to stand at room temperature for ten hours. The clear solution was then acidified with dilute nitric acid and allowed to stand for three hours in a dark place. The precipitated silver cyanide was filtered into a weighed Gooch crucible, washed, dried at 100° and weighed. Calcd.: —CN, 3.85. Found: —CN, 3.60.

Degradation of Gentiobionic Acid Nitrile Octaacetate to 5-D-Glucosido-D-arabinose Heptaacetates.—Four grams of the nitrile was dissolved in 10 cc. of dry chloroform and a solution of 0.2 g. of sodium in 15 cc. of absolute methanol added, after cooling both in ice-water. The mixture gelatinized in one minute, but was allowed to stand in the bath for an additional five minutes. The gel was shaken with 15 cc. of water and immediately acidified with 5 cc. of acetic acid. After diluting with 15 cc. of water, the solution was extracted with 25 cc. of chloroform. A suspension of 5 g. of silver acetate in 10 cc. of glacial acetic acid was added to the water layer, with shaking. After ten minutes, the silver cyanide and excess silver acetate were removed by filtration, the filtrate giving no precipitate with a drop of fresh silver acetate solution. The filtrate was then warmed and dilute hydrochloric acid added dropwise to precipitate the Ag^+. After filtration, the colorless solution was treated with a small amount of sodium bicarbonate to reduce the acidity, then concentrated to a sirup *in vacuo*. This sirup was dried by repeatedly evaporating to dryness with absolute ethanol. To the dried sirup was added 20 cc. of acetic anhydride and 3 g. of freshly fused

(5) V. Deulofeu, *Nature*, **131**, 548 (1933).

sodium acetate, the mixture placed in a boiling water-bath and kept at that temperature for one hour. The dark solution was then poured into 125 cc. of cold water and stirred for one hour. The granular material was filtered off and dissolved in chloroform, dried over anhydrous sodium sulfate and treated with carboraffin. Upon concentrating *in vacuo*, a yellow sirup was obtained, which was subjected to fractional precipitation from ethanol–water. Two products were finally obtained in the crystalline state: I, (less alcohol-soluble fraction), rhombohedra, m. p. 161–162° (cor.); $[\alpha]^{25}D$ −14.4° ($CHCl_3$, c = 4.2); yield 1.2 g. (32%).

Anal. Calcd. for $C_{25}H_{34}O_{17}$: C, 49.50; H, 5.61; acetyl, 11.6.[6] Found: C, 49.51, 49.25; H, 5.56, 5.67; acetyl, 11.7, 11.7.

II. (More alcohol-soluble fraction), needles; m. p. 132–133° (cor.); $[\alpha]^{25}D$ +23.1° ($CHCl_3$, c = 3.8.)

Anal. Calcd. for $C_{25}H_{34}O_{17}$: C, 49.50; H, 5.61. Found: C, 49.51, 49.40; H, 5.88, 5.82.

Such a small amount of this material was obtained that a satisfactory acetyl number could not be determined.

Preparation of 5-D-Glucosido-D-arabinose.—The free sugar was prepared in an amorphous condition by deacetylation of the heptaacetate I. To a cooled solution of 0.78 g. of the acetate in 30 cc. of absolute methanol was added 0.05 g. of sodium in 5 cc. of absolute methanol. After standing in the ice-box for two hours, and concentrating to a volume of 15 cc., a precipitate appeared. This material was filtered rapidly and washed with cold absolute methanol. The amorphous powder reduces Fehling's solution and is very hygroscopic; yield 0.25 g.; equilibrium rotation $[\alpha]^{30}D$ −3.14° (H_2O, c = 4.1).

Phenylosazone of 5-D-Glucosido-D-arabinose.—To the water solution of the free sugar, used for the determination of the optical rotation, was added a mixture of 0.3 g. of phenylhydrazine and 8 cc. of glacial acetic acid. After warming on the water-bath for forty-five minutes, the dark solution was diluted with 20 cc. of water and allowed to stand overnight. The crude material so precipitated was recrystallized by dissolving in the smallest possible amount of pyridine, diluting with a ten-fold volume of acetone, and adding ligroin to turbidity. A crop of yellow needles was obtained; m. p. 209–210° (cor.); mixed m. p. with glucose phenylosazone 198–200°.

Anal. Calcd. for $C_{25}H_{30}O_8N_4$: N, 11.43. Found: N, 11.17, 11.02.

Estimation of Pentose in 5-D-Glucosido-D-arabinose Heptaacetate.—The method used was a modification of the standard procedure for pentose determination[7] as developed by Tollens. Sixty-eight milligrams of the material (I) was transferred to a 20-cc. distilling flask equipped with a 25-cc. dropping funnel in the neck and a short water jacket for the arm. The acetate was dissolved in 8 cc. of absolute methanol and 1.0 cc. of a sodium methylate solution (1%) added. It was found that unless the material was deacetylated and thus rendered water soluble, before the acid distillation, results were not reproducible. After three minutes, 10 cc. of 12% hydrochloric acid was added, boiling stones dropped in and the distillation begun gently. After 10 cc. had come over, the distillate gave a red color to paper moistened with aniline acetate, a positive test for the presence of furfural. The distillate was allowed to drop through a filter into a graduated cylinder and 100 cc. was collected, fresh 12% hydrochloric acid being added to maintain a constant level in the distilling flask. To the colorless distillate was added a solution of 0.05 g. of phloroglucinol in 10 cc. of warm 12% hydrochloric acid. A yellow color developed immediately, which darkened rapidly. Within ten minutes, a blue-black precipitate appeared. The mixture was diluted to 150 cc. with water and allowed to stand twelve hours at room temperature, after which it was filtered into a weighed Gooch crucible, dried and weighed. By applying empirical correction factors,[7] the weight of pentose is calculated from the weight of furfural-phloroglucide obtained: weight of arabinose calcd., 0.017 g.; weight of pentose found, 0.016 g.

Control.—A mixture of 0.036 g. of D-arabinose tetraacetate and 0.052 g. of D-glucose pentaacetate was treated in exactly the same manner: weight of arabinose calcd., 0.017 g.; weight of pentose found, 0.016 g. In order to make sure that hydroxymethylfurfural, obtainable from the glucose section, did not interfere, 0.05 g. of gentiobiose octaacetate was subjected to exactly the same treatment. No coloration of aniline acetate and no precipitate with phloroglucinol were obtained under these conditions.

(6) A. Kunz and C. S. Hudson, THIS JOURNAL, **48**, 1982 (1926).

(7) "Allen's Commercial Organic Analysis," 5th ed., Vol. I, p. 498.

Summary

1. Crystalline gentiobionic acid nitrile octaacetate was prepared by the removal of the elements of water from amorphous gentiobiose oxime. The sign of its optical rotation agrees with that predicted from the Hudson–Levene hydrazide rule, as extended to sugar acid nitriles by Deulofeu.

2. 5-D-Glucosido-D-arabinose heptaacetate was prepared by the degradation of gentiobionic acid nitrile octaacetate with sodium methoxide and the acetylation of the resulting compound.

3. Since the free sugar is mutarotatory in aqueous solution and shows no reaction with Schiff reagent, it is concluded that the arabinose section of this compound contains the furan ring.

4. The presence of arabinose was established by the detection of furfural in the products of the acid hydrolysis of the disaccharide.

5. The phenylosazone of 5-D-glucosido-D-arabinose was prepared from the amorphous free sugar.

6. It is suggested that the two acetylated compounds obtained from the degradation constitute an α,β-isomeric pair.

COLUMBUS, OHIO RECEIVED SEPTEMBER 5 1942

[CONTRIBUTION FROM THE DEPARTMENT OF ANIMAL AND PLANT PATHOLOGY OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

Basic Amino Acids in Strains of Tobacco Mosaic Virus

BY C. A. KNIGHT

It was shown in a recent communication from this Laboratory that the Holmes ribgrass strain of tobacco mosaic virus differs strikingly from ordinary tobacco mosaic virus in aromatic amino acid content.[1] It was also shown that cucumber viruses 3 and 4, which are related to tobacco mosaic virus, possess the same amount of tyrosine as the latter but contain distinctly different amounts of tryptophane and phenylalanine. These results demonstrated clearly for the first time the nature of some of the chemical differences between strains of tobacco mosaic virus. However, no distinctive difference was detected between the aromatic amino acid composition of ordinary tobacco mosaic virus and that of the yellow aucuba, green aucuba, J14D1, or masked strains of the virus. These strains are serologically, and in certain other respects, much more closely related to the common tobacco mosaic virus than are the other strains mentioned above. It seemed desirable, therefore, to extend the original investigation to include other amino acids, in order to determine whether there are demonstrable chemical differences between tobacco mosaic virus and some of its more closely related strains. The present report deals with analyses of the 8 previously described strains of tobacco mosaic virus[1] for arginine and histidine.

Experimental

Preparations of the viruses were made by purely physical methods involving filtration and differential centrifugation of the juices from infected Turkish tobacco plants, or from cucumber plants in the cases of cucumber viruses 3 and 4. Highly purified solutions of each virus in distilled water were frozen, dried *in vacuo*, and then further dried to constant weight at 110° in a drying oven. The white fluffy material thus obtained was used for amino acid analyses.

Arginine.—Arginine was determined by a colorimetric procedure based on the Sakaguchi reaction and by a gravimetric method involving precipitation of arginine as the flavianate.[2,3]

For the colorimetric test, 15 to 20 mg. of virus was hydrolyzed in 1 ml. of concentrated hydrochloric acid in a sealed tube in an oven at 110° for twenty hours. The hydrolysate thus obtained was transferred quantitatively to a 100 ml. volumetric flask, the solution was made to volume with distilled water, and 1 ml. aliquots were taken for analysis. The Sakaguchi reaction was carried out essentially as described by Thomas and co-workers,[2] with the exception that readings were made with a Klett-Summerson photoelectric colorimeter using Green Filter 54. The method used for the gravimetric determination of arginine involved a preliminary isolation of the basic amino acids by the electrolytic procedure of Albanese.[3]

The arginine content of tobacco mosaic virus was found by colorimetric and gravimetric methods to be 9.2 ± 0.1%. As may be observed in Table I, the arginine values obtained by the two different methods agreed remarkably well for all of the strains. Four of the 8 strains were found to contain about 9.2% arginine. On the other hand, cucumber viruses 3 and 4 were found to contain significantly less arginine than ordinary tobacco mosaic virus, while the green and yellow aucuba viruses were found to contain significantly more arginine than the type strain.

TABLE I

ARGININE AND HISTIDINE IN STRAINS OF TOBACCO MOSAIC VIRUS

Virus	Arginine: No. of preparations	Arginine: Sakaguchi method, %[a]	Arginine: No. of preparations	Arginine: Flavianate method, %[a]	Histidine, %
Tobacco mosaic	7	9.2	8	9.2	None
Yellow aucuba	7	10.0	2	10.0	None
Green aucuba	7	10.0	1	10.0	None
Holmes' ribgrass	4	9.1	1	9.2	0.55
Holmes' masked	2	9.2	1	9.0	None
J14D1	2	9.2	1	9.2	None
Cucumber virus 4	5	8.7	2	8.7	None
Cucumber virus 3	1	8.7	1	8.8	None

[a] The results of individual analyses for arginine showed a maximum deviation from the averages listed of ±0.2% for the Sakaguchi method and ±0.1% for the flavianate method.

Histidine.—Ross was unable to detect histidine in ordinary tobacco mosaic virus upon examination of whole hydrolysates of the virus or portions of hydrolysates obtained by chemical fractionation, although an amount of histidine equivalent to less than 0.1% of the virus could be recovered when added to various fractions.[4] Hence, it was concluded that histidine is not present in the tobacco mosaic virus molecule. The present experiments confirm this conclusion.

The Albanese technique for the estimation of histidine[3] was found to be quite unreliable for the determination of very small amounts of histidine in mixtures which contained large amounts of arginine. On the other hand, the conditions required in the Jorpes modification of the Pauly reaction[5] seemed admirably suited to such analyses and

(1) C. A. Knight and W. M. Stanley, *J. Biol. Chem.*, **141**, 39 (1941).

(2) L. E. Thomas, J. K. Ingalls, and J. M. Luck, *ibid.*, **129**, 263 (1939).

(3) A. A. Albanese, *ibid.*, **134**, 467 (1940).

(4) A. F. Ross, *ibid.*, **138**, 741 (1941).

(5) E. Jorpes, *Biochem. J.*, **26**, 1507 (1932).

particularly adaptable to the determination of small amounts of histidine in the histidine–lysine fraction obtained from tobacco mosaic virus by the electrolytic method. In the present investigation, the Jorpes procedure was slightly modified by substituting for the Zeiss photometer a Klett–Summerson photoelectric colorimeter with Green Filter 54. Results of tests with a standard solution of histidine showed that a true proportionality was obtained between the colorimeter reading and the amount of histidine present in the range 0.005 to 0.05 mg. per ml.

Application of the Pauly test to the histidine–lysine fractions of the strains indicated the absence of histidine from all except the ribgrass strain (Table I). Analyses on 2 different preparations of the ribgrass virus gave histidine values of 0.39 and 0.43%.

It has been suggested that the presence of carbohydrate may result in the destruction of histidine during the acid hydrolysis of proteins.[6] In order to evaluate fairly the apparent absence of histidine from all except one of the strains, the destructive effect of the virus carbohydrate was tested in two ways. In the first, small amounts of histidine were added to tobacco mosaic virus during hydrolysis and the recovery of histidine was noted, and, in the second, nucleic acid was removed from tobacco mosaic and the ribgrass viruses before hydrolysis and the effect on the histidine analyses was observed. In two trials in which small amounts of histidine were added to tobacco mosaic virus during hydrolysis, recoveries of 36 and 64% were made. In the other approach, tobacco mosaic and the ribgrass viruses were freed from nucleic acid by treatment with alkali. Negative phosphorus and carbohydrate tests on 25- to 30-mg. portions of the proteins indicated that essentially all of the nucleic acid had been removed. Five hundred and ten mg. of nucleic acid-free tobacco mosaic virus protein and 470 mg. of the corresponding preparation of ribgrass virus protein were then hydrolyzed as usual and the basic amino acids were isolated by the electrolytic procedure. No histidine could be demonstrated in the histidine–lysine fraction of the tobacco mosaic virus protein by the Pauly reaction, but 0.55% of histidine (calculated on the basis of the intact virus) was detected by the same method in a similar fraction of the ribgrass virus protein.

The histidine–lysine fraction of the nucleic acid-free ribgrass virus protein was also analyzed for histidine by the nitranilic acid gravimetric procedure as described by Block.[6] After allowance was made for the 6% nucleic acid in the ribgrass virus, a histidine value of 0.57% was obtained, in good agreement with the 0.55% found by the colorimetric procedure, and both figures are almost one-third greater than the highest value obtained on whole virus.

In general, the results of the above experiments appear to confirm earlier observations regarding the destruction of histidine in the presence of carbohydrate during acid hydrolysis of proteins. In particular, the data emphasize the absence of histidine from tobacco mosaic virus and its presence in the ribgrass virus. This is the first demonstration of the presence in a strain of tobacco mosaic virus of a constituent which is apparently entirely lacking in the common strain.

(6) R. J. Block, *J. Biol. Chem.*, **133**, 67 (1940).

Lysine.—If the amino nitrogen of the intact virus[7] is attributed to epsilon amino groups of lysine, tobacco mosaic virus contains about 1.35% of lysine. However, the experiments of Ross[8,9] have led him to conclude that tobacco mosaic virus contains very little, if any, lysine. In the present investigation, analyses of the electrolytically obtained lysine fractions of eight strains of tobacco mosaic virus indicated the presence of amino nitrogen which was unattributable to known constituents of the virus and which might therefore represent lysine. The amounts of this nitrogen were too small to permit the confirmatory isolation of lysine derivatives, but attempts to isolate such derivatives starting with considerably larger samples of virus are now in progress and will be described in detail in a later communication.

Discussion

Analysis of eight strains of tobacco mosaic virus indicated that each strain possesses a characteristic and constant amount of arginine. Thus, in seven preparations of tobacco mosaic virus obtained from different groups of diseased tobacco plants over a period of two to four years, the arginine content was found to be 9.2 ± 0.1%. On the other hand, seven preparations of green aucuba virus and seven of yellow aucuba virus obtained over a similar period of time were found to contain 10.0 ± 0.1% of arginine. The difference between the compositions of the aucuba viruses and ordinary tobacco mosaic virus is particularly striking in view of the very close relationship of these strains. For example, it is almost impossible to distinguish between the symptoms produced by ordinary tobacco mosaic virus and the green aucuba strain in diseased Turkish tobacco plants. It is generally necessary to inoculate to *Nicotiana sylvestris* Spegaz. and Comes to differentiate between the two strains. The green aucuba strain produces local lesions on *N. sylvestris*, whereas the ordinary strain does not. It is now possible, on the basis of arginine content, to distinguish definitely between these strains with considerably less than the amount of virus obtained from a single diseased plant. The significantly lower amounts of arginine found in cucumber viruses 3 and 4 than in ordinary tobacco mosaic virus are somewhat less surprising because the relation of the cucumber strains to the latter is less close.

In general, the data from the basic amino acid analyses of the virus strains support and extend the observations resulting from the aromatic

(7) G. L. Miller and W. M. Stanley, *ibid.*, **141**, 905 (1941).

(8) A. F. Ross and W. M. Stanley, *Proc. Am. Soc. Biol. Chem.*, *J. Biol. Chem.*, **128**, p. lxxxiv (1939).

(9) A. F. Ross, *J. Biol. Chem.*, **143**, 685 (1942).

amino acid analyses.[1,10] It is quite clear that the protein components of strains of tobacco mosaic virus differ in their amino acid compositions. Whether or not these differences are responsible for the different biological properties of the various strains remains to be shown. In any case, they must be considered when sufficient data have been gathered to permit an intelligent correlation of biological properties with chemical structure. The nucleic acid components of the viruses cannot, of course, be entirely neglected. There is no unequivocal evidence at present that the nucleic acids of various strains of tobacco mosaic virus differ either quantitatively or qualitatively. On the other hand, the results of phosphorus analyses indicate that 8 of the strains contain essentially the same amount of nucleic acid, and colorimetric tests show that all of these 8 strains contain ribose nucleic acid.[1] Nevertheless, it will not be certain that the nucleic acids of strains of tobacco mosaic virus are identical until thorough analytical studies have been completed.

The discovery of the presence of histidine in the ribgrass virus is especially interesting, for it represents the first case in which one strain of tobacco mosaic virus has been found to contain a constituent apparently lacking in another. The ribgrass virus has not yet been obtained directly by mutation of ordinary tobacco mosaic virus, as have certain yellow strains[11,12] and the Holmes masked strain.[13] Thus, the ribgrass strain may represent a stable product resulting from many variations rather than from one. However, if the ribgrass strain developed originally from ordinary tobacco mosaic virus, it is necessary to assume that at one stage some histidine was added to a virus molecule which previously contained none. Unless it can be established experimentally that direct changes of this type can occur in completely formed virus molecules, it seems reasonable to assume that the introduction of a new amino acid occurred as a result of a departure from the usual pattern of the synthetic process of virus multiplication. On this basis the phenomena of virus multiplication and virus variation become directly related, the latter representing simply a modification of the former.

(10) W. M. Stanley and C. A. Knight, *Cold Spring Harbor Symposia on Quant. Biol.*, **9**, 255 (1941).

(11) J. H. Jensen, *Phytopathology*, **23**, 964 (1933).

(12) J. H. Jensen, *ibid.*, **26**, 266 (1936).

(13) F. O. Holmes, *ibid.*, **24**, 845 (1934).

The author is indebted to Dr. W. M. Stanley for his interest and encouragement during the course of this investigation.

Summary

Eight strains of tobacco mosaic virus were analyzed for arginine and histidine. Analyses by two methods of seven different preparations of tobacco mosaic virus indicated that this virus contains 9.2 ± 0.1% of arginine. A similar amount of arginine was found in the Holmes masked, Holmes ribgrass, and J14D1 strains. On the other hand, the green and yellow aucuba strains were found to contain 10.0% of arginine and the cucumber viruses 3 and 4, 8.7% of arginine. No histidine could be detected in seven of eight strains, but about 0.55% of histidine was found in the ribgrass strain. Indirect analyses indicated that the eight strains contain a small amount of lysine, but this finding has not yet been verified by isolation methods.

PRINCETON, NEW JERSEY RECEIVED JULY 29, 1942

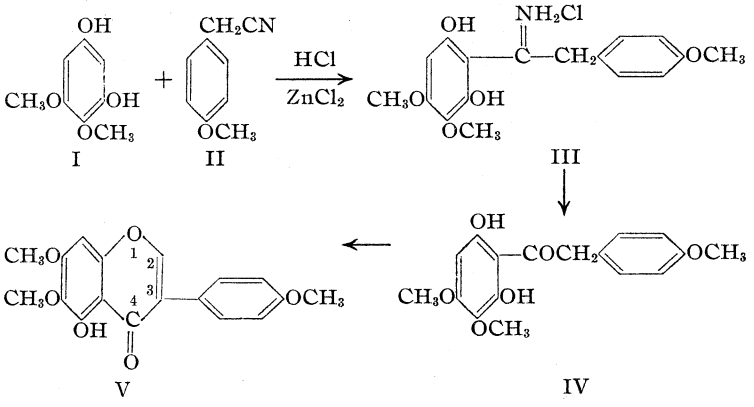
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

Synthesis of Tectorigenin Dimethyl Ether

BY R. L. SHRINER AND R. W. STEPHENSON

An isoflavone structure has been suggested for tectorigenin, the aglucone of the naturally occurring glucoside, tectoridin. This structure was deduced from its degradation products,[1] absorption spectra[2] and general chemical properties.[2,3] Two other possible substituted coumaran structures were shown to be quite different from the natural aglucone.[4] The present paper reports the synthesis of the dimethyl ether of tectorigenin (V).

The starting materials are 4,5-dimethoxyresorcinol (I) and homoanisonitrile (II). The first was prepared by the sequence: guaiacol → 4,6-dinitroguaiacol → 3,5-dinitroveratrole → 3,5-diaminoveratrole → 4,5-dimethoxyresorcinol, according to the directions of Baker and Robinson.[5] Homoanisonitrile has been synthesized repeatedly by a number of methods; for instance, recently by Julian and Sturgis, and by Lapine.[6] The direct chloromethylation of anisole to *p*-methoxybenzyl chloride[7] followed by reaction with sodium cyanide[8] in the presence of an emulsifying agent to promote rapid reaction of the chloride with the cyanide was found to be a time saving procedure, although the yields were low (29%).



Condensation of 4,5-dimethoxyresorcinol (I) with homoanisonitrile (II) was effected by means of hydrogen chloride and zinc chloride. Hydrolysis of the intermediate iminohydrochloride (III) yielded the substituted desoxybenzoin (IV). A Claisen condensation of the latter compound with ethyl formate and sodium followed by acidification yielded 5-hydroxy-4′,6,7-trimethoxyisoflavone (V). This compound melted at the same temperature as dimethyltectorigenin[4] and a melting point of a mixture of the two samples showed no depression. The acetyl derivative of the synthetic isoflavone (V) was identical with the acetate prepared from the methylated tectorigenin.[4]

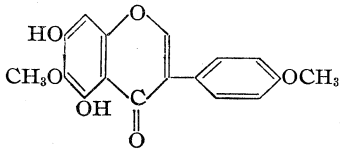
In the first step in the above synthesis, the Hoesch reaction is shown taking place in the 2-position of 4,5-dimethoxyresorcinol (I) rather than the 6-position. The reactivity of the 2-position in substituted resorcinols of this type has been previously pointed out by Baker and Robinson[5] who have shown that 3,4,5-trimethoxyphenylacetonitrile condenses in the 2-position. Methoxyacetonitrile also reacted with the 2-position of 4,5-dimethoxyresorcinol.[9] Hence it seems very probable that the condensation with homoanisonitrile also takes place in the 2-position especially since the properties of the isoflavone (V) indicate an hydroxyl group in the 5-position.[4]

The second step in the synthesis of tectorigenin dimethyl ether involves the Claisen condensation with ethyl formate and ring closure with the 6-hydroxyl of the substituted desoxybenzoin (IV) and not with the 2-hydroxyl. The fact that ring closure in compounds of this type always appears to involve the unhindered 6-hydroxyl group has been well established by previous work by Baker and Robinson,[5] Bargellini[10] and Chapman, Perkin and Robinson.[11]

The present synthesis of tectorigenin dimethyl

(1) Shibata, *J. Pharm. Soc. Japan*, **47**, 380 (1927).
(2) Asahina, Shibata and Ogawa, *ibid.*, **48**, 1087 (1928).
(3) Mannich, Schumann and Lin, *Arch. Pharm.*, **275**, 317 (1937).
(4) Shriner, Matson and Damschroder, THIS JOURNAL, **61**, 2322 (1939).
(5) Baker and Robinson, *J. Chem. Soc.*, 152 (1929).
(6) Julian and Sturgis, THIS JOURNAL, **57**, 1126 (1935); Lapine, *Bull. soc. chim.*, **6**, 390 (1939).
(7) Quelet and Anglade, *Compt. rend.*, **203**, 262 (1936).
(8) Cannizzaro, *Ann.*, **117**, 243 (1861); Levy, *Ann. chim.*, **9**, 5 (1938).
(9) Baker, Nodzu and Robinson, *J. Chem. Soc.*, 74 (1929).
(10) Bargellini, *Gazz. chim. ital.*, **45**, 69 (1915); **49**, 47 (1919).
(11) Chapman, Perkin and Robinson, *J. Chem. Soc.*, 3015 (1927).

ether coupled with the fact that iretol (2,4,6-trihydroxyanisole) is one of the degradation products of tectorigenin[1] shows that tectorigenin possesses the isoflavone structure (VI).



VI

Experimental

Homoanisonitrile.—One hundred fifty grams of anisole, 150 g. of 40% formalin, 15 cc. of petroleum ether, and 15 g. of zinc chloride were placed in a three-necked flask equipped with a mercury-sealed stirrer. The flask was placed in an ice-bath, and hydrogen chloride gas was added with stirring at such a rate that the temperature remained at 15°. After one hour and fifteen minutes the gas addition was stopped, and 30 g. of cracked ice was added. The stirring was continued for five minutes. After stopping the stirring, an oily layer rose to the top of the solution. This layer was separated, dissolved in 200 cc. of benzene, and washed with 100 cc. of 10% sodium carbonate. The benzene solution was then washed once with 100 cc. of water and added to a solution of 70 g. of sodium cyanide in 180 cc. of water. One gram of sodium laurylsulfate (Dupanol WA) was added and stirring and heating were started. The benzene was distilled out by steam developed in the flask. After the distillation of the benzene was complete the condenser, which had been set downward for distillation, was raised to a vertical position and the solution heated at the boiling point until the solution had boiled with stirring, a total of three and one-half hours. After cooling, the solution was extracted with 800 cc. of ether in three portions. The ether solution was dried with sodium sulfate, and the ether was distilled off. The residue was distilled under diminished pressure. The first fraction (26 g.) was anisole b. p. 53–55° at 20 mm. The second fraction was homoanisonitrile b. p. 154–56° at 20 mm. Sixty grams (29%) of the nitrile was obtained.

The first step in this synthesis must be carried out quickly. The chloromethylanisole must be freed from hydrogen chloride and added to the sodium cyanide as quickly as possible. Otherwise polymerization or hydrolysis of the chloromethylanisole to methoxybenzyl alcohol occurs.

2,6-Dihydroxy-3,4-dimethoxy-α-(*p*-methoxyphenyl)-acetophenone (IV).—A 1.45-g. quantity of 4,5-dimethoxyresorcinol, 1.8 g. of homoanisonitrile, and 0.5 g. of anhydrous zinc chloride were dissolved in 60 cc. of dry ether. Dry hydrogen chloride gas was passed into the solution at 0°. The hydrogen chloride was added rapidly for one hour, then slowly for two hours. The flask was then stoppered and allowed to stand overnight. After the flask had stood for twenty hours, 100 cc. of dry ether was added and the flask again allowed to stand overnight. The ether was then poured off the viscous oil and the oil washed with dry ether. Approximately 100 cc. of 10% hydrochloric acid was added to the oil and the solution boiled under reflux for one-half hour. After cooling, the solution was extracted with ether and the ether solution dried with anhydrous sodium sulfate. Removal of the ether left a red oil which became crystalline upon the addition of methyl alcohol. Recrystallization from methyl alcohol gave 0.8 g. (29%) of white crystals melting at 116.5°.

Anal. Calcd. for $C_{17}H_{18}O_6$: C, 64.15; H, 5.66. Found: C, 64.32; H, 5.99.

Dimethyltectorigenin.—To 0.20 g. of powdered sodium at 0° was added 0.28 g. of 2,6-dihydroxy-3,4-dimethoxy-α-(*p*-methoxyphenyl)-acetophenone in 4.5 cc. of redistilled ethyl formate. The mixture was stirred for four and one-half hours at 0°. Then about 10 g. of crushed ice was added, and the stirring was continued for three hours. After the solution had stood overnight without stirring so that the ethyl formate had evaporated, the solid was filtered off. This solid was dissolved in pyridine and precipitated with water. Repeated precipitation gave 0.04 g. (14%) of light tan colored microscopic needles m. p. 186°. Recrystallization of this material from methanol gave silvery white needles melting at 188°. A mixed melting point of this material with a sample of dimethyltectorigenin prepared by Matson[4] (from natural tectorigenin) gave no alteration in melting point.

Anal. Calcd. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.87. Found: C, 65.69; H, 5.06.

Dimethyltectorigenin Acetate.—In 0.6 cc. of dry pyridine was dissolved 0.026 g. of dimethyltectorigenin and 0.26 cc. of acetic anhydride. The stoppered tube was allowed to stand at room temperature for three days. Then 5 cc. of water was added to the mixture. After standing several hours light tan crystals had formed. These were purified by dissolving in pyridine and precipitating with water. After several crystallizations silvery-white crystals melting at 213° were obtained. A mixed melting point of this material with a sample of dimethyltectorigenin acetate, prepared by Matson[4] (from natural tectorigenin) gave no alteration in melting point.

Anal. Calcd. for $C_{20}H_{18}O_7$: C, 64.86; H, 4.86. Found: C, 65.00; H, 4.95.

In order to establish the validity of the use of melting points of mixtures in the isoflavone field, five different synthetic isoflavones were found to exhibit depressions in melting point when any two of them were mixed together.

Summary

A synthesis of tectorigenin dimethyl ether has been carried out which provides additional evidence that tectorigenin possesses the isoflavone structure.

BLOOMINGTON, INDIANA RECEIVED JULY 24, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

Refractive Indices and Densities of Normal Saturated Fatty Acids in the Liquid State

BY A. DORINSON, M. R. MCCORKLE AND A. W. RALSTON

Few systematic studies of the refractive indices of the saturated fatty acids are found in the literature; there is the classical work of Eijkman,[1] the investigation of Scheij[2] on the naturally occurring fatty acids, and the more modern work of Waterman and Bertram.[3] Determinations were made at arbitrary and scattered temperatures; only the work of Falk[4] on butyric acid embraces a large number of determinations over a wide range of temperature. We have measured the refractive indices of the normal saturated fatty acids in the liquid state, from caproic to stearic inclusive, at a sufficient number of temperatures between 20 and 80° to enable us to plot the variation of refractive index with temperature for each acid, as shown in Fig. 1. In addition, the densities of these acids were determined at 80° and these data were used to calculate the molar volume and the molar refractivity of each acid at that temperature. The refractive indices are listed in Table I and the densities in Table II. The values listed in Table I have not been corrected for the effect of temperature on the refractometer prism, since we feel that less confusion will arise among investigators using these figures if they are left uncorrected. Whenever we shall have occasion here to treat the refractive indices as functions of the homologous series, a correction given by

$$0.00006\ (t - 20) \qquad (1)$$

where t is the temperature at which the refractive index was determined, will be added. This is the correction for the refractometer prism only. A correction should also be applied for the effect of temperature on the compensating prisms in the refractometer, but since their temperature could be estimated only crudely, this correction will be omitted. Since the compensating prisms do not deviate the sodium D line, the correction is probably very small.

Experimental

The acids used were carefully purified; their preparation is described in another communication from this Laboratory.[5] Refractive indices were measured with an Abbe type refractometer, the temperature of whose prisms could be held constant to ±0.05. A calibrated thermometer was used. Densities were determined in a modified Ostwald pycnometer at 80 ± 0.05°. Weighings were corrected for the buoyancy of air.

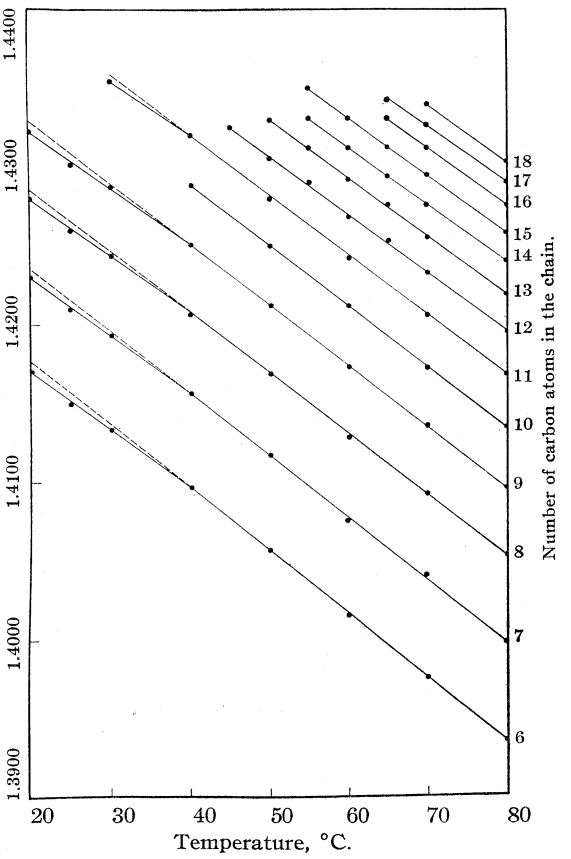


Fig. 1.—The variation of refractive index with temperature. Change of slope is shown by comparison with the extrapolation from the curve at higher temperatures. Extrapolation is represented by a dotted line.

Discussion

Molar Volumes.—The molar volumes at 80° of the acids from caproic through stearic were calculated from the densities determined in this work. By taking advantage of the fact that the densities of the straight chain saturated acids are linear functions of temperature, we were able to

(1) Eijkman, *Rec. trav. chim.*, **12**, 157 (1893).
(2) Scheij, *ibid.*, **18**, 182 (1899).
(3) Waterman and Bertram, *ibid.*, **46**, 699 (1927).
(4) Falk, THIS JOURNAL, **31**, 96 (1909).
(5) Hoerr, Pool and Ralston, *Oil and Soap*, **19**, 126 (1942).

TABLE I

REFRACTIVE INDICES (n^tD) OF NORMAL SATURATED FATTY ACIDS

Acid	20.0°	25.0°	30.0°	40.0°	45.0°	50.0°	55.0°	60.0°	65.0°	70.0°	80.0°
Caproic	1.4170	1.4150	1.4132	1.4095		1.4054		1.4012		1.3972	1.3931
Enanthic	1.4230	1.4209	1.4192	1.4155		1.4114		1.4073		1.4037	1.3993
Caprylic	1.4280	1.4260	1.4243	1.4205		1.4167		1.4125		1.4089	1.4049
Pelargonic	1.4322	1.4301	1.4287	1.4250		1.4210		1.4171		1.4132	1.4092
Capric				1.4288		1.4248		1.4210		1.4169	1.4130
Hendecanoic				1.4319		1.4279		1.4240		1.4202	1.4164
Lauric					1.4323	1.4304	1.4288	1.4267	1.4250	1.4230	1.4191
Tridecanoic						1.4328	1.4310	1.4290	1.4272	1.4252	1.4215
Myristic							1.4329	1.4310	1.4291	1.4273	1.4236
Pentadecanoic							1.4348	1.4329	1.4310	1.4292	1.4254
Palmitic									1.4328	1.4309	1.4272
Margaric									1.4340	1.4324	1.4287
Stearic										1.4337	1.4299

TABLE II

DENSITIES OF NORMAL SATURATED FATTY ACIDS AT 80°

Acid	d^t_4	Acid	d^t_4
Caproic	0.8751	Tridecanoic	0.8458
Enanthic	.8670	Myristic	.8439
Caprylic	.8615	Pentadecanoic	.8423
Pelargonic	.8570	Palmitic	.8414
Capric	.8531	Margaric	.8396
Hendecanoic	.8505	Stearic	.8390
Lauric	.8477		

convert data already in the literature[2,4,6–11] to the proper temperature and to extend this series of calculations at 80° down to acetic acid, and also to make a series of calculations from formic acid to pelargonic acid at 20° (see Table III). At 20° the molar volumes from acetic acid to pelargonic acid are adequately expressed by

$$V_m = 16.89n + 23.62 \qquad (2)$$

where n is the number of carbon atoms in the chain. At 80° the equation

$$V_m = 17.25n + 28.88 \qquad (3)$$

holds for butyric and higher acids. The deviation of the first three members of the series from linearity is quite sharp and the addition of a term of the form k/n does not extend the validity of the equation to include these three members. The molar volumes of the normal saturated acids, arranged serially, do not show as much deviation from a linear relation as noticed by Huggins[12] for the normal saturated hydrocarbons, nor does this deviation extend as far up the series for the acids as for the hydrocarbons.

(6) Timmermans and Hennaut-Roland, *J. chim. phys.*, **27**, 420, 422, 425 (1930); **29**, 550 (1932).
(7) Merry and Turner, *J. Chem. Soc.*, **105**, 758 (1914).
(8) Eijkman, *Chem. Zentr.*, **78**, II, 1210 (1907).
(9) Dunstan, *J. Chem. Soc.*, **107**, 667 (1915).
(10) Deffet, *Bull. soc. chim. Belg.*, **40**, 385 (1931).
(11) Garner and Ryder, *J. Chem. Soc.*, **127**, 728 (1925).
(12) Huggins, THIS JOURNAL, **63**, 116 (1941).

TABLE III

MOLAR VOLUMES OF NORMAL SATURATED FATTY ACIDS

Acid	V_m at 20° Exptl.[a]	V_m at 20° Calcd.[b]	V_m at 80° Exptl.	V_m at 80° Calcd.[c]
Formic	37.71	40.51	....	....
Acetic	57.21	57.40	61.11[a]	63.38
Propionic	74.55	74.29	79.68[a]	80.63
Butyric	91.93	91.18	97.95[a]	97.88
Valeric	108.69	108.07	115.33[a]	115.13
Caproic	125.04	124.96	132.67[d]	132.38
Enanthic	141.89	141.85	150.07	149.63
Caprylic	158.57	158.74	167.30	166.88
Pelargonic	174.53	175.63	184.50	184.13
Capric			201.80	201.38
Hendecanoic			218.90	218.63
Lauric			236.29	235.88
Tridecanoic			253.27	253.13
Myristic			270.41	270.38
Pentadecanoic			287.61	287.63
Palmitic			304.56	304.88
Margaric			321.90	322.13
Stearic			338.85	339.38

[a] Calculated from densities obtained from references 2, 4, 6–11. [b] Calculated from equation (2). [c] Calculated from equation (3). [d] This figure and subsequent figures in this column were computed from densities in Table II.

Refractivities.—In Fig. 1 we have plotted the refractive indices of the acids, corrected according to equation (1), against temperature. The refractive indices for each acid fall upon a straight line between 40 and 80°. Below this temperature a change of direction is observed. A plausible explanation of this phenomenon can be found in the theory of molecular refractivity and in current viewpoints on the structure of liquids consisting of polar molecules. To begin with, the molar refraction for visible light, calculated by the Lorentz–Lorenz equation, is equal to the electron polarization. A collection of molecules which are inherent dipoles, such as the molecules of a fatty acid, act on each other to cause more or less orien-

tation, even in the liquid state, and consequently produce an electric field within the body of the liquid. Onsager[13] has published a theoretical treatment of this effect on the determination of dipole moments of polar substances by means of an external electrical field. It is beyond the scope of this paper to attempt a quantitative treatment of the effect of the internal electric field on the bonding electrons in the relatively non-polar part of the fatty acid chain, and hence on the refractivity, but qualitatively we would expect the electron polarization of a substance such as a fatty acid to depend on the statistical orientation of the individual molecules within the body of the liquid. On the other hand, the thermal motions of these molecules will tend to produce disorder, and at some temperature they should be vigorous enough to completely overcome the restraints caused by dipole interaction. The molecules within the liquid will then exhibit a perfectly random configuration and the net field there will be zero. On these grounds we would expect to find a temperature for each acid above which the molar refractivity will be constant and below which it will depend on temperature. We have taken the data of Falk[4] for butyric acid and instead of smoothing out the values of the refractive index, we have calculated the molar refractivities from the data as they stand. This examination shows that the molar refractivity is practically constant above 42° and a linear function of the temperature below this point. This is the only fatty acid reported for which a sufficient number of molecular refractivities could be calculated from the original data over a wide temperature range.

To eliminate the possibility that the discontinuities in the plot of the refractive indices of the acids might be due to some systematic defect in the refractometer or in the calibration of the thermometer, the refractive index of *n*-heptane was determined between 20 and 50°. The data so obtained lie on a straight line and the data of Shepard, Henne and Midgley[14] also lie on this line in full agreement with ours.

If a plot of the molar refractivity of a normal fatty acid shows discontinuity with temperature, it can be shown that a plot of the refractive indices will also exhibit discontinuity. The densities of the fatty acids are continuous linear functions of the temperature from zero to at least 80°. The density factor, then, will produce no discontinuity in the molar refractivity as calculated from the Lorentz–Lorenz formula

$$\frac{n^2 - 1}{n^2 + 2}\frac{M}{d}$$

but any discontinuity in the temperature variation of n will show up in the molar refractivity and *vice versa*, since it is impossible to eliminate n from the ratio $n^2 - 1/n^2 + 2$.

The molar refractivities of the normal saturated fatty acids, from caproic to stearic inclusive, can be expressed as a function of the number of carbon atoms in the chain by

$$R_m = 4.654n + 3.83 \qquad (4)$$

The observed values and those calculated from this formula are listed in Table IV.

TABLE IV

MOLAR REFRACTIVITIES OF NORMAL SATURATED FATTY ACIDS AT 80°

Acid	R_m (exptl.)[a]	R_m (calcd.)[b]
Caproic	31.70	31.75
Enanthic	36.34	36.40
Caprylic	41.08	41.06
Pelargonic	45.66	45.71
Capric	50.36	50.37
Hendecanoic	55.02	55.02
Lauric	59.73	59.68
Tridecanoic	64.35	64.33
Myristic	69.00	68.99
Pentadecanoic	73.65	73.64
Palmitic	78.30	78.30
Margaric	83.01	82.95
Stearic	87.59	87.61

[a] Computed from the formula $R_m = \frac{n^2 - 1}{n^2 + 2}\frac{M}{d}$, refractive indices corrected. [b] Calcd. from equation (4).

Summary

1. The refractive indices of the normal saturated fatty acids from caproic to stearic inclusive have been determined at a number of temperatures between 20 and 80°. For each acid the refractive indices are straight line functions of the temperature with an abrupt change of a slope at 40°.

2. An explanation of this change of slope has been presented.

3. The densities of these acids at 80° have also been determined. Molar volumes and molar refractivities for the homologous series have been computed and shown to be linear with respect to the number of carbon atoms in the chain.

CHICAGO, ILLINOIS RECEIVED JUNE 24, 1942

(13) Onsager, THIS JOURNAL, **58**, 1486 (1936).
(14) Shepard, Henne and Midgley, *ibid.*, **53**, 1948 (1931).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Solubility Studies. VII. The Solubilities of Some Isomeric Ketones in Water

BY JOHN H. SAYLOR, VICTOR J. BAXT[1] AND PAUL M. GROSS

The possible existence of a linear relationship between the heats and entropies of solution of organic compounds has been suggested by several investigators[2,3] and is of considerable interest from the standpoint of the energy relationships involved in the solution process.

In a previous communication from this Laboratory[4] it was shown that a linear relationship between the heats and entropies of solution existed for three of the ketones studied. These ketones, methyl propyl, methyl isopropyl and diethyl, have approximately the same molar volumes at the temperatures of the measurements. It was suggested that equality of solute volumes as well as chemical similarity may well be a prerequisite for the existence of such a linear relationship between the heats and entropies of solution. The present investigation of the solubilities of the three isomeric ketones, dipropyl, diisopropyl and methyl *n*-amyl, was undertaken with this suggestion in mind.

Experimental

The saturated solutions were prepared and analyzed by means of a Zeiss combination liquid and gas interferometer as previously described.[4,5]

The ketones were obtained from the Carbide and Carbon Chemical Company. They were purified by repeated shaking with ammoniacal silver nitrate until no discoloration appeared on allowing the ketone to stand for thirty minutes in contact with fresh reagent. Then they were washed, dried over calcium sulfate and fractionated in a 50-cm. Widmer still using calibrated thermometers. The boiling points of the fractions used are given in Table I.

TABLE I

BOILING POINTS OF THE COMPOUNDS

Substance	B. p. at 760 mm., °C.	Previously observed b. p., °C.	Ref.
Dipropyl ketone	144.00–144.10	144.1	6
Diisopropyl ketone	124.06 ± 0.05	124.0 123.7	7, 8
Methyl *n*-amyl ketone	150.18–150.32	150.2	9

It was necessary to determine the densities of diisopropyl and methyl *n*-amyl ketone in order to calculate the corresponding molar volumes. This was done at 10, 30, 50 and 75° by means of appropriate specific gravity bottles.

Results

The observed solubilities are listed in Table II. Vapor solubilities,[4,10] C_s, were calculated from these and are listed in Table II along with the vapor pressures, P_L, of the solute. The vapor solubility is defined as that concentration C_s in equilibrium with the vapor of the substance under a standard pressure of 100 mm. at the particular temperature in question. It is calculated by means of Henry's law from the observed solubilities and the vapor pressure of the liquid solute at the same temperature.

Table II also lists the mole fraction, N, corresponding to C_s as well as the densities and molar volumes, V_m, at each temperature.

The free energies of hydration as given by the relation $\Delta F = RT \ln (P/N)$ have been calculated from the mole fractions, N, given in Table II. The corresponding entropy of hydration ΔS was evaluated graphically from a plot of ΔF *vs.* T. The heats of hydration ΔH were calculated from the values of ΔF and ΔS by means of the relation

$$\Delta F = \Delta H - T\Delta S$$

These quantities are listed in Table III.

Figure 1 is a plot of ΔS *versus* ΔH for dipropyl, diisopropyl and methyl *n*-amyl ketones as well as for methyl propyl, methyl isopropyl and diethyl ketones taken from the previous investigation. The linear relationship is not as good in the present investigation. Nevertheless, within the limits of experimental error and the assumptions involved the data point to its validity. It is likely that the relation may have limited validity for the longer carbon chains with their many possible configurations. Butler[3] has shown that such a linearity exists in a series of alcohols. It

(1) This paper was taken in part from the thesis submitted by Victor J. Baxt to the Graduate School of Duke University in partial fulfillment of the requirements for the degree of Master of Arts, June, 1940.

(2) Evans and Polanyi, *Trans. Faraday Soc.*, **32**, 1333 (1936).

(3) Butler, *ibid.*, **33**, 229 (1937).

(4) Gross, Rintelen and Saylor, *J. Phys. Chem.*, **43**, 197 (1939).

(5) Gross and Saylor, THIS JOURNAL, **53**, 1747 (1931).

(6) Timmermans, *Bull. soc. chim. belg.*, **30**, 62 (1931).

(7) Mailhe, *Bull. soc. chim.*, [4] **5**, 620 (1909).

(8) "International Critical Tables."

(9) Park and Hoffman, *Ind. Eng. Chem.*, **24**, 132 (1932).

(10) Saylor, Stuckey and Gross, THIS JOURNAL, **60**, 373 (1938).

TABLE II

SOLUBILITIES AND RELATED QUANTITIES

Ketone	t, °C.	Moles per 1000 g. H_2O	C_s molality	$N \times 10^3$	dt_4	P_L, (mm.)	V_m, (ml.)
Dipropyl[a]	0	0.0643	4.02	69.1	0.8340[11]	1.6[12]	136.9
	10	.0466	1.55	27.2	.8248	3.0	138.4
	30	.0331	0.348	6.23	.8081	9.5	141.3
	50	.0288	.113	2.03	.7913	25.5	144.3
	75	.0254	.336	0.604	.7702	75.6	148.2
Diisopropyl	10	.0587	.858	15.2	.8139	6.8[13]	140.3
	30	.0404	.201	3.60	.7968	20.1	143.3
	40	.0392	.118	2.12	.7869	33.2	145.1
	50	.0350	.0668	1.20	.7792	52.4	146.5
	55	.0339	.0562	1.01	.7734	65.5	147.6
	65	.0331	.0335	0.603	.7645	98.8	149.3
	75	.0376	.0255	.459	.7560	147.3	151.0
Methyl *n*-amyl	10	.0472	3.35	56.8	.8245	1.41[14]	138.5
	30	.0355	.668	11.9	.8072	5.32	141.4
	50	.0319	.216	3.86	.7898	14.8	144.6
	60	.0308	.110	1.97	.7809	28.0	146.2
	65	.0315	.0890	1.60	.7761	35.4	147.1
	75	.0339	.0610	1.10	.7676	55.6	148.7

[a] Data at 0 and 10° from the data of Gross, Rintelen and Saylor, ref. 4.

TABLE III

VALUES OF ΔF, ΔH AND ΔS

Ketone	t, °C.	ΔF, kcal.	$-\Delta S$, cal./degree	$-\Delta H$, kcal.
Dipropyl	0	3.95	65.8	14.01
	10	4.62	64.5	13.63
	30	5.84	58.1	11.76
	50	6.93	54.1	10.54
	75	8.31	53.0	10.13
Diisopropyl	10	4.94	62.1	12.63
	30	6.16	58.1	11.44
	40	6.70	58.1	11.49
	50	7.27	55.1	10.47
	55	7.50	52.5	9.68
	65	8.07	46.6	7.68
	75	8.50	41.0	5.81
Methyl *n*-amyl	10	4.20	60.2	12.84
	30	5.44	59.7	12.65
	50	6.52	56.7	11.79
	60	7.17	53.3	10.58
	65	7.42	52.7	10.39
	75	7.90	50.2	9.57

appears, however, that the alcohols with the longest carbon chains do not follow the relationship as closely.

Figure 2 is a plot of vapor solubility against molar volume. There is a still greater temperature dependency in the solubility of these compounds than that found previously for ketones of lower molecular weight. At 10° methyl *n*-amyl ketone is 3.9 times more soluble than diisopropyl ketone but this ratio diminishes with increase in temperature until at 75° it is 2.4. This greater temperature dependency would be predicted from the explanation previously offered.

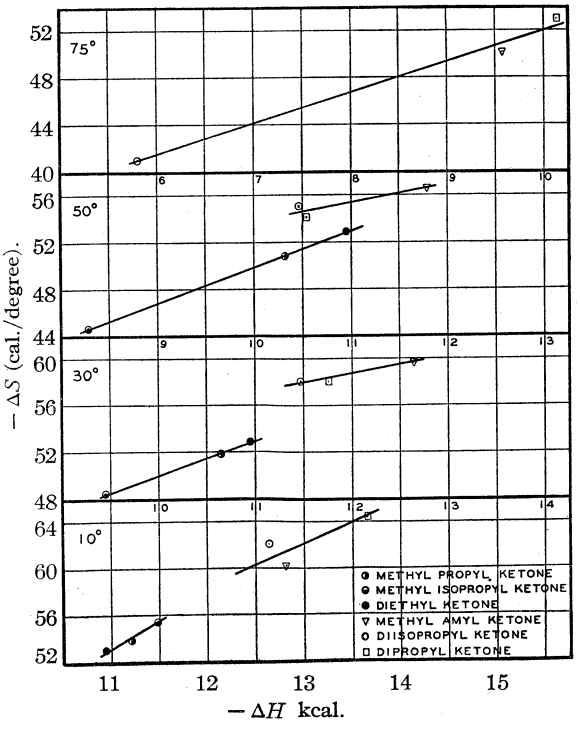


Fig. 1.—Relation between heats and entropies of solution.

According to this, compounds such as methyl *n*-amyl ketone with longer unbranched side-chains

(11) F. K. Beilstein, "Handbuch der organischen Chemie," 4th ed., Julius Springer, Berlin, Vol. 1, p. 700, appendix 1, Vol. I, p. 359.

(12) Rintelen, Saylor and Gross, THIS JOURNAL, **59**, 1129 (1937).

(13) Aston and Mayberry, *ibid.*, **56**, 2682 (1934).

(14) Stuckey and Saylor, *ibid.*, **62**, 2922 (1940).

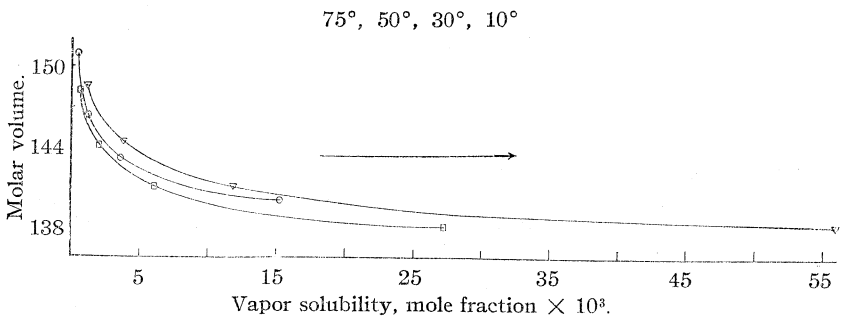


Fig. 2.—Effect of temperature on solubilities in relation to volume: ▽, methyl amyl ketone; O, diisopropyl ketone; □, dipropyl ketone.

may be stretched out at low temperatures so that the CH_2 groups are surrounded by the maximum possible number of water molecules, the attractive forces between these groups and water thus adding to the main interaction between the carbonyl dipole and water. When the temperature increases, the molecule may assume other more compact configurations which will be such as to decrease the number of water molecules adjacent to the CH_2 groups. On the other hand, molecules such as that of diisopropyl ketone having compact branched structures can only assume a limited number of configurations and, hence, their solubilities are less temperature dependent.

Summary

The solubilities in water of dipropyl, diisopropyl and methyl *n*-amyl ketones have been determined at various temperatures from 10 to 75° and vapor solubilities have been computed.

Free energies, heats and entropies of solution have been calculated. Additional evidence was obtained which tends to confirm the previous suggestion that equality of solute volume as well as chemical similarity is necessary for a linear relation to exist between entropies and heats of solution.

Large solubility differences and a large temperature dependence of these differences were noted in agreement with those previously found for other isomeric ketones.

DURHAM, NORTH CAROLINA RECEIVED SEPTEMBER 2, 1942

[CONTRIBUTION FROM THE MALLINCKRODT CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Surface Tension of Solutions of Electrolytes as a Function of the Concentration. IV. Magnesium Sulfate

BY GRINNELL JONES AND WENDELL A. RAY

This paper is a continuation of work previously reported[1] on the surface tensions of aqueous solution of electrolytes relative to that of pure water. These earlier papers should be consulted for a description of the experimental technique and a discussion of the historical and theoretical background of the problem. The data given are "apparent relative surface tensions" in the sense defined in the second paper of this series.

Magnesium sulfate was chosen for this work because none of the salts already studied belonged to this valence type. The measurements have been carried out at 25.00° over a concentration range of 0.0001 up to 2 molar.

Analytical reagent grade magnesium sulfate was purified by two recrystallizations from water. The crystals were washed by centrifugation and slowly dried in an electric oven. As the salt was hygroscopic each sample before final weighing was kept in an electric furnace at 475° for several hours or until constant weight was assured. At this temperature the anhydrous salt was formed. The samples were weighed in platinum boats in stoppered weighing bottles. A saturated solution showed no red coloration with phenolphthalein. Two 50-ml. Ostwald type pycnometers were used for the density measurements and gave duplicate results differing by not more than a few parts per million. The surface tension measurements were made by the differential capillary rise method as described in the first and second papers of this series. The figures given in Table I are the mean of at least two independent determinations for each concentration. The results are shown graphically in Figs 1 and 2.

(1) Grinnell Jones and Wendell A. Ray, THIS JOURNAL, **59**, 187 (1937); **63**, 288, 3262 (1941); Grinnell Jones and L. D. Frizzell, *J. Chem. Phys.*, **8**, 986 (1940).

TABLE I

DENSITY AND APPARENT RELATIVE SURFACE TENSION OF MAGNESIUM SULFATE SOLUTIONS AT 25°

Concentration, molar	Density d^{25}_4	Apparent relative surface tension	$(\sigma_c - \sigma_0)/c\sigma_0$
0.000100	0.997085	0.99997	−0.3
.000200	.997096	.99994	− .3
.000500	.997131	.99993	− .14
.001000	.997190	.99997	− .03
.002000	.997322	1.00003	+ .15
.005000	.997694	1.00022	+ .044
.010000	.998319	1.00046	+ .046
.020000	.999544	1.00087	+ .0435
.050000	1.003198	1.00195	+ .0390
.10000	1.009195	1.00345	+ .0345
.20000	1.021005	1.00638	+ .0319
.49647	1.055099	1.01435	+ .02890
1.0000	1.110781	1.02836	+ .02836
1.98720	1.214289	1.06603	+ .03323

Interpretation of the Data

The densities of magnesium sulfate may be expressed over the range studied by an equation of the form suggested by Root.[2]

$$d^{25}_4 = 0.997074 + 0.124469c - 0.010756c^{3/2}$$

This equation agrees with the data with an average deviation of less than 0.001%.

From the curve it may be seen that the apparent relative surface tension of magnesium sulfate in the extreme dilute range becomes less than unity giving a minimum. The surface tension at the minimum is about 0.010% below that of pure water. The minimum occurs at about 0.0005 molar. This minimum is similar to that found by us for the other salts studied. At higher concentrations the surface tension is nearly a linear function of the concentration but a slight positive curvature may be noted at the highest concentrations which has been found typical of all the salts studied in this Laboratory in the past.

(2) W. C. Root, THIS JOURNAL, **55**, 850 (1933).

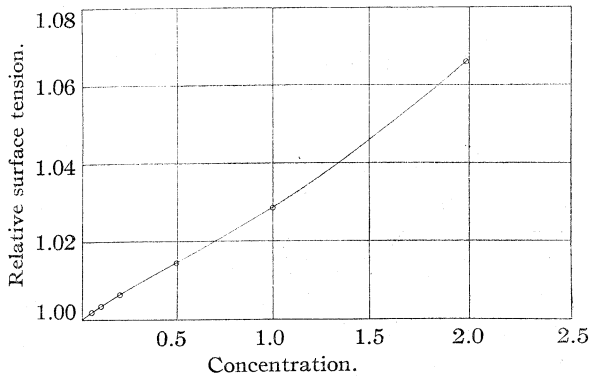


Fig. 1.

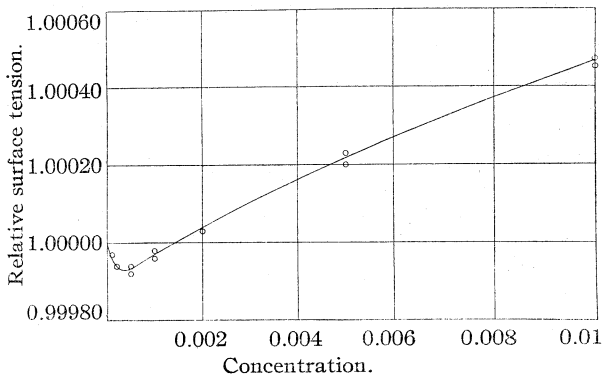


Fig. 2.

Summary

The apparent relative surface tensions of aqueous solutions of magnesium sulfate have been measured from 0.0001 to 2 molar at 25.00°.

At extreme dilution magnesium sulfate apparently gives a minimum in the surface tension–concentration curve. This same type of minimum has been observed for all of the other salts so far reported in this series.

At moderate and high concentrations magnesium sulfate increases the surface tension of water almost linearly with concentration and behaves as a typical "capillary-inactive" substance.

CAMBRIDGE, MASSACHUSETTS RECEIVED AUGUST 25, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY]

Some Isotherms of the System Sodium Chromate–Sodium Chlorate–Water

BY J. E. RICCI AND C. WELTMAN

Solubility measurements in the ternary system sodium chromate–sodium chlorate–water have been made with the purpose of testing any possible similarity with the behavior of the related system sodium sulfate–sodium chlorate–water, which forms a double salt of the formula $NaClO_3 \cdot 3Na_2SO_4$.[1] The present measurements, however, reveal neither compound formation nor solid solution between the salts Na_2CrO_4 and $NaClO_3$ over the temperature range studied, 19–50°.

Materials.—A C. P. grade of sodium chlorate was used, found to be 100.0% pure by reduction and precipitation of silver chloride. Recrystallized C. P. potassium dichromate was used for the standardization of the 0.2 *N* sodium thiosulfate titrating solution. Other chemicals used, such as sulfur dioxide and silver nitrate, were similarly of C. P. grade. The sodium chromate was used in the form of the tetrahydrate, supplied by the Mackay Company; the percentage of Na_2CrO_4 in this material, found by titration, was 69.15, and by dehydration, 69.25, as compared with the theoretical value of 69.21. The purity of this salt is further confirmed by the agreement of the solubility at 25° as determined by evaporation, with the value obtained by titration (see Table I): 45.63 and 45.59%, respectively.

Solubility Determinations.—Complexes were made up by weight from sodium chlorate, tetrahydrate and water, and rotated in a thermostat at the specified temperature (±0.02°), about three days being allowed for the attainment of equilibrium. Samples for analysis were taken in the usual way by means of pipets fitted with filter paper.

Analysis.—1. Sodium chromate in the presence of sodium chlorate. Gravimetric determination as barium chromate or as lead chromate (using excess of barium chloride or of lead nitrate) gave consistently high results in the determination of about 0.5 g. of potassium chromate in the presence of 0.5 to 2 g. of sodium chlorate, the errors being about +15 and +6 parts per 1000, respectively. These errors may indicate co-precipitation of the respective chlorates. A volumetric analysis was therefore employed, involving precipitation as barium chromate, filtration, re-solution in nitric acid and iodometric titration of the chromate with standard thiosulfate. The use of hydrochloric acid in re-dissolving the precipitate of barium chromate gave irregular, low results, by as much as thirty parts per thousand, apparently because of some reduction of chromate by the hydrochloric acid, during the process of solution of the precipitate. Nitric acid, however, gave satisfactory results (±0.5 part per thousand); the procedure was tested on samples of ~0.35 g. of potassium chromate in the presence of 1–4 g. of sodium chlorate, the final titration being carried out with 3 g. of potassium iodide and 8 cc. of 6 *N* nitric acid in a total volume of 200 cc. Whatever small amounts of chlorate may have accompanied the precipitated barium chromate apparently caused no measurable interference under these conditions.

2. Sodium chlorate can be determined by difference from the percentage of total solid obtained by evaporation of the saturated solution at 110°. But because of some difficulty and uncertainty in the complete drying of sodium chromate residues, it was decided to supplement this indirect determination of sodium chlorate by the following direct analysis.

3. Direct gravimetric determination of the chlorate, by reduction with sulfur dioxide gas followed by the usual gravimetric determination of the resulting chloride as silver chloride. This procedure gave exact results both on pure sodium chlorate and in the presence of sodium chromate, as can be seen of course in the close agreement of the algebraic extrapolation of tie-lines for the identification of solid phases in the ternary system, described below.

Results.—The results for the solubility determinations for three isotherms, 19, 25 and 50°, are given in Table I. All compositions are in weight per cent. The first two columns under the caption "saturated solution" are the directly determined percentages of the two individual salts, and the percentage of water for the actual phase diagram was calculated by difference, using the sum of these percentages for the total solid. The percentage of total solid obtained by direct evaporation was considered probably slightly less dependable than the sum of the separate determinations. The third column under "saturated solution" gives the percentage of water determined by evaporation, and it may be seen that the total solid so determined is nevertheless in good agreement in general with the sum of the first two columns. The average discrepancy is +0.8 to 1.0 part per thousand for the evaporation figure, the maximum difference being six parts per thousand. All but eight of the analytical values given in Table I are averages of at least two duplicates; the average disagreement of duplicates was 1.3 parts per thousand. The sodium chlorate solubilities given in parentheses were determined by evaporation. Table II compares the solubilities of the single salts here reported with values from the literature.

The results, shown graphically for two temperatures in Fig. 1, indicate that in the range of temperature studied, the system is simple, the only solid phases being anhydrous sodium chlorate and one of the hydrates of sodium chromate. This is

(1) Ricci and Yanick, THIS JOURNAL, **59**, 491 (1937).

TABLE I

SYSTEM Na_2CrO_4–$NaClO_3$–H_2O

Original complex		Saturated solution			
Wt., % Na_2CrO_4	Wt., % $NaClO_3$	Wt., % Na_2CrO_4	Wt., % $NaClO_3$	Wt., % H_2O by evapn.	Solid phases
			At 50°		
0.00	...	0.00	55.49	44.51	$NaClO_3$
5.00	60.00	6.36	48.49	45.11	$NaClO_3$
13.94	51.78	18.37	36.71	44.94	$NaClO_3$
23.00	44.00	31.45	23.55	44.69	$NaClO_3$
30.00	38.00	40.80	15.81	43.32	$NaClO_3$
39.00	25.00	43.13	13.87	42.90	$NaClO_3$ + $Na_2CrO_4 \cdot 4H_2O$
53.00	10.00	43.15	13.85	42.89	$NaClO_3$ + $Na_2CrO_4 \cdot 4H_2O$
Av.		43.14	13.86	42.90	$NaClO_3$ + $Na_2CrO_4 \cdot 4H_2O$
54.00	7.00	44.21	11.54	44.21	$Na_2CrO_4 \cdot 4H_2O$
55.00	4.00	47.32	6.20	46.47	$Na_2CrO_4 \cdot 4H_2O$
...	0.00	50.66	0.00	49.34	$Na_2CrO_4 \cdot 4H_2O$
			At 25°		
0.00	...	0.00	(50.06)	49.94	$NaClO_3$
5.00	53.00	5.95	43.88	50.17	$NaClO_3$
9.98	49.87	12.45	37.06	50.36	$NaClO_3$
15.00	48.00	20.42	29.30	50.27	$NaClO_3$
20.00	44.99	28.51	21.50	50.03	$NaClO_3$
25.00	40.00	35.18	15.65	49.16	$NaClO_3$
34.00	33.00	36.43	14.43	49.04	$NaClO_3$ + $Na_2CrO_4 \cdot 4H_2O$
36.00	20.00	36.44	14.44	49.00	$NaClO_3$ + $Na_2CrO_4 \cdot 4H_2O$
46.88	10.00	36.43	14.43	49.04	$NaClO_3$ + $Na_2CrO_4 \cdot 4H_2O$
Av.		36.43	14.43	49.03	$NaClO_3$ + $Na_2CrO_4 \cdot 4H_2O$
48.00	7.00	39.47	9.82	50.71	$Na_2CrO_4 \cdot 4H_2O$
49.96	4.99	41.04	7.34	51.59	$Na_2CrO_4 \cdot 4H_2O$
...	0.00	45.59	0.00	54.37	$Na_2CrO_4 \cdot 6H_2O$
			At 19°		
0.00	...	0.00	48.28	51.62	$NaClO_3$
4.93	55.01	6.43	41.91	51.64	$NaClO_3$
11.00	50.01	14.56	33.59	51.71	$NaClO_3$
20.00	42.00	27.00	21.57	51.39	$NaClO_3$
27.00	36.00	35.05	15.01	49.96	$NaClO_3$ + $Na_2CrO_4 \cdot 6H_2O$
35.00	21.00	35.03	15.03	49.96	$NaClO_3$ + $Na_2CrO_4 \cdot 6H_2O$
Av.		35.04	15.02	49.96	$NaClO_3$ + $Na_2CrO_4 \cdot 6H_2O$
43.00	8.00	37.26	10.70	51.99	$Na_2CrO_4 \cdot 6H_2O$
44.95	4.01	40.60	5.14	54.27	$Na_2CrO_4 \cdot 6H_2O$
45.00	2.00	42.26	2.31	55.35	$Na_2CrO_4 \cdot 6H_2O$
...	0.00	43.63	0.00	56.33	$Na_2CrO_4 \cdot 10H_2O$

TABLE II

INDIVIDUAL SOLUBILITIES

Salt	Temp., °C.	Observed	Literature	Solid phase
$NaClO_3$	19	48.3	48.75[2]	$NaClO_3$
	25	50.1	50.1[2,3]	$NaClO_3$
	50	55.5	55.2[3]	$NaClO_3$
Na_2CrO_4	19	43.6	43.3[4]	$Na_2CrO_4 \cdot 10H_2O$
	25	45.6	45.8[4,5]	$Na_2CrO_4 \cdot 6H_2O$
	50	50.7	51.0[6]	$Na_2CrO_4 \cdot 4H_2O$

the tetrahydrate for the whole sodium chromate solubility curve at 50°. The binary transition temperature to the hexahydrate is 25.9°, and that between the hexahydrate and the decahydrate lies at 19.5°.[7] The stable solid phases for the solubility of the pure salt at the lower temperatures, 25 and 19°, are therefore the hexahydrate and the decahydrate, respectively, and they are so reported in the table. Apparently, however, these phases are in each case dehydrated to the next lower hydrate in the presence of even small concentrations of sodium chlorate, since the tie-lines for the ternary system in this region show only the tetrahydrate as the solid phase at 25° and

(2) Interpolated from: Bell, *J. Chem. Soc.*, **123**, 2713 (1923); and Ricci and Yanick, ref. 1.

(3) Ricci, THIS JOURNAL, **60**, 2040 (1938).

(4) Interpolated from Salkowski, *Ber.*, **34**, 1947 (1901).

(5) Takeuchi, *Mem. Kiyoto Imp. Univ.*, **1**, 249 (1916); cited in "Int. Crit. Tables," Vol. IV, p. 347 (1926).

(6) Interpolated from Mylius and Funk, *Wiss. Abh. Reichanstalt*, **3**, 451 (1900); cited in Seidell "Solubilities, etc.," 1940, Vol. I, p. 1255.

(7) Richards and Kelley, THIS JOURNAL, **33**, 847 (1911).

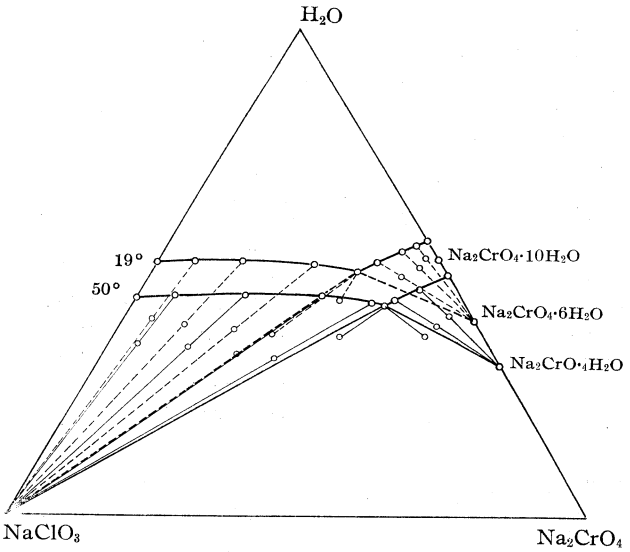


Fig. 1.—The system Na_2CrO_4–$NaClO_3$–H_2O at 19 and 50°.

only the hexahydrate at 19°. The isothermally invariant points for equilibrium, at each of these two temperatures, between the two adjacent hydrates in the ternary system were not determined.

The identity of the solid phases as reported is based on graphical and algebraic extrapolation of tie-lines. For the case of sodium chlorate as solid phase these tie-lines extrapolate to 100% sodium chlorate with an average absolute error, for all three isotherms, of 0.16%, calculated as % water. For the sodium chromate phases, the average error of extrapolation to the theoretical percentage of sodium chromate in the respective hydrates, is 0.11%, calculated as % sodium chlorate. There is consequently no indication, within the experimental error, of any solid solution formation between the equilibrium phases of the system.

Summary

Solubility determinations are reported for the ternary system sodium chromate–sodium chlorate–water at 19, 25 and 50°. No evidence is found for any compound formation or solid solution between the two salts in this temperature range.

NEW YORK, N. Y. RECEIVED AUGUST 6, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

Absorption Spectra of Some Double Salts Containing Cobaltous Chloride*

BY MELVIN L. SCHULTZ AND ERNEST F. LILEK

The blue color of solutions containing cobaltous chloride and hydrochloric acid or certain other chlorides in large excess has been shown by ion migration experiments[1] to be due to an anion of which cobalt is a constituent. It has been suggested frequently,[2] on the basis of indirect physico-chemical evidence, that this ion may be represented as $CoCl_4^{--}$.

The absorption spectra of solutions containing the ion in question have been observed, the most accurate measurements being those of Brode,[3] Brode and Morton,[4] and Kiss and Gerendas.[5] The spectrum consists of many relatively narrow bands extending from the near infra-red through the visible into the ultraviolet. In the present paper, the results of the comparison of the portion of this spectrum lying within the visible region with spectra of several blue double salts containing cobaltous chloride are reported.

The structure of one of these double salts, Cs_3CoCl_5, has been determined by X-ray diffraction measurements.[6] These experiments have shown that in the crystal there exists an approximately regular tetrahedral arrangement of four chloride ions about each cobalt ion, the cobalt–chlorine distance being 2.34 Å. The fifth chloride ion is separated from the cobalt ion by a much greater distance, about 6.0 Å. The absorption spectrum responsible for the blue color of this crystal may be ascribed to the presence of the tetrahedral $CoCl_4^{--}$ group.

If this same complex is present in other crystals or in solution the absorption spectra ought to re-

* Presented before the Division of Physical and Inorganic Chemistry at the Buffalo meeting of the American Chemical Society, September, 1942.

(1) F. G. Donnan and H. Bassett, *J. Chem. Soc.*, **81**, 939 (1902).

(2) See "Gmelins Handbuch der anorganischen Chemie, System-Nummer 58, Kobalt, Teil A," Verlag Chemie G. m. b. H., Berlin, 8 aufl., 1932, p. 490 for a summary of the work done before 1932. W. Feitknecht, *Helv. Chim. Acta*, **20**, 659 (1937), has summarized the more recent results and has presented a critical discussion of the relationship between color and constitution for a number of cobaltous compounds.

(3) W. R. Brode, *Proc. Roy. Soc.* (London), **118A**, 286 (1928).

(4) W. R. Brode and R. A. Morton, *ibid.*, **120A**, 21 (1928).

(5) A. v. Kiss and M. Gerendas, *Z. physik. Chem.*, **180A**, 117 (1937).

(6) H. M. Powell and A. F. Wells, *J. Chem. Soc.*, 359 (1935).

semble one another closely. It need not be expected, however, that the positions and relative intensities of corresponding absorption bands be identical. For the crystals, differences in the identity of the surrounding ions and differences in their arrangement about the $CoCl_4^{--}$ complex would be expected to give rise to differences in the spectra. The absorption bands for the solution should be more diffuse than those for the crystals with fewer details of structure resolved because of the less regular arrangement of neighbors about the complex ions and because of the effect of thermal agitation upon the arrangement. Any change in the binding energy between cobalt and chlorine for the complex in solution as compared with the crystal might produce shifts in the positions of the absorption bands. If, however, the complex responsible for the absorption, either in solution or in a crystal other than Cs_3CoCl_5, has a different composition or structure the absorption spectrum should be qualitatively different. From the results of measurements by Brode[7] it may be inferred that the blue color of solutions of cobalt chloride in various solvents is not always due to the same complex since the spectra of such solutions do show characteristic differences in their structure.

We have found that the absorption spectra of crystals of Cs_3CoCl_5, Cs_2CoCl_4, $(PyH)_2CoCl_4$, $(QuH)_2CoCl_4$ and $(QuH)_2CoCl_4 \cdot H_2O$, in which PyH represents the pyridinium ion and QuH the quinolinium ion, are nearly identical. Furthermore, there is a close correspondence between these spectra and the spectrum of the hydrochloric acid solution of cobalt chloride. It may be concluded, therefore, that in these crystals and in the blue aqueous cobalt chloride solutions containing large excess of chloride ion the characteristic color is due to a tetrahedral $CoCl_4^{--}$ complex ion.

Experimental

The spectra were photographed using a Hilger constant deviation wave length spectrometer, fitted with a camera of 30 cm. focal length, and Eastman Spectroscopic Plates types IV B, IV F and 144 N. The linear dispersion at 4500 Å. was about 50 Å. per mm. An image of the source, an automobile headlight bulb operated from a small motor generator, was focused on the crystal. An image of the illuminated crystal was then focused on the spectrograph slit which was set at a width of about 0.02 mm. Exposure times varied from a few seconds to about nine hours.

The double salts used were prepared by methods described in the literature.[8] The composition of each was confirmed by determination of chloride. Single crystals up to about 2 mm. in thickness were used in photographing the weak absorption bands. For the more intense bands the material was powdered and pressed between microscope slides whose surfaces had been ground with fine carborundum. With $(PyH)_2CoCl_4$ and $(QuH)_2CoCl_4 \cdot H_2O$ large single crystals could not be obtained. In order to photograph the weak bands of these two substances relatively thick layers of the powdered material were used which made long exposure times necessary.

The wave lengths of the bands were determined by first spotting visually on the plates the centers of the bands and by then determining the positions of the spots with respect to the comparison spectrum using a measuring microscope. For each band, with the exception of a few which were very weak, the value reported is the mean of at least five independent measurements. The average deviation, from the chosen value, of the individual measurements on a given band varied from about 1.5 Å. in the blue to about 6 Å. in the far red. The relative intensities of the bands were estimated visually from the plates and are expressed on a scale of 0–10. Since the absorption bands observed were rather sharp with clearly defined edges the band widths were estimated roughly by spotting, on the plates, the band edges. The values reported for the widths have been rounded off to the nearest 10 $cm.^{-1}$.

Results and Discussion

The wave numbers, calculated from the measured wave lengths, of the band centers for the five double salts studied are listed in Table I together with the band widths and estimated intensities. These data are plotted in Fig. 1, in which the vertical lines represent the positions of the band centers and the heights of the lines represent the relative intensities. The only marked differences among these spectra occur in the group of weak bands lying between 19,200 $cm.^{-1}$ and 20,300 $cm.^{-1}$. The remaining bands appear in all the spectra with nearly the same positions and relative intensities. Evidently, the energy levels characteristic of the complex ion are not very sensitive to changes in the surroundings.

The absorption curve for the solution of cobalt chloride in concentrated hydrochloric acid is plotted also in Fig. 1 with wave numbers as abscissas and log ϵ as ordinates. This curve was constructed from the data of Brode[3] and Brode and Morton.[4] The similarity between the curve for the solution and the spectra of the crystals is apparent. Each consists of four regions of absorption: a group of intense bands in the red, a group of smaller intensity in the green and yellow and two groups of weak bands in the blue. The

(7) W. R. Brode, THIS JOURNAL, **53**, 2457 (1931).

(8) H. W. Foote, *Am. J. Sci.*, **13**, 158 (1927); E. G. V. Percival and W. Wardlaw, *J. Chem. Soc.*, 1505 (1929).

TABLE I

ABSORPTION BANDS OF COBALT CHLORIDE DOUBLE SALTS

Cs_3CoCl_5			Cs_2CoCl_4			$(PyH)_2CoCl_4$			$(QuH)_2CoCl_4$			$(QuH)_2CoCl_4 \cdot H_2O$		
ν, cm.$^{-1}$	Width, cm.$^{-1}$	Int.	ν, cm.$^{-1}$	Width, cm.$^{-1}$	Int.	ν, cm.$^{-1}$	Width, cm.$^{-1}$	Int.	ν, cm.$^{-1}$	Width, cm.$^{-1}$	Int.	ν, cm.$^{-1}$	Width, cm.$^{-1}$	Int.
14258	200	10	14258	230	10	14299	290	10	14242	220	10	14269	310	10
15021	190	10	14988	220	10	15000	180	10	15000	220	10	15036	220	10
15403	130	8	15393	130	9	15524	170	8	15496	180	8	15496	140	8
15783	140	9	15803	140	10	15881	210	9	15811	230	9	15868	220	9
16238	110	9	16242	120	9	16311	140	8	16281	160	8	16314	170	8
16583	90	8	16570	180	8	16725	140	7	16698	140	7	16681	100	7
17262	200	4	17198	170	3	17308	150	4	17227	120	3	17246	120	4
17703	180	2	17635	150	2	17698	120	3	17698	120	2	17684	90	3
18073	90	3	18072	140	3	18066	130	4	18067	170	3	18053	130	4
18642	180	6	18600	120	6	18623	180	5	18621	140	5	18606	110	5
18872	160	6	18837	120	6	18915	130	6	18897	190	6	18867	160	6
19273	130	1				19305	180	4				19258	100	2
19659	160	2	19559	180	5	19684	170	2	19667	220	3	19647	180	3
20153	340	1				20284	350	1	20320	270	2	20243	260	1
21909	110	4	21889	180	2	21918	170	4	21896	160	2	21876	170	2
22155	100	5	22143	130	5	22210	200	3	22152	160	2	22148	140	3
22410	140	4	22444	160	4	22498	180	3	22462	120	3	22446	120	3
22843	160	0	22832	170	0	22856	100	0	22800	120	1	22765	110	1
24044	100	1	24040	110	2	24026	110	2	24018	100	0	23996	120	0
24510	110	2	24497	120	1	24489	90	1	24462	130	0	24442	140	0

number of components, six, of the group in the red is the same for the solution and for the crystals although the bands in solution are somewhat more diffuse. The remaining groups of bands show less structure in the spectrum of the solution than in the spectra of the crystals. For these groups, however, the curve for the solution follows approximately the envelope of the bands for the crystals if slight shifts in the positions of some of the groups are made. This comparison indicates that the differences between the two spectra are due principally to the effects of thermal agitation in solution. Therefore, the conclusion that the same complex is responsible for the absorption by the solution and by the crystals may be drawn.

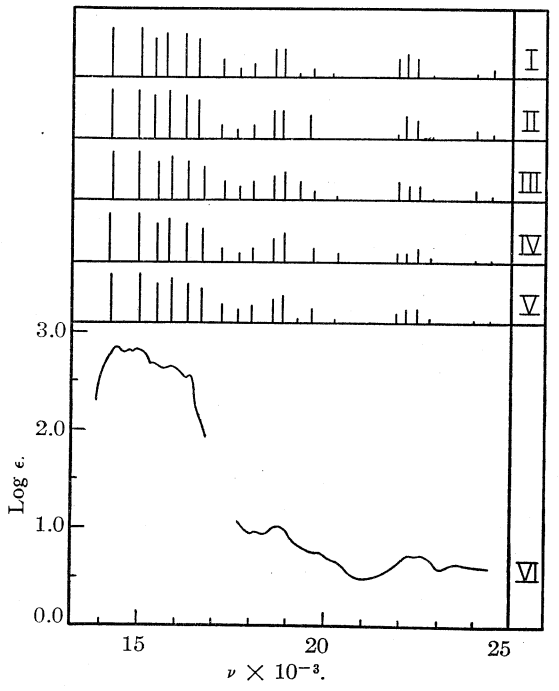


Fig. 1.—The absorption spectrum of $CoCl_4^=$ in: I, Cs_3CoCl_5; II, Cs_2CoCl_4; III, $(PyH)_2CoCl_4$; IV, $(QuH)_2CoCl_4$; V, $(QuH)_2CoCl_4 \cdot H_2O$; VI, cobalt chloride in hydrochloric acid (from data of Brode and Morton[3,4]).

Brode[3] and Brode and Morton[4] have shown that their absorption curve for the solution may be analyzed into components each of which is a multiple of a frequency of 409 cm.$^{-1}$. Although there are minor discrepancies between their data and those of Kiss and Gerendas,[5] the spectrum reported by the latter for these same solutions may be analyzed in the same fashion. The wave numbers, ν, of the bands found, including those in the ultraviolet which were not studied by Brode and Morton, may be represented by an expression of the form

$$\nu = a + bn$$

in which a and b are constants and n is a running positive integer. The values of a and b which give the best fit between the calculated and experimental wave number values are found in Table II. The constant frequency difference, 416 cm.$^{-1}$, is in approximate agreement with the value of Brode and Morton.

The absorption spectra of the crystals may be represented by similar expressions. The con-

TABLE II [*]

	a, cm.$^{-1}$	b, cm.$^{-1}$	Av. dev., cm.$^{-1}$
$CoCl_2$ in HCl[a]	14302	416	68
Cs_3CoCl_5	14225	393	57
Cs_2CoCl_4	14231	391	69
$(PyH)_2CoCl_4$	14304	390	73
$(QuH)_2CoCl_4$	14236	391	64
$(QuH)_2CoCl_4 \cdot H_2O$	14282	389	74

[a] Analysis based on the data of Kiss and Gerendas.[5]

stants, together with the average deviations between the calculated and experimental values of ν, are listed in Table II. The latter are somewhat larger than the experimental uncertainties in the wave number values of the bands but are of the same order of magnitude. Since the bands are from 100 to 300 cm.$^{-1}$ in width, the deviation might be due, in part, to slight systematic errors in picking out the band maxima.

In view of these regularities, following a suggestion made recently by one of us[9] for several other complex ions, these spectra may be interpreted as having originated in electronic transitions for which vibrational structure characteristic of the $CoCl_4^{--}$ complex ion is developed. It may be noted that the average frequency for the complex in solution, 413 cm.$^{-1}$, differs by 22 cm.$^{-1}$ from the average value of the crystals, 391 cm.$^{-1}$. Since the frequencies of the normal vibrations of the complex depend on the force constant of the cobalt–chlorine bond and since the frequency found here is probably that of the totally symmetric vibration, the existence of this difference indicates that the binding energy of the complex ion in the crystal is smaller than in solution.

(9) M. L. Schultz, *J. Chem. Phys.*, **10**, 194 (1942).

Although each observed band in the spectra of the crystals (and in the solution as well) is represented by an integral value of n, not all values of n represent observed bands. This, together with the somewhat unsatisfactory fit of the group of bands at 22,000 cm.$^{-1}$ into the suggested analysis, indicates that this analysis is too simple. Probably several electronic transitions, each with its associated vibrational structure, occur. With the data at present available, no reliable energy level diagram can be constructed. It is the intention in this Laboratory to study the spectra of these crystals at low temperatures in order to obtain information which might permit the construction of such a diagram and also in order to study in more detail the effect of the environment upon the spectrum.

Summary

1. The absorption spectra of crystals of two cesium cobaltous chlorides, dipyridinium cobaltous chloride, diquinolinium cobaltous chloride and diquinolinium cobaltous chloride monohydrate have been measured.

2. Comparison of the spectra of these crystals with the spectrum of the solution of cobaltous chloride in concentrated hydrochloric acid shows that the same complex ion, $CoCl_4^{--}$, is present in all.

3. A tentative analysis of the spectra of the crystals has been made. This analysis suggests that the spectra may be considered to originate in coupled electronic-vibrational transitions.

CHICAGO, ILLINOIS RECEIVED JULY 27, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

Some Boron Trifluoride Catalyzed Alkylations of Halobenzenes[1]

BY G. F. HENNION AND V. R. PIERONEK

Introduction

Previous work in this Laboratory has shown that boron trifluoride, in the presence of a strong dehydrating agent such as phosphoric anhydride or sulfuric acid, is an excellent catalyst for the alkylation of benzene[2] and its homologs[3] with alcohols. This method was extended in the present work to the halobenzenes.

In many respects boron trifluoride has been found superior to aluminum chloride for these alkylations. With aluminum chloride there may be considerable halogen migration to produce benzene, dihalobenzene and alkylbenzene as well as the desired alkylhalobenzene.[4,5] Furthermore, the aluminum chloride methods result in both meta and para substitution,[6,7] thus giving an

(1) Paper XXVII on organic reactions with boron trifluoride; XXVI delayed in press; XXV, THIS JOURNAL, **63**, 2603 (1941).

(2) Toussaint and Hennion, *ibid.*, **62**, 1145 (1940).

(3) Welsh and Hennion, *ibid.*, **63**, 2603 (1941).

(4) Dumreicher, *Ber.*, **15**, 1866 (1882).

(5) Berry and Reid, THIS JOURNAL, **49**, 3146 (1927).

(6) Tsukervanik, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 1512 (1938); *C. A.*, **33**, 4587 (1939).

(7) Dreisbach, Britton and Perkins, U. S. Patent 2,193,760 (1940).

TABLE I

PHYSICAL CONSTANTS AND ANALYSES OF *p*-*s*-ALKYLHALOBENZENES

Compound	Yield, %	B. p., °C.	Mm.	$n^{20}D$	d^{20}	Mol. wt. Calcd.	Mol. wt. Obsd.[a]	% Halogen Calcd.	% Halogen Obsd.[b]
2-*p*-Chlorophenylpropane	63.0[c]	66–72	11	1.5109	1.0190	152.5	150.5	23.30	22.77
2-*p*-Chlorophenylbutane	66.4	81–82	8	1.5095	1.0122	166.5	167	21.29	21.28
2-*p*-Chlorophenylpentane	35.0	93–96	9	1.5040	0.9951	180.5	173	19.65	19.30
3-*p*-Chlorophenylpentane	33.6	95	10	1.5049	0.9934	180.5	177	19.65	19.50
p-Chlorophenylcyclohexane	34.0	145–7	19	1.5585	1.0753	194.5	192	18.34	18.20
2-*p*-Chlorophenyloctane	45.0	106–8	3	1.4971	0.9553	223.5	220	15.88	15.75
2-*p*-Bromophenylpropane	31.7	58–60	3	1.5379	1.2936	197	195	40.61	40.54
2-*p*-Bromophenylbutane	35.3	96–98	8	1.5290	1.2225	211	211	36.92	36.70
2-*p*-Bromophenylpentane	27.3	68–72	3	1.5240	1.1988	225	219	36.00	35.90
2-*p*-Iodophenylbutane	31.7	92–94	3	1.5651	1.4438	258	260	49.30	48.90
2-*p*-Iodophenylpentane	19.1	94–97	3	1.5538	1.3636	272	268	46.67	46.20

[a] Cryoscopic in cyclohexane. [b] Sodium-liquid ammonia method. [c] Polyalkylation product 15.1%.

undesirable mixture. Boron trifluoride is a less drastic catalyst. No migrations of the halogen on the benzene nucleus were observed, nor were any dehalogenated products isolated. Moreover, oxidation of the alkylhalobenzenes to the *p*-halobenzoic acids reveals that the orientation of the product is entirely para when boron trifluoride is used as a catalyst.

The reactions were found to proceed analogously to those described in previous papers.[2,3] The yields decrease with the increasing molecular weight of the alcohol or halobenzene used, and with the increasing tendency of the alcohol toward dehydration. Isomeric primary and secondary alcohols were found to give the same product, *p*-*s*-alkylhalobenzene. This was proved by the reaction of *p*-*s*-butylchlorobenzene (from *n*-butyl alcohol) with sodium in liquid ammonia at −34°, which gave a 10% yield of *p*-*s*-butylaniline and a 50% yield of *s*-butylbenzene. The various reaction products are described in Table I.

Experimental

Procedure.—The halobenzene was weighed into a one-liter, three-neck, round-bottom flask, equipped with an efficient oil-sealed stirrer, a reflux condenser and a thermometer. The alcohol was then added and mixed with the halobenzene. The flask was cooled in ice-water and boron trifluoride introduced below the liquid surface until the appearance of white fumes above the condenser indicated that the reactants were saturated. It was found, in every case, that the mixture at this point had absorbed one mole of boron trifluoride per mole of alcohol. Phosphorus pentoxide (0.25 mole per mole of alcohol) was then added as quickly as possible. The temperature was raised *slowly* to about 75–85° and maintained there for about six hours. The heating was then stopped, the mixture cooled with ice-water and then poured into a separatory funnel. The lower layer was discarded and the upper washed with water, twice with 10% solution of sodium carbonate, and finally with water. After drying with calcium chloride the material was distilled through an efficient column. The yields in Table I represent products of narrow refractive index range after two distillations.

Oxidation.—Small samples (0.2 to 0.3 g.) were oxidized with sodium dichromate (3.5 g.) and sulfuric acid (5.0 ml.) in (6.0 ml.) acetic acid solution at 70–75°. Melting points of the *p*-halobenzoic acids agree with literature values: *p*-chloro, 242°; *p*-bromo, 252°; *p*-iodo, 269–270°.

Summary

1. Boron trifluoride, with phosphoric anhydride as an adjunct, has been shown to be an effective catalyst in the condensation of alcohols with chloro-, bromo- and iodobenzenes.

2. Satisfactory yields of *p*-*s*-alkylhalobenzenes are readily obtained in this manner.

NOTRE DAME, INDIANA RECEIVED JULY 27, 1942

[CONTRIBUTION NO. 304 FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF TEXAS]

The Nitrogen Compounds in Petroleum Distillates. XXIV. Isolation and Identification of a $C_{11}H_{17}N$ Base from California Petroleum

BY H. L. LOCHTE, W. W. CROUCH[1] AND E. D. THOMAS

The identification of the $C_{16}H_{25}N$ base isolated by Thompson and Bailey[2] from the kerosene distillates of California petroleum as 2-(2,2,6-trimethylcyclohexyl)-4,6-dimethylpyridine[3] suggests that the so-called "non-aromatic" bases of Perrin and Bailey[4] might consist of mixtures of highly substituted pyridines. These bases are separated from the other bases present in kerosene distillates by extraction of an aqueous solution of the mixed base hydrochlorides with chloroform, the "non-aromatic" base hydrochlorides being found in the chloroform layer. The mixture of bases remaining in the water layer always has the higher refractive index and density, and a number of these compounds have been identified by Bailey and co-workers as alkylated quinolines.

Besides the $C_{16}H_{25}N$ base, two other bases having physical constants and chemical properties similar to the known alkylated pyridines have been isolated previously from the chloroform-soluble hydrochlorides of petroleum bases. These are a $C_{10}H_{15}N$ base isolated by Roberts[5] and a $C_{13}H_{21}N$ base isolated by Armendt,[6] neither of which has been identified.

The bases used in this study were recovered from the hydrochlorides found in the chloroform layer after extraction of an aqueous solution of the hydrochlorides of kerosene bases boiling at 210–213°. After fractional distillation and fractional extraction with hydrochloric acid, the fractions were sufficiently pure to form crystalline picrates from which pure bases were recovered. A $C_{11}H_{17}N$ base was isolated and identified as *dl*-2-*s*-butyl-4,5-dimethylpyridine by the following facts: (1) condensation of the base with benzaldehyde to form a mono-addition compound indicated that one methyl group was in position 2, 4 or 6 on the pyridine ring. (2) Failure of the base to condense with acetic anhydride to form a picolide showed that the reactive methyl group was not in position 2 or 6. (3) Ozonolysis to produce diacetyl indicated that two methyl groups were present in adjacent positions. (4) Isolation of the amide of *dl*-methylethylacetic acid after ozonolysis showed that a secondary butyl group was at position 2. (5) The structure was confirmed by permanganate oxidation to give pyridine-2,4,5-tricarboxylic acid.

Small quantities of two other bases were isolated by means of crystalline picrates analysis of which corresponded to formulas of $C_{12}H_{19}N$ and $C_{13}H_{21}N$ for the bases. While not obtained in sufficient quantities for identification, the physical characteristics and formulas of the bases suggest that they are probably alkylated pyridines.

Experimental

The material for this investigation consisted of 6.8 liters of bases that had been obtained from kerosene distillates, carefully fractionated and donated to this Laboratory in 1940 by the Union Oil Company of California. The boiling point of the material used ranged from 210–213° and the index of refraction at 20° from 1.4982 to 1.5040. The mixture was acidified with 3750 cc. of concentrated hydrochloric acid in 4 kg. of chipped ice, then divided into six aliquots and extracted by stirring successively with six portions of 1500 cc. of chloroform, the chloroform then being washed with 800-cc. portions of water similar to the multiple-fractional-extraction method described by Morton.[7] The chloroform was distilled off and the base was recovered by addition of sodium hydroxide solution. In this way there was obtained 2 liters of material with $n^{20}D$ 1.4922–1.4904. It was combined and distilled at 20 mm. through a 12-ft. packed column with 10:1 reflux ratio; b. p. 99–103° (20 mm.).

Fractional Acid Extraction.—The highest boiling material from the distillation, 190 g. with $n^{20}D$ 1.4916, was dissolved in 500 cc. of petroleum ether and extracted in thirteen fractions using the apparatus of Fig. 1. A 1.5 *N* solution of hydrochloric acid was introduced into the top flask, extracting the base from the solvent and passing down the spinner[8] column. At the bottom of the column, 1.5 *N* sodium hydroxide solution was added at one-half the rate of addition of the acid so that one-half of the base was released and carried up the column by the rising stream of petroleum ether, thus furnishing reflux for the descending salt solution. The aqueous extract was taken off in 300-cc. portions from which the base was recovered, volume and refractive indices of the fractions being shown in Table I.

(1) Research Assistant, University Research Institute Project No. 49.

(2) Thompson and Bailey, THIS JOURNAL, **53**, 1002 (1931).

(3) Shive, Roberts, Mahan and Bailey, *ibid.*, **64**, 909 (1942).

(4) Perrin and Bailey, *ibid.*, **55**, 4136 (1933).

(5) Roberts, Ph.D. Thesis, The University of Texas, 1939.

(6) Armendt, Ph.D. Thesis, The University of Texas, 1932.

(7) Morton, "Laboratory Technique in Organic Chemistry, McGraw-Hill Book Co., Inc., New York, N. Y., 1938, p. 200.

(8) Schutze and Lochte, *Ind. Eng. Chem., Anal. Ed.*, 10 675 (1938).

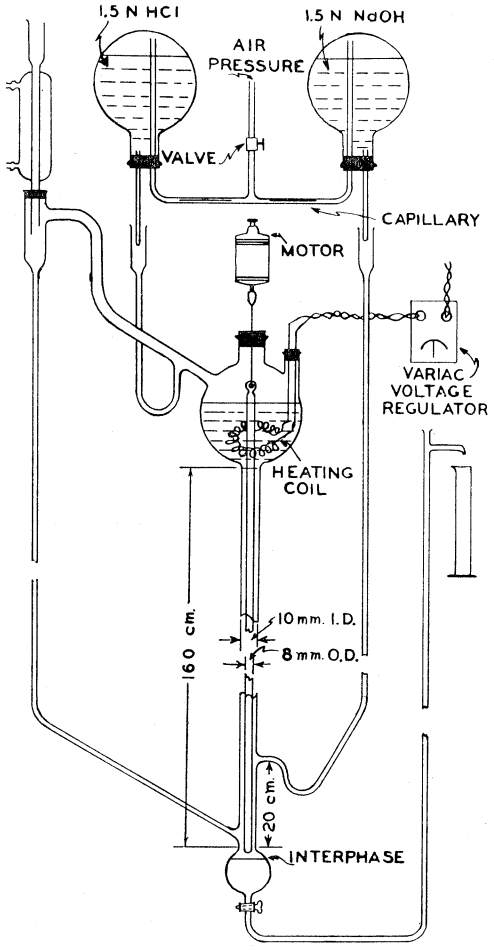


Fig. 1.

Isolation of the $C_{11}H_{17}N$ Base.—To one-gram samples of these fractions dissolved in sulfurous acid solution, 1.5 g. of picric acid in saturated aqueous solution was added. Oily picrates formed but after several days in the icebox the picrate of fraction 6 crystallized. It was recrystallized from ethyl alcohol and dilute acetic acid to a constant melting point of 127–128°.

Anal. Calcd. for $C_{17}H_{20}O_7N_4$: C, 52.04; H, 5.14; N, 14.28. Found: C, 52.12; H, 4.99; N, 14.13.

By seeding the other fractions with the pure picrate,

TABLE I

Fraction no.	Volume, cc.	$n^{20}D$
1	8	1.4943
2	12	1.4921
3	12	1.4921
4	13	1.4931
5	10	1.4938
6	14	1.4938
7	14	1.4936
8	13	1.4925
9	13	1.4907
10	15	1.4901
11	14	1.4880
12 (Residue)	33	1.4871

crystals were obtained from fractions 4–8. They were recrystallized until pure and warmed with excess concentrated ammonium hydroxide to give the free base which was separated, washed, dried over solid sodium hydroxide and distilled; b. p. 214° (752 mm.); d^{20}_4 0.8991; $n^{20}D$ 1.4947.

Anal. Calcd. for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58. Found: C, 80.89; H, 10.44; N, 8.47.

From fractions 5 and 6, 40% by weight of the mixture was recovered as pure base. More of the base was obtained by processing in a similar way petroleum bases from the same source boiling at 214–215.5°.

Condensation of the $C_{11}H_{17}N$ Base with Benzaldehyde.—Two grams of the base, 4 g. of benzaldehyde and 0.5 g. of zinc chloride were heated for twenty-four hours at 200° in a sealed tube. The dark, viscous product was shaken with 2 *N* hydrochloric acid but only a few drops of base was recovered from the water layer. The residue was washed twice with ether to remove benzaldehyde, made alkaline with sodium hydroxide solution, separated, dissolved in alcohol and added to two grams of picric acid in alcohol. Three grams of the picrate of the benzal derivative was obtained which was recrystallized to a constant melting point of 143°.

Anal. Calcd. for $C_{24}H_{24}O_7N_4$: C, 59.99; H, 5.03. Found: C, 59.98; H, 5.05.

Attempted Condensation of the $C_{11}H_{17}N$ Base with Acetic Anhydride.—Following the procedure employed by Scholtz[9] for the condensation of acetic anhydride with 2-methyl- and 2,4-dimethylpyridine, 1.7 g. of the natural base was heated with 10 g. of acetic anhydride for eight hours at 210° in a sealed tube. The dark, resinous product was heated with water, alcohol and chloroform in an attempt to obtain a crystalline picolide. No such compound was obtained by cooling or evaporating the solvents.

Ozonolysis of the $C_{11}H_{17}N$ Base.—Through 4 g. of the $C_{11}H_{17}N$ base dissolved in 20 cc. of carbon tetrachloride and cooled to 0° there was passed a stream of 10% ozone at a rate of 1200 cc. per hour for four hours. Five grams of 30% sodium hydroxide solution was added and the mixture shaken vigorously for ten minutes, during which white crystals separated. They were filtered off, the carbon tetrachloride layer was dried, and the ozonolysis repeated. In this way, 250 mg. of amide was obtained melting, after recrystallization from benzene–petroleum ether, at 112°. A mixed melting point showed it to be the amide of *dl*-methylethylacetic acid.

Anal. Calcd. for $C_5H_{11}ON$: N, 13.85. Found: N, 13.71.

The ozonolysis was repeated, the ozonide was decomposed by adding water and stirring, and *p*-nitrophenylhydrazine hydrochloride solution was added to the product. The mixture was warmed and the dark red crystals of the *p*-nitrophenylosazone of diacetyl separated. It was recrystallized from nitrobenzene and melted with decomposition at 332°. The melting point and mixed melting point of this derivative of synthetic diacetyl showed the two compounds to be identical.

Permanganate Oxidation of the $C_{11}H_{17}N$ Base.—Ten grams of the base was added to two liters of 2% potassium

(9) Scholtz, *Ber.*, **45**, 734 (1912).

permanganate solution and the mixture was stirred on a steam-bath with reflux. After twelve hours the solution was decolorized and 40 g. more of potassium permanganate was added in concentrated solution. After twelve hours the addition was repeated, after which the solution was not completely decolorized by heating for four days. The excess permanganate was reduced with formaldehyde, the solution was filtered, concentrated to 200 cc. and neutralized with dilute nitric acid. Silver nitrate solution was added and the flocculent precipitate of silver salt was filtered, washed, dissolved in ammonium hydroxide and reprecipitated in three fractions by the slow addition of 1 *N* nitric acid. The second fraction was suspended in water and hydrogen sulfide passed into the mixture. The silver sulfide was removed and the solution evaporated to leave white crystals of pyridine-2,4,5-tricarboxylic acid, melting with decomposition at 242–243°. It was recrystallized from dilute hydrochloric acid from which it precipitated slowly. The air-dried sample was heated one hour at 120° to remove water of crystallization.[10]

Anal. Calcd. water of crystallization for $C_8H_5O_6N \cdot H_2O$: H_2O, 7.86. Found: H_2O, 7.90.

The anhydrous acid was analyzed for nitrogen.

Anal. Calcd. for $C_8H_5O_6N$: N, 6.63. Found: N, 6.69.

The acid was readily soluble in water and gave a dark red color with ferrous sulfate solution. It was heated to 170° without appreciable carbon dioxide evolution, a reaction that is reported[11] to be rapid above 140° for pyridine-2,3,6-tricarboxylic acid. It was apparently unaffected by boiling for two hours with acetic anhydride, giving none of the chloroform-soluble cinchomeronic anhydride which is formed[12] by this treatment of pyridine-2,3,4-tricarboxylic acid.

Isolation of a $C_{12}H_{19}N$ Base.—An intermediate fraction of bases from the distillation described above, 80 g. with $n^{20}D$ 1.4904 and b. p. 101° (20 mm.), was extracted from 500 cc. of petroleum ether in seven fractions using the apparatus of Fig. 1. Fraction 6 was converted to the picrate as described above, giving a crude picrate which was recrystallized repeatedly from dilute ethanol and dilute acetic acid to a constant melting point of 174°.

Anal. Calcd. for $C_{18}H_{22}O_7N_4$: C, 53.20; H, 5.46. Found: C, 53.20; H, 5.51.

One-half gram of the picrate was heated with concentrated ammonium hydroxide to liberate the base which was extracted in ether, dried and distilled in a semi-micro distillation apparatus. A middle fraction gave the following constants: b. p. 214° (754 mm.); $n^{20}D$ 1.4832.

Anal. Calcd. for $C_{12}H_{19}N$: N, 7.90. Found: N, 7.79.

Isolation of a $C_{13}H_{21}N$ Base.—Fraction 7 of the extraction series described above from which the $C_{12}H_{19}N$ base was obtained was converted to the picrate and recrystallized repeatedly to give yellow needles having a constant melting point of 121°.

Anal. Calcd. for $C_{19}H_{24}O_7N_4$: C, 54.28; H, 5.75; N, 13.33. Found: C, 53.87; H, 5.74; N, 13.52.

Summary

1. A sample of California petroleum bases boiling at 210–213° has been fractionated by efficient methods of extraction and distillation to yield products of sufficient purity that crystalline picrates of three new bases were obtained.

2. By a process of degradation a $C_{11}H_{17}N$ base has been identified as *dl*-2-*s*-butyl-4,5-dimethylpyridine.

3. Two other bases having molecular formulas of $C_{12}H_{19}N$ and $C_{13}H_{21}N$ were isolated in quantities too small for identification. It is believed that they are also alkylated pyridines.

AUSTIN, TEXAS RECEIVED JULY 31, 1942

(10) Weidel, *Ber.*, **12**, 410 (1879).
(11) Weiss, *ibid.*, **19**, 1310 (1886).
(12) Kirpal, *Monatsh.*, **26**, 53 (1905).

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 909]

Stereoisomeric Diphenyloctatetraenes

BY L. ZECHMEISTER AND A. L. LEROSEN

While some earlier authors[1] have denied the existence of *cis–trans*-isomers in the case of an extended conjugated double bond system, Kuhn[2] correctly summarized the situation in 1933 by the following statement: ". . . according to the available evidence a strong accumulation of double bonds does not exclude the occurrence of *cis–trans*-isomerism. That the higher diphenylpolyenes are known only in one spatial form is due to the inadequacy of the preparative methods." In the series mentioned, $C_6H_5(CH{=}CH)_nC_6H_5$, so far as we know, stereoisomeric forms have been obtained[3] only in the case $n < 3$. According to X-ray studies by Hengstenberg and Kuhn[4] the prepa-

(1) G. Wittig and W. Wiemer, *Ann.*, **483**, 144 (1930).
(2) R. Kuhn, in Freudenberg's "Stereochemie," F. Deuticke, Vienna, 1933, p. 915.
(3) F. Straus, *Ann.*, **342**, 190 (1905). An alleged white modification of diphenyl-octatetraene (H. Stobbe, *Ber.*, **42**, 567 (1909)) was later identified as stilbene by R. Kuhn and A. Winterstein (footnote 5). Accordingly, text and formulas on pp. 179–180 of the following book should be corrected: G. Egloff, G. Hulla and V. I. Komarewsky, "Isomerization of Pure Hydrocarbons," Reinhold Publishing Corp., New York, N. Y., 1942.
(4) J. Hengstenberg and R. Kuhn, *Z. Krystall. Miner.*, **75**, 301 (1930).

rations of Kuhn and Winterstein[5] represent all-*trans* forms in case of $n = 3$ or 4.

In contrast, the existence of a great number of stereoisomers has recently been demonstrated for naturally occurring polyenes, the carotenoids. For example, 14 stereoisomeric lycopenes, $C_{40}H_{56}$, have been reported, and one of them, prolycopene containing 4 or 5 *cis*-double bonds, has been isolated from natural sources.[6] A partially *cis* γ-carotene, *viz.*, *pro*-γ-carotene,[7] $C_{40}H_{56}$, also occurs in nature. Many stereoisomers can be obtained from β-carotene[8] in addition to Gillam's pseudo-α-carotene.[9]

Considering these facts a stereochemical reinvestigation of diphenylpolyenes was desirable. We have mentioned briefly[10] that some methods in use for the isomerization of carotenoids are applicable to synthetic polyenes.

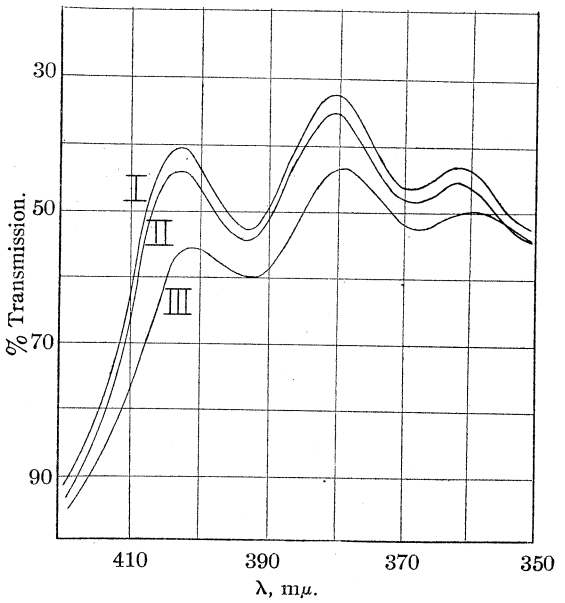


Fig. 1.—Isomerized diphenyloctatetraene in benzene. Light absorption curves of a chromatographic filtrate containing chiefly zone 2. The curves III, II, and I were taken after zero, one, and two days, respectively. Curve I remained constant on the fourth day. (Abscissa: wave length, ordinate: percentage transmission measured in the Beckman photoelectric spectrophotometer.[11])

The stereochemical homogeneity and the all-*trans* configuration of 1,8-diphenyloctatetraene (prepared according to Kuhn and Winterstein[5]) can be demonstrated chromatographically. A single zone, showing an intense light yellow fluorescence in ultraviolet light, appeared on the lime column. When, however, a benzene solution of this zone was refluxed, irradiated, or treated with iodine, or if crystals were melted for a short time, subsequent chromatography gave three well separated, fluorescing zones in each case. The upper one was identical with the single all-*trans* zone mentioned. The two other fractions possess *cis*-configurations of some double bonds which will be designated below.

It is easy to isomerize about one-sixth of the starting material, *e. g.*, the weight ratio of the three isomers was 83:15:2 from top to bottom of the Tswett column (weighed in form of the regenerated all-*trans* isomer). In some favorable cases two additional minor isomers appeared below the main zones. In this way five of the ten theoretically possible isomers were observed. They are designated as zones 1–5 (no. 1 = all-*trans* top zone).

All diphenyloctatetraenes containing *cis*-double bonds are labile. Their solutions when kept at room temperature contain a gradually increasing quantity of the all-*trans* form. The conversion becomes manifest by a decreasing light-transmission until a constant end value is reached (Fig. 1). This conversion has been followed and confirmed chromatographically.

Analogous changes were observed by starting from solid samples obtained by almost instantaneous evaporation of solutions of the zones 2–5 which had been washed through the column. Adsorption analysis showed that the fresh solution of the dry residue contained very little of the all-*trans* isomer, the quantity of which, however, rapidly increased on standing. Because of these circumstances we were unable (even working at 5°) to isolate samples of a *cis*-isomer for which the absence of the all-*trans* compound could be conclusively proved. Attempts to crystallize individual *cis*-compounds, contained in chromatographic zones, using the ordinary methods of elution and isolation so far gave only crystals of the *trans*-isomer. Combustion analysis of some isomerized, chromatographed and reconverted

(5) R. Kuhn and A. Winterstein, *Helv. Chim. Acta*, **11**, 87, 116, 123, 144 (1928).

(6) L. Zechmeister, A. L. LeRosen, F. W. Went and L. Pauling, *Proc. Nat. Acad. Sci.*, **27**, 468 (1941); A. L. LeRosen and L. Zechmeister, THIS JOURNAL, **64**, 1075 (1942); L. Zechmeister and R. B. Escue, *J. Biol. Chem.*, **144**, 321 (1942).

(7) L. Zechmeister and W. A. Schroeder, *Science*, **94**, 2452 (1941); THIS JOURNAL, **64**, 1173 (1942); *J. Biol. Chem.*, **144**, 315 (1942); W. A. Schroeder, THIS JOURNAL, **64**, 2510 (1942).

(8) A. Polgár and L. Zechmeister, THIS JOURNAL, **64**, 1856 (1942). The same statement is valid for α-carotene.

(9) A. E. Gillam and M. S. El Ridi, *Biochem. J.*, **30**, 1735 (1936); *ibid.*, **31**, 1605 (1937) [with S. K. Kon]; G. R. Carter and A. E. Gillam, *ibid.*, **33**, 1325 (1939).

(10) L. Zechmeister and A. L. LeRosen, *Science*, **95**, 587 (1942).

(11) H. H. Cary and A. O. Beckman, *J. Opt. Soc. Am.*, **31**, 682 (1941).

samples (zones 2 and 3) proved, however, that no other change but a spatial shift within the molecule had taken place during the operations.

Another characteristic feature showing the lability of the new isomers is the very rapid reconversion of adsorbed material under the quartz lamp. In a suitably developed chromatogram those portions of zone 2 which were adsorbed on the cylindrical surface of the column, when exposed to ultraviolet light for a minute, showed on further washing a division into two fluorescing layers. The inside of the column showed only the original zone but none of the all-*trans* zone formed locally by the irradiation of the surface.

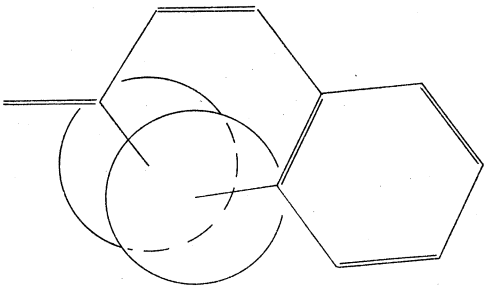


Fig. 2.—Model of one molecule end of diphenyloctatetraene (values used: C=C, 1.33 Å.; C—C, 1.46 Å.; C_6H_5—C, 1.44 Å.; C_6H_5—H, 1.08 Å.; C—H, 1.09 Å.; H-radius, 1.20 Å.; angles C=C—C and C=C—H, 124°20′.

With reference to the configuration of the individual diphenyloctatetraenes the following remarks can be made. Figure 2 shows that if an end double bond of the aliphatic chain assumes *cis*-configuration, a hydrogen atom of the nucleus, in opposition to the side chain, is spatially hindered by one of the hydrogens of the latter so that planar or approximately planar configuration becomes impossible for the molecule. The calculated deviation is about 52.5°. Therefore if the all-*trans* compound is isomerized, great preference will be given to the formation of stereoisomers in which the two end double bonds remain in *trans*-position. Instead of nine isomeric tetraenes possessing *cis*-bonds only two will be formed in any substantial quantity. We believe that these are contained in the two main zones produced by isomerization for which we suggest the following probable configurations

Zone 1 (top) *trans–trans–trans–trans*
Zone 2 (middle) *trans–cis–trans–trans*
Zone 3 (bottom) *trans–cis–cis–trans*

As with *cis*-stilbene, $C_6H_5CH{=}CHC_6H_5$, and *cis*-diphenylbutadiene, $C_6H_5(CH{=}CH)_2C_6H_5$, "hindered" isomers are also formed; this is shown by the minor zones 4 and 5 of the isomerized tetraene chromatogram. In the case of the octatetraene, isomerization is distributed between the several sterically possible types, some of which may be formed without significant steric hindrance others of which may involve definite spatial conflicts. Since the former types provide preferred configurations which may be assumed by the molecule, the sterically "hindered" types will not have the opportunity to play the prominent role which they have been found to assume in the case of stilbene (and diphenylbutadiene) in which the "hindered" isomer is without competition from other and more stable forms.

In the field of the carotenoids, according to Pauling,[12] the group >C=CH—C(CH$_3$)< constitutes a complete hindrance for a *trans–cis*-shift. The number of the expected *cis–trans*-isomers (occurring in substantial quantities) can be reduced on the basis of spatial considerations both in the class of natural and synthetic polyenes.

Acknowledgment.—The authors wish to thank Dr. R. B. Corey for valuable advice and Dr. G. Oppenheimer as well as Mr. G. Swinehart for microanalyses.

Experimental

1,8-Diphenyloctatetraene was synthesized according to Kuhn and Winterstein.[5] After recrystallization from

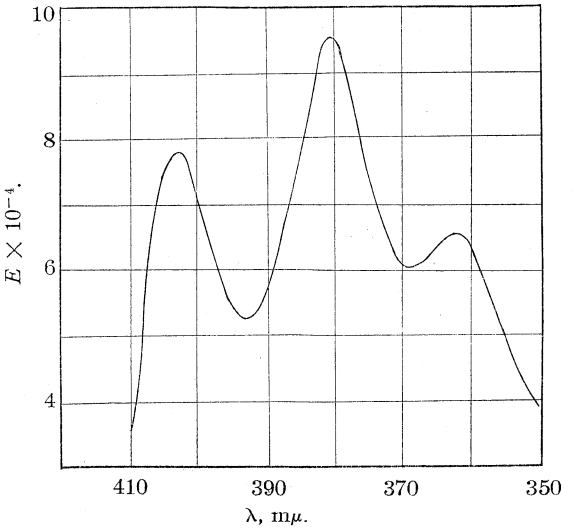


Fig. 3.—Absorption curve of all-*trans*-diphenyloctatetraene in benzene. (Abscissa, wave length; ordinate, mol. extinction coefficient.) $E = \frac{1}{Lc}\log\frac{I_o}{I}$.

(12) L. Pauling, *Fortschr. Chem. Organ. Naturstoffe*, **3**, 203 (1939).

chloroform the yellow plates melted at 235–237° (cor.). The absorption curve is given in Fig. 3.

Anal. Calcd. for $C_{20}H_{18}$: C, 92.97; H, 7.03. Found: C, 93.27; H, 7.23.

Chromatographed on calcium hydroxide (Shell brand chemical hydrate, 98% through 325 mesh) as described below, a solution of the crude or of the purified crystals showed homogeneity. The zones as well as those of stereoisomers are best located during the development on a Tswett column by means of a portable quartz lamp in the dark. Intense light yellow fluorescence appears.

1. Isomerization in Solution by Heat.—A solution of 0.4 g. of diphenyloctatetraene in about 200 ml. of benzene was gently refluxed for several hours, brought to 225 ml. (in order to prevent precipitation) and diluted with 3 volumes of light petroleum (b. p. 60–70°). The solution was immediately poured on the adsorbent in a percolator (40 × 16 × 8 cm.) under suction. After washing with light petroleum the chromatogram was developed with benzene–light petroleum 1:10 within a few hours. Below the main zones of unchanged all-*trans* compound a second and a smaller third zone appeared, followed by traces of two minor fractions. All zones (termed 1–5, from top to bottom) were well separated by non-fluorescing intermediate sections. Each of the main zones was cut out, eluted with benzene-methanol 3:1, quickly washed alcohol-free in a special apparatus,[13] dehydrated with sodium sulfate within a few minutes and completely evaporated *in vacuo*. Each dry residue was dissolved in dioxane and precipitated with water. The zones 1–3 yielded 0.25 g., 0.05 g. and 0.005 g. of substance, respectively. All were identified as all-*trans* compounds by mixing them together and chromatographing; only one zone appeared.

Anal. Calcd. for $C_{20}H_{18}$: C, 92.97; H, 7.03. Found (zones 1–3): C, 92.72, 93.07, 92.43; H, 7.72, 7.37, 7.94.

In other experiments the elution of the isomers formed was made with ether which was evaporated directly. Each residue when chromatographed gave only a zone of the all-*trans* form.

2. Isomerization by Melting.—A sealed tube containing several milligrams of diphenyloctatetraene was kept in a bath of boiling diphenyl ether (b. p. 259°) for fifteen minutes. After rapid cooling in ice-water the material was dissolved in cold benzene and diluted with light petroleum. The chromatogram showed two isomers below the main zone of unchanged starting material. A second adsorption of the lower zones revealed the presence of a strong zone of the all-*trans* isomer, formed during the operations (elution, filtration, washing, drying).

Similar results were obtained by heating diphenyloctatetraene in melted diphenyl at 140° for five hours.

3. Isomerization by iodine catalysis in benzene solution at 25° in the dark produced the zones 1–3 within fifteen minutes as demonstrated chromatographically.

4. Photochemical Isomerization.—A benzene solution containing 2 mg. of diphenyloctatetraene per ml. was divided into two parts. One part was kept in diffuse light at 25° while the other was irradiated for twelve hours with a mercury quartz lamp (4 amp. d. c., voltage drop 32 v.) in a quartz tube. A half ml. of the irradiated solution, chromatographed on a column (25 × 1.7 cm.), after suitable development showed the following zones from top to bottom (the figures on the left side denote width of zones, in mm.):

10 *zone 1* (all-*trans*), strongly fluorescing
5 dark interzone
20 *zone 2*, fluoresced more weakly than 1, contained much less material
5 dark interzone
2.5 *zone 3*, well defined, similar to 2 in fluorescence
2 dark interzone
2 *zones 4 and 5*, not well differentiated (traces), easily washed into the filtrate.

The non-irradiated portion showed a similar chromatogram but a much smaller fraction of the adsorbed material was contained in the zones 2–5 than after irradiation.

In another set of experiments the modifications *a* and *b* were made:

a. The irradiated solution was poured on a short column prepared in a Gooch funnel (8 × 4 cm.) which was attached to a side neck of a three-neck flask (1 liter). Three fluorescing layers were visible. The two lower zones were slowly washed into the flask with benzene-light petroleum (1:1). The flask was immersed in hot water; each drop of the filtrate was rapidly evaporated by a current of air under reduced pressure. The whole procedure was followed by an ultraviolet lamp in the dark. In this way a solid residue was obtained consisting of a mixture of all-*trans* diphenyloctatetraene and a preponderant quantity of its steroisomers. A subsequent chromatogram showed a narrow top zone 1 of the all-*trans* form while zone 2 was four times broader. It was followed by a smaller layer, all separated by non-fluorescing sections.

A portion of the solid mixture was investigated spectrophotometrically in benzene solution, immediately and after twenty-four hours of standing. It shows considerably decreased transmission, corresponding to the formation of more *trans*-isomer.

b. In other experiments the first portion of the chromatographic filtrate was rechromatographed and the two lowest isomers were washed through with pure benzene. The light absorption curve was determined immediately as well as after one, two and three days of standing at room temperature. The transmission decreased considerably in the course of the first day, less in the second day and thereafter it remained constant. An equilibrium had been reached in which the all-*trans* form was predominant (Fig. 1).

Summary

Ordinary (all-*trans*) 1,8-diphenyloctatetraene, $C_6H_5(CH{=}CH)_4C_6H_5$ when heated, irradiated or treated with iodine in benzene solution is partially converted into two main stereoisomers which can also be obtained by melting of crystals. These labile isomers are adsorbed below the unchanged, all-*trans* compound in the lime column. Their solution re-isomerize spontaneously at room temperature. This has been followed chromatographically and photometrically. A similar but

(13) A. L. LeRosen, *Ind. Eng. Chem., Anal. Ed.*, **14**, 165 (1942).

more rapid change occurs on irradiation of adsorbed material. The configurations *trans–cis–trans–trans* and *trans–cis–cis–trans* are suggested for the new isomers mentioned. As two minor isomers also appear, five out of the ten possible steric forms of diphenyloctatetraene have been observed. It is shown that the formation of substantial quantities of certain isomers is prevented by spatial conflicts.

PASADENA, CALIFORNIA RECEIVED AUGUST 27, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF RADCLIFFE COLLEGE AND HARVARD UNIVERSITY AND THE DEPARTMENT OF BIOLOGICAL CHEMISTRY OF THE HARVARD MEDICAL SCHOOL]

Does the Parathyroid Hormone Influence Phosphatase Activity?

BY THOMAS R. WOOD AND WILLIAM F. ROSS

It is well established that serum phosphatase is markedly increased in rickets, hyperparathyroidism and other diseases characterized by lesions in the bones.[1,2,3] It has even been suggested that the action of phosphatases on organic phosphate compounds in bone "is the factor that controls the direction and intensity of calcification in bone."[3] This concept is supported by the increased serum phosphatase activity after parathyroid hormone injection,[4] and by similar changes in bone phosphatase of rats following injection of the hormone.[5,6]

The question arises, as to whether there is an *in vitro* influence of the parathyroid hormone on the activity of phosphatase. Such an effect, if reasonably pronounced, would afford a simple, economical, and rapid assay method for the hormone, which is sorely needed at the present time. Heymann[7] reported that glycerophosphatase and hexosediphosphatase of bone are inhibited by parathyroid extract, but Bakwin and Bodansky,[8] drew the opposite conclusion, that rat and cattle bone phosphatases are not affected. Both of the above studies involved the use of very small amounts of impure parathyroid preparations.

The effect of a very active parathyroid extract[9] on the hydrolysis of glycerophosphate by a kidney phosphatase preparation has therefore been investigated. The hormone concentrate had a nitrogen potency of 300 units per mg. of nitrogen, thus being three times as active as any preparation hitherto reported,[10] and many times more active than those used in the phosphatase studies referred to above.[7,8] At the same time experiments were carried out in which two other proteins, thrice-crystallized egg albumin and crystalline, carbohydrate-free horse serum albumin[11] were substituted for the hormone. Other conditions such as *p*H, temperature, and magnesium ion concentration were identical in all experiments.

The data obtained from these studies give the curves of Fig. 1. Under our conditions each of the three proteins has an activating effect upon phosphatase, and the parathyroid hormone is not unlike the other two substances in any respect. Characteristic of the curves is the tendency to approach a constant maximum, which is not followed by a subsequent decline in activity.

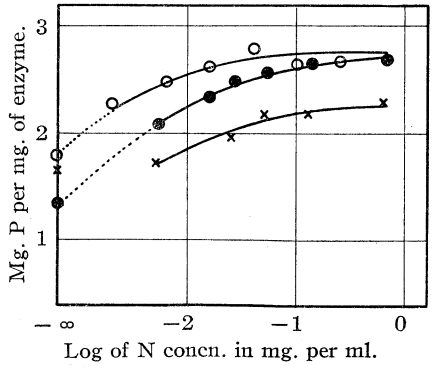


Fig. 1.—The *in vitro* effect of parathyroid hormone (O), horse serum albumin (●), and egg albumin (X) on phosphate liberation by kidney phosphatase.

This behavior of phosphatase recalls its activation by other nitrogen containing compounds, such as ammonia, amino acids and veronal. The activity in the presence of these substances, however, passes through a maximum and then decreases.

(1) Roe and Whitman, *Am. J. Clin. Path.*, **8**, 233 (1939).
(2) Bodansky and Jaffe, *Arch. Internal Med.*, **54**, 88 (1934).
(3) Peters, Robbins and Lavietes, *Ann. Rev. Biochem.*, **5**, 295 (1936).
(4) Page and Reside, *Biochem. Z.*, **226**, 273 (1930).
(5) Williams and Watson, *Endocrinology*, **29**, 250 (1941).
(6) Page, *Biochem. Z.*, **223**, 222 (1930).
(7) Heymann, *ibid.*, **227**, 1 (1930).
(8) Bakwin and Bodansky, *Proc. Soc. Exptl. Biol. Med.*, **31**, 64 (1933).
(9) Ross and Wood, *J. Biol. Chem.*, **146**, 49 (1942).
(10) Collip and Clark, *ibid.*, **66**, 133 (1925).
(11) McMeekin, THIS JOURNAL, **61**, 2884 (1939).

The published data for glycine[12,13] illustrate this quite satisfactorily, and we have obtained similar data for ammonia and veronal. On the basis of these results the nature of the activation by these simple organic compounds appears to differ from that caused by proteins, but the parathyroid hormone, even in the high concentrations employed (as much as 75 units per ml. of digest solution) has no individual and characteristic effect of its own.

Experimental

A concentrate of "alkaline" phosphatase was prepared from beef kidney cortex by the method of Albers and Albers.[14] The resulting solution was evaporated to dryness in the frozen state; such preparations are stable for months at 5°.

The digest solutions were 0.025 *M* in borate buffer of *p*H 9.75, 0.0005 *M* in magnesium chloride, and 0.015 *M* in sodium glycerophosphate (52% β); the enzyme was present in a concentration of 0.004%. The thoroughly dialyzed protein solutions were adjusted to *p*H 9.75 immediately before incorporation in the above mixture. The total volume was 10 ml.; hydrolysis was allowed to proceed at 30° for sixty minutes. The final values of *p*H were 9.55 ± 0.05 unit. Inorganic phosphate liberated during the digestion was estimated by the method of Fiske and Subbarow.[15] Control experiments in the presence of each of the three proteins demonstrated that no inorganic phosphate appeared if enzyme or substrate was omitted.

(12) Bodansky, *J. Biol. Chem.*, **115**, 101 (1936).
(13) Williams and Watson, *ibid.*, **135**, 337 (1940).
(14) Albers and Albers, *Z. physiol. Chem.*, **232**, 189 (1935).

Summary

The parathyroid hormone, like two other typical proteins, egg and serum albumins, accelerates the liberation of phosphate by kidney phosphatase. It has no peculiar effect which can be attributed to its function as a hormone.

(15) Fiske and Subbarow, *J. Biol. Chem.*, **66**, 375 (1925).

BOSTON AND CAMBRIDGE, MASSACHUSETTS
RECEIVED SEPTEMBER 1, 1942

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

The Structure of Riddelliine, the Alkaloid in *Senecio Riddellii*. I

BY ROGER ADAMS, K. E. HAMLIN, JR., C. F. JELINEK AND R. F. PHILLIPS

The similarity of the alkaloids occurring in the plant genera *Senecio*, *Trichodesma*, *Heliotropium*, and *Crotalaria* has previously been discussed.[1] As was pointed out, these alkaloids are esters which on alkaline hydrolysis yield an acid and an alkanolamine, retronecine or some other closely related bicyclic base.

As a result of investigations on the alkaloid Riddelliine, obtained by ethanolic extraction of *Senecio Riddellii*, it can be stated that this compound possesses the properties characteristic of the group. Riddelliine was first isolated from the plant by Manske,[2] who reported a molecular formula of $C_{18}H_{23}O_6N$. His directions for extraction and isolation were followed and as a result of analytical data on the pure riddelliine, its hydrochloride and methiodide, Manske's formula was confirmed. Hydrolysis of riddelliine indicated that this alkaloid was typical of the *Senecio* group. Alkaline cleavage yielded a basic product, which proved to be retronecine, and a crystalline acid, $C_{10}H_{14}O_6$, designated as riddellic acid.

$$C_{18}H_{23}O_6N + 2H_2O \xrightarrow{Ba(OH)_2} C_8H_{13}O_2N + C_{10}H_{14}O_6$$

(1) Adams and Rogers, THIS JOURNAL, **61**, 2815 (1939).
(2) Manske, *Can. J. Res.*, **B17**, 1 (1939).

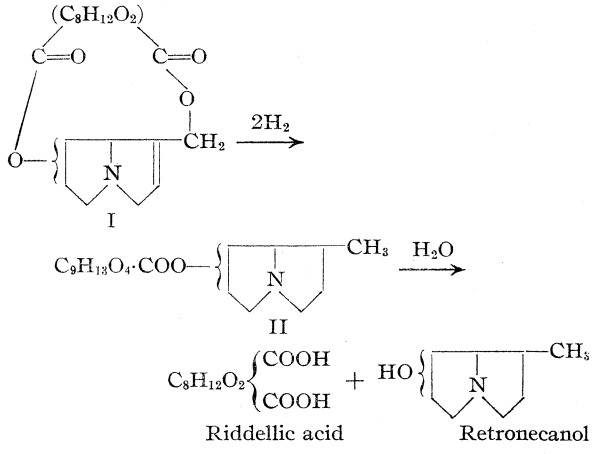
From the above equation it is to be noted that in common with most of the other *Senecio* alkaloids, water enters into the reaction with no loss of carbon dioxide and that the acid product contains ten carbon atoms. The retronecine, which was isolated in a nearly quantitative yield, was identified by comparison with an authentic sample.

Riddellic acid was obtained in both an anhydrous and hydrated form. It is optically active and is shown by direct titration to be dibasic. However, by addition of excess alkali and back titration, evidence for a third carboxyl was found which indicates the probability of the presence of a lactone linkage. The acid formed a dimethyl ester on treatment with diazomethane. Molecular weight determinations in dioxane and benzene indicate that dimethyl riddellate is a monomer, although in the latter solvent apparently one molecule of benzene associates with a molecule of solute. Preliminary hydrogenation experiments show that with a platinum oxide catalyst, two moles of hydrogen are absorbed to give a product which as yet has not been obtained in a pure state. Significantly, when the dimethyl ester of riddellic acid was hydrogenated with platinum oxide, only

one mole equivalent of hydrogen was absorbed to give a nearly quantitative yield of dimethyl dihydroriddellate.

On alkaloids analogous to riddelliine catalytic hydrogenation has also been employed as a degradative procedure. In the case of monocrotaline,[1] hydrogenolysis takes place upon absorption of one molecule of hydrogen followed by absorption of a second molecule and the reduction of the double bond in the basic portion of the molecule. Thus, monocrotalic acid and retronecanol are isolated.

Reduction of riddelliine using Raney nickel resulted in the absorption of two molecules of hydrogen. A single product was isolated in excellent yield, which indicated that no cleavage had occurred. This tetrahydroriddelliine (II), ($C_{18}H_{27}O_6N$), is optically active and possesses the physical properties of an amino acid. Hydrolysis by means of barium hydroxide yielded an acid identical with riddellic acid and a base identified as retronecanol. On the basis of this evidence riddelliine exists as a cyclic diester (I), one molecule of the dibasic riddellic acid being linked to the two hydroxyls of a molecule of retronecine. Thus it is an alkaloid similar in general structure to grantianine.[3] The first molecule of hydrogen apparently attacks the labile ester linkage and the second reduces the double bond of the basic moiety. Using the formulas recently proposed for retronecine and retronecanol,[4] the following equations may be written



If hydrogenation is carried out using a platinum oxide catalyst, somewhat different results are obtained. In this case, four mole equivalents of hydrogen are rapidly absorbed. The octahydroriddelliine has not yet been obtained in a pure state. However, alkaline hydrolysis of the crude reduction product has yielded an acid and the base retronecanol. Although the acid has not been purified, the additional two moles of hydrogen must have reacted with the acid portion of the molecule, a fact which agrees with the hydrogenation experiment on riddellic acid itself.

(3) Adams, Carmack and Rogers, THIS JOURNAL, **64**, 571 (1942).

(4) Adams, Carmack and Mahan, *ibid.*, **64**, 2593 (1942); Adams and Hamlin, *ibid.*, **64**, 2597 (1942).

Experimental

Extraction of Riddelliine from *Senecio Riddellii*.—About 1.41 kg. of dried, finely ground *Senecio Riddellii* (entire plant) was extracted by percolation with 95% ethanol over a forty-eight hour period. Most of the solvent was removed *in vacuo* and the concentrate was poured into a large evaporating dish. After acidification to congo red with citric acid, the extract was mixed with water to precipitate the resins and the remaining ethanol was boiled off over a steam-cone. The mixture was then allowed to stand at room temperature overnight to permit caking of the resinous material. The solution was decanted from the resin and extracted with successive portions of ether until the ether extracts were colorless, then with two 50-cc. portions of chloroform. The aqueous solution was now made alkaline to litmus with aqueous ammonia and extracted with successive portions of chloroform until evaporation of the extract left no residue. After distilling off the solvent, 11.3 g. of crude, crystalline riddelliine was obtained. Recrystallization from absolute ethanol yielded 6.4 g. (0.45%) of product, m. p. 193–195° (cor.) with decomposition in an evacuated tube. It was noted that for several experiments, the yield of pure alkaloid varied from 0 to 0.70% depending on the plant material. Further purification from absolute ethanol produced white prisms, m. p. 197–198° (cor.) with decomposition in an evacuated tube.

Anal. Calcd. for $C_{18}H_{23}O_6N$: C, 61.92; H, 6.64; N, 4.01. Found: C, 61.87; H, 6.69; N, 4.00.

Rotation. 0.0889 g. made up to 5 cc. with chloroform at 25° gave α_D −3.90; *l*, 1; $[\alpha]^{25}D$ −109.5°.

These results are in satisfactory agreement with the work of Manske[2] who has reported 196° (cor.) as the melting point of the alkaloid and an analysis corresponding to the formula, $C_{18}H_{23}O_6N$.

Riddelliine Hydrochloride.—A solution of 0.5 g. of riddelliine in a slight excess of 0.1 *N* hydrochloric acid was evaporated under reduced pressure with gentle heating on the water-bath. The residue was recrystallized from absolute ethanol, m. p. 225–226° (cor.) with decomposition in an evacuated tube.

Anal. Calcd. for $C_{18}H_{24}O_6NCl$: C, 56.03; H, 6.27; N, 3.63. Found: C, 55.86; H, 6.40; N, 3.62.

Rotation. 0.0900 g. made up to 5 cc. with water at 25° gave α_D −1.45; *l*, 1; $[\alpha]^{25}D$ −80.6°.

Riddelliine Methiodide.—To a solution of 1 g. of riddelliine in 4 cc. of chloroform and 3 cc. of methanol was added 1.5 cc. of methyl iodide. After warming a few minutes, the mixture was cooled and filtered; yield 1.2 g. After recrystallization from water, the methiodide melts with decomposition at 260–262° (cor.) after beginning to

darken at 235°. Manske[2] has reported the melting point of riddelliine methiodide to be 259° (cor.) with decomposition.

Anal. Calcd. for $C_{19}H_{26}O_6NI$: C, 46.44; H, 5.29; N, 2.85. Found: C, 46.67; H, 5.55; N, 2.82.

Alkaline Hydrolysis of Riddelliine

A. Riddellic Acid ($C_{10}H_{14}O_6$).—A mixture of 5 g. of riddelliine, 10 g. of barium hydroxide octahydrate and 70 cc. of water was heated under reflux for one hour and cooled. The solution was saturated with carbon dioxide and the precipitated barium carbonate filtered off. After acidification to congo with hydrochloric acid, the solution was extracted continuously with ether for seventy-two hours. The ether extract, which contained an appreciable aqueous layer, was evaporated to dryness *in vacuo*. The residue was a viscous orange glass which began to crystallize after standing in a vacuum desiccator at refrigerator temperature. After recrystallization from ether-petroleum ether (b. p. 30–60°), the product was obtained as colorless needles, m. p. 62° (cor.); yield, 3.02 g. (85%).

Anal. Calcd. for $C_{10}H_{14}O_6 \cdot H_2O$: C, 48.40; H, 6.50. Found: C, 48.52; H, 6.63.

Rotation. 0.2038 g. made up to 5 cc. with absolute ethanol at 31° gave α_D −0.08; *l*, 1; $[\alpha]^{31}D$ −1.96°.

The anhydrous form of riddellic acid resulted if the ether extracts were withdrawn periodically from the continuous extraction, were dried over anhydrous magnesium sulfate and the ether removed *in vacuo*. Also the monohydrate was converted readily into anhydrous riddellic acid by boiling with benzene or by fractional crystallization from ether–petroleum ether. Recrystallization from ether–petroleum ether gave colorless prisms, m. p. 102–103° (cor.).

Anal. Calcd. for $C_{10}H_{14}O_6$: C, 52.17; H, 6.08. Found: C, 52.11; H, 6.21.

Rotation. 0.2644 g. made up to 5 cc. with absolute ethanol at 32° gave α_D −0.14; *l*, 1; $[\alpha]^{32}D$ −2.65°.

The neutral equivalents for both the hydrated and anhydrous forms of riddellic acid always ran about 5% high for a dibasic acid. However, the values for the hydrate checked satisfactorily those for the anhydrous form.

Hydrogenation of Riddellic Acid (PtO_2 Catalyst).—A solution of 1 g. of riddellic acid monohydrate in 25 cc. of absolute ethanol was hydrogenated at 2–3 atmospheres pressure using 0.05 g. of platinum oxide. Within fifteen minutes, hydrogenation was complete, a total of two mole equivalents being absorbed. After filtering the catalyst and removing the solvent *in vacuo*, a reddish glass remained. This product has not been obtained in a pure state.

Dimethyl Riddellate.—A suspension of 5 g. of riddellic acid monohydrate in 30 cc. of chloroform was treated with an excess of an ethereal solution of diazomethane. During the addition of the diazomethane, the mixture was shaken continuously and the temperature maintained below 10°. The solvents were distilled *in vacuo* leaving a yellow oil which readily distilled at 144–145° (1 mm.); yield, 5.10 g. (98%). This product was redistilled at 0.075 mm. to yield a pale yellow, viscous oil; d^{20}_4 1.171; $n^{20}D$ 1.4870.

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.80; H, 7.03. Found: C, 55.96; H, 6.86.

Rotation. 0.4931 g. made up to 5 cc. with absolute ethanol at 32° gave α_D −0.28; *l*, 1; $[\alpha]^{32}D$ −2.84°.

Molecular weight determinations by the cryoscopic method in dioxane gave a value of 265; theoretical for dimethyl riddellate is 258. Using benzene as the solvent, a value of 340 was obtained. Assuming a molecule of benzene to be associated, the actual molecular weight would be 262.

Dimethyl Dihydroriddellate.—A solution of 5.1 g. of dimethyl riddellate in 50 cc. of absolute ethanol was hydrogenated at 2–3 atmospheres pressure using 0.1 g. of platinum oxide catalyst. Exactly one mole equivalent of hydrogen was absorbed within one hour and although shaking was continued one-half hour no additional hydrogenation occurred. The catalyst was filtered and the solvent removed *in vacuo*. The pale yellow oil remaining was distilled, b. p. 146–147° (1 mm.). The product was a colorless viscous oil; yield 5.0 g. (97%); $n^{20}D$ 1.4682; d^{20}_4 1.153.

Anal. Calcd. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.37; H, 7.84.

Rotation. 0.4577 g. made up to 5 cc. with absolute ethanol at 32° gave α_D −1.40; *l*, 1; $[\alpha]^{32}D$ −15.3°.

B. Retronecine Hydrochloride.—The aqueous solution, remaining after ether extraction of the riddellic acid, was evaporated *in vacuo* to dryness. The crystalline residue was extracted with boiling absolute ethanol and the extracts concentrated. The crystalline product after recrystallization from absolute ethanol melted at 160–161° (cor.). A mixed melting point with an authentic sample of retronecine hydrochloride showed no depression; yield, 2 5 g. (91%).

Tetrahydroriddelliine.—A solution of 5 g. of riddelliine in 150 cc. of ethanol and 25 cc. of water[5] was hydrogenated at 2–3 atmospheres in the presence of 3 g. of Raney nickel. After three hours, two mole equivalents of hydrogen had been absorbed and the reduction was complete. The catalyst was filtered off and the solvent removed *in vacuo*. A white crystalline solid remained which was purified by dissolving in a little hot glacial acetic acid and adding absolute ethanol until the solution became cloudy. White microscopic prisms were obtained, m. p. 205° (cor.) with decomposition; yield 4.4 g. (87%).

Anal. Calcd. for $C_{18}H_{27}O_6N$: C, 61.17; H, 7.70; N, 3.96. Found: C, 60.75; H, 7.55; N, 4.05.

Rotation. 0.0944 g. made up to 5 cc. with absolute ethanol at 31° gave α_D −0.18; *l*, 1; $[\alpha]^{31}D$ −9.5°.

Tetrahydroriddelliine is fairly soluble in water, easily soluble in glacial acetic acid but practically insoluble in ethanol.

When first prepared by hydrogenation of riddelliine in absolute ethanol, the tetrahydroriddelliine was an amorphous solid, very hygroscopic and easily soluble in ethanol. However, after once obtaining the crystalline product, the original experiment could not be duplicated.

Alkaline Hydrolysis of Tetrahydroriddelliine

A. Riddellic Acid.—A mixture of 1 g. of tetrahydroriddelliine, 2 g. of barium hydroxide octahydrate and 15 cc. of water was refluxed for one hour and cooled. After

(5) It is necessary to have sufficient water present to dissolve the tetrahydroriddelliine formed during the reaction. If this precaution is not taken the precipitate formed inactivates the catalyst thus stopping hydrogenation.

saturating with carbon dioxide, the solution was filtered and made acid to congo. Continuous ether extraction for twenty-four hours and removal of the solvent *in vacuo*, yielded an oil which crystallized after seeding with riddellic acid. Recrystallization from ether–petroleum ether (b. p. 30–60°) gave 0.35 g. of a white crystalline solid melting at 61–62° (cor.). A mixed melting point with riddellic acid monohydrate (m. p. 62°) gave no depression.

B. Retronecanol.—The aqueous solution remaining after ether extraction of the acid just described was made alkaline with 10% aqueous sodium hydroxide and extracted with ether. After drying the ether extracts over anhydrous magnesium sulfate and distilling the ether, a solid remained. This product, recrystallized from petroleum ether (b. p. 30–60°), melted at 95–96° (cor.) which is identical with the melting point of retronecanol.

A picrate was prepared from water which melted at 211° with decomposition. A mixed melting point with retronecanol picrate (m. p. 211°) showed no depression.

Hydrogenation of Riddelliine (PtO_2 Catalyst).—A solution of 5 g. of riddelliine in 150 cc. of ethanol and 25 cc. of water was hydrogenated at 2–3 atmospheres pressure using 0.1 g. of platinum oxide catalyst. A total of four mole equivalents of hydrogen was absorbed within one hour. The catalyst was filtered off and the solvent removed *in vacuo*. A white amorphous solid material remained which was very hygroscopic and soluble in ethanol. Attempts to obtain a crystalline product failed.

One gram of this material was taken up in 5 cc. of water and 10 cc. of 50% aqueous sodium hydroxide added. After refluxing one hour and cooling, the mixture was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and the ether distilled. A solid product remained which after one recrystallization from petroleum ether melted at 95–96°. Retronecanol melts at 95–96°. A picrate of the above base was prepared in ethanol and melted at 213°. A mixed melting point with authentic retronecanol picrate showed no depression.

Acidification and continuous ether extraction of the aqueous solution remaining after removal of the retronecanol yielded an acid fraction as a brown viscous oil. This has not been obtained in a pure state.

Summary

1. Riddelliine, the alkaloid of *Senecio Riddellii*, has been isolated and shown to have the molecular formula reported by Manske, $C_{18}H_{23}O_6N$.

2. Upon saponification, riddelliine gives a molecule of retronecine and one molecule of a crystalline acid, $C_{10}H_{14}O_6$, designated as riddellic acid. It is dibasic and with diazomethane gives a dimethyl ester.

3. Riddellic acid, upon reduction with hydrogen and platinum oxide, absorbs two moles of hydrogen but no pure product was isolated. Dimethyl riddellate under similar conditions absorbs only one mole of hydrogen to give dimethyl dihydroriddellate.

4. Riddelliine, upon reduction with hydrogen and Raney nickel, absorbs two moles of hydrogen to form tetrahydroriddelliine which has the properties of an amino acid and can be hydrolyzed to retronecanol and riddellic acid. With platinum oxide as a catalyst, four moles of hydrogen are absorbed but the product has not been obtained in a pure state. On saponification the crude octahydroriddelliine yields retronecanol.

5. Riddelliine is thus shown to be an ester from one mole of the dibasic acid, riddellic acid, and one mole of retronecine, each of the two hydroxyls in the molecule being utilized.

URBANA, ILLINOIS RECEIVED SEPTEMBER 18, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE CALCO CHEMICAL DIVISION OF THE AMERICAN CYANAMID COMPANY]

Sulfanilamide Derivatives. VIII. Sulfanilylamidines[1]

BY E. H. NORTHEY, ALAN E. PIERCE AND D. J. KERTESZ

In view of the fact that most of the recently developed chemotherapeutic agents of high potency, including sulfapyridine, sulfathiazole and sulfadiazine, have the structure of sulfanilyl cyclic amidines, $4\text{-}(NH_2)C_6H_4SO_2NHC(=N-)$ it was thought desirable to prepare an analogous series of amidine derivatives of the type $4\text{-}(NH_2)\text{-}C_6H_4SO_2NHC(R)=NR'$. A number of such compounds have been made, however, the structure appears to be better represented by the formula $4\text{-}(NH_2)C_6H_4SO_2N=C(R)NHR'$, because the monosulfanilylamidines did not form alkali salts corresponding to the well known sodium salts of the above sulfanilamido heterocycles. This would indicate lack of ionizable hydrogen associated with the amide nitrogen. Also, while sulfapyridine is stable to alkaline hydrolysis and is cleaved by mineral acids to sulfanilic acid and 2-aminopyridine,[2] the sulfanilylamidines are cleaved to sulfanilamide by either

(1) Presented in part before the Division of Medicinal Chemistry, A. C. S., Buffalo, N. Y., September, 1942.

(2) Crossley, Northey and Hultquist, THIS JOURNAL, **62**, 372 (1940).

TABLE I

Compound (S=$H_2NC_6H_4SO_2$—)	Formula	Melting range, °C. Int. nitro cpd.[a]	Melting range, °C. Finished product	% Assay by nitrite	Analyses, % Calculated C	H	N	S	Found C	H	N	S
S-Acetamidine[5]	$C_8H_{11}N_3O_2S$	190.7–191.3	151.4–152.0[b]	100.6	45.0	5.2	19.7	15.0	45.0	5.3	19.7	14.9
Di-S-acetamidine	$C_{14}H_{16}N_4O_4S_2$	189.0–190.7	191.6–191.8	100.5	45.6	4.4	15.2	17.4	45.5	4.7	15.3	17.2
S-Isocaproamidine	$C_{12}H_{19}N_3O_2S$	247.0–250.0 dec.	126.0–127.2	99.3	53.4	7.1	15.6	11.9	52.7	7.0	15.9	11.9
S-α-Phenylacetamidine[c]	$C_{14}H_{15}N_3O_2S$	194.3–195.8	177 –179		52.6	3.8	13.2	10.0	51.8	4.0	12.9	10.0
S-Benzamidine[5]	$C_{13}H_{13}N_3O_2S$	180.3–181.0	210.2–210.7[d]	100.3	56.8	4.8	15.3	11.6	56.4	5.0	15.4	11.5
Di-S-benzamidine	$C_{19}H_{18}N_4O_4S_2$	241.8–242.6	206.4–207.6 dec.	100.3	53.0	4.2	13.0	14.9	53.0	4.2	13.3	15.2
S-p-Toluamidine	$C_{14}H_{15}N_3O_2S$	149.5–160	234.9–235.4	100.3	58.0	5.2	14.6	11.1	57.4	5.1	14.7	11.2
Di-S-p-toluamidine	$C_{20}H_{20}N_4O_4S_2$	213.7–214.9	166.9–167.5	100.3	54.0	4.5	12.6	14.4	52.4	4.7	12.9	14.2
S-Nicotinamidine	$C_{12}H_{11}N_4O_2S$	232.5–233.5	208.1–208.2	100.0	51.4	4.0	20.4	11.6	52.1	4.5	20.4	11.5
N-S-N′-Methylbenzamidine	$C_{14}H_{15}N_3O_2S$	181.2 dec.	228.1–229.2	100.0	58.1	5.2	14.5	11.1	57.9	5.0	14.6	11.1
N-S-N′-Diethylbenzamidine	$C_{17}H_{21}N_3O_2S$		193.7–194.0	100.0	61.5	6.4	12.7	9.7	61.1	6.4	12.6	10.0
N-S-N′-α-Pyridylbenzamidine	$C_{18}H_{16}N_4O_2S$	180.7 dec.	206.8–207.5	99.8	61.3	4.6	15.9	9.1	61.7	4.5	16.3	8.7

[a] Melting point taken on samples crystallized from alcohol or from water. [b] Melting point, lit. 149°. [c] Analysis given for the nitro compound. [d] Melting point, lit. 203°.

acid or alkaline hydrolysis, indicating a different type of linkage between amide nitrogen and carbon.

Further information on structure was given by synthesis from the corresponding imido chloride, —SO_2N=C(R)Cl, by reaction with secondary amines giving compounds of the type, —SO_2N=C(R)N(R′)R″, where the possibility of tautomerism was eliminated.

As by-products in the reaction of unsubstituted amidines with sulfonyl chlorides, we isolated disulfonyl derivatives of the probable structure —SO_2N=C(R)NHSO_2—, which formed neutral alkali salts with one equivalent of base.

Preliminary pharmacological tests[3] showed low chemotherapeutic activities for all of the compounds with the possible exception of sulfanilylacetamidine which was approximately equal to sulfanilamide.

After the work here reported was completed, two patents[4,5] came to our attention. However, the preparation of disulfanilylamidines was not described in these references.

In preliminary work, acetylsulfanilylacetamidine was prepared from acetylsulfanilyl chloride and acetamidine, but it was not found possible to hydrolyze this product to sulfanilylacetamidine. Hence, this method of preparation was abandoned in favor of the preparation of nitrobenzene sulfonylamidines as intermediates. These were prepared in two ways. Amidine hydrochlorides, where readily available, were treated in acetone with *p*-nitrobenzenesulfonyl chloride, in the presence of excess sodium hydroxide. Both mono- and *bis*-nitrobenzenesulfonylamidines were formed in this reaction, the proportion varying with the amount of *p*-nitrobenzenesulfonyl chloride used in excess. The two types of products were easily separated, since only the latter were soluble in alkali. The first eight compounds in Table I were prepared through the use of this procedure. The second method involved the preparation of aromatic or heterocyclic N-acyl-*p*-nitrobenzenesulfonamides from the acid chloride and *p*-nitrobenzenesulfonamide in dry pyridine. The acyl sulfonamides were treated with phosphorus pentachloride to yield the corresponding imido chlorides which with ammonia or amines were converted to amidines. This method, as applied to N-benzoylbenzenesulfonamide, has been previously described[6,7,8] and was used for the preparation of the last four compounds listed in Table I.

All nitro compounds were reduced with iron to give the corresponding sulfanilylamidines, which were obtained as white microcrystalline substances upon purification by crystallization from alcohol or precipitation from acid or alkaline solution.

Experimental

N^4-Acetylsulfanilylacetamidine.—To 9.5 g. of acetamidine hydrochloride and 19.5 g. of 50% sodium hydroxide solution in 75 cc. of acetone, was added 25.2 g. of 95% acetylsulfanilyl chloride in portions, with vigorous stirring, over twenty minutes, at 10–20°. Cooling was necessary. After further stirring for twenty minutes, the slurry was diluted with 2 volumes of cold water, filtered, and the solid washed and dried. The yield of acetylsulfanilylacetamidine was 16.0 g., or 62.5%. A small sample recrystallized from hot water melted at 244.2 to 244.7° (all m. p.'s corrected).

Anal. Calcd. for $C_{10}H_{13}N_3O_3S$: C, 47.0; H, 5.1; N, 16.5; S, 12.6. Found: C, 47.0; H, 4.5; N, 16.8; S, 12.5.

Hydrolysis of acetylsulfanilylacetamidine was carried out in six moles of 7.5 *M* hydrochloric acid at 60°. Solu-

(3) Pharmacological tests were carried out under the direction of W. H. Feinstone at the Stamford, Conn., Laboratories of the American Cyanamid Co.

(4) Hungarian Patent 127,837, 1941; *C. A.*, **36**, 2271 (1942).

(5) British Patent 538,822, 1941; *Brit. Chem. Abs.*, **BIII**, 344 (1941).

(6) Gerhardt, *Ann.*, **108**, 214 (1858).

(7) Wolkoff, *Ber.*, **5**, 137 (1872).

(8) Wallach and Gossman, *ibid.*, **11**, 753 (1878).

tion was complete in two and three-fourths hours, but hydrolysis of the acetyl group was not complete, as determined by titration with sodium nitrite, until the end of three and one-half hours, when heating was stopped. Sulfanilamide was isolated in 90% yield. No sulfanilylacetamidine was identified.

p-Nitrobenzenesulfonylamidines from Amidines.—The procedure given above for acetylsulfanilylacetamidine was followed using a 5–10% excess of *p*-nitrobenzenesulfonyl chloride instead of acetylsulfanilyl chloride. In the alkaline filtrate from the mono-nitrobenzenesulfonylamidines, the *bis*-nitrobenzenesulfonylamidines were precipitated by acidification with hydrochloric acid. The yields ranged from 40–80% for the monosubstituted amidines and 20 to 35% for the disubstituted derivatives.

p-Nitrobenzenesulfonylamidines from Imido Chloride.—This method is illustrated by the preparation of *p*-nitrobenzenesulfonylnicotinamidine. 76.8 g. of N^1-nicotinyl-*p*-nitrobenzenesulfonamide[9] was mixed with 57 g. of phosphorus pentachloride and 100 cc. of phosphorus oxychloride, then heated at 80–85° for five hours. The excess phosphorus oxychloride was removed by distillation at reduced pressure and by washing the residue with petroleum ether. The imido chloride was added with stirring to 300 cc. of 15% aqueous ammonia. The *p*-nitrobenzenesulfonylnicotinamidine was filtered off, in 44% yield, and the corresponding amide was recovered, in 50% yield, by acidification of the filtrate.

The preparation of N^1-substituted *p*-nitrobenzenesulfonylbenzamidines was analogous. Aqueous methylamine and an acetone solution of diethylamine or 2-aminopyridine was used instead of ammonia for reaction with the imido chloride.

Reduction of Nitro Compounds.—All the nitro compounds were reduced with iron. The procedure for preparation of sulfanilylbenzamidine is illustrative. A mixture of 84 g. of finely divided iron and 19 cc. of 5 *N* hydrochloric acid in 500 cc. of water was stirred at 95–100°. The mixture was alkaline to congo red. To the slurry was added 91.5 g. of *p*-nitrobenzenesulfonylbenzamidine. There was slight heat evolution, and the color of the insoluble substance changed from yellow to gray. After two hours of stirring at a temperature near the boiling point the mixture was made just alkaline with sodium carbonate solution, cooled and filtered. The dried iron sludge was extracted with 3A alcohol, which on evaporation yielded 73 g. of crude product. This was purified by crystallization from glacial acetic acid and from 3A alcohol, using decolorizing carbon; 35 g. of pure sulfanilylbenzamidine was obtained.

The disulfanilyl compounds were dissolved by the sodium carbonate addition, and were obtained by making the filtrate slightly acid. The other sulfanilylamidines were practically insoluble in hot water, except sulfanilylacetamidine.

The products were purified by reprecipitation from acid or alkaline solution, by crystallization from 60–95% ethyl alcohol or acetic acid, or by both methods.

Hydrolysis of Sulfanilylacetamidine.—Sulfanilylacetamidine (1.066 g., 0.005 mole) was distilled in a Kjeldahl distillation apparatus with 100 cc. of 0.25 *N* sodium hydroxide, catching the ammoniacal distillate in standard acid. During forty-five minutes, the still solution was evaporated to 15–25 cc., and 0.00496 mole of ammonia was distilled. The contents of the still were filtered and neutralized to *p*H 9; the white precipitate obtained was filtered off, washed, and dried. The product weighed 0.66 g. and was identified as sulfanilamide by m. p. and mixed m. p. with an authentic sample.

Sulfanilylacetamidine (1.066 g., 0.005 mole) was gently boiled for half an hour with 60 cc. of 2 *N* hydrochloric acid. The solution was made strongly alkaline and distilled as described in the preceding paragraph. The titer of the distillate corresponded to an evolution of 0.00498 mole of ammonia. No sulfanilic acid was detected in the still contents. The acid hydrolysis was repeated on another 1.066-g. sample of sulfanilylacetamidine. The resulting solution was concentrated and neutralized. The solid which precipitated was recrystallized from hot water and dried. The white crystalline product weighed 0.63 g. and was identified as sulfanilamide, as previously described.

Summary

1. A series of sulfanilylamidines of the structure 4-$(NH_2)C_6H_4SO_2N{=}C(R)N(R')R''$ were prepared, where R was alkyl, aryl, aralkyl or heterocyclic, and R′ and R″ were hydrogen, alkyl or heterocyclic. None of these compounds formed sodium salts.

2. As by-products in some preparations disulfanilylamidines were isolated having the probable structure, 4-$(NH_2)C_6H_4SO_2N{=}C(R)NHSO_2C_6H_4$-$(NH_2)$-(4)′. These formed neutral sodium salts.

3. None of the compounds was more active than sulfanilamide in preliminary chemotherapeutic studies.

BOUND BROOK, N. J. RECEIVED JULY 25, 1942

(9) Prepared in the manner described for N^1-nicotinyl-N^4-acetylsulfanilamide but starting with *p*-nitrobenzenesulfonamide, see Crossley, Northey and Hultquist, THIS JOURNAL, **61**, 2950 (1939).

[CONTRIBUTION FROM WESTINGHOUSE RESEARCH LABORATORIES]

Ionization and Dissociation by Electron Impact: Normal Propyl Chloride and Tertiary Butyl Chloride

BY D. P. STEVENSON[1,2] AND JOHN A. HIPPLE

In an effort to gain further insight into the unimolecular dissociation reactions of hydrocarbons and related molecules which follow ionization by electron impact, we undertook a mass-spectroscopic investigation of some alkyl halides. Due to circumstances beyond our control, the research was terminated with the work on *n*-propyl and *t*-butyl chlorides only partially completed. Since the data which have been acquired seem of interest, we report them herewith.

The apparatus and technique have been briefly described in an earlier paper.[3] The *n*-propyl and *t*-butyl chlorides were Eastman Kodak Co. white label compounds, used without further purification. The electrons were obtained from the same oxide-coated platinum filament used in the preceding work.[3] This pair of halides very markedly decreased the activity of the filament. When the vapors were removed from the tube the filament regained its original activity. A similar, but less pronounced, effect had been noted with the unsaturated hydrocarbons, propylene and isobutylene. The latter, however, left the voltage scale calibration (correction for contact potentials) unchanged. The propyl chloride decreased the correction, as determined from the ionization efficiency curve of argon, by a little over one volt. This effect provides full justification for the extra effort involved in admitting the calibration gas, argon, simultaneously with the substance under investigation.

The relative intensities of the principal ions in the mass spectrum of *t*-butyl chloride are given in Table I for some round values of the bombarding electron energy. Due to the almost immeasurably small current of the parent ion, $C_4H_9Cl^+$, the principal ion in the spectrum, $C_4H_9^+$, has been used as the reference standard. The complete lack of stability of the *t*-butyl chloride ion was both surprising and irritating. It precluded the measurement of the appearance potential of this ion and thus the vertical ionization potential of the molecule.

(1) Westinghouse Research Fellow.

(2) Present address, Shell Development Co., Emeryville, California.

(3) D. P. Stevenson and J. A. Hipple, THIS JOURNAL, **64**, 1588 (1942).

It will be noted that even though the breaking of a carbon–carbon bond (loss of a methyl radical) is favored by the greater number of such bonds,[3] the molecular ion has a greater tendency to lose a chlorine atom. Similarly, the isobutane molecular ion loses a methyl radical more readily than a hydrogen atom,[3] despite the greater number of C–H than C–C bonds. These reaction probabilities of the molecular ions are apparently directly related to the strength of the bond that breaks since in the order of their decreasing strength the bonds are C–H, C–C, and C–Cl.

One of the more characteristic reactions of propane and the butanes is the one giving rise to a lower olefinic ion and methane, ethane or hydrogen. By analogy one would expect the reactions

$$\text{(a)}\quad t\text{-BuCl} \longrightarrow C_3H_5Cl^+ + CH_4 + \epsilon^-$$
$$\text{(b)}\quad t\text{-BuCl} \longrightarrow C_3H_6^+ + CH_3Cl + \epsilon^-$$

to contribute to the spectrum of *t*-butyl chloride to a much greater extent than is observed. As in the isobutane spectrum, the relative abundance of the allene (or methylacetylene) ion, $C_3H_4^+$ is much smaller than those of the ions $C_3H_5^+$ and $C_3H_3^+$, and the ethylene (or ethylidene) ion is less abundant than $C_2H_5^+$ and $C_2H_3^+$.

The mass spectrum of normal propyl chloride, given in Table II, presents a marked contrast to that of tertiary butyl chloride. In the first place, the parent ion, $C_3H_7Cl^+$, is present in quite large abundance. Because of the apparent similarity of the dissociation reactions involved, one would expect $C_3H_7^+$ to be much more abundant than $C_3H_6^+$, since the current of $C_4H_9^+$ from *t*-butyl chloride is about twelve times as great as that of $C_4H_8^+$. That our expectation is not fulfilled is the more surprising when it is noted that the relative abundances of $C_2H_5^+$, $C_2H_4^+$ and $C_2H_3^+$ have the same pattern in both chlorides.

Although their relative abundances are not very large, it is to be noted that both $C_2H_5Cl^+$ and CH_3Cl^+ are present in the spectrum of the propyl chloride. Although methane and ethane are formed in the dissociation of the butane ions, careful search failed to reveal any trace of the ions CH_4^+ or $C_2H_6^+$ in the spectra.[3] It is conceivable

TABLE I

MASS SPECTRUM OF *t*-BUTYL CHLORIDE (INCOMPLETE[a])

V⁻ (volts)	$C_4H_9Cl^+$	$C_3H_6Cl^+$	$C_3H_5Cl^+$	$C_3H_4Cl^+$	$C_2H_3Cl^+$	HCl^+	Cl^+
30	<0.1	39	...	...	...	<0.1	<0.1
50	<0.1	43	3.4	0.5	<1	<0.1	<0.1
100	<0.1	47	3.5	...	...	<0.1	<0.1

V⁻ (volts)	$C_4H_9^+$	$C_4H_8^+$	$C_3H_7^+$	$C_3H_6^+$	$C_3H_5^+$	$C_3H_4^+$	$C_3H_3^+$	$C_2H_5^+$	$C_2H_4^+$	$C_2H_3^+$
30	99	...	...	...	55	...	7.3	..	...	..
50	100	7.9	4.5	0.7	73	2.7	23	32	6.6	20
100	107	...	...	...	78	...	23	..	...	..

[a] Absence of an ion from table does not necessarily imply absence from spectrum. The relative abundances have been corrected for C^{13} in its natural abundance, 1.1%.

TABLE II

MASS SPECTRUM OF *n*-PROPYL CHLORIDE[a]

V⁻ (volts)	$C_3H_7Cl^+$	$C_2H_4Cl^+$	CH_2Cl^+	$C_3H_7^+$	$C_3H_6^+$	$C_3H_5^+$	$C_3H_4^+$	$C_3H_3^+$
30.0	100	51.3	14.8	108	368	102	..	26.7
40.0	107	57.0	25.6	114	382	116	..	60.1
60.0	111	59.0	28.3	118	392	124	14.5	63.2
100.0	113	60.0	27.2	121	412	129	..	60.5

V⁻ (volts)	$C_2H_5^+$	$C_2H_4^+$	$C_2H_3^+$	$C_2H_2^+$	C_2H^+	CH_3^+
30.0	184	60.5	163	..	..	7.6
40.0	204	87.5	216	..	..	24.7
60.0	219	96.5	250	32.0	3.5	31.1
100.0	224	100	255	..	..	29.5

V⁻ (volts)	$C_3H_6Cl^+$	$C_3H_5Cl^+$	$C_3H_4Cl^+$	$C_2H_5Cl^+$	$C_2H_3Cl^+$	$C_2H_2Cl^+$	C_2HCl^+	Cl^+
60.0	3.9	2.2	2.4	0.9	8.8	4.3	1.9	2.5

V⁻ (volts)	CH_3Cl^+	$CHCl^+$	CCl^+	$C_3H_2^+$	C_3H^+	C_3^+	HCl^+
60.0	3.0	2.8	3.1	4	2	2	2

[a] The relative abundances have been corrected for isotopic effects.

that the $C_2H_5Cl^+$ and CH_3Cl^+ are present in the spectrum of C_3H_7Cl because of ethyl and methyl chloride impurities. For this to be the case one would expect the relative abundances to be in the reverse order, *i. e.*, $C_2H_5Cl^+ > CH_3Cl^+$, rather than the observed $C_2H_5Cl^+ < CH_3Cl^+$.

The appearance potentials, which were determined from the "initial breaks"[3] of the ionization efficiency curves are listed in Table III. When two values are noted, the second refers to the position of a marked inflection in the ionization efficiency curve. The ionization potential of argon was taken equal to 15.76 e. v.[4] for calibration purposes.

TABLE III

APPEARANCE POTENTIALS IN THE *t*-BuCl AND *n*-PrCl SPECTRA

	Process	$A(X^+)$
t-C_4H_9Cl	$\longrightarrow C_3H_6Cl^+ + CH_3 + \epsilon^-$	10.7 ± 0.1 e.v.
	$\longrightarrow C_4H_9^+ + \epsilon^- + Cl$	10.2 ± 0.2; 18.5 ± 1
	$\longrightarrow C_3H_6^+ + \ldots + \epsilon^-$	12.4 ± 0.2; 16.0 ± 1
	$\longrightarrow C_3H_5^+ + \ldots + \epsilon^-$	16.1 ± 1
n-C_3H_7Cl	$\longrightarrow C_3H_7Cl^+ + \epsilon^-$	10.7 ± 0.2 e. v.
	$\longrightarrow C_2H_4Cl^+ + CH_3 + \epsilon^-$	12.0 ± 0.3 e. v.
	$\longrightarrow C_3H_7^+ + Cl + \epsilon^-$	11.1 ± 0.3 e. v.

(4) R. F. Bacher and S. Goudsmit, "Atomic Energy States," McGraw-Hill Book Co., New York, N. Y., 1932. See footnote to Table I of the preceding paper on isobutylene, etc.

The value $A(C_3H_7Cl^+) = 10.7$ e. v. in the *n*-C_3H_7Cl spectrum is to be associated with the vertical ionization potential of this molecule. The vertical ionization potential of *t*-butyl chloride must be less than the appearance potential of the ion $C_4H_9^+$ in its spectrum, that is, I_{vert}-(*t*-BuCl) < 10.2 e. v. These values stand in contradiction to the suggestion made by Price[5] that there should be no further reduction in the ionization potentials of the alkyl chlorides beyond that found in going from methyl chloride to ethyl chloride. In the light of the large decrease in the vertical ionization potential in the sequence ethane, propane, butane (11.6, 11.0, 10.2, respectively[3]), the results on the propyl and butyl chlorides are not entirely surprising.

By use of the rules formulated by Kistiakowsky and co-workers[6] in combination with the data summarized by Rossini[7] one can estimate the heat of the reaction *n*-C_4H_{10} + HCl = *n*-C_3H_7Cl + CH_4, to be $\Delta H^\circ_{298.1} = 0.15 \pm 0.05$ e. v. From Table III we have *n*-$C_3H_7Cl \rightarrow$ *n*-$C_3H_7^+ + Cl +$

(5) W. C. Price, *J. Chem. Phys.*, **4**, 539, 547 (1936).

(6) J. B. Conn, G. B. Kistiakowsky and E. A. Smith, THIS JOURNAL, **60**, 2764 (1938).

(7) F. D. Rossini, *Chem. Rev.*, **27**, 1 (1940).

ϵ^-, $A(C_3H_7^+) = 11.1$ and from earlier work,[3] $n\text{-}C_4H_{10} \rightarrow n\text{-}C_3H_7^+ + CH_3 + \epsilon^-$, $A(C_3H_7)^+ = 11.2_1$. Herzberg[8] gives 4.43 e. v. for the dissociation energy of HCl. Combining these data with the assumptions described elsewhere,[9] we find $4.4_2 \pm 0.2$ e. v. for the strength of the first carbon–hydrogen bond in methane. The excellence of the agreement of this estimate of $D(CH_3\text{–}H)$ with that made from other similar pairs of appearance potentials, $4.3_8 \pm 0.2$ e. v., provides further justification for an assumption there made, namely, that in the reaction $C_3H_8 \rightarrow C_3H_7^+ + H + \epsilon^-$, the $C_3H_7^+$ is the isopropyl rather than the normal propyl ion.

If the value of $A(C_4H_9^+)$ in the *t*-BuCl spectrum is combined with that of the same ion in the isobutane spectrum and the heats of formation of isobutane[7] and tertiary butyl chloride,[10] one finds 3.7 e. v. for the dissociation energy of HCl. This value is 0.7 e. v. lower than the accurate value quoted above.[8] In making this estimate, we have assumed that the $C_4H_9^+$ in the isobutane spectrum has the tertiary structure. If the appearance potential $A(C_4H_9^+) = 11.6 \pm 0.3$ e. v.[3] corresponds to the formation of the isobutyl ion from isobutane, the calculated value of the dissociation energy of HCl would be too low by an amount equal to the energy of the isomerization process, $i\text{-}C_4H_9^+ \rightarrow t\text{-}C_4H_9^+$. Since this latter quantity is probably of the order of 0.4 e. v., the assumption that isobutane yields the isobutyl ion would explain most of the discrepancy. The determination of the appearance potential of $C_4H_9^+$ in the isobutyl chloride spectrum would make possible a decision as to whether or not the explanation of the discrepancy is the correct one.

The reaction giving rise to $C_3H_5^+$ in the spectrum of *t*-BuCl may be either of the following pair

$$t\text{-}C_4H_9Cl \longrightarrow \begin{cases} C_3H_5^+ + CH_3 + HCl + \epsilon^- \\ C_3H_5^+ + CH_4 + Cl + \epsilon^- \end{cases}$$

since the two pairs of un-ionized fragments are of very nearly the same energy. The following simple calculation shows the observed value of $A(C_3H_5^+)$ to be consistent with either of the reactions. From reference 10 we have

$$i\text{-}C_4H_8 + HCl = t\text{-}C_4H_9Cl \quad \Delta H^\circ_{298} = -0.73 \text{ e. v.}$$

while

$$i\text{-}C_4H_8 = C_3H_5^+ + CH_3 + \epsilon^- \quad A(C_3H_5^+) = 11.5_1 \text{ e. v.}[11]$$

Adding, we find, $t\text{-}C_4H_9Cl \rightarrow C_3H_5^+ + CH_3 + HCl + \epsilon^-$, $A_{\text{calcd.}}(C_3H_5^+) = 12.2_5$ e. v. in excellent agreement with the observed value. Since $D(CH_3\text{—}H)$ and $D(H\text{—}Cl)$ are equal to within 0.1 e. v., the products could also be CH_4 and Cl. A possible reaction which can be eliminated is

$$t\text{-}C_4H_9Cl \longrightarrow C_3H_5^+ + CH_3Cl + H + \epsilon^-$$

From the data given by Bichowsky and Rossini[12] one finds $CH_4 + HCl = CH_3Cl + H$, $\Delta H^\circ_{291} = 0.91$ e. v. Thus $A_{\text{calcd.}}(C_3H_5^+)$ for the latter un-ionized products is 0.8 e. v. greater than the observed value.

Until further data on related molecules are acquired, it is not profitable to discuss the reactions $t\text{-}C_4H_9Cl \rightarrow C_3H_6Cl^+ + CH_3 + \epsilon^-$ and $n\text{-}C_3H_7Cl \rightarrow C_2H_4Cl^+ + CH_3 + \epsilon^-$, further than to state that the appearance potentials observed seem to be consistent with the reactions as written.

In closing, we should remark that no search was made for negative ions, which undoubtedly are formed.

Summary

The mass spectra of tertiary butyl and normal propyl chloride are tabulated and briefly discussed. The appearance potentials of a few ions in these spectra were measured. The vertical ionization potential of normal propyl chloride is 10.7 ± 0.2 e. v. An estimate of $D(CH_3\text{—}H)$ from the present data leads to the value $4.4_2 \pm 0.2$ e. v. in agreement with the value deduced from other electron impact data.

EAST PITTSBURGH, PA. RECEIVED JULY 28, 1942

(8) G. Herzberg, "Molecular Spectra," Prentice-Hall, Inc., New York, N. Y., 1939.

(9) D. P. Stevenson, *J. Chem. Phys.*, **10**, 291 (1942).

(10) G. B. Kistiakowsky and C. H. Stauffer, THIS JOURNAL, **59**, 165 (1937).

(11) D. P. Stevenson and J. A. Hipple, *ibid.*, **64**, 2769 (1942).

(12) F. R. Bichowsky and F. D. Rossini, "Thermochemistry," Reinhold Publishing Co., New York, N. Y., 1936.

[CONTRIBUTION FROM WESTINGHOUSE RESEARCH LABORATORIES]

Ionization and Dissociation by Electron Impact: Isobutylene, Propane, and Propylene

BY D. P. STEVENSON[1] AND JOHN A. HIPPLE

In a recent paper the results of a mass-spectroscopic investigation of the dissociation products of normal and isobutane were reported.[2] We present here the results of a similar investigation of isobutylene. As a part of an extensive study of the form of ionization efficiency curves, we have examined certain processes in propane and propylene. Inasmuch as our results on these latter molecules differ from those of a previous investigation, we also report appearance potentials of some of the ions in the mass spectra of propane and propylene.

The instrument and general technique have been described in the preceding article.[2] The gas samples were given to us by the Standard Oil Company of Indiana.

The appearance potentials, determined from the "initial breaks,"[2] are summarized in Table I. The results of Delfosse and Bleakney[3] on propane and propylene are included for comparison. We can offer no explanation for the discrepancies between our results and those of Delfosse and Bleakney. Careful checks show the results we report are consistent with our previously reported work on ethane and the butanes.

The significance of the appearance potentials of the various ions in the spectra of propylene and propane has been discussed by Delfosse and Bleakney.[3] Our values are not sufficiently different to change their interpretation in any significant detail.

The value of the appearance potential of the parent ion in the isobutylene spectrum, $A(C_4H_8^+) = 8.9$ e. v., which is to be associated with I_{vert}-(i-C_4H_8) is surprisingly low. The substitution of two methyl groups in ethylene reduces $I_{vert}(\pi + \pi, \pi_u)$ by $\sim$2.0 e. v. The effect of methyl for hydrogen substitution is more marked in the ethylene series than in the corresponding ethane series, since $I_{vert}(C_2H_6) = 11.7$ e. v. and $I_{vert}(C_4H_{10}) = 10.4$ e. v.[2] The I_{vert}(ethylenes) decrease more or less smoothly with methyl substitution, while the ethane series shows a greater decrease from propane to butane than from ethane to propane.

It will be noted that while in the ethylene series there is a difference of over 2.2 volts between the appearance potentials of R–H$^+$ and R$^+$ + H, the difference is less than 1.2 e. v. for the saturated hydrocarbons. A similar situation obtains when one compares the appearance potentials of R–CH_3^+ and R$^+$ + CH_3 for R olefin or saturate. These observations are consistent with the assumption which is usually made with respect to the relative strengths of single bonds to unsaturated and saturated carbon atoms.[4]

The ionization efficiency curve for $C_4H_8^+$ from isobutylene shows inflections at $\sim$12.5 e. v. and at $\sim$18 e. v. The inflection at 12.5 probably is to be attributed to the removal of the electron from a C–H bond orbital instead of from a C–C double bond orbital. Although we can make no assignment of the higher ionization potential ($\sim$18 e. v.), it should be remarked that isobutane also has an ionization potential about 9 volts above the appearance potential. The ionization efficiency curves for $C_4H_8^+$ from i-C_4H_8 and for $C_4H_{10}^+$ from i-C_4H_{10} are shown in Fig. 1.

Barring molecular rearrangement, the ion $C_3H_5^+$ formed from isobutylene has the structure $CH_3CCH_2^+$. One might expect the $C_3H_5^+$ formed from propylene to be the isomeric CH_2-$CHCH_2^+$ since the bonds to carbon atoms attached to unsaturated carbon atoms are generally weaker (more reactive) than the bonds to an unsaturated atom. The fact that $A(C_3H_5^+)$ from C_3H_6 is 2.2 e. v. greater than $A(C_3H_6^+)$ while $A(C_3H_7^+)$ from C_3H_8 is but 0.5 e. v. greater than $A(C_3H_8^+)$ suggests that the hydrogen atom lost by propylene was attached to one of the ethylenic carbon atoms. In either case we can write

(a) $C_3H_6 \longrightarrow CH_3CCH_2^+ + H + \epsilon^-$ $\quad A(C_3H_5^+) \geq 11.9_6$

(b) i-$C_4H_8 \longrightarrow CH_3CCH_2^+ + CH_3 + \epsilon^-$ $\quad A(C_3H_5)^+ = 11.5_1$

(c)[5] i-$C_4H_8 + 2H = C_3H_6 + CH_4$ $\quad \Delta H^\circ_{298.1} = -4.93$

These equations lead to D(CH_3—H) $\leq$ 4.48 e. v. This is in good agreement with the value of 4.38 e. v. deduced from other data.[6] This agreement

(1) Westinghouse Research Fellow. Present address, Shell Development Co., Emeryville, California.

(2) D. P. Stevenson and J. A. Hipple, THIS JOURNAL, **64**, 1588 (1942).

(3) J. Delfosse and W. Bleakney, *Phys. Rev.*, **56**, 256 (1939).

(4) F. O. Rice and K. K. Rice, "The Aliphatic Free Radicals," Johns Hopkins Press, Baltimore, Md., 1935, p. 75.

(5) F. D. Rossini, *Chem. Rev.*, **27**, 1 (1941), 1 kcal./mole = 0.04337 e. v.

(6) D. P. Stevenson, *J. Chem. Phys.*, **10**, 291 (1942).

TABLE I

APPEARANCE POTENTIALS OF VARIOUS IONS IN C_3H_6, C_3H_8 AND IN C_4H_8

Process	$A(X^+)$, e. v.[a]	$A(X^+)$, e. v.[b]
$C_3H_6 \longrightarrow C_3H_6^+ + \epsilon^-$	9.76 ±0.1	10.0 ±0.2
$C_3H_6 \longrightarrow C_3H_5^+ + H + \epsilon^-$	11.96 ± .1	11.8 ± .2
$C_3H_8 \longrightarrow C_3H_8^+ + \epsilon^-$	11.21 ± .1	11.3 ± .2
$C_3H_8 \longrightarrow C_3H_7^+ + \epsilon^-$	11.67 ± .1	11.9 ± .2
$C_3H_8 \longrightarrow C_2H_5^+ + CH_3 + \epsilon^-$	12.21 ± .1	12.3 ± .2
$C_3H_8 \longrightarrow C_2H_4^+ + CH_4 + \epsilon^-$	11.81 ± .1	12.2 ± .2
$C_3H_8 \longrightarrow CH_3^+ + \ldots + \epsilon^-$	17 ±2	...
i-$C_4H_8 \longrightarrow C_4H_8^+ + \epsilon^-$	8.86 ±0.1; 12.5 ±1	
i-$C_4H_8 \longrightarrow C_4H_7^+ + H + \epsilon^-$	11.32 ± .1	
i-$C_4H_8 \longrightarrow C_3H_5^+ + CH_3 + \epsilon^-$	11.51 ± .1	
i-$C_4H_8 \longrightarrow C_3H_4^+ + CH_4 + \epsilon^-$	11.62 ± .1	
i-$C_4H_8 \longrightarrow C_3H_3^+ + \ldots + \epsilon^-$	14.2 ± .5	
i-$C_4H_8 \longrightarrow C_2H_5^+ + \ldots + \epsilon^-$	15 ±1	
i-$C_4H_8 \longrightarrow C_2H_4^+ + C_2H_4 + \epsilon^-$	12.1 ±0.5	
i-$C_4H_8 \longrightarrow C_2H_3^+ + C_2H_4 + H + \epsilon^-$	15.2 ± .5	

[a] The ionization potential of argon, $I = 15.76$ e. v., was taken in accordance with the new conversion factor, 1 e. v. = 8066 cm.$^{-1}$. The appearance potentials in reference 2 should all be raised 0.07 e. v. We should like to thank the referee who called attention to the inconsistency on this point which existed in our original manuscript. [b] Ref. 3 of text.

suggests either that the unsymmetrical structure for the $C_3H_5^+$ from C_3H_6 is correct or that the isomerization energy of the reaction $CH_2CHCH_2^+ \rightarrow CH_3CCH_2^+$ is quite small. The latter seems very likely, since the allene → methylacetylene reaction involves but −0.07 e. v.

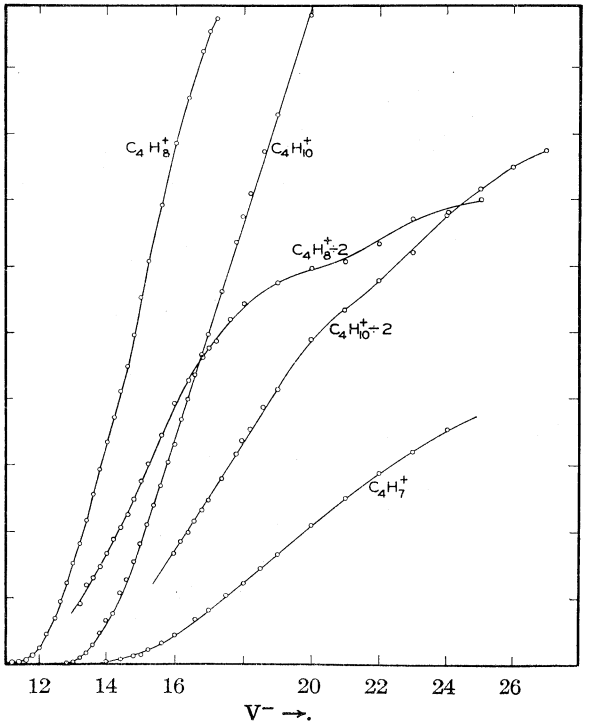


Fig. 1.—Ionization efficiency curves for the reactions i-$C_4H_8 \rightarrow C_4H_8^+$; i-$C_4H_8 \rightarrow C_4H_7^+ + H$; i-$C_4H_{10} \rightarrow C_4H_{10}^+$. The voltage scale is uncorrected. The ordinates for isobutylene and isobutane are not comparable.

The $C_3H_4^+$ from isobutylene may have either the allene or the methylacetylene structure. From the data summarized by Rossini,[5] we can write

(d) i-$C_4H_8 = CH_2CCH_2 + CH_4 \quad \Delta H^\circ_{298.1} = 1.36$ e. v.

or

(d′) i-$C_4H_8 = CH_3CCH + CH_4 \quad \Delta H^\circ_{298.1} = 1.29$ e. v.

Subtracting from i-C_4H_8; $A(C_3H_4^+) = 11.62$, we have either $I(CH_2CCH_2) = 10.26$ or $I(CH_3CCH) = 10.33$ e. v. Delfosse and Bleakney[3] found from direct measurement on allene, $A(C_3H_4^+) = 9.9$ e. v. The ionization potential of methylacetylene has not been measured. In acetylene, $A(C_2H_2^+) = 11.2$ e. v.[7] By analogy with the observed decreases in the vertical ionization potential brought about by substituting a methyl group into ethane and ethylene, one may guess that $I_{vert}(CH_3CCH)$ is 1 e. v. less than $I_{vert}(C_2H_2)$ or $I_{vert}(CH_3CCH) = 10.2$ e. v. Thus we are unable to reach a decision with regard to the structure of the $C_3H_4^+$ in the isobutylene spectrum. It may be noted that regardless of the structure of this ion, the methyl and hydrogen which form the methane come from adjacent carbon atoms rather than from the same atom.[8]

The relatively low values of the appearance potentials of the ions $C_2H_5^+$ and $C_2H_4^+$ in the isobutylene spectrum indicate that a minimum number of bonds are lost in the course of the rearrangement and dissociation reactions through which they are formed. The essential sharpness

(7) J. T. Tate, P. T. Smith and A. L. Vaughan, *Phys. Rev.*, **48**, 525 (1935).

(8) See the discussion in refs. 2 and 3.

with which the ionization efficiency curves (see Fig. 2) rise to their maximum values suggests that but one process is involved in each case, *i. e.*, one set of products. The low precision of $A(C_2H_5^+)$ precludes the unique assignment of the un-ionized fragments which accompany the formation of $C_2H_5^+$.

From the data of Rossini[5] we can write

(e) $i\text{-}C_4H_8 = 2C_2H_4$ $\quad \Delta H^\circ_{298.1} = 1.23$ e. v.

while Tate and co-workers[9] give

(f) $C_2H_4 \longrightarrow C_2H_4^+ + \epsilon^-$ $\quad A(C_2H_4^+) = 10.8$ e. v.

Adding, we find

(g) $i\text{-}C_4H_8 \longrightarrow C_2H_4^+ + C_2H_4 + \epsilon^-$

$A_{\text{calcd.}}(C_2H_4^+) = 12.0$ e. v.

in excellent agreement with the observed value (Table I). If, instead of the electron impact value of $A(C_2H_4^+)$, we had used Price's[10] spectroscopically determined $I^z(C_2H_4) = 10.4$ e. v., the value of $A(C_2H_4^+)$ calculated for (g) would be 0.4 e. v. below the observed value. This suggests 0.4 e. v. as a limit to the activation energy of the reverse of reaction (g). We have assumed that the products are of the ethylene rather than the ethylidene structure, an assumption which is unwarranted at present. Until the energies of ethylidene and its ion are known from other data, this ambiguity in the foregoing discussion must remain unresolved.

The ionization efficiency curve of the ion of mass 27 (primarily $C_2H_3^+$) of the isobutylene spectrum is similar in form to the curves for this ion in the spectra of ethane and the butanes. The rather large range of electron energies through which the slope increases suggests that one or more secondary processes, involving more fragmentation than the primary process, are involved. Combining reaction (e) with C_2H_4, $A(C_2H_3^+) = 14.1$ e. v.,[9] we find

(h) $i\text{-}C_4H_8 \longrightarrow C_2H_4 + C_2H_3^+ + H + \epsilon^-$

$A_{\text{calcd.}}(C_2H_3^+) = 15.3$ e. v.

in good agreement with the observed value of $A(C_2H_3^+) = 15.(2)$ e. v. We cannot exclude C_2H_5 as the un-ionized product which accompanies the $C_2H_3^+$. The association of C_2H_4 and H to C_2H_5 gives off about 1.7 e. v., thus for the reaction

(h′) $i\text{-}C_4H_8 \longrightarrow C_2H_5 + C_2H_3^+ + \epsilon^-$

one would estimate $A(C_2H_3^+) \cong 13.6$ e. v., well below the observed value. The 1.5 e. v. discrepancy could easily be assigned to an activation energy of the reverse of reaction (h′).

(9) P. Kusch, A. Hustrulid and J. T. Tate, *Phys. Rev.*, **52**, 843 (1937).
(10) W. C. Price, *ibid.*, **47**, 444 (1935).

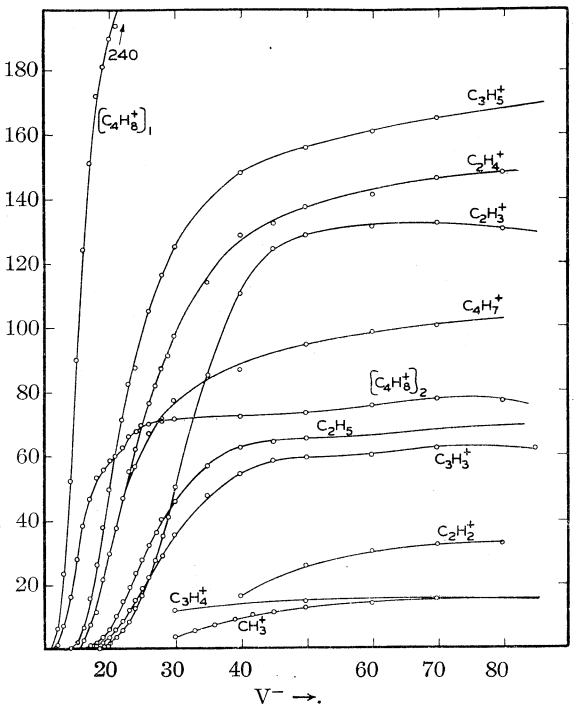


Fig. 2.—Ionization efficiency curves for various processes in isobutylene. $(C_4H_8^+)_1$ is to be compared with the C_2 masses. $(C_4H_8^+)_2$ is to be compared with the C_3 masses.

The form of the ionization efficiency curve of CH_3^+ from propane is of a character intermediate to those of this ion in ethane and the butanes. The formation of the methyl ion in the ethane spectrum involves mainly single ionization and in the butanes only double ionization. The value of $A(CH_3^+)$ from propane, while only rough, indicates that a process involving only single ionization contributes. The very pronounced curvature of the ionization efficiency curve in the vicinity of 26 volts indicates double ionization to be the more important source of methyl ions. The CH_3^+ current from propane attains about 10% of its maximum value for 30 volt electrons, while for similar electrons in ethane, CH_3^+ is 50% of its maximum value. The methyl ion current is but 6% of its maximum value for 30 volt electrons in the butanes.

The relative abundances of the various ions in the mass spectrum of isobutylene are given, for round values of the bombarding electron energy in Table II. Qualitatively, the distribution of intensities is very like that observed in the butane spectra. As is the case in the spectra of propylene, propane and the butanes, the principal reaction is

$$R\text{–}CH_3 \longrightarrow R^+ + CH_3 + \epsilon^-$$

In the C_4 region of the spectrum, isobutylene

TABLE II

THE MASS SPECTRUM OF ISOBUTYLENE[a]

m/e =	56	55	54	53	52	51	50	49	48
V⁻ ion =	$C_4H_8^+$	$C_4H_7^+$	$C_4H_6^+$	$C_4H_5^+$	$C_4H_4^+$	$C_4H_3^+$	$C_4H_2^+$	C_4H^+	C_4^+
30	100	33.3	3.9	..	..	..	..	..	..
50	103	40.8	4.9	11.0	2.5	8.6	8.4	1.6	0.22
70	108	43.6	4.8	10.8	2.3	8.5	9.7	2.6	.38
100	107	45.1	5.2	11.2	2.2	8.3	10.3	3.2	.54

m/e =	42	41	40	39	38	37	36
V⁻ ion =	$C_3H_6^+$	$C_3H_5^+$	$C_3H_4^+$	$C_3H_3^+$	$C_3H_2^+$	C_3H^+	C_3^+
30	16.1	175	16.9	50.1	..	..	..
50	18.2	218	21.4	83.8	11.3	5.1	0.25
70	18.7	231	22.4	87.4	12.7	7.5	.88
100	17.2	243	22.6	87.0	12.7	8.1	1.33

m/e =	29	28	27	26.5	26	25.5	25	24	15	14
V⁻ ion =	$C_2H_5^+$	$C_2H_4^+$	$C_2H_3^+$	$C_4H_5^{++}$	$C_2H_2^+$	$C_4H_3^{++}$	C_2H^+	C_2^+	CH_3^+	CH_2^+
30	18.8	42.2	21.4	..	..	..	..	..	1.4	0.09
50	28.1	59.5	55.1	..	11.0	0.5	..	..	5.5	1.9
70	29.1	63.3	56.6	..	13.9	..	..	..	6.5	..
90	29.9	64.8	55.7	0.22	14.3	2.8	2.3	0.25	6.7	..

[a] No correction for C^{13} in its natural abundance, 1.1%.

shows its generic relationship to isobutane. The manner in which the spectrum changes with electron energy is illustrated in Fig. 2.

Summary

The results of a mass-spectroscopic investigation of the ionization and dissociation of propylene, propane and isobutylene by electron impact are reported. The vertical ionization potentials of these three molecules were found to be $I_v(C_3H_6) = 9.8 \pm 0.1$ e. v., $I_v(C_3H_8) = 11.2 \pm 0.1$ e. v., and $I_v(i\text{-}C_4H_8) = 8.9 \pm 0.1$ e. v. The significance of some of the observed appearance potentials of ions in the isobutylene spectrum is discussed. The mass spectrum of isobutylene is given in detail.

EAST PITTSBURGH, PA. RECEIVED JULY 28, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

Reactions of Cobalt(III), Cobalt(II), and Iron(II) Oxides in Liquid Ammonia

BY THOMAS E. MOORE AND GEORGE W. WATT

With the single exception of the reduction studies described by Watt and Fernelius,[1] the only available information relative to reactions of metal oxides in liquid ammonia consists of a number of incidental qualitative observations[2] together with certain partially erroneous[3] results on reactions of the acidic oxides of chromium, molybdenum and tungsten published by Rosenheim and Jacobssohn.[4] The experiments described in this paper represent the first of a series of studies initiated for the purpose of providing information on the behavior of metal oxides toward liquid ammonia and liquid ammonia solutions of ammonium salts (acids), alkali amides (bases) and strong reducing agents.

(1) Watt and Fernelius, THIS JOURNAL, **61**, 2502 (1939).

(2) For primary references see Fernelius and Watt, *Chem. Rev.*, **20**, 213 (1937).

(3) Davies and Watt, forthcoming publication.

(4) Rosenheim and Jacobssohn, *Z. anorg. allgem. Chem.*, **50**, 297 (1906).

Experimental

Methods.—Unless otherwise indicated, the experimental techniques were those employed by Watt and Fernelius.[1] All analytical data were obtained using standard methods of analysis.

Materials.—All materials were carefully dried before use. All chemicals other than the oxides were either reagent grade materials or consisted of commercial products which were subjected to careful purification.

Cobalt(III) Oxide.—Baker "reagent grade" oxide was dried for ten hours at 100° and used without further treatment.

Anal. Calcd. for Co_2O_3: Co, 71.06. Found: Co, 70.75.

Cobalt(II) Oxide.—The most satisfactory method for the preparation of this material was found to be that of Le Blanc and Möbius.[5] However, the use of this method in the original or in modified form, as well as other known methods,[6] failed to yield a product of the desired composi-

(5) Le Blanc and Möbius, *Z. physik. Chem.*, **A142**, 151 (1929).

(6) For details see Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans, Green and Co., New York, N. Y., 1937, Vol. XIV, pp. 558–563.

TABLE I

REACTIONS WITH AMMONIUM SALTS AT 100°

Oxide		Salt				Oxide dissolved	
Formula	Wt., g.	Formula	Wt., g.	NH_3, ml.	Time, hr.	Wt., g.	%
Co_2O_3	0.4186	NH_4Cl	11.00	20	36	0.0000[a]	0.00
Co_2O_3	.4979	NH_4NO_3	36.80	30	36	.0000[a]	.00
CoO	.1960	NH_4Cl	12.90	20	20	.0163	8.32
CoO	.1896	NH_4NO_3	25.80	25	20	.0083	4.38
FeO	.4596	NH_4Cl	11.50	20	24	.0082	1.80
FeO	.3878	NH_4NO_3	20.00	25	24	.0049	1.26

[a] The aqueous extracts failed to give positive tests for cobalt with α-nitroso-β-naphthol reagent which, according to Atack [*J. Soc. Chem. Ind.*, **34**, 641 (1915)] will detect one part of cobalt in one million parts of solution.

tion. The best product obtained contained 75.0% cobalt as compared with a calculated cobalt content of 78.7% for CoO.

Iron(II) Oxide.—Kahlbaum iron(II) oxide was used. The chief impurity in this material was found to be elemental carbon. *Anal.* Calcd. for FeO: Fe, 77.71. Found: Fe, 73.64. The method of Chaudron[7] and other known methods[8] failed to provide a product of purity greater than that of the Kahlbaum product.

Reactions with Liquid Ammonia.—Weighed quantities of the oxides were allowed to remain in contact with a large excess of liquid ammonia in sealed tubes at 25° over a period of twenty-four hours. After removal of the ammonia, the oxides were shown by analysis to have undergone no change in composition. For example, a sample of iron(II) oxide (0.5388 g.) contained 73.81% iron before treatment and was found to contain 73.84% iron after treatment with ammonia.

Reactions with Ammonium Salts.—Weighed samples of the oxides were treated with liquid ammonia solutions containing large excesses of ammonium salts in sealed "Pyrex" tubes which were heated to 100° in an autoclave of the type described by Bergstrom.[9] After removal of the solvent, unchanged oxides of cobalt were separated by extraction with water. Both the soluble and insoluble portions were thereafter analyzed for cobalt. Unchanged iron(II) oxide was separated on the basis of its insolubility (as shown by preliminary experiments) in 1.2 *N* hydrochloric acid solution. In each case the identity of the unchanged oxide was established by analysis. Results of these experiments are given in Table I.

Reactions with Potassium Amide.—The methods used were those employed by Watt and Fernelius[10] with the exception that the stopcocks were removed from the Faraday tubes prior to mixing the reactants. This procedure was found necessary in order to avoid loss of solvent due to leakage over the long periods of time and under the pressures developed due both to solvent vapor pressure and that of gases evolved during the reactions. This practice, however, suffers a disadvantage in that it does not permit of the ready collection and identification of insoluble gaseous reaction products.

Cobalt(III) Oxide.—When treated with a liquid ammonia solution of potassium amide (from 1.3110 g. of potassium) at room temperature for ten days, cobalt(III) oxide (0.5847 g.) reacted slowly to form an apparently complex mixture of insoluble products. The only product identified was elemental cobalt which was deposited on the walls of the tube in the form of a thin bright metallic mirror. This deposit was dissolved by hydrochloric acid with evolution of hydrogen. In any case, the quantity of elemental cobalt isolated was small; for example, in a typical case 0.0085 g. of cobalt was separated from the heterogeneous insoluble products.

Cobalt(II) Oxide.—Treatment of 0.2984 g. of cobalt (II) oxide with an ammonia solution of the potassium amide from 1.1847 g. of potassium over a period of ten days at room temperature resulted in a three-fold increase in the bulk of the insoluble solid phase, the liberation of small quantities of an insoluble gas, and the production of an intensely green colored ammonia solution. Following separation of the ammonia solution from the insoluble material, the former was cooled to −70°, whereupon deep blue crystals separated together with crystals of potassium amide. Attempts to separate the blue crystalline product by fractional crystallization from ammonia were unsuccessful. The heterogeneous insoluble material reacted with hydrochloric acid with liberation of hydrogen. A representative sample of this material (0.3231 g.) was found to contain: N, 5.76; K, 17.49; Co, 58.94.

Iron(II) Oxide.—Potassium amide (from 1.4111 g. of potassium) in liquid ammonia solution was allowed to remain in contact with iron(II) oxide (0.4286 g.) at room temperature over a period of ten days, without any visible evidence of reaction. However, the insoluble black solid phase (after thorough washing with liquid ammonia) was found to contain: N, 7.73; K, 5.40; Fe, 73.80.

Reduction Reactions.—Cobalt(III) and iron(II) oxides were reduced by liquid ammonia solutions of potassium at 0° using the same procedures as those employed by Watt and Fernelius[1] with the exception that provision was made for the collection of hydrogen resulting from the interaction of potassium and ammonia under the catalytic influence of the oxides and/or reduction products. In effecting several reactions involving the heterogeneous reduction of a given oxide, efforts were made (but none too successfully) to control (a) the concentration of the potassium solutions, (b) the rate of addition of the reducing agent, and (c) the uniformity of agitation of the reactants. After washing each insoluble product, the tube was evacuated at 80–90° at an oil pump to remove adsorbed ammonia and hydrogen.

Unchanged cobalt(III) oxide was separated from the insoluble reduction products on the basis of its insolubility (as shown by preliminary experiments) in 1 *N* hydrochloric

(7) Chaudron, *Ann. chim.*, **16**, 272 (1921).
(8) Mellor, "A Comprehensive Treatise," 1937, Vol. XIII, p. 709.
(9) Bergstrom, *J. Org. Chem.*, **2**, 424 (1937).
(10) Watt and Fernelius, THIS JOURNAL, **61**, 1692 (1939).

acid. It was found impossible to separate iron(II) oxide by any similar procedure even when buffered acetic acid solutions were employed. Consequently, the gross insoluble product was analyzed as such. Data relevant to reduction reactions are given in Tables II and III.

TABLE II[a]

REDUCTION OF COBALT(III) OXIDE BY POTASSIUM IN LIQUID AMMONIA AT 0°

Co_2O_3, g.	Potassium G.	Potassium Equivalents	H_2, cc. at S. T. P.	Co (g.) in acid-soluble[b] product	Reduction,[c] %
0.5248	0.7559	6.1	157	0.1860	50.1
.2572	0.7429	12.0	163	.1328	74.5
.2569	1.4453	23.9	341	.1700	93.6

[a] Data recorded in this table represent the average results of at least three independent experiments which agreed as well as could be expected in view of the variables previously indicated. [b] In each case, the *acid-insoluble* product was shown to consist of unchanged cobalt(III) oxide. For example, *Anal.* Calcd. for Co_2O_3: Co, 70.75. Found: Co, 70.59. [c] Based on soluble cobalt.

TABLE III

REDUCTION OF IRON(II) OXIDE BY POTASSIUM IN LIQUID AMMONIA AT 0°

FeO, g.	Potassium G.	Potassium Equivalents	Analysis of insoluble products[a] Weight, g.	Fe, %	K, %
0.8732	0.9590	1.41	0.8914	72.01	4.42
.6112	1.3361	2.81	.6015	74.52	2.20
.4659	2.0496	5.66	.4594	74.04	2.73

[a] Analysis showed that nitrogen was absent or present only in traces.

Discussion

With regard to the preparation of the oxides of divalent cobalt and iron, this study has confirmed conclusions reached by earlier investigators[6,8] to the effect that pure compounds corresponding to the formulas CoO and FeO cannot be produced by at present available methods. Apparently the most that can be accomplished is the preparation of materials in which the lower oxides predominate.

That these oxides, and cobalt(III) oxide as well, are insoluble in and unreactive toward liquid ammonia is in full accord with the earlier observations of Franklin and Kraus.[11] In their reactions with ammonium salts, the behavior of the oxides included in this work parallels their behavior toward the corresponding aquo acids. If it may be assumed that the ability of a liquid ammonia solution of an onium type salt to dissolve metal oxides may be looked upon as a true manifestation of acidity, then it may be concluded that the acidic solutions employed in this investigation are of considerably lesser acidic strength than the corresponding aqueous acid solutions and that (in liquid ammonia) ammonium chloride is a stronger acid than ammonium nitrate. That cobalt(III) oxide proved to be entirely unreactive even at 100° is not surprising since this oxide is dissolved only very slowly by hot concentrated hydrochloric acid.

The reactions with potassium amide proved to be slow, very complex, and probably incomplete. The presence of elemental cobalt among the reaction products provides new evidence of the reducing action of the amide ion. The insoluble heterogeneous products also may have contained unchanged oxides, lower oxides, potassium hydroxide, and possibly salts of amphoteric bases resulting from the interaction of the reduced metals and potassium amide.[12] That mixtures were produced is shown by the fact that in every one of a considerable number of cases, the analytical data failed to conform to the composition of any known or probable compound.

The reduction of cobalt(III) oxide is believed to occur in two stages

$$Co_2O_3 + 2K + NH_3 \longrightarrow 2CoO + KOH + KNH_2$$
$$CoO + 2K + NH_3 \longrightarrow Co + KOH + KNH_2$$

This view is supported by the physical appearance of the products obtained when six, twelve and twenty-four equivalents of potassium are used, and by the fact that the insoluble product obtained using six equivalents of potassium is dissolved by hydrochloric acid without appreciable liberation of hydrogen whereas hydrogen is evolved extensively when the products obtained using twelve or twenty-four equivalents of potassium are treated similarly. Furthermore, the weights of potassium amide found by analysis[13] of the ammonia-soluble products were found to agree only with the theoretically possible weights of amide corresponding to the assumption that cobalt(II) oxide is the principal product of reactions involving six equivalents of potassium. Similarly, the weights of potassium amide found in reactions involving twenty-four equivalents of potassium agree only with values calculated on the assumption of essentially complete reduction to elemental cobalt. Of the possible bases for the determination of extent of reduction, analysis for soluble cobalt is believed to be the most reliable. Reproducible values for hydrogen evolved by the catalyzed reaction between potassium and

(11) Franklin and Kraus, *Am. Chem. J.*, **20**, 827 (1898).

(12) *Cf.* Bergstrom and Fernelius, *Chem. Rev.*, **12**, 43 (1933).

(13) Data available but not included in this paper.

TABLE IV

THE EXTENT OF REDUCTION OF IRON(II) OXIDE BY POTASSIUM

K (equivalents)	Insol. prod., g.	KOH,[a] g.	Cor. wt. of insol. prod.,[b] g.	Fe, g.	FeO, g.	Reduction, %	FeO accounted for, %
1.41	0.8914	0.0565	0.8349	0.1050	0.7299	16.4	99.9
2.81	.6015	.0190	.5825	.0742	.5083	16.5	99.5
5.66	.4594	.0180	.4414	.0582	.3832	17.1	99.2

[a] Calculated on the basis of potassium found by analysis of the insoluble products. [b] Corrected by subtraction of the weight of KOH—column 3.

ammonia could not be obtained due probably to leakage around the stopcocks and to the absorption of hydrogen by the reduction products.[14] Calculations based on analyses of ammonia-soluble products also led to divergent results probably as a result of difficulty encountered in complete removal of the solvent ammonia.

Iron(II) oxide is incompletely reduced to elemental iron in accordance with the equation

$$FeO + 2K + NH_3 \longrightarrow Fe + KOH + KNH_2$$

If it is assumed that the insoluble product consists of iron, iron(II) oxide, and potassium hydroxide, the values given in Table IV may be calculated from the data of Table III. The validity of this interpretation is supported by the excellent agreement between the weights of iron(II) oxide used initially and that accounted for in terms of the analytical data.

The fact that the extent of reduction of iron(II) oxide does not increase appreciably [as in the case of cobalt(III) oxide] with increase in the quantity of potassium used provides evidence that iron(II) oxide (or its reduction products) is a much more active catalyst for the conversion of potassium to potassium amide than is cobalt(III) oxide (or its reduction products). Although no rate measurements were made, it was observed that evolution of hydrogen is, in either case, relatively slow until some of the oxide has been reduced. Hence, it seems likely that the observed catalytic activity is to be attributed more to the reduction products than to the parent oxides.

(14) *Cf.* Burgess and Eastes, THIS JOURNAL, **63**, 2674 (1941).

Summary

1. Cobalt(III), cobalt(II) and iron(II) oxides are insoluble in and unreactive toward liquid ammonia at room temperature.

2. Cobalt(III) oxide is unreactive toward liquid ammonia solutions of ammonium chloride or nitrate at 100° while, under the same conditions, cobalt(II) and iron(II) oxides are partially dissolved.

3. Cobalt(III), cobalt(II) and iron(II) oxides react slowly with liquid ammonia solutions of potassium amide at room temperature to form complex mixtures of soluble and/or insoluble products.

4. Cobalt(III) oxide is reduced to cobalt(II) oxide and finally to elemental cobalt by liquid ammonia solutions of potassium at 0° to an extent dependent upon the Co_2O_3/K ratio. Under the same conditions, iron(II) oxide is reduced to elemental iron only to a very limited extent.

AUSTIN, TEXAS RECEIVED JUNE 22, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

The Vapor Pressure of Phenylhydrazine as a Function of the Temperature[1]

BY GLENN E. WILLIAMS AND E. C. GILBERT

Work now in progress in this Laboratory required a knowledge of the vapor pressure and latent heat of vaporization of phenylhydrazine. A search of the literature revealed an almost total lack of information based on any adequately purified and protected sample. The present work was therefore undertaken to obtain the required data over a considerable range of temperature.

Procedure and Apparatus.—The isoteniscopic apparatus of Smith and Menzies[2] was used, suitably modified so that samples could be introduced by distillation at reduced pressure and protected during the experimental manipulation in an atmosphere of dry nitrogen. Temperatures were controlled to ±0.02° and the thermometers had been compared with standards calibrated by the National Bureau of Standards. The manometer was of the Germann[3] design and was read to 0.1 mm. with a cathetometer, the readings being corrected to 0°, sea level, and latitude of 45°.

As a check on the accuracy of the procedure, the vapor pressure of water was measured in the temperature range 20–75°, and that of aniline in the range 100–150°. The arithmetical mean deviation of the twelve measurements with water was ±0.24 mm., with a maximum deviation of ±0.40 mm. The results for aniline agreed with the data of Ramsay and Young[4] rather than with those of Garrick,[5] obtained with a different type of apparatus unsuitable for use with phenylhydrazine. The maximum deviation of our experimental points from the smoothed values of Ramsay and Young at eight temperatures was 0.8 mm., the mean being ±0.3 mm.

Materials.—The nitrogen supply was passed through sodium pyrogallate to remove oxygen, and dried over a long column of calcium chloride and "anhydrone." The phenylhydrazine was prepared by the method of Coleman[6] and purified by fractionation under reduced pressure (18 mm.) in an atmosphere of nitrogen. The middle fraction from 250 cc. was distilled onto crushed stick sodium hydroxide. After standing, the phenylhydrazine was redistilled and a 20-cc. middle fraction was introduced into the isoteniscope. Four different samples were used including one from the Eastman Kodak Company. All were purified in the same manner. The aniline (Eastman Kodak Company) was purified in essentially the same manner as the phenylhydrazine.

Results and Discussion.—Fifty-five values of the vapor pressure were obtained between 100 and 192° using the four samples. Some sets of readings were taken with falling temperatures and some rising. It was found that these data fitted well an empirical equation of the form used by Cox[7] and Davis[8] and shown by them to be valid with a considerable variety of substances over a range of 340°. This equation is essentially $\log P = A - B/(t + 230)$, where t = centigrade temperature and P is the pressure in mm. Utilizing the 50 experimental points between 105 and 150°, the values of the constants A and B of this equation were derived by the method of least squares and found to be as follows: $A = 7.9046$; $B = 2366.4$.

The arithmetical mean deviation of the vapor pressures calculated by this formula from those observed was ±0.4 mm., with a maximum deviation of ±1.0 mm. In terms of percentage, the mean deviation above 125° was ±1.0%, while at lower temperatures the smaller absolute values of the vapor pressure (7–17 mm.) resulted in a larger mean deviation, approximately 3.0%.

As a further test of the adequacy of the equation, the vapor pressures measured at the five higher temperatures in the range 160–192° were compared with those calculated. The average arithmetical mean deviation of these measurements was ±0.7 mm. or ±0.5%, the maximum deviation being +0.75%. This showed that a fit, practically equal to the precision of the measurements was afforded by this equation.

The normal boiling point of phenylhydrazine calculated from the equation was 241°, slightly lower than the highest value given in the literature,[9] but in good agreement with others.

For the estimation of the latent heat of vaporization, values of the vapor pressure were calculated at 10° intervals, and from adjacent pairs the latent heat was calculated by the Clausius–Clapeyron equation, which is the best approximation that can be had, lacking critical data. The results are shown in Table I.

(1) Based on Thesis for the Master's Degree by G. E. Williams, 1942. Published with the approval of the Monographs Publication Committee, Oregon State College, as Research Paper No. 66, School of Science.

(2) Smith and Menzies, THIS JOURNAL, **32**, 897, 997, 1412 (1910).

(3) Germann, *ibid.*, **36**, 2456 (1914).

(4) Ramsay and Young, *J. Chem. Soc.*, **47**, 640 (1885).

(5) Garrick, *Trans. Faraday Soc.*, **23**, 560 (1927).

(6) "Organic Synthesis," Coll. Vol. I, second edition, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 442.

(7) Cox, *Ind. Eng. Chem.*, **15**, 592 (1923).

(8) Davis, *ibid.*, **17**, 735 (1925); **22**, 380 (1930).

(9) Perkin, *J. Chem. Soc.*, **69**, 1209 (1896); Blanksma, *Chem. Weekblad.*, **7**, 418 (1910); Fischer, *Ann.*, **236**, 198 (1896); Heilbron, "Dictionary of Organic Compounds," Oxford University Press, N. Y., 1938, Vol. 3, p. 419.

TABLE I

THE HEAT OF VAPORIZATION OF PHENYLHYDRAZINE

Temp., °C.	25	95	105	115
	125	135	145	240
Heat of vaporization, cal./mole	(14690)	13886	13788	13693
	13610	13526	13455	(12903)

Summary

The vapor pressure of phenylhydrazine has been measured by means of the isoteniscope over the range 105–192° with a precision of about ±0.4 mm. From the resulting data an empirical equation was derived by the method of least squares which reproduced these values to within the experimental precision.

From these values of the vapor pressure the latent heat of vaporization at temperatures from 25–240° has been computed and tabulated.

CORVALLIS, OREGON RECEIVED JUNE 22, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Kinetics of the Transformation of Hydrazine Cyanate into Semicarbazide[1]

BY ELTON M. BAKER AND E. C. GILBERT

The transformation of ammonium cyanate into urea has been the subject of numerous and exhaustive studies but the analogous reaction of hydrazine cyanate to form semicarbazide has never been subjected to critical examination. Such examination is complicated by the reactive nature of the substances involved and also by the fact that semicarbazide is definitely basic whereas urea is so weakly basic that for practical purposes its proton affinity in dilute aqueous solution is entirely negligible. The present work, however, represents a study of the kinetics of the reaction, simple salt effects, equilibrium measurements and the effect of temperature on the rate.

Experimental Part

Preparation of Materials.—Potassium Cyanate (Baker C. P.) was suspended in absolute ethanol by vigorous shaking, to dissolve any small amount of cyanide present. It was then collected on a filter, washed with ether and dried. It was then preserved in a vacuum desiccator and stored in the dark. Prepared in this manner, analysis by the Volhard method showed a purity of 99.6%.

Two neutral salts of hydrazine, the perchlorate and monohydrochloride, were prepared from Kahlbaum 100% hydrazine hydrate and the corresponding pure acids. These salts were recrystallized from 80% methanol and dried over sulfuric acid. They were analyzed by the iodate method.

For equilibrium measurements semicarbazide was necessary. Eastman Kodak Co. semicarbazide hydrochloride was recrystallized from 80% methanol, and checked for purity by Volhard analysis for chloride content. Foreign salts added to increase ionic strength were Baker C. P. quality.

Procedure.—The unexpected rapidity of the reaction precluded the preparation of pure hydrazine cyanate (free from other ions) from silver cyanate and hydrazine chloride in a manner analogous to that used by Warner and Stitt[2] to prepare ammonium cyanate.

All solutions were made up by adding hydrazine monochloride or perchlorate in solution to exactly equivalent amounts of potassium cyanate. This was accomplished by a vessel of special design which permitted almost instantaneous mixing of small amounts of these solutions. Measurements were made at 25 and 15° in a bath controlled to ±0.05°.

The progress of the reaction was followed by withdrawing samples which were added to excess standard silver nitrate solution. The precipitated silver salts were filtered out and the excess silver ions in an aliquot portion were determined by titration with standard thiocyanate using ferric alum indicator.

From these results the amount of unreacted cyanate present at any time was calculable.

Equilibrium measurements were made from both forward and backward directions. Reaction mixtures of hydrazine and cyanate were allowed to react until the cyanate titer was constant. Similarly semicarbazide solutions of equivalent concentrations were allowed to stand at constant temperature and analyzed for cyanate from time to time. Equilibrium lies so far toward completion that the reverse reaction has no detectable effect in the early stages of the process.

Discussion

The rapidity of the reaction as measured was quite unexpected as the laboratory directions for the preparation of semicarbazide by this method[3] called for elevated temperature and twenty to twenty-four hours of standing. It was therefore thought desirable to demonstrate that the reaction being followed was actually that which was postu-

(1) Taken from the thesis presented by Elton M. Baker in partial fulfillment of requirements for the Ph.D., Oregon State College, 1942. Published with the approval of the Monographs Publication Committee, O. S. C. Research Paper 67.

(2) Warner and Stitt, THIS JOURNAL, **55**, 4807 (1933).

(3) Beilstein, 4th edition, Vol. III, p. 98.

lated. This was done by adding benzaldehyde solution at intervals to samples of reaction mixture. With unchanged hydrazine the yellow insoluble compound benzalazine was formed, while with semicarbazide the white semicarbazone of the benzaldehyde was formed. This was also insoluble. The two were readily separated by differential solubility in ether and their identity established by mixed melting points with known samples. As the reaction proceeded the amount of yellow benzalazine rapidly decreased and that of the semicarbazone increased. Had it not been for the time lag in formation of these compounds it would have provided an excellent method of following the reaction. There thus is no reason to doubt that the reaction measured is that of the formation of semicarbazide. No evidence was ever found indicating the presence of carbonate, which is known to be a disturbing factor in the urea reaction.[2] This is probably due to the lower temperatures and shorter times used in this work.

The main points of interest lie in the conclusions that may be drawn concerning the possible mechanism of the reaction, the possibility of general or specific ion catalysis and the energy of activation.

The assumption that the process would likely prove to be bimolecular was borne out by the fact that in all cases the graph of time against the reciprocal of cyanate concentration was a very satisfactory straight line (Fig. 1) until the reaction was at least 50% complete.

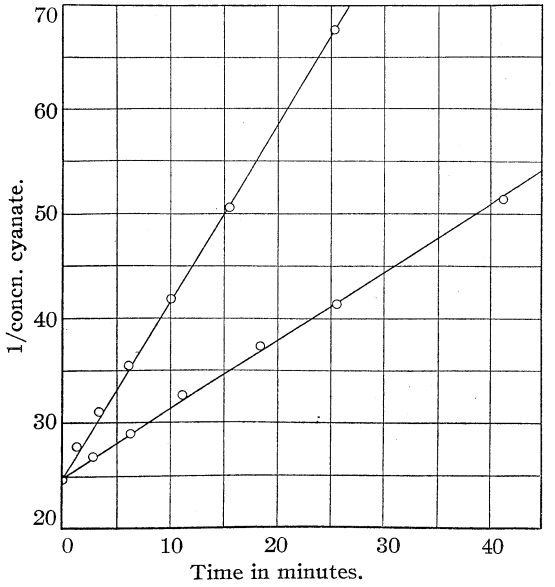


Fig. 1.—Graph showing bimolecular characteristics of reaction, also temperature effect: upper curve, temp. 25°; lower curve, temp. 15°.

For the elucidation of the mechanism useful evidence is obtainable from the effect of ionic strength on the velocity, as shown in Table I. Since the ionic strength diminished due to the disappearance of the hydrazine and cyanate ions during the reaction it was necessary to approximate the mean ionic strength during the time over which the constant was determined.

TABLE I

CONVERSION OF HYDRAZINE CYANATE INTO SEMICARBAZIDE AT 25°, DEPENDENCE OF THE BIMOLECULAR RATE CONSTANT UPON THE IONIC STRENGTH

Run	Initial molality	Molality of added salts	Mean[a] μ	Bimolecular k, mole liter^{-1} sec.$^{-1}$
19	0.0250	0.0250 (1)	0.0488	0.0390
24	.0250	.0250 (1)	.0435	.0300
25	.0250	.0250 (2)	.0453	.0298
63	.0403	.0403 (1)	.0700	.0286
10	.0500	.0500 (1)	.0858	.0286
18	.0500	.0500 (2)	.0860	.0283
12	.0500	.0500 (3)	.0860	.0282
11	.0500	.0500 (1)	.0860	.0278
17	.0500	.1000 (3)	.1360	.0275
16	.0500	.1500 (3)	.1865	.0260
15	.0500	.2500 (3)	.2870	.0238
14	.0500	.4500 (3)	.4887	.0220

[a] Mean ionic strength taking into account salts present plus mean concentration of hydrazine and cyanate ions during time used in establishing bimolecular constant, k: (1) potassium chloride only; (2) potassium perchlorate only; (3) potassium nitrate and chloride.

There was a definitely negative primary salt effect though the concentrations which it was necessary to use were too high to expect quantitative agreement with the limiting law. When the expression for the limiting law, modified to allow for higher ionic strength

$$\log k = \log k_0 + Z_1 Z_2 \frac{\sqrt{\mu}}{1 + A\sqrt{\mu}}$$

is used, excellent agreement is obtained even at the higher concentrations.

According to Brönsted's theory such a negative salt effect is to be expected for a reaction between ions of unlike charge, whereas if uncharged molecules were involved the salt effect should be negligible. The effect is shown graphically in Fig. 2, in which has been shown also the limiting slope (−1) predicted for a reaction in which the ions have unit positive and negative charges, in solutions of low ionic strength.

This evidence, like that in the urea conversion, points strongly to the theory that the rate governing step is one between ions, presumably hydrazine and cyanate.

The effect of temperature is also illustrated in Fig. 1 showing runs at 15 and 25° for solutions of low ionic strength. The mean k_{15} for 5 runs was 0.0107 and the mean k_{25} for 4 runs was 0.0284 giving a temperature coefficient of 2.65 for ten degrees, and a calculated energy of activation of 16,600 cal./mole. The data probably do not possess sufficient precision to merit calculation of the entropy of activation.

Equilibrium data are shown in Table II. Due to the greater time required for attainment of equilibrium at lower temperatures with the attendent complications of side reactions and oxidation only measurements at 25° are reported. Equilibrium is apparently reached only when approximately 97% of the hydrazine cyanate has reacted.

TABLE II

EQUILIBRIUM CONSTANT, AT 25°

$$K = \frac{(\text{MOLALITY OF CYANATE})^2}{(\text{MOLALITY OF SEMICARBAZIDE})}$$

Run	Molality of semicarbazide	Molality of cyanate	$K \times 10^5$
60	0.02409	0.00091	3.44
61[a]	.03903	.00124	3.94
62[a]	.03924	.00111	3.14
62[a]	.03927	.00108	2.97
64	.03907	.00128	4.19

[a] Semicarbazide was allowed to decompose into hydrazine cyanate. In all other runs the reactant was hydrazine cyanate.

Using the equilibrium data, in equations of Walker and Appleyard[4] it was possible to calculate k_2 for the postulated reverse unimolecular decomposition of semicarbazide. This is shown in the summarizing table, Table III.

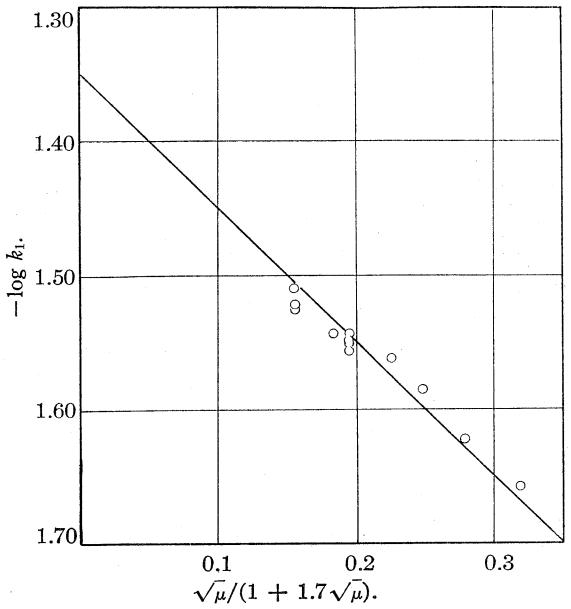


Fig. 2.—Change of velocity constant k_1 at 25° with change in ionic strength. Solid line is limiting slope for reaction between univalent ions of opposite charge.

the hydrazine salts were of the monovalent series and the potassium cyanate neutral the reaction mixture at the start was at a *p*H of approximately 6. As semicarbazide was formed, there was a gradual increase in *p*H. At this *p*H, calculation shows that the semicarbazide is practically entirely in the basic form. Buffers which are effective in this range have the disadvantage that practically without exception their silver salts are insoluble, unless acid is added, in which case error is introduced by the concomitant solubility of the silver cyanate.

TABLE III

SUMMARY OF CONSTANTS

Conversion of Hydrazine Cyanate to Semicarbazide

Equilibrium constant K_{25}	(μ = *ca.* 0.05)	3.5×10^{-5}
Equilibrium constant K_{15}	(μ = *ca.* .05)	(2.9×10^{-5})
k_1 forward at 25°	(μ = *ca.* .08)	2.85×10^{-2} mole liter^{-1} sec.$^{-1}$
k_2 reverse at 25°		9.98×10^{-7} mole liter^{-1} sec.$^{-1}$
k_1 forward at 15°	(μ = *ca.* .08)	1.07×10^{-2} mole liter^{-1} sec.$^{-1}$
k_2 reverse at 15°		4.93×10^{-8} mole liter^{-1} sec.$^{-1}$
k_0 (extrap.) at 25°	(μ = 0)	4.46×10^{-2} mole liter^{-1} sec.$^{-1}$
Temperature coefficient k_{25}/k_{15}		2.65
Energy of activation		16,600 cal. mole^{-1}

Due to limitations imposed by the method of analysis which so far have not seemed avoidable, and the basicity of the semicarbazide, investigation of possible specific or general catalysis was confined to qualitative observations. Since one set of experiments using an acetate buffer at *p*H 5 (slightly lower than that of the unbuffered mixture) showed apparently an increase in reaction rate which might indicate a hydrogen ion catalysis. There was no change in the bimolecular characteristics, however. So far as could be de-

(4) Walker and Appleyard, *J. Chem. Soc.*, **69**, 193 (1896).

termined, an increase in buffer concentration caused no increase in rate, indicating no general catalysis at least for the acetate–acetic acid buffer.

To convert semicarbazide predominantly into its salt requires a *p*H of about 2. Efforts were made to study the rate of reaction in this *p*H range by adding acid from a micro buret at a rate sufficient to keep the *p*H at 2.2 (in which case the acid added is a measure of the semicarbazide formed) following the procedure of earlier work.[5] Evidence showed however that the cyanic acid was decomposing with little semicarbazide being formed, and this approach was not carried further.

(5) Gilbert, THIS JOURNAL, **51**, 3394 (1929).

Summary

1. The formation of semicarbazide from hydrazine cyanate takes place readily at room temperature.

2. Increase in ionic strength reduces the velocity of reaction in a manner which agrees with the postulate that the rate determining process is the reaction between the hydrazine and cyanate ions.

3. The reaction reaches an equilibrium far to the side of formation of semicarbazide.

4. Quantitative results are presented on the velocity constants of the reaction at 15 and 25°, the equilibrium constant, salt effects, temperature coefficient and heat of activation.

CORVALLIS, OREGON RECEIVED AUGUST 6, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY, THE ILLINOIS INSTITUTE OF TECHNOLOGY, AND THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

The Role of Neighboring Groups in Replacement Reactions. I. Retention of Configuration in the Reaction of Some Dihalides and Acetoxyhalides with Silver Acetate[1]

BY S. WINSTEIN[2] AND R. E. BUCKLES

Three mechanisms for nucleophilic replacement reactions at a saturated carbon atom are currently recognized.[3,4] One is the now familiar[5] bimolecular (S_N2) substitution with complete Walden inversion. A second mechanism (S_Ni) involves the rearrangement of an intermediate product[3,6] in such a way that retention of configuration is the steric result.

The third mechanism has been termed unimolecular[3] (S_N1) or polymolecular.[3,4,7] It seems to consist of at least two steps, the most probable rate-determining step being an ionization. There are several indications that the carbonium ion intermediate is, in some respects, quite unfree.[4] For example, the steric result of reaction by this mechanism generally is predominant inversion. Quite analogous to the S_N1 mechanism is a process involving the electrophilic attack of a reagent such as silver ion on a halogen atom.[3,4]

Ionization to an ion-pair, solvated in a way characteristic of ions, may be thought to be the rate-determining step in the S_N1 mechanism. Solvation of the ions makes this step feasible; therefore, the rate varies with the arrangement of solvent molecules around what is to be the ion-pair. Solvent molecules must be included in the transition state, without, however, drawing bonds between the solvent molecules and the carbonium ion.[8,9,10] If the carbonium ion is very reactive it will react preferentially with a molecule in the solvation cluster to give inversion as the major steric result.[3] There may thus be some connection between rates and final product compositions in mixed solvents.[3,8] If reaction of the carbonium ion takes place after dissociation of the ion-pair, complete racemization is the steric result.[7]

(1) A portion of the material reported in this paper was presented before the Organic Division at the St. Louis meeting of the American Chemical Society, April, 1941.

(2) National Research Fellow in Chemistry, Harvard University, 1939–1940.

(3) (a) Cowdrey, Hughes, Ingold, Masterman and Scott, *J. Chem. Soc.*, 1252 (1937); (b) Bateman, Church, Hughes, Ingold and Taher, *ibid.*, 979 (1940).

(4) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapters V and VI.

(5) (a) Olson, *J. Chem. Phys.*, **1**, 418 (1933); (b) Bergmann, Polanyi and Szabo, *Z. physik. Chem.*, **20**, 161 (1933).

(6) Hughes, Ingold and Whitfield, *Nature*, **147**, 206 (1941).

(7) (a) Steigman and Hammett, THIS JOURNAL, **59**, 2536 (1937); (b) Farinacci and Hammett, *ibid.*, **59**, 2542 (1937); (c) Beste and Hammett, *ibid.*, **62**, 2481 (1940).

(8) Winstein, *ibid.*, **61**, 1635 (1939).

(9) Balfe and Kenyon, *ibid.*, **62**, 445 (1940).

(10) It is possible that the failure of a tertiary halide with the halogen atom on a bridge-head to undergo solvolytic reaction, as demonstrated by Bartlett and co-workers, [THIS JOURNAL, **61**, 3184 (1939); **62**, 1183 (1940)] should be ascribed partly to the fact that the solvation energy of the cationic end of the ion-pair to be formed is apt to be much smaller than usual. Solvent is kept away from the cationic carbon atom by the hydrocarbon cage more effectively than is possible with the most highly hindered open-chain compounds in which the cationic carbon atom can flatten out.

To understand the rates and steric results of nucleophilic replacement reactions of the most complex compounds (perhaps with several functional groups) it is necessary to demonstrate and understand the effects of substituent groups other than their supply or withdrawal of electrons to the seat of substitution by induction and resonance.[3] One of the most interesting effects is that of participation of a group on a neighboring or more distant carbon atom in a replacement process at a carbon atom. Thus, a replacement reaction might really consist of two steps, the first one an intramolecular S_N2 reaction, the second the opening of a ring. Two inversions or apparent retention will be the steric result.

Even more interesting is the involvement of a neighboring group in a replacement reaction which appears to be of the S_N1 type. In this connection, several reactions have been found to proceed with retention of configuration because of an extra functional group.[3,11,12,13]

In this article we present and discuss several additional examples of reactions which similarly involve participation of a neighboring group and we include a discussion of general expectations as to the scope and results of such participation.

We have now studied the steric result of the reaction of silver acetate in dry acetic acid with the *threo*- and *erythro*-2-acetoxy-3-bromobutanes, the *dl*- and *meso*-2,3-dibromobutanes, *trans*-1-acetoxy-2-bromocyclohexane and *trans*-1,2-dibromocyclohexane. Table I gives a summary of the results of the conversions. The steric results are based on configurations of the starting materials and products which are either proved or highly probable.[12,14,15,16,17]

It is seen that the acetoxybromobutanes and the butene dihalides react with silver acetate to give diacetates with quite high retention of configuration. Thus, retention of configuration is the steric result in the replacement of both the first and second bromine atom of the dibromide by the acetoxy group. Similarly the cyclohexene derivatives react with retention of configuration to give *trans*-diacetate under conditions which cause no configurational change of *cis*-diacetate.

TABLE I

SUMMARY OF STERIC RESULTS OF REACTION OF SILVER ACETATE WITH SOME HALIDES IN ACETIC ACID

Starting halide	Diacetate[a] M. p., °C.	Config.	Corrected[b] steric result
trans-1-Acetoxy-2-bromocyclohexane	102[c]	97% *trans*	97% Retention
threo-2-Acetoxy-3-bromobutane	41	95.5% *dl*	98% Retention
erythro-2-Acetoxy-3-bromobutane	0.5	91% *meso*	91% Retention
trans-1,2-Dibromocyclohexane	103[c]	98% *trans*	98% Retention
dl-2,3-Dibromobutane	39	91% *dl*	94% Retention
meso-2,3-Dibromobutane	−1.5	87% *meso*	>87% Retention[d]

[a] Melting point of *dl*-2,3-diacetoxybutane, 42.9°; *meso* isomer 3.0°. [b] There is included a correction for slight configurational impurity of two starting materials. [c] Melting point of glycol from saponification of the diacetate. Melting point of *trans*-1,2-cyclohexanediol, 104°. [d] This result is a lower limit since it was obtained early in the course of the work and the acetic acid solvent was not freed from water as thoroughly as in later work; see ref. 18.

The retentions of configuration are almost complete and would appear even better were one able to eliminate small configurational impurity of starting materials; also, if one were able completely to eliminate another reaction to be discussed elsewhere,[18] which gives rise to inverted products and which can be made predominant under other conditions. Also, there is the possibility that the halides are to a very small degree isomerized to diastereomers by silver halide in the course of the conversions. This would give rise to a small amount of apparent inversion in the steric result.

Besides acetic acid as a solvent medium for the reaction of the cyclohexene derivatives with silver acetate, acetic anhydride was also employed. The results obtained were entirely similar in steric result to those in acetic acid but the yields of diacetate were much inferior and it was difficult to fractionate out pure material.

The retentions of configuration observed are best accounted for by the participation in the replacement process of the —Br atom or —OAc group on the carbon atom neighboring the seat of substitution. This participation involves bond formation to the carbon atom being substituted either simultaneously with or very shortly after the removal of halide ion by silver ion in some form with the production of intermediate I or II with quite complete inversion. The reaction of these intermediates with acetate ion[19] with a

(11) Cowdrey, Hughes and Ingold, *J. Chem. Soc.*, 1208 (1937).

(12) (a) Winstein and Lucas, THIS JOURNAL, **61**, 1576 (1939); (b) Winstein and Lucas, *ibid.*, **61**, 2845 (1939).

(13) Lucas and Gould, *ibid.*, **63**, 2541 (1941).

(14) Bartlett, *ibid.*, **57**, 224 (1935).

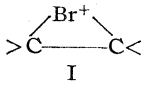
(15) Lucas and Gould, *ibid.*, **64**, 601 (1942).

(16) Winstein, *ibid.*, **64**, 2792 (1942).

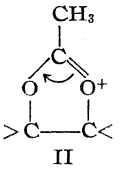
(17) Rothstein, *Ann. Chim.*, **14**, 461 (1930).

(18) Winstein and Buckles, *ibid.*, **64**, 2787 (1942).

(19) Although the reaction is formulated in this way, it is not entirely clear whether acetate ion or acetic acid[12b] is the reagent in this case. This point will be settled later.



I

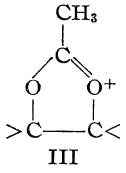


II

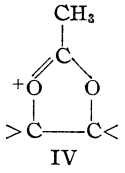
second inversion gives a net apparent retention of configuration as the steric result.

The bromonium ion I has been considered an intermediate in the reaction of the 3-bromo-2-butanols with hydrobromic acid[12] and in one ionic mechanism of addition of bromine to the ethylenic linkage.[12,20] Lucas and Gould have recently presented evidence for an analogous chloronium ion.[13]

For two reasons, the ion II is chosen as the intermediate when a neighboring acetoxy group participates in the replacement process. First, II should be energetically preferable over other possible forms because of freedom from strain and because of resonance between equivalent forms III and IV. The arrow in formula II indicates



III



IV

the symmetrical nature of II. Secondly, in reactions similar to the one being dealt with, ortho-acetate derivatives are often isolated.

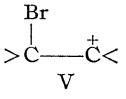
The argument in favor of the mechanism involving intermediates I and II for the retentions of configuration is strengthened by the results with some optically active materials (Table II). 2-Bromoöctane with α_D (1 dcm.) 5.39° was converted by silver acetate in acetic acid to an acetate with α_D (1 dcm.) − 0.61°. On the basis of densities and specific rotations in the literature[3a,21] for 2-bromoöctane and 2-acetoxyoctane, it appears that 72% of the optical activity survives in the process and that the results correspond to 86% inversion and 14% retention. Thus, in the absence of a neighboring group the reaction conditions lead to a typical[3,4] S_N1 steric result. 2,3-Dibromobutane with α_D (1 dcm.) − 2.43° yielded a diacetate which was completely inactive in spite of the fact that active diacetate did not lose its activity under the conditions of the experiment. Also, *trans*-1-acetoxy-2-bromocyclohexane with α_D (1 dcm.) −0.19° yielded a completely inactive diacetate. These results are in perfect accord with the prediction[12] of complete loss of activity for a mechanism involving an inactive internally compensated intermediate (I or II).

TABLE II

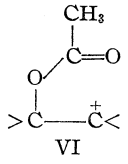
SUMMARY OF THE RESULTS OF THE TREATMENT OF ACTIVE COMPOUNDS WITH SILVER ACETATE IN DRY ACETIC ACID

Name	Starting compound α_D (1 dcm.)°	Final product α_D (1 dcm.)°
2-Bromoöctane	5.39	−0.61
2,3-Dibromobutane	−2.43	.00±0.01
trans-1-Acetoxy-2-bromocyclohexane	−0.19	.00± .01
2,3-Diacetoxybutane	− .48	− .45

We are still inquiring into the question whether the closings of the rings in intermediates I and II are one-stage[12] or two-stage[3] processes. The two-stage processes would involve the bromine-substituted carbonium ion V and the acetoxy-substituted carbonium ion VI. In this connection



V



VI

some relative reactivities are pertinent. There is a tremendous difference in reactivity of the 2-butene chlorohydrins and bromohydrins toward fuming hydrobromic acid. This has been mentioned by Lucas and Gould[13] and we have independently noticed it. A similar difference in reactivity appears in the cyclohexene series.[22] It does not appear reasonable that inductive effects can account for such a large difference. Bromine and chlorine atoms generally have effects of comparable magnitude[23] and thus would hinder about equally well the formation of conjugate acid from halohydrin and the departure of a water molecule with the shared pair of electrons from the halohydrin-conjugate acid. Thus, the bromine atom is able to meet much better than the chlorine atom a demand of the carbon atom being substituted. This effectiveness of the bromine atom must rest in its larger size and larger polarizability.

Also, there is a tremendous difference in the reactivity of the *cis*- and *trans*-1-acetoxy-2-chlorocyclohexanes toward silver acetate.[24] Under conditions more drastic than those needed to

(20) Roberts and Kimball, THIS JOURNAL, **59**, 947 (1937).

(21) (a) Hughes, Ingold and Masterman, *J. Chem. Soc.*, 1196 (1937); (b) Pickard and Kenyon, *ibid.*, 45 (1911); (c) Pickard and Kenyon, *ibid.*, 830 (1914).

(22) Winstein, unpublished work.

(23) See, for example, Branch and Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, p. 204.

(24) Winstein and Buckles, unpublished work.

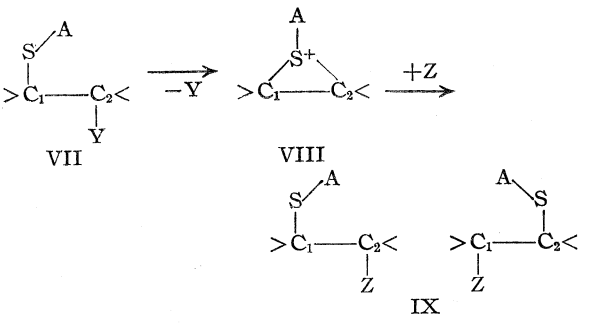
bring about reaction of the *trans*-compound, the *cis*-compound is completely unreactive. The *trans*-acetoxy group seems to be able to supply some driving force for the reaction and the *cis*-acetoxy group is essentially unable to do this. These relative reactivities are more easily understood on the basis of a one-stage closing of the ring in intermediates like I or II than on another basis. This holds also for the rather complete inversion accompanying the formation of I or II together with the rather complete lack of competition of outside reagents (solvent, AcO^-, etc.) with the neighboring group for attachment to the carbon atom being substituted.

We are also attempting to decide whether the opening of the ring in intermediates like I or II occurs in one or two stages.[25]

Participation of Neighboring Groups.—The observed retentions of configuration due to the participation of a neighboring group in an S_N1-like replacement process involve the effect of a carboxylate ion group[11] in solvolytic and analogous reactions of salts of α-halogen acids; the effect of a neighboring bromine atom in the reaction of a bromohydrin with hydrogen bromide[12] and in the reaction of a dibromide with silver acetate; the effect of a neighboring chlorine atom in the reaction of a chlorohydrin with thionyl chloride[13]; and the effect of a neighboring acetoxy group in the reaction of acetoxybromides with silver acetate. One would expect this effect to be very general, likely neighboring groups for such participation, including those already mentioned, being $-O^-$ of a carboxylate ion group, halogen, —OCOR, $-NH_2$ or $-NR_2$, —SR, —OR, —OH and of course $-O^-$.

It is worth pointing out briefly some expected results of the participation of neighboring groups in replacement processes of the S_N1 type. We will symbolize VII as the starting compound with Y the group to be replaced and AS the neighboring group, Z being the entering group.

First, if VII is the derivative of an unsymmetrical olefin, it becomes possible for some or most of



the product IX to have Z on a different carbon atom than the one left by Y.

A second expectation involves the results when VII is either the *cis*- or *trans*-derivative of a cyclic olefin. If the new ring in the intermediate VIII is a small one, it is possible for the neighboring group to participate in the replacement process only when one starts with *trans*-VII and not when one starts with *cis*-VII. Thus, retention of configuration will be the steric result when one starts with *trans*-VII and the usual predominating inversion will be the steric result when one starts with *cis*-VII. There will then be a tendency for both isomeric VII's to give, in reactions of the S_N1 type, a product with the groups Z and SA *trans* to each other.[26]

A situation which appears to illustrate this point arises in the reaction of silver acetate with acetohalogen sugars to form normal polyacetates. Tipson[27] has made the generalization that acetate groups 1 and 2 in the product are *trans* to each other and Isbell[28] has pointed out that this result arises because of the ability of acetate group 2 to enter into the replacement process if it is *trans* to the original halogen and not if it is *cis* to the original halogen.

Somewhat the same differences which are foreseen for *cis*- and *trans*-derivatives of cyclic olefins may be looked for in the case of pairs of open-chain diastereomers where rotation is seriously restricted about the bond between carbon atoms C-1 and C-2. The configurations about this bond might be so preferred[29] that it is easy for a neighboring group to participate in a replacement process of one diastereomer and difficult in the case of the other.

(25) If generalizations such as rate sequences, *t*-Bu > *i*-Pr > Et > Me for S_N1 reactions and *t*-Bu < *i*-Pr < Et < Me for S_N2 reactions hold[13] for intermediates like I or II it would be possible to learn the nature of a reaction from the direction of the opening of the ring of an unsymmetrical intermediate. Considerable success[22] can be attained in this way in understanding the direction of opening of oxide rings but even with oxides one generalization, at least, does not hold. For S_N2 reactions, hydroxide ion should be a reagent superior to a water molecule. However, in kinetic work on reactions of oxides which appear to be S_N2, hydroxide ion has proved to be an ineffective reagent while water is an effective one [Brönsted, Kilpatrick and Kilpatrick, THIS JOURNAL, **51**, 428 (1929)].

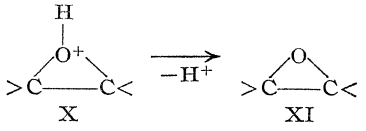
(26) The effect of the neighboring group might contribute toward the existence of a large difference in reactivity of *cis*- and *trans*-VII in S_N1 type reactions.

(27) Tipson, *J. Biol. Chem.*, **130**, 55 (1939).

(28) (a) Isbell, "Annual Review of Biochemistry," Annual Reviews, Inc., Stanford Univ. Press, Stanford Univ. P. O., Calif., 1940, page 65; (b) Frush and Isbell, *J. Research Natl. Bur. of Standards*, **27**, 413 (1941).

(29) Weissberger, *J. Org. Chem.*, **2**, 245 (1937).

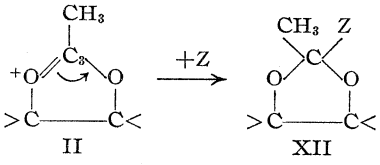
Finally, reactions involving the intermediate VIII might yield products other than IX in view of the ability of VIII to undergo other reactions. Thus, if VIII were to become X, we might expect to get oxide XI by the loss of a proton. Indeed



X XI

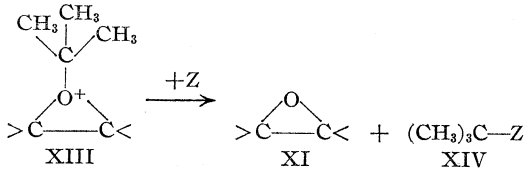
oxides are often isolated from S_N1 or analogous reactions of halohydrins, monotosylates of glycols, etc.

If II is the intermediate, then reaction at carbon C-3 should give an orthoacetate derivative XII. Isbell[28] has pointed out that acetohalogen sugars often give rise to orthoacetate derivatives, and that these orthoacetate derivatives are obtained only when the neighboring acetate group is *trans* to the halogen and not when it is *cis*. This is because an intermediate like II is easily possible only for the *trans*-compound.



II XII

It seems possible that other intermediates might discard, instead of a proton, some other group. Thus, it seems possible that an intermediate such as XIII might give rise to oxide XI and a tertiary butyl derivative XIV.



XIII XI XIV

Experimental

trans-**2-Bromocyclohexanol.**—This material was prepared from cyclohexene and acetbromamide.[30] 1.56 moles of cyclohexene and an equivalent amount of acetbromamide were stirred under reflux with 1200 ml. of water for one and one-half hours. The reaction was controlled by addition of concd. sulfuric acid, 2 ml. at the start, 2 ml. after one half hour and 1 ml. at the end of an hour. The temperature of the reaction mixture was kept below 50° with an ice-bath. At the end of the one and one-half-hour period the mixture had returned to room temperature. The bromohydrin layer was separated and the aqueous layer was extracted with 150 ml. of ether. The extract and bromohydrin were combined and washed with 250 ml. of water to remove acetamide. The ether was distilled off and the bromohydrin was distilled rapidly through a Weston-type[31] column at reduced pressure. The yield was 219 g. (79%), b. p. 86.6–88.4° (10 mm.), $n^{25}D$ 1.5184.

trans-**1-Acetoxy-2-bromocyclohexane.**—Acetylation of the bromohydrin was carried out with a 20% excess of acetic anhydride. To 45 g. of bromohydrin, acetic anhydride and 2 drops of concd. sulfuric acid were added. The mixture warmed up and soon returned to room temperature. The mixture was shaken with a little calcium carbonate to neutralize the catalyst, filtered and distilled at reduced pressure through a short column. 48 g. (87%) of the acetate was obtained; b. p. 109–110° (12 mm.), $n^{25}D$ 1.4857.

trans-**1,2-Dibromocyclohexane.**—Bromine was added to cyclohexene by the method of Greengard.[32] Material, b. p. 99.6–99.9° (13 mm.), $n^{25}D$ 1.5506, was used in this work.

trans-**1,2-Cyclohexanediol.**—This material was some prepared from cyclohexene oxide in connection with other work[16] and some prepared by saponification of the diacetate obtained from the action of silver acetate on dibromocyclohexane in dry acetic acid. Recrystallization from carbon tetrachloride yields a product, m. p. 104°.

cis-**1,2-Cyclohexanediol.**—This material was some prepared in another study.[18]

cis- **and** *trans*-**1,2-Diacetoxycyclohexanes.**—These substances were prepared by acetylation of the glycols by the procedure used with the bromocyclohexanol. The diacetates were obtained in 90 to 95% yield, the *cis*, b. p. 117.8–118.0° (12 mm.), $n^{25}D$ 1.4475, the *trans*, b. p. 120° (12 mm.), $n^{25}D$ 1.4457.

threo-**3-Bromo-2-butanol.**—This substance was prepared from the reaction of acetbromamide and *cis*-2-butene[12] obtained from *meso*-2,3-butanediol by way of the diacetate and dibromide.[33] The general procedure has been described previously.[12] The reaction was controllable when 0.4 mole of butene was added to the acetbromamide in 250 ml. of water to which 4 ml. of 6 *N* sulfuric acid had been added. Under these conditions the reaction mixture was worked up after one and one-quarter to two hours and the yield, 82%, (107 g. bromohydrin from a total of 0.855 mole of butene used in two runs) was superior to that formerly obtained.[12]

erythro-**3-Bromo-2-butanol.**—This material was prepared from pure oxide.[12]

threo- **and** *erythro*-**2-Acetoxy-3-bromobutanes.**—These substances were prepared by acetylation of the corresponding bromohydrins as previously described.[34] In the acetylation of bromohydrins from the reaction of olefin with acetbromamide, a drop or two of concd. sulfuric acid was needed as a catalyst, and the reaction mixture was shaken with a little calcium carbonate before distillation.

dl-**2,3-Dibromobutane.**—This material was prepared from *meso*-diacetate.[33,34]

meso-**2,3-Dibromobutane.**—This dibromide was some prepared by the action of fuming hydrobromic acid on pure oxide or the bromohydrin or the acetoxybromobutane derived from it.[12,34]

(30) Schmidt, Knilling and Ascherl, *Ber.*, **59B**, 1280 (1926).

(31) Weston, *Ind. Eng. Chem., Anal. Ed.*, **5**, 179 (1933).

(32) Greengard, Org. Syntheses, **XII**, 26 (1932).

(33) Wilson and Lucas, THIS JOURNAL, **58**, 2396 (1936).

(34) Winstein and Lucas, *ibid.*, **61**, 1581 (1939).

Reaction of the Dibromides and Acetoxy-bromides with Silver Acetate.—The reaction of the halides with silver acetate in acetic acid at 100–110° with automatic stirring yielded results superior to some[35] reported for other conditions. Silver acetate (approximately 25% excess) was precipitated by adding excess aqueous sodium or potassium acetate to aqueous silver nitrate. It was filtered and washed carefully three times with glacial acetic acid on a Büchner funnel. The moist mass was then transferred to the reaction flask equipped with a mercury-sealed stirrer and reflux condenser protected by a drying tube. 100 ml. of reagent grade glacial acetic acid for each 0.1 mole of halide was added and the mixture was stirred for fifteen minutes. Then a sample of the acetic acid solvent was pipetted through cotton and the water content of the acid estimated from the melting point. An amount of acetic anhydride, in excess by 2 or 3 ml. of the amount necessary to react with the water in the solvent, was then added and the mixture was kept warm for about two hours[36] with stirring with an oil-bath at 100–110°. Then the halide was added and to insure complete reaction the mixture was stirred for eight hours in the case of the butene derivatives and eleven hours for the cyclohexene derivatives, the oil-bath being maintained at 100–110°. Sometimes the reaction was vigorous at the start and it was necessary to interrupt the heating for a short while. At the end of the proper time, the reaction mixture was allowed to cool and it was filtered. The filtrate was distilled at reduced pressure through the Weston-type column to isolate the diacetates. Starting with 0.1-mole quantities of the halides the yields averaged 70%, and they were better on larger runs. The products agreed within experimental error in boiling point, refractive index and saponification equivalent with authentic samples.

When acetic anhydride was used as a reaction medium in the case of the cyclohexene derivatives the procedure was the same in preparing and washing the silver acetate. Then acetic anhydride was added instead of acetic acid, the mixture was heated for a time to remove water, and the reaction was then carried on as usual and the product was isolated as usual. A good deal of high-boiling residue was formed in these reactions and only a 30–40% yield of somewhat impure diacetate could be distilled out with difficulty.

Analysis of Products.—The 1,2-diacetoxycyclohexane samples were identified by saponification to the glycol. 1 ml. of the ester was refluxed two hours with 2 ml. of 35% aqueous sodium hydroxide and 2 ml. of pure alcohol. The solution was washed into a separatory funnel with a minimum of water (1 or 2 ml.). Then the glycol was extracted with five 25-ml. portions of pure chloroform, the extracts were dried over potassium carbonate, distilled to a small volume and the residue was allowed to evaporate to dryness. The solid glycol was thus obtained in nearly quantitative yield. The melting points of the glycol and its mixtures with authentic specimens yielded an estimate of the composition of the glycol. Recrystallization of the crude glycols from carbon tetrachloride yielded pure *trans*-glycol. The saponification procedure was carried out on mixtures of *cis*- and *trans*-diacetates made up by weight, the temperatures of disappearance of solid when the glycol was melted being summarized in Table III.

The diacetoxybutanes were identified by melting point and mixed melting point with the aid of melting point-composition data of Lucas and Mitchell.[37]

TABLE III

MELTING POINTS OF GLYCOLS FROM THE SAPONIFICATION OF MIXTURES OF THE *cis*- AND *trans*-1,2-DIACETOXYCYCLOHEXANES

% *trans*	M. p., °C.	% *trans*	M. p., °C.
0	98	45	72
4	93.5	51	74
5.7	91	66	82
8.7	89	83	92.5
12	88	89	99
23	80.5	93	100.5
35	71.5	100	103.5

The melting points of the solid diacetate were taken by melting the whole sample in a flask or test-tube. In the case of the liquid diacetate, the dependence of composition on melting point is so sensitive that some standardization of the procedure was necessary. About a 10-g. sample of the diacetate was frozen in a test-tube and then with stirring at room temperature allowed to melt, the melting point being taken with a thermometer in the melt. With this technique and the thermometer in use, the very purest diacetate (prepared from glycol, m. p. 34.5°, by acetylation, removal of the sulfuric acid catalyst with calcium carbonate, and careful purification) gave a temperature 0.5° below the value of Lucas and Mitchell. Thus 0.5° was added to the temperature values near the melting point of *meso*-diacetate. To discover on what side of the eutectic a low-melting sample was it was sufficient to add a small amount of *meso*-diacetate and notice whether a decrease or increase in melting point was observed.

The products from the reaction of the cyclohexene derivatives in acetic anhydride gave glycols a little less pure than those obtained from the acetic acid reaction, the acetoxybromocyclohexane product giving a glycol, m. p. 101.5° and the dibromocyclohexane product giving a glycol m. p. 96°. These glycols were again predominantly *trans*.

Corrections for Slight Impurity of Starting Isomers.—In the preparation of *threo*-2-acetoxy-3-bromobutane (from the butene from the dibromide) and the *dl*-2,3-dibromobutane, *meso*-diacetate of slightly low melting point was used. This impurity was partly due to impurity of the glycol used and perhaps partly due to the failure to neutralize the sulfuric acid, used as a catalyst in the acetylation of the glycol, before distillation. This impurity in the starting diacetate is corrected for in Table I.

Preparation of Active 2-Bromoöctane and its Reaction with Silver Acetate.—5.0 ml. of active 2-octanol (kindly supplied by Dr. P. D. Bartlett) α_D (1 dcm.) −7.38°, was mixed with 15.0 ml. of Eastman Kodak Co. *dl*-2-octanol and the mixture was sealed up with hydrobromic acid which was prepared by saturating[12,34] 130 g. of 48% acid with hydrogen bromide gas at 0°. The reaction mixture was left at room temperature with occasional shaking for several days when the reaction vessel was opened and the

(35) Bainbridge, *J. Chem. Soc.*, **105**, 2291 (1914).

(36) For the reaction of *meso*-2,3-dibromobutane the water was removed by allowing the mixture to stand nearly two days at room temperature before the dibromide was added.

(37) Private communication.

bromide layer separated. The bromide was washed with water, twice with 10 ml. of concd. sulfuric acid, then with water and finally with potassium carbonate solution. The bromide was dried over potassium carbonate and the 21.5 g. of crude material was then distilled through the Weston-type column. 18.5 g., b. p. 74.7–75.3° (14 mm.), α_D (1 dcm.) 5.39°, was obtained. The bromide, 18.0 g., was converted to acetate with silver acetate in dry acetic acid as for the butene and cyclohexene derivatives. Distillation through the Weston-type column yielded 9.5 g. (59%) of acetate, b. p. 81.3–82.0° (12.5 mm.), $n^{22}D$ 1.4140, α_D (1 dcm.) −0.61°.

Active 2,3-Dibromobutane and its Conversion to Diacetate.—Partial resolution of a 2,3-dibromobutane which was mostly the *dl*-isomer was accomplished by the method of Lucas and Gould.[15] 64.8 g. (0.30 mole) of the dibromide and 39.5 g. of brucine were mixed and allowed to stand for eighteen hours. The brucine was dissolved in excess hydrochloric acid and the dibromide was removed with the aid of 200 ml. of petroleum ether. The extract was washed with water and dried over potassium carbonate. The dibromide was obtained by distillation at reduced pressure; 46 g., b. p. 73.0–73.5° (50 mm.), α_D (1 dcm.) − 2.43°. When this material was converted to diacetate in the usual way, the product proved to be completely inactive.

A 2,3-diacetoxybutane with α_D −0.48° (mostly diacetate of Lucidol glycol) was subjected to the reaction conditions using a mixture of silver acetate and bromide. The recovered diacetate α_D − 0.45° showed a change in the rotation no larger than one would expect due to fractionation.

Active 1-Acetoxy-2-bromocyclohexane and its Conversion to Diacetate.—The method of treating the bromohydrin with a deficiency of acetic anhydride in the presence of brucine as described previously[12b] for butene derivatives yielded a slight resolution. A solution of 30 g. of brucine, 54 g. of 2-bromocyclohexanol and 13 ml. of acetic anhydride in 300 ml. of carbon tetrachloride was refluxed for two hours. The reaction mixture was treated as before and fractionation at 12 mm. yielded 23.2 g. of bromohydrin, b. p. 88.5–91.0°, α_D (1 dcm.) − 0.20° and 17.8 g. of acetoxybromocyclohexane, b. p. 106.0–107.2°, α_D (1 dcm.) − 0.19°. Each fraction was treated with acetic anhydride to convert all the bromohydrin to acetate. The bromohydrin fraction yielded 23.6 g. of acetate, b. p. 109–110° (12 mm.), α_D (1 dcm.) − 0.19°. The bromoacetate fraction[38] yielded 14 g., b. p. 109–110° (12 mm.), α_D (1 dcm.) − 0.17°.

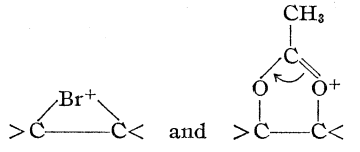
When the acetoxybromocyclohexane, α_D (1 dcm.) − 0.19° was converted to diacetate with silver acetate in dry acetic acid in the usual way the diacetate, b. p. 120.0–120.5° (12 mm.) showed no activity at all. The intermediate fraction lower-boiling than the diacetate also showed no activity.

Behavior of *cis*-1,2-Diacetoxycyclohexane under the Reaction Conditions.—A small quantity of *cis*-1,2-diacetoxycyclohexane was heated eleven hours in dry acetic acid with a mixture of silver acetate and silver bromide. The reaction mixture was filtered and diluted with water. The diacetate was then extracted with ether. The ether extract was neutralized with carbonate solution and then dried over potassium carbonate. Evaporation of the ether and saponification of the ester by the procedure in use gave *cis*-glycol, m. p. 97.5° before recrystallization. Thus at least 99% of the glycol maintains its configuration.

It is a pleasure to thank Professor H. J. Lucas and Messrs. C. W. Gould and F. W. Mitchell, Jr., of the California Institute of Technology for data in advance of publication and Professor P. D. Bartlett of Harvard University for the optically active 2-octanol used. Also, one of us (S. W.) wishes to acknowledge several helpful discussions with Professors P. D. Bartlett and H. J. Lucas.

Summary

The reactions of silver acetate in dry acetic acid with the *erythro*- and *threo*-2-acetoxy-3-bromobutanes, *trans*-1-acetoxy-2-bromocyclohexane, the *meso*- and *dl*-2,3-dibromobutanes, and *trans*-1,2-dibromocyclohexane proceed with predominant retention of configuration. Also, optically active 2,3-dibromobutane and *trans*-1-acetoxy-2-bromocyclohexane give rise to completely inactive diacetates. The steric results are believed due to the participation of a neighboring bromine or acetoxy group in the replacement processes, with production of the intermediates



A discussion of the scope of this kind of participation of neighboring groups in replacement processes and the results to be expected from such participation is included.

LOS ANGELES, CALIFORNIA RECEIVED APRIL 14, 1942

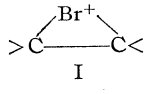
(38) The fact that the same sign of rotation is displayed by the acetoxybromocyclohexanes from both fractions shows that the slight resolution obtained by this procedure is not due to a selective acetylation but to some other reaction.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY, THE ILLINOIS INSTITUTE OF TECHNOLOGY, AND THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

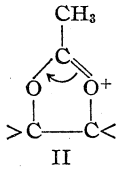
The Role of Neighboring Groups in Replacement Reactions. II. The Effects of Small Amounts of Water on the Reaction of Silver Acetate in Acetic Acid with Some Butene and Cyclohexene Derivatives[1]

BY S. WINSTEIN[2] AND R. E. BUCKLES

In a previous[3] publication on the effects of neighboring groups in replacement reactions we reported that the reaction of silver acetate in dry acetic acid with *trans*-1-acetoxy-2-bromocyclohexane, *threo*- and *erythro*-2-acetoxy-3-bromobutane, *trans*-1,2-dibromocyclohexane and *dl*- and *meso*-2,3-dibromobutane proceeded with what appears to be quite complete retention of configuration. This and other evidence pointed to the participation of the neighboring —Br and —OAc groups in the replacement process, intermediates I and II being involved.



I



II

In the course of this investigation, we noticed a pronounced and interesting effect of the presence of water in the acetic acid on the nature of the product and the steric result. The presence of water causes the appearance of roughly 65–75% of the equivalent amount of monoacetate in the product and shifts the steric result to as much as 95–98% of inversion of configuration. This is shown in Table I.

That monoacetate of the glycol is the direct product of the reaction in the presence of water is shown by the behavior of some of the monoacetates and diacetates toward the reaction conditions (Table II). The monoacetates are converted to diacetates to a considerable extent, while the diacetates are converted to monoacetates to only a negligible extent.

Since monoacetate is the direct product of reaction, the presence of water is able to cause the introduction of an hydroxyl group instead of an acetate group by the action of silver acetate on the bromoacetates. However, it appears unlikely

(1) A large portion of the material reported in this paper was presented before the Organic Division at the St. Louis meeting of the American Chemical Society, April, 1941.

(2) National Research Fellow in Chemistry, Harvard University, 1939–1940.

(3) Winstein and Buckles, THIS JOURNAL, **64**, 2780 (1942).

TABLE I

THE EFFECT OF WATER ON THE REACTION OF SOME HALIDES WITH SILVER ACETATE IN ACETIC ACID

Compound	Moles H_2O	N[a]	Diacetate[b] m. p., °C.	Corrected steric result % inversion
threo-2-Acetoxy-3-bromobutane	0	0	41	2
	0.25	0.10	34.8	19
	.50	.39	15.7	55
	.75	.58	−4.5	82
	1.0	.70	0.5	94
	1.0[c]	.72	2.1	95
erythro-2-Acetoxy-3-bromobutane	1.0		41.3	96
dl-2,3-Dibromobutane	0.5	.39	14.2	57
	1.0	.65	2.0	96
meso-2,3-Dibromobutane	1.0	.67	40.5	96
dl-trans-1-Acetoxy-2-bromocyclohexane	0.00[c]	0		7
	0.51	.37		67
	1.0	.65		92
	1.0[d]	.64		94
	1.0[c]	.52		92
	2.0	.65		98
dl-trans-1,2-Dibromocyclohexane	1.0	.64		90
	2.0			98

[a] Mole fraction of monoacetate in reaction product. [b] *dl*-2,3-Diacetoxybutane melts at 42.9°, the *meso*-isomer at 3.0°. [c] 1 mole of potassium acetate per mole of halide was used in the reaction mixture. [d] Volume of reaction mixture was twice as large as usual so that the initial concentration of water was half as large.

TABLE II

THE BEHAVIOR OF MONO- AND DIACETATES TOWARD THE CONDITIONS FOR REACTION OF HALIDES WITH SILVER ACETATE

Compound	Moles H_2O	Hours of heating	N	% retention
meso-2,3-Diacetoxybutane	1.0[b]	11	0.02	100
erythro-3-Acetoxy-2-butanol	0.3	7.5	.76	100
cis-1,2-Diacetoxycyclohexane	1.0	11	.03	...
cis-2-Acetoxycyclohexanol[a]	0.51	11	.51	...
trans-1,2-Diacetoxycyclohexane	2.0	11	..	99

[a] This material was 84 mole % monoacetate, 16 mole % diacetate. [b] In all these experiments an equimolar mixture of silver acetate and silver bromide was added.

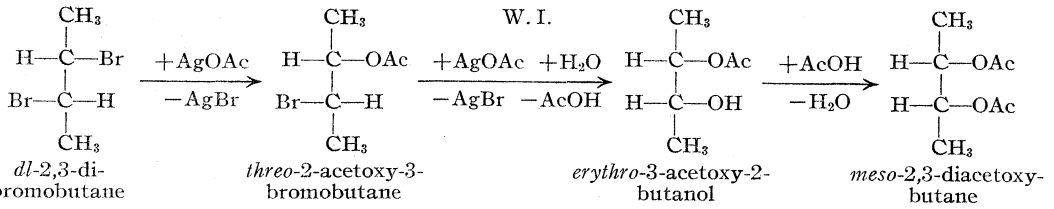


Fig. 1.—*erythro*-3-Acetoxy-2-butanol and *meso*-2,3-diacetoxybutane from *dl*-2,3-dibromobutane or *threo*-2-acetoxy-3-bromobutane.

that water causes the introduction of an hydroxyl group instead of an acetate group when silver acetate reacts to replace the first bromine atom of the dibromides. This is evident from the behavior of the bromohydrins which would thus be formed (Table III).

TABLE III

THE BEHAVIOR OF BUTENE AND CYCLOHEXENE BROMOHYDRINS TOWARD SILVER ACETATE IN ACETIC ACID

Compound	Moles H_2O	N	% retention
threo-3-Bromo-2-butanol	1.0	..	75[a]
trans-2-Bromocyclohexanol	1.0	78	92
trans-2-Bromocyclohexanol	0.64[b]	71	93

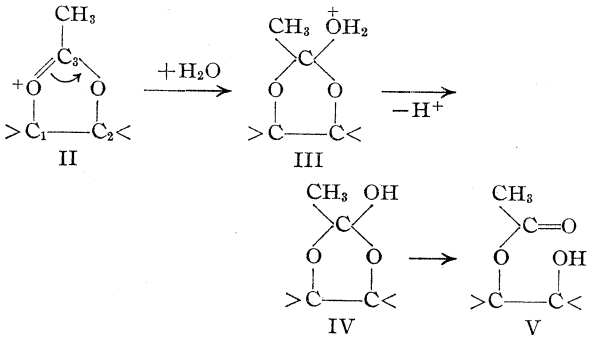
[a] The yield of diacetate on acetylating the crude ester product of the reaction was only 26%. [b] One mole of silver bromide was added also.

Firstly, *threo*-3-bromo-2-butanol gives only a poor yield[4] of expected product with silver acetate in acetic acid. Secondly, with the butene bromohydrin, the steric result is 75% retention,[5] while with the cyclohexene bromohydrin it is at least 93% retention. All our experience[3,6] would lead us to expect bromohydrin to be formed from dibromide with retention of configuration, so retention of configuration should be the steric result for the conversion of dibromide to monoacetate by way of bromohydrin. Actually inversion is the major steric result in the presence of enough water.

Figure 1 illustrates the reaction course for the preparation of a mixture of monoacetate and diacetate from one of the dibromides or bromoacetates with silver acetate in wet acetic acid containing moderate amounts of water.[7] If dibromide is the starting material, bromoacetate is produced with retention of configuration just as in the absence of water.[3] Then bromoacetate gives rise to monoacetate with inversion of configuration, the monoacetate then slowly being acetylated. The inversion of configuration is denoted by W. I.

In the presence of small amounts of water the scheme shown in Fig. 1 apparently proceeds until the water is largely consumed and then the scheme for dry acetic acid (with retention of configuration) operates. Since water is slowly produced from the monoacetate, it becomes clear why there is a tendency for the amount of inversion of configuration to run somewhat higher than equivalent to the amount of water in the original reaction mixture.

The most probable explanation of the effect of the water involves the formation of intermediate II even when some water is present. Then intermediate II reacts with water at carbon atom C-3 to give the conjugate acid of the orthomonoacetate of the glycol III which by loss of a proton



gives rise to the orthomonoacetate of the glycol IV.[8] The orthomonoacetate IV and the ordinary

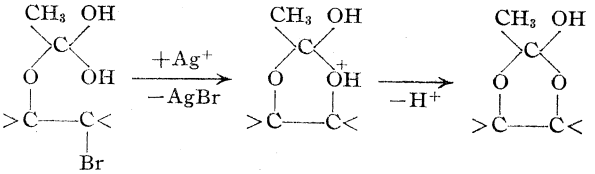
(4) With the cyclohexene bromohydrin the yield of expected product was not much inferior to that obtained from dibromide.

(5) The reason for this steric result in the case of the butene bromohydrin is not yet clear. In view of the poor yield, the amount of inversion observed could be due to reaction of a small amount (*ca.* 7%) of bromoacetate produced from bromohydrin.

(6) (a) Winstein and Lucas, THIS JOURNAL, **61**, 1576 (1939); (b) Winstein and Lucas, *ibid.*, **61**, 2845 (1939).

(7) Mr. Robert Henderson has found that very much larger amounts of water in the reaction mixture for the treatment of the dibromobutanes have some marked effects such as depressing the yield of product greatly.

(8) At least part of the orthomonoacetate formation in the presence of water may arise from reaction of molecules of acetoxybromide, to which water has already added, according to the scheme shown.



This scheme involves the participation of a neighboring orthoacetate group in the process of replacement of the bromine atom.

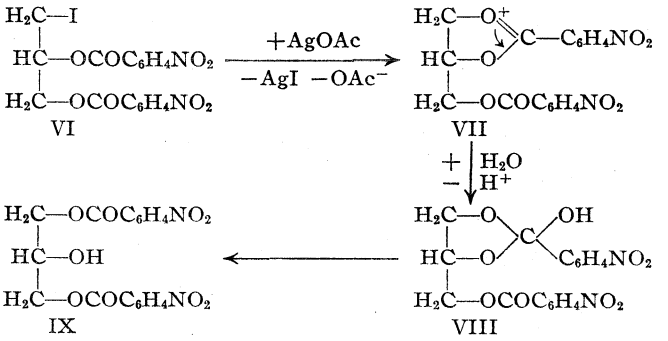
monoacetate V are presumed to be readily interconvertible without any configurational changes under the conditions of the replacement reaction.[9] Thus, the preparation of monoacetate is attended by one Walden inversion which occurs in the formation of intermediate II.

There are several favorable aspects to this explanation. First, intermediates of type II must be reactive at carbon atom C-3, for acetohalogen sugars in which the neighboring acetoxy group is *trans* to the halogen atom often give rise to orthoacetate derivatives in reactions similar in nature to the one discussed in this paper.[10,11] Secondly, the ability of water to affect the reaction only when the acetoxy group is the neighboring group becomes understandable. Thirdly, the very high percentage of inversion of configuration that occurs when enough water is present is to be expected from a process involving the production of an intermediate such as II.

Other Halides with Silver Acetate in Wet Acetic Acid.—Rothstein[12] obtained *cis*-ester from cyclohexene dibromide and Brunel[13] obtained what is now known to be *cis*-ester from 1-acetoxy-2-iodocyclohexane,[14] 1-bromo-2-iodocyclohexane,[14] and 1-chloro-2-iodocyclohexane.[14] These results demand the presence of water in the acetic acid used as solvent, by analogy with the results we have reported.

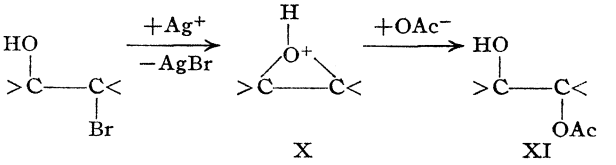
A case which comes to mind of the introduction of an hydroxyl group on treatment of an acyloxyhalide with silver acetate in acetic acid is the conversion[15] of such compounds as 1-iodo-2,3-di-*p*-nitrobenzoxypropane VI to 1,3-di-*p*-nitrobenzoxypropanol-2 IX.

This work is interesting here not only because an hydroxyl group is introduced instead of an acetoxy group but because an acyl group has migrated[3] in the process. If our mechanism for the effect of water in acetic acid on the course of the reaction of acyloxyhalide with silver acetate is correct, the transformation VI → IX proceeds according to the scheme[16] VI → VII → VIII → IX.



Form VIII was suggested by E. Fischer[15] as an intermediate for the migration of acyl groups in partially acylated polyhydroxy compounds.

The Neighboring Hydroxyl Group.—The quite high retention of configuration observed in the treatment of cyclohexene bromohydrin with silver acetate in acetic acid and the predominating retention of configuration in the similar treatment of the butene bromohydrin suggest that the ester product XI is produced chiefly by way of the conjugate acid of the oxide X, the opening of



the oxide ring occurring with inversion.[17] Thus, it would appear that a neighboring hydroxyl group can be similar in action to a bromine or acetoxy group.[3]

Experimental

***trans*-2-Bromocyclohexanol, *threo*-3-Bromo-2-butanol, *trans*-1-Acetoxy-2-bromocyclohexane, *trans*-1,2-Dibromocyclohexane, *erythro*- and *threo*-2-Acetoxy-3-bromobutane and *dl*-2,3-Dibromobutane.**—These substances were either the same as or prepared similarly to the ones used in the previous work.[3]

***meso*-2,3-Dibromobutane.**—This material, b. p. (50 mm.) 73.3–73.5°, was prepared by the action of fuming hydrobromic acid[17,18] on the *dl*-2,3-diacetoxybutane which was obtained in the course of this and the previous[3] work and which was purified by recrystallization from petroleum ether.

***cis*-1,2-Cyclohexanediol.**—This substance, m. p. 98°, was prepared by saponification of esters obtained in the

(9) The ready interconversion of IV to V would be expected from the available work on compounds such as these (Meerwein and Sönke, *J. prakt. Chem.*, **137**, 295 (1933); Hibbert and Greig, *Can. J. Research*, **4**, 254 (1931)).

(10) (a) Isbell, Annual Review of Biochemistry, Annual Reviews, Inc., Stanford Univ. Press, Stanford Univ. P. O., Calif., 1940, page 65; (b) Frush and Isbell, *J. Research Natl. Bur. of Standards*, **27**, 413 (1941).

(11) Generalizations are still lacking as to the factors which determine relative reactivity at carbons C-1 and C-2 as compared to C-3. In the present work it seems necessary to say that acetate ion reacts at C-1 and C-2, while water reacts very rapidly at C-3.

(12) Rothstein, *Ann. chim.*, **14**, 461 (1930).

(13) Brunel, *ibid.*, [8] **6**, 200 (1905).

(14) These compounds are all presumably *trans*.

(15) E. Fischer, *Ber.*, **53**, 1621 (1920).

(16) One desirable support for this scheme would be to show that the α,β-diglyceride does not proceed rapidly enough to the α,α'-glyceride by way of the ortho form VIII.

(17) Winstein and Lucas, THIS JOURNAL, **61**, 1581 (1939).

(18) Wilson and Lucas, *ibid.*, **58**, 2396 (1936).

present work. It was purified by recrystallization from carbon tetrachloride. When prepared in large batches by saponification of the ester from the reaction of 1 mole of dibromide with silver acetate in wet acetic acid, the glycol was sometimes not as pure as from the 0.1-mole runs. It was helpful to dissolve the glycol in acetone, filter off an acetone-insoluble impurity, evaporate the acetone from the filtrate and then recrystallize the residue from carbon tetrachloride.

cis- and *trans*-**1,2-Diacetoxycyclohexanes.**—These substances were the same ones used before.[3]

Monoacetate of *meso*-2,3-Butanediol.—This material was the one previously[17] prepared. Most of it, b. p. 79.2° (10 mm.), $n^{25}D$ 1.4215 was from butene oxide and a little, b. p. 74.5–75.5° (8 mm.),[19] was from *meso*-glycol.

Monoacetate of *cis*-1,2-Cyclohexanediol.—A mixture of 29 g. (0.25 mole) of *cis*-glycol, 25.5 g. (0.25 mole) of acetic anhydride, and 25 ml. of acetic acid was treated with several drops of concd. sulfuric acid. After the heat evolution had ceased and the solution had returned to room temperature, the mixture was diluted with 300 ml. of water and extracted with three 100-ml. portions of ether. The ether extracts were washed with carbonate solution and dried over potassium carbonate. Distillation at 12 mm. through the Weston-type[20] column yielded 27.5 g., 67%, of product boiling at 114–115°, $n^{25}D$ 1.4607. This product had a saponification equivalent weight of 142, indicating a composition of 84 mole per cent. monoacetate and 16 mole per cent. diacetate.

Conversion of Dibromides and Acetoxybromides to Mixtures of Mono- and Diacetates.—The halogen compounds were allowed to react with silver acetate in acetic acid as described previously.[3] The amount of water in the reaction mixture before addition of the halogen compound was estimated as before. Enough additional water was added to make up the desired quantity and the halogen compound was added after the mixture was stirred for a few minutes. Sometimes potassium acetate was added along with the water. The product was isolated as before except when potassium acetate was used in the experiment. Then, the reaction mixture was filtered as before and concentrated at reduced pressure. Ether was added to enable separation from solid potassium acetate. Then the ether was distilled off and the product isolated at reduced pressure.

The mixtures of mono- and diacetates distilled over a small range of temperatures but the mono- and diacetates boil sufficiently near the same temperature to enable sharp separation from acetic acid and high-boiling residue. The yields in the presence of water were about the same as in its absence.

Analysis of Ester Mixtures.—Usually a small portion of the mono- and diacetate mixture obtained by distillation was used for a determination of the saponification equivalent of the sample by the method of Redemann and Lucas.[21] Then the mole fraction of monoacetate in the sample could be calculated.

To obtain a configurational analysis of the ester product, the procedure was similar to the one used before.[3] The cyclohexene derivatives were saponified to glycol. The butene derivatives were acetylated, distilled and the diacetates analyzed as before.

Behavior of Mono- and Diacetates.—The behavior of mono- and diacetates toward the reaction conditions was studied by using a mixture of silver acetate and bromide to best simulate the actual reaction conditions and isolating and analyzing the products as for the conversion reactions.

With *trans*-1,2-diacetoxycyclohexane only a very small amount of ester was treated. It was not distilled but separated with ether after diluting the filtered acetic acid solution with water. The ether solution was neutralized and dried, the ether was evaporated and the residue was subjected to the saponification procedure.

The diacetates on treatment with silver salts in wet acetic acid, gave rise to products with refractive indices and saponification equivalents slightly high. The values of N, the mole fraction of monoacetate in the product, are given in Table II. There seems to be a very slight change to monoacetate, but it is not possible to estimate such small changes very accurately with the methods we used.

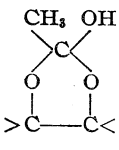
Behavior of Butene and Cyclohexene Bromohydrins.—The bromohydrins were treated with silver acetate and silver bromide in wet acetic acid in the same way as for an acetoxybromide. The *threo*-3-bromo-2-butanol yielded only a small amount of ester product which was at once acetylated. The cyclohexene bromohydrin gave products which, in spite of the approximate character of the temperature control of the bath, etc., seemed definitely higher in monoacetate content than the *cis*-products obtained from dibromide and acetoxybromide.

Summary

The presence of small amounts of water in the acetic acid used as a medium for the action of silver acetate on the *erythro*- and *threo*-2-acetoxy-3-bromobutanes, *trans*-1-acetoxy-2-bromocyclohexane, the *meso*- and *dl*-2,3-dibromobutanes, and *trans*-1,2-dibromocyclohexane, gives rise to a steric result shifted toward inversion and a product containing monoacetate. The percentage of inversion is usually slightly greater than equivalent to the water present in the acetic acid solvent and approaches 100 quite closely.

There is evidence that monoacetate is directly produced when water is involved in the replacement process and that the monoacetate is slowly esterified. Also, water seems to be involved in the replacement process for only the second bromine atom of the dibromides.

All the facts are best accounted for by the idea that the water exerts its effect through formation of the orthoester intermediate,



(19) Previously incorrectly reported as b. p. 74.5–75.5° (10 mm.) [THIS JOURNAL, **61**, 1583 (1939)].

(20) Weston, *Ind. Eng. Chem., Anal. Ed.*, **5**, 179 (1933).

(21) Redemann and Lucas, *ibid.*, **9**, 521 (1937).

LOS ANGELES, CALIFORNIA RECEIVED APRIL 14, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE ILLINOIS INSTITUTE OF TECHNOLOGY AND THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

The Role of Neighboring Groups in Replacement Reactions. III. Retention of Configuration in the Reaction of the 3-Bromo-2-butanols with Phosphorus Tribromide

BY S. WINSTEIN

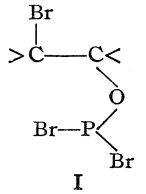
When the *erythro*- and *threo*-3-bromo-2-butanols react with phosphorus tribromide, the steric result is predominant retention of configuration. This is clear from Table I which lists the properties and compositions of the dibromobutanes derived from the bromohydrins.[1] It is seen that *erythro*-3-bromo-2-butanol gives a dibromide which is 95% *meso* and *threo*-3-bromo-2-butanol yields one which is approximately 90% *dl*. Thus, the retention of configuration in the reaction is rather high. Perhaps it would be higher if one learned if there should be made a correction for stereomutation of the dibromides under the reaction conditions.

TABLE I

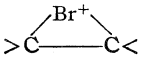
PROPERTIES AND COMPOSITIONS OF 2,3-DIBROMOBUTANES PREPARED FROM 3-BROMO-2-BUTANOLS AND PHOSPHORUS TRIBROMIDE

Bromohydrin	*erythro*	*threo*
Dibromide, b. p., °C.	74.0–74.2 (51 mm.)	76.0–76.7 (50 mm.)
Dibromide, $n^{25}D$	1.5087	1.5115
Dibromide, K_2[2]	0.0531	0.0324
Dibromide, % *meso*	95	11
Dibromide, % *dl*	5	89

The steric result of predominant retention of configuration may be accounted for by the operation, for the most of the reaction, of one or the other of two mechanisms. One mechanism is the cyclic rearrangement[3] of an intermediate compound such as I.



I



II

The other mechanism involves the formation of the bromonium ion[1,4] II. Then II reacts with bromide ion with another inversion.

A definite choice between these two mechanisms would be possible from the results with active *threo*-3-bromo-2-butanol.[1,4] However, it seems very probable that the retention of configuration observed is another result of the participation of a neighboring group (Br) in the replacement process. Lucas and Gould[5] have shown that the 3-chloro-2-butanols react with thionyl chloride by way of a chloronium ion, in spite of the small tendency for a chlorine atom to participate in this manner.[1,5] Thionyl chloride is the type reagent most addicted to the cyclic mechanism; thus there seems to be no great tendency for the cyclic rearrangement mechanism to operate in systems such as those under consideration.

It is interesting to compare the present results with the findings of Lucas and Gould[5] for the reaction of phosphorus trichloride with the 3-chloro-2-butanols. Phosphorus trichloride reacted with the 3-chloro-2-butanols with predominant inversion of configuration, whereas phosphorus tribromide reacted with the bromohydrins with predominant retention of configuration. This would seem to be at least partly due to the greater tendency to participate in a replacement process that a neighboring bromine atom displays relative to a chlorine atom.

Experimental

***erythro*- and *threo*-3-Bromo-2-butanols.**—The *erythro*-bromohydrin was an old sample prepared from pure low-boiling 2,3-epoxybutane.[1] It was quite dark by the time it was used in this work. The *threo*-bromohydrin was prepared as previously described[1] by way of 2-butene starting with *meso*-diacetate.

Conversion of Bromohydrins to Dibromides with Phosphorus Tribromide.—The bromohydrin (0.1–0.15 mole) was added dropwise with cooling and stirring to a 50% excess of phosphorus tribromide in a 3-necked flask equipped with a mercury-sealed stirrer, a reflux condenser and a dropping funnel and protected against moisture. With the *threo*-bromohydrin the addition was too rapid at first and the reaction mixture erupted once, causing some loss. There appears to be considerable heat evolution in some reaction step before the one producing the final products. After the bromohydrin was added, the reaction mixture was surrounded by a bath which was brought to 100° and kept at this temp. for one and one-half hours. Then the

(1) For a discussion of configuration see (a) Winstein and Lucas, THIS JOURNAL, **61**, 1576 (1939); (b) Winstein and Buckles, *ibid.*, **64**, 2780 (1942).

(2) Dillon, Young and Lucas, *ibid.*, **52**, 1953 (1930).

(3) (a) Cowdrey, Hughes, Ingold, Masterman and Scott, *J. Chem. Soc.*, 1252 (1937); (b) Hughes, Ingold and Whitfield, *Nature*, **147**, 206 (1941).

(4) Winstein and Lucas, THIS JOURNAL, **61**, 2845 (1939).

(5) Lucas and Gould, *ibid.*, **63**, 2541 (1941).

reaction mixture was cooled and poured onto ice. The dibromide was separated with the aid of some carbon tetrachloride and the extract was washed with potassium carbonate. Distillation at reduced pressure through a Weston-type[6] column yielded 39 and 42% yields of dibromides, from *threo-* and *erythro*-bromohydrins, respectively.

Analysis of Dibromides.—Comparison of the boiling points and refractive indices of the dibromides with the known[2,7] properties of the 2,3-dibromobutanes indicates that the dibromide samples are largely either *meso-* or *dl*-2,3-dibromobutane. Also, the samples are contaminated with a trace of some low-refractive index impurity, possibly bromohydrin. For samples not absolutely free of foreign materials, the best method of analyzing a mixture of *meso-* and *dl*-2,3-dibromobutanes is by way of the rate constant K_2 for the reaction of the sample with potassium iodide in methanol.[2] Mr. Harold Pokras kindly determined these rates and they are included in Table I along with the calculated compositions for the dibromide samples. The values of K_2 are slightly in doubt because of an uncertainty about the solvent correction of the solvent used in the rate measurements. The uncertainty in the compositions is about 4%.

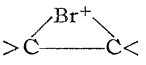
(6) Weston, *Ind. Eng. Chem., Anal. Ed.*, **5**, 179 (1933).

(7) Wilson and Lucas, THIS JOURNAL, **58**, 2396 (1936).

Summary

The *erythro-* and *threo*-3-bromo-2-butanols are converted to dibromides by the action of phosphorus tribromide with a steric result of predominant retention of configuration.

It is considered probable that the steric result is due to the participation of the neighboring bromine atom in the replacement process with the formation of the bromonium ion



as an intermediate.

LOS ANGELES, CALIFORNIA RECEIVED APRIL 14, 1942

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, AND THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

The Role of Neighboring Groups in Replacement Reactions. IV. The Identity of Various Preparations of 1,2-Dibromocyclohexane

BY S. WINSTEIN

A number of reactions leading to 1,2-dibromocyclohexane have been investigated as to the steric result because of the interest in effects[1,2] of neighboring groups on replacement processes.

All of the preparations of 1,2-dibromocyclohexane, summarized in Table I, have been compared with the dibromide from cyclohexene. The latter dibromide has been assigned the *trans*-configuration for the following reasons. First, the predominance of *trans*-addition of halogen to olefins[3] leads one to this configuration. Further, the second-order rate constant at 74.90° for the reaction of cyclohexene dibromide with potassium iodide in methanol is 0.0204.[4] This value compares favorably with 0.0301 for *dl*-2,3-dibromobutane[5] and 0.0562 for *meso*-2,3-dibromobutane.[5] Since the favored mechanism[6] of the reaction is a *trans*-elimination of bromine by potassium iodide, the *trans*-configuration for cyclohexene dibromide is strongly indicated.

TABLE I

PROPERTIES OF DIFFERENT PREPARATIONS OF 1,2-DIBROMOCYCLOHEXANE

Prepn. no.	Source	$n^{25}D$	M. p., °C.
1[a]	Cyclohexene + Br_2	1.5507	−4.5
2[b]	*trans*-Diacetate + HBr − AcOH	1.5498	−6
3	*cis*-Diacetate + HBr − H_2O	1.5506	−4
4	*cis*-Diacetate + HBr − AcOH	1.5504	−4
5[c]	Oxide + HBr − H_2O	1.5504	−5
6	Bromohydrin from olefin + HBr − H_2O	1.5506	−4
7	Bromohydrin from ketone + HBr − H_2O	1.5490	−6
8	Bromohydrin from oxide + PBr_3	1.5497	−8
9	Bromohydrin *p*-toluenesulfonate + HBr − H_2O	1.5504	−4

[a] d^{25}_4 1.7826, MR_D 43.28. [b] K_2 at 74.90° for reaction with KI is 0.0203. [c] K_2 at 74.90°, 0.0205.

One group of dibromocyclohexane samples was prepared from 2-bromocyclohexanol. The 2-bromocyclohexanol, which is prepared from cyclohexene and which is presumably[2,7] of the *trans*-configuration, reacts smoothly with fuming hydrobromic acid to yield dibromide. In preparing

(1) (a) Winstein and Lucas, THIS JOURNAL, **61**, 1576 (1939); (b) Winstein and Lucas, *ibid.*, **61**, 2845 (1939).

(2) Winstein and Buckles, *ibid.*, **64**, 2780 (1942).

(3) (a) Michael, *J. prakt. Chem.*, **52**, 344 (1893); (b) Terry and Eichelberger, THIS JOURNAL, **47**, 1067 (1925).

(4) Kindly determined by Dr. D. Pressman.

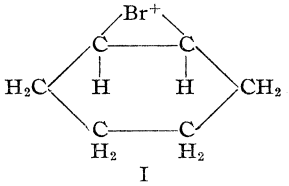
(5) Dillon, THIS JOURNAL, **54**, 952 (1932).

(6) Winstein, Pressman and Young, *ibid.*, **61**, 1645 (1939).

(7) Bartlett, *ibid.*, **57**, 224 (1935).

cyclohexene dibromide in this manner, one can treat cyclohexene oxide directly with fuming hydrobromic acid without first converting it to bromohydrin.[8] Phosphorus tribromide reacts with *trans*-bromohydrin[2,7] from cyclohexene oxide to yield, along with what is probably some elimination product, considerable 1,2-dibromocyclohexane. Cyclohexene bromohydrin can be converted to dibromide by way of the *p*-toluenesulfonate. The *p*-toluenesulfonate was non-crystalline but its behavior on treatment with fuming hydrobromic acid was reasonable for the *p*-toluenesulfonate of the bromohydrin. Smooth conversion to dibromide occurred.

The products of these three reactions are almost indistinguishable, on the basis of physical properties and mixed melting points, from the dibromide prepared directly from cyclohexene. Thus complete retention of configuration obtains in these reactions. It would seem that all three reactions proceed by way of the cyclohexene bromonium[1,2] ion I.



I

The reaction[2] of I with bromide ion with inversion gives a net apparent retention of configuration as the steric result.

The bromohydrin from the reduction of 2-bromocyclohexanone with aluminum isopropoxide[9] was also converted to dibromide with fuming hydrobromic acid. Whether the bromocyclohexanol, a somewhat impure product which did not keep well, contained any *cis*-compound[7] is uncertain. The dibromide was almost identical with the dibromides from the other reactions.

The *cis*- and *trans*-1,2-diacetoxycyclohexanes yielded the other preparations of cyclohexene dibromide by some reactions which merit further investigation.[8] Both esters yield dibromide smoothly on treatment with hydrogen bromide in acetic acid. The *cis*-diacetate yields dibromide on treatment with fuming hydrobromic acid. All three of these dibromides are almost indistinguishable from the dibromide from cyclohexene.

On treatment with fuming hydrobromic acid, *trans*-1,2-diacetoxycyclohexane behaves differently from the *cis*-isomer. The reaction mixture turns very dark and yields no dibromide. Possibly the diacetate yields the glycol, which undergoes rearrangement.

The various preparations of 1,2-dibromocyclohexane all appeared to be quite pure *trans*-isomer. A similar tendency for the production of only one dihalide of a cyclic olefin by replacement reactions is seen in the results of other workers. Thus, Mousseron and Granger[10] report that 2-bromocyclohexanol and phosphorus pentabromide and 2-chlorocyclohexanol and phosphorus pentachloride give rise to the same dihalides obtained from the fixation of halogen to cyclohexene. Also, Suter and Lutz[11] have reported that the treatment of *trans*-indene chlorohydrin with phosphorus pentachloride and both *cis*- and *trans*-indene chlorohydrins with thionyl chloride gives one and the same dichloride. This dihalide is apparently the same as indene gives with chlorine. Suter and Lutz[11] have drawn attention to the fact that apparently the only report of a pair of isomeric dihalides of a simple cyclic olefin is that of the cyclohexene dichlorides.[12]

The factors operating to make one dihalide, the *trans*-isomer, the favored product in nucleophilic replacement reactions have been partly discussed already.[2] Thus it has been pointed out that S_Ni type replacement reactions with *cis*- and *trans*-derivatives of cyclic olefins will tend to give *trans*-product if a neighboring group such as a halogen atom is available for participation in the replacement process.

It is possible that a neighboring halogen atom contrives in another way to make the *trans*-dihalide the favored product of replacement reactions. Evidence from studies on restricted rotation[13] of dihalides leads to a considerable barrier for passage through a configuration with two bromine atoms *cis* to each other. With this kind of energy effect to modify the activation energy of an S_Ni or S_N2 reaction leading to *cis*-dihalide, it is possible for the S_Ni or the S_N2 mechanism to disappear to the exclusive operation of mechanisms leading to *trans*-product.

This latter kind of effect of a β-halogen atom we hope to demonstrate independently. This is desirable first, because it is not clear to what

(8) Winstein and Lucas, THIS JOURNAL, **61**, 1581 (1939).
(9) Winstein, *ibid.*, **61**, 1610 (1939).
(10) Mousseron and Granger, *Compt. rend.*, **205**, 327 (1937).
(11) Suter and Lutz, THIS JOURNAL, **60**, 1360 (1938).
(12) Komatsu and Kawamoto, *C. A.*, **26**, 5080 (1932).
(13) (a) Beach and Palmer, *J. Chem. Phys.*, **6**, 639 (1938); (b) Beach and Turkevich, THIS JOURNAL, **61**, 303 (1939).

extent S_N2[14] and S_Ni mechanisms operate in cyclic systems such as those being discussed. Secondly, except for the above-postulated effect, a β-halogen atom would be expected to increase[15] the rate of an S_N2 process.

Experimental

Cyclohexene Oxide.—Cyclohexene was converted to chlorohydrin, which, without being isolated as a pure product, was converted to oxide. 123 g. (1.5 moles) of cyclohexene was treated with hypochlorous acid solution.[16] The chlorohydrin layer was separated, the aqueous layer was extracted with a 300-ml. portion of isopropyl ether and the chlorohydrin and ether extracts were stirred for one and one-quarter hours with a solution of 80 g. of sodium hydroxide in 400 ml. of water. The ether layer was then separated, usually dried over potassium carbonate and distilled through a Vigreux column. There was obtained 53–66 g. of oxide, b. p. 127–130°, 69.5–71.0° (100 mm.), yield 36–45%.

trans-**1,2-Cyclohexanediol.**—Cyclohexene oxide, 114.5 g., was shaken with 330 ml. of water to which 8 drops of 60% perchloric acid had been added. The mixture became warm and was homogeneous after about a half hour. The solution was neutralized with sodium hydroxide, the water was distilled off at reduced pressure, and the residue was recrystallized from 300 ml. of benzene. 108 g., 80%, of glycol, m. p. 103–104°, was obtained without working up the mother liquor.

trans-**1,2-Diacetoxycyclohexane.**—This substance was prepared from glycol as described previously.[2]

cis-**1,2-Diacetoxycyclohexane.**—This substance was some prepared previously.[2] Most of the work with *cis*-diacetate was performed on the product of the reaction of 1,2-dibromocyclohexane with silver acetate in acetic acid on the basis of Rothstein's report.[17] We have since[2,18] investigated this reaction and now know that the product must have been a mixture of mono- and diacetates of the *cis*-glycol, the mole per cent. of monoacetate being about 65.

2-Bromocyclohexanol from Oxide.—This was carried out in the same manner in which butene oxide was converted to bromohydrin.[1] Forty-nine grams of oxide and 100 ml. of 48% hydrobromic acid yielded 65 g., 73%, of bromohydrin, b. p. (10 mm.) 86°, $n^{25}D$ 1.5178.

2-Bromocyclohexanol from Cyclohexene.—Cyclohexene was converted to bromohydrin by treatment with acetbromamide as directed by Schmidt, Knilling and Ascherl.[19] The product was obtained in 60% yield, b. p. (10 mm.) 86°, $n^{25}D$ 1.5165. Later,[2] the use of acid as a catalyst in this reaction was found advantageous, but it is possible that these conditions give rise to a little dibromide with the bromohydrin.

2-Bromocyclohexanol from 2-Bromocyclohexanone.—The reduction of 2-bromocyclohexanone with aluminum isopropoxide has already been described.[9] The product from this method darkened rapidly and underwent some change for, on redistillation after ten days, it showed $n^{25}D$ 1.5142 instead of $n^{25}D$ 1.5165 first obtained. The density was now d^{25}_4 1.3990 compared to d^{25}_4 1.4542 for the product from cyclohexene. When samples of about 0.8 g. of this material were left in 20 ml. of 0.4 *N* sodium hydroxide diluted with 20 ml. of alcohol and the mixtures then back-titrated with standard acid, the sample was found to use up 88% of the theoretical amount of alkali in four minutes at room temperature, 90% in twenty-four minutes at room temperature, and 91% in six minutes at the boiling point. The bromohydrin from cyclohexene, similarly treated, consumed 98% of the theoretical amount of alkali in five minutes at room temperature.

1,2-Dibromocyclohexane from Cyclohexene.—Cyclohexene was converted to dibromide by the method of Greengard.[20] The dibromide turns dark rapidly on standing, as is reported, due to impurities. When the impure material is stored over potassium carbonate and fractionated twice through a Weston[21] column, the bulk of the material distils at 99.6–99.9° (13 mm.). This substance remains colorless indefinitely whether exposed to air or not.

Preparation of 1,2-Dibromocyclohexane from Diacetates and Hydrogen Bromide in Acetic Acid.—The method was the same as for the diacetoxybutanes.[8] A heating period of ten hours on a water-bath was used. The crude yield of product was approximately 85%, the bulk of material distilling at constant temperature at reduced pressure.

Preparation of 1,2-Dibromocyclohexane Using Fuming Hydrobromic Acid.—The procedure was the same as for the butene derivatives.[1,8] The reaction mixtures became cloudy in a half hour or less and were left at room temperature several days. Crude yields were about 90% for the products except the one from bromohydrin from bromoketone. These products distilled sharply through the Weston column. In the case of the experiment with bromohydrin from bromoketone the yield was lower and the reaction mixture was very dark. The product was separated with the aid of some carbon tetrachloride. On distillation, the yield of product, not as pure as some of the others, was 55%.

cis-1,2-Diacetoxycyclohexane, on treatment with fuming hydrobromic acid, behaved, from external appearances, just as the monoacetate–diacetate mixture.

When *trans*-1,2-diacetoxycyclohexane was dissolved in fuming hydrobromic acid and the mixture left at room temperature, no dibromide layer formed, but instead, the reaction mixture became somewhat colored in one day and extremely dark in a week. Heating a small portion of the reaction mixture after two days at room temperature at 75° in a sealed tube for one and one-quarter hours and steam-distilling afterwards yielded only traces of oil, $n^{22}D$ 1.527.

Dibromocyclohexane from Bromohydrin and Phosphorus Tribromide.—26.8 g., 0.15 mole, of bromohydrin was dropped with stirring into 6 ml. of phosphorus tribromide in a three-necked 100-ml. flask equipped with a dropping funnel, a mercury-sealed stirrer, a drying tube and an ice-bath. The bromohydrin was added over a period of twenty minutes and a little hydrogen bromide

(14) Bartlett and Rosen, THIS JOURNAL, **64**, 544 (1942).
(15) Hughes, *Trans. Faraday Soc.*, **37**, 625 (1941).
(16) Coleman and Johnstone, "Organic Syntheses," Coll. Vol. I, 1932, p. 151.
(17) Rothstein, *Ann. chim.*, **14**, 461 (1930).
(18) Winstein and Buckles, THIS JOURNAL, **64**, 2787 (1942).
(19) Schmidt, Knilling and Ascherl, *Ber.*, **59B**, 1280 (1926).
(20) Greengard, "Org. Syntheses," **12**, 26 (1932).
(21) Weston, *Ind. Eng. Chem., Anal. Ed.*, **5**, 179 (1933).

was evolved at the end of the addition. After a half-hour at the ice-bath temperature the material in the reaction flask was still one phase. The ice-bath was removed. After two hours' standing, there was still no change. Then, 5 ml. more of phosphorus tribromide was added and the reaction mixture was warmed. After one and one-half hours the temperature had been raised to 100°, with slight evolution of hydrogen bromide. A gummy viscous deposit had formed on the walls. Two hours further heating at 95–100° was allowed. The reaction mixture was then cooled and poured onto ice and sodium bicarbonate with which it was well stirred. The dibromide was separated with the aid of 25 ml. of carbon tetrachloride after hydrochloric acid was added to break an emulsion. The extract of the dibromide was washed with potassium carbonate solution, dried over potassium carbonate, filtered and distilled through the Weston column. There were obtained 15 g., 41%, of dibromide, b. p. 93.1–94.1° (10 mm.) as well as 7 g. of a low boiling fraction, b. p. 50.3–51.0 (13 mm.), $n^{25}D$ 1.4941, d^{24}_4 1.325 (in a 2-ml. pycnometer). The low boiling fraction gave an immediate precipitate with aqueous 1 *N* silver nitrate and it absorbed bromine in carbon tetrachloride, not instantaneously but at a moderate rate, without evolution of hydrogen bromide.

1,2-Dibromocyclohexane from Bromohydrin *p*-Toluenesulfonate.—Ten grams, 0.056 mole, of cyclohexene bromohydrin from the oxide, 10.9 g. of *p*-tosyl chloride and 4.4 ml. of pyridine were mixed, whereupon the mixture warmed up to 40 or 50° and cooled off after about an hour. Solid precipitated. After two days the mixture was poured into dilute hydrochloric acid and stirred well. An oil settled out which was not induced to crystallize. The oil was separated and added to 30 ml. of 48% hydrobromic acid. The oil remained as an upper layer after the mixture was saturated with hydrogen bromide gas at 0° and sealed off in an ampoule. After several hours at room temperature, a good deal of solid seemed to have formed, presumably *p*-toluenesulfonic acid. After several days of standing at room temperature, the ampoule was cooled and opened, and the contents were poured into water. The dibromide was washed with potassium carbonate and dried over potassium carbonate, 11.0 g. (81% yield) of crude product being obtained. The bulk of this material distilled at 110.8–111.0° at 16 mm.

Properties of Dibromide Preparations.—About 90 ml. combined preparations 1, 2, 3, 4, 5 and 6, Table I, in a large test-tube equipped with a thermometer, mercury-sealed stirrer and a drying tube was frozen out and allowed to melt while the test-tube was kept in a Dewar flask for insulation. The temperature was −5.0° when the mixture was too thick to stir even by hand and all the solid was gone at −4.0°, so the combined material melted substantially over a range of 1.0° and negligible amounts of isomeric impurities were indicated.

The melting points of individual preparations were taken by freezing about 10-ml. portions in test-tubes and warming the portions with stirring. The points of disappearance of solid are given in Table I. Mixed melting points were taken on various pairs of samples and no melting point lowerings were ever experienced.

Boiling ranges of the dibromides were very narrow and the spread in the values was from 98.6–99.9° at 13 mm., mostly because of difficulty in reproducing pressures.

It is a pleasure to acknowledge the many suggestions of Professor H. J. Lucas and Dr. E. R. Buchman of the California Institute of Technology.

Summary

Preparations of 1,2-dibromocyclohexane from the action of: fuming hydrobromic acid on cyclohexene oxide, 2-bromocyclohexanol derived from cyclohexene, and 2-bromocyclohexanol derived from 2-bromocyclohexanone; phosphorus tribromide on 2-bromocyclohexanol derived from oxide; fuming hydrobromic acid on 2-bromocyclohexyl *p*-toluenesulfonate; fuming hydrobromic acid on *cis*-1,2-diacetoxycyclohexane; and hydrogen bromide in acetic acid on *cis*- and *trans*-1,2-diacetoxycyclohexane all proved to be essentially pure and identical with the known dibromide derived from cyclohexene.

The known 1,2-dibromocyclohexane is assigned the *trans*-configuration. It is pointed out how a β-halogen atom contrives to make the *trans*-dihalide the favored product of nucleophilic replacement reactions.

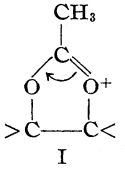
LOS ANGELES, CALIFORNIA RECEIVED APRIL 14, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES AND THE ILLINOIS INSTITUTE OF TECHNOLOGY]

The Role of Neighboring Groups in Replacement Reactions. V. The Effect of the Neighboring Acetoxy Group on the Course of the Replacement of the Tosylate Group of *trans*-2-Acetoxycyclohexyl *p*-Toluenesulfonate[1]

BY S. WINSTEIN, H. V. HESS AND R. E. BUCKLES

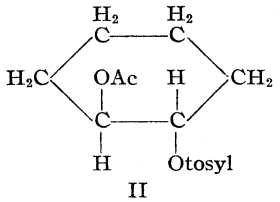
In a recent communication it was reported that the *erythro*- and *threo*-2-acetoxy-3-bromobutanes and *trans*-1-acetoxy-2-bromocyclohexane are converted by silver acetate in dry acetic acid to diacetates with retention of configuration.[2] This steric result and the loss of optical activity when active 1-acetoxy-2-bromocyclohexane was treated with silver acetate in dry acetic acid led to the idea that the acetoxy group participated in the replacement process to give rise to the intermediate I. The presence of enough water in the acetic



I

acid used as a medium for the action of silver acetate on the halides mentioned gave rise to an odd number of inversions[3] in contrast to the even number of inversions under anhydrous conditions.

We now report quite analogous results in the homogeneous solvolysis of *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate[4] II in acetic acid containing potassium acetate.



II

When *trans*-2-acetoxycyclohexyl tosylate is refluxed with potassium acetate in dry acetic acid a diacetate is produced which is at least 93% *trans* so that retention of configuration is by far the predominant steric result.[5] Thus the bulk of the replacement process must be by way of the intermediate I, which reacts with acetate ion.[2] This is further indicated by the loss of activity[2] which is experienced when the replacement process is carried out with the acetate-tosylate derived from active *trans*-1,2-cyclohexanediol by first tosylating and then acetylating the glycol. Almost pure levorotatory glycol, m. p. 111°, $[\alpha]D$ 30.2°, (0.221 g. in 25.0 ml. solution, chloroform as solvent) when converted to active acetate–tosylate, then to diacetate and then back to glycol, gave rise to completely inactive, almost pure *trans*-glycol. This, on recrystallization, yielded pure inactive *trans*-glycol, m. p. 104°. This is a more satisfactory demonstration of the loss of activity due to a neighboring acetoxy group than was possible before.[2]

In the presence of enough water in the acetic acid, the acetate-tosylate gave rise to the ester of pure *cis*-glycol, and intermediate amounts of water caused the production of esters of both *cis*- and *trans*-glycol.[6] A series of experiments was carried out in which small amounts of acetate–tosylate were treated with potassium acetate in acetic acid of varying water content. The crude diacetate was saponified and the resulting crude glycol was recrystallized. Under the conditions of concentration employed, acetic acid of higher melting point than 15.75° yielded a glycol mixture from which *trans*-glycol could be obtained by recrystallization. Acetic acid of melting point below 15.50° yielded a mixture from which *cis*-glycol was obtained.

Table I summarizes the results of the series of experiments. The third column indicates where very low recoveries of pure glycol were obtained by the recrystallization. The arrows indicate the directions of increase in these recoveries. Included in Table I are the results of three other qualitative experiments which yielded glycols very largely *cis*.

Several larger runs were made in which the acetate–tosylate was treated with potassium acetate in acetic acid of varying water content and

(1) A portion of the material reported in this paper was presented before the Organic Division at the St. Louis meeting of the American Chemical Society, April, 1941.

(2) Winstein and Buckles, THIS JOURNAL, **64**, 2780 (1942).

(3) Winstein and Buckles, *ibid.*, **64**, 2787 (1942).

(4) Criegee and Stanger, *Ber.*, **69B**, 2753 (1936).

(5) *cis*-Diacetate is not transformed to *trans* under the conditions of the replacement process.

(6) Criegee and Stanger[4] have recommended the reaction of the *trans*-acetate–tosylate with potassium acetate in acetic acid for preparing *cis*-1,2-cyclohexanediol. These authors must have used acetic acid with a considerable water content.

TABLE I

SUMMARY OF QUALITATIVE EXPERIMENTS ON THE EFFECT OF WATER CONTENT OF ACETIC ACID ON THE STERIC RESULT OF CONVERSION OF *trans*-2-ACETOXYCYCLOHEXYL *p*-TOLUENESULFONATE TO MONO- AND DIACETATE

M. p. of AcOH, °C.	Config. of recryst. glycol	Recovery on recryst.
16.7[a]	*trans*	↑
16.0	*trans*	
15.85	*trans*	
15.75	*trans*	low
15.50	*cis*	low
15.30	*cis*	
15.0	*cis*	
14.6	*cis*	
14.1	*cis*	
13.1	*cis*	
10.4	*cis*	↓
16.7[a,b]	*cis*	high
14.6[b]	*cis*	high
[c]	*cis*	high

[a] Small excess of acetic anhydride present. [b] No potassium acetate added. [c] Solvent was absolute alcohol.

the ester was isolated by distillation. Here it is possible to estimate the steric results quite accurately.[2] Table II summarizes some of the results.

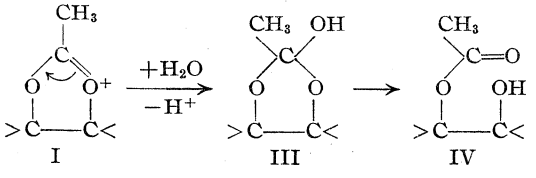
TABLE II

STERIC RESULTS AND PRODUCTS OF REACTION OF *trans*-2-ACETOXYCYCLOHEXYL TOSYLATE WITH POTASSIUM ACETATE IN ACETIC ACID

M. p. of AcOH, °C.	% H_2O	Mole ratio H_2O/-tosylate	Mole % mono-acetate	M. p. of glycol,[a] °C.	Steric result
..	0	0	0	100	93% Retention
16.0	0.35	0.20	16	85	68% Retention
10.3	4.0	2.3	65	98	100% Inversion

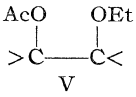
[a] M. p. of *trans*-glycol, 104°; *cis*-glycol, 98°.

In line with the previous discussion,[3] the most likely explanation of the effect of water is that it reacts with intermediate I to give orthomonoacetate III which isomerizes to ordinary monoacetate IV. The validity of this explanation has

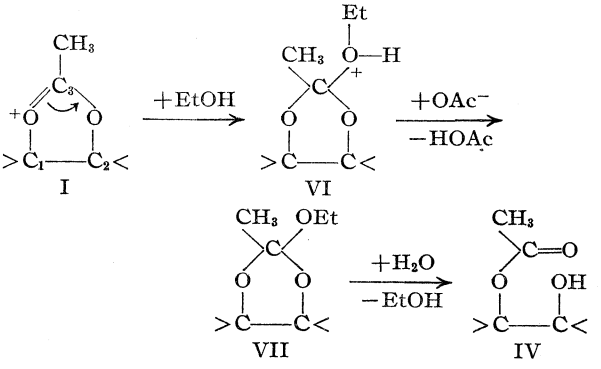


been indicated by the study of the acetate-tosylate II in alcohol. Criegee and Stanger[4] have already reported that the acetate–tosylate gives rise to quite pure *cis*-ester on refluxing with potassium acetate in absolute alcohol. We have confirmed this steric result in alcohol (see Table I and experimental part). Also, we have isolated the ester product and found it to be pure monoacetate. Potassium acetate can be dispensed with. When the *trans*-acetate–tosylate is heated in absolute alcohol, to which a trace of water is added and in which calcium carbonate is suspended, a product is obtained which can be saponified directly to quite pure *cis*-glycol without being isolated.

The facts that acetate ion may be dispensed with in alcohol and that little or no ethyl ether V is produced are consistent only with the following mechanism for the replacement process.

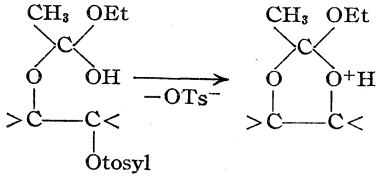


There is formed intermediate I which reacts with ethyl alcohol to give VI.[7] This loses a proton to give an orthoacetate derivative VII which eventually[8] gives the ordinary monoacetate IV. We plan to prepare VII and show whether the conversion to monoacetate does indeed proceed. Also we shall attempt to isolate VII from the reaction mixtures.

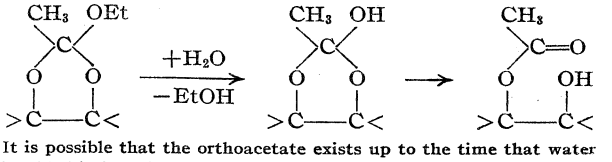


From the previous[3] and the present work, it appears that intermediate I reacts with water and alcohol at carbon atom C-3 and with acetate ion

(7) It must be noticed that part, at least, of VI might be formed from reaction of molecules to which alcohol has already added, as follows



(8) A possible route from VII to IV is as follows



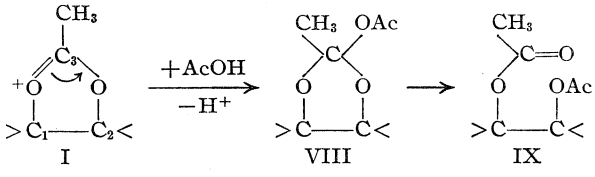
It is possible that the orthoacetate exists up to the time that water is added in isolating monoacetate from the reaction mixture.

TABLE III

SOME REPLACEMENT REACTIONS WITH A STERIC RESULT OF RETENTION OF CONFIGURATION BECAUSE OF PARTICIPATION OF NEIGHBORING GROUPS

Neighboring group	Compound	Diastereomer used: *dl* or *trans* or *threo* inactive	*dl* or *trans* or *threo* active	*erythro* or *meso* inactive	*erythro* or *meso* active	Leaving group	Extracting reagent	Entering group	Ref.
—O⁻ of —COO⁻	RCHBrCOO⁻					Br⁻	Solvent Ag⁺	OH⁻ $OC_2H_5^-$	10
—Br	$CH_3CHBrCH(OH)CH_3$	√	√	√	√	OH_2	Solvent	Br⁻	11, 12
	2-Bromocyclohexanol	√							
—Cl	$CH_3CHClCH(OH)CH_3$	√	√	√	√	$OSOCl^-$?		Cl⁻	13
—Br	2-Bromocyclohexyl *p*-Toluenesulfonate	√				OTs^-	Solvent	Br⁻	12
—Br	$CH_3CHBrCHBrCH_3$	√	√	√		Br⁻	AgOAc	OAc⁻	2
	1,2-Dibromocyclohexane	√							
—Br	$CH_3CHBrCH(OH)CH_3$	√		√		$OPBr_2^-$?		Br⁻	12, 14
	2-Bromocyclohexanol	√							
—OH	$CH_3CH(OH)CHBrCH_3$	√				Br⁻	AgOAc	OAc⁻	3
	2-Bromocyclohexanol	√							
—OAc	$CH_3CH(OAc)CHBrCH_3$	√		√		Br⁻	AgOAc	OAc⁻	2
	1-Acetoxy-2-bromocyclohexane	√	√						
—OAc	2-Acetoxycyclohexyl *p*-Toluenesulfonate	√	√			OTs^-	Solvent	OAc⁻	Present work

at carbon atoms C-1 and C-2. Also, the reactions with water and alcohol are very much faster than with acetate ion. One more reaction of intermediate I seems indicated. In dry acetic acid in the absence of potassium acetate, the acetate–tosylate II yields, on heating, a diacetate which is about 90% *cis*, so that predominant inversion is the steric result (see Table I and experimental part). Apparently, without any acetate ions to react with intermediate I at carbon atoms C-1 or C-2, a reaction path to *cis*-diacetate is available. This may be as follows



I reacting at carbon atom C-3 with even the poor electron-donor, acetic acid. The subsequent loss of a proton gives the orthodiacetate VIII which, under the conditions prevailing, is isomerized to the normal diacetate IX.[9] The only inversion in the whole process is during the formation of intermediate I. We may attempt to synthesize and study VIII.

(9) If the mechanisms we have outlined are correct, acetate ion reacts with intermediate I at C-1 and C-2 faster than acetic acid at C-3. Therefore, it must react at C-1 and C-2 very much faster than acetic acid at C-1 and C-2. This seems to be evidence that the opening[2] of the ring of I by acetate ion is S_N2 in character. Also, it would appear that in the previous[2] work with silver acetate, the intermediate I reacts with acetate ion and not acetic acid. In the reaction mixtures using silver acetate, acetate ion is as effective as it is in 1 *M* potassium acetate solution in the homogeneous work.

Summary of Retentions of Configuration.—There has been reported by us and others a number of S_N1 type replacement reactions which have a steric result of predominant retention of configuration. These have been discussed from the standpoint of the role of a neighboring group in causing this steric result and they are summarized in Table III.

Experimental

***cis*- and *trans*-1,2-Cyclohexanediol.**—These substances were the same as those previously used.[2,3,12]

***cis*- and *trans*-1,2-Diacetoxycyclohexane.**—These materials were prepared as before.[2]

Cyclohexene Oxide.—This material was prepared as before.[12]

***dl-trans*-2-Hydroxycyclohexyl-*p*-toluenesulfonate.**—The monotosylate of *trans*-1,2-cyclohexanediol was produced from cyclohexene oxide and purified by the method of Criegee and Stanger.[4]

As mentioned by Criegee and Stanger,[4] the glycol monotosylate may also be prepared from *trans*-1,2-cyclohexanediol. To 1.00 g. of glycol in 10 ml. of dry pyridine was added 1.64 g. of good grade tosyl chloride and the mixture was allowed to stand overnight. Treatment of the mixture with dilute sulfuric acid and stirring yielded after several minutes a solid product, 1.58 g., 68%, after washing and drying. This product was suitable to acetylate without further purification.

***dl-trans*-2-Acetoxycyclohexyl-*p*-toluenesulfonate.**—The acetylation of the glycol monotosylate was performed with excess acetic anhydride containing a trace of concentrated sulfuric acid (1 drop in 10 ml.). After the mixture had

(10) Cowdrey, Hughes and Ingold, *J. Chem. Soc.*, 1208 (1937).
(11) Winstein and Lucas, THIS JOURNAL, **61**, 1576, 2845 (1939).
(12) Winstein, *ibid.*, **64**, 2792 (1942).
(13) Lucas and Gould, *ibid.*, **63**, 2541 (1941).
(14) Winstein, *ibid.*, **64**, 2791 (1942).

stood overnight, it was poured into water. There was obtained a nearly quantitative yield of product which soon crystallized; m. p. 73–76°; recryst. from ligroin, m. p. 78°. The acetates from the monotoluenesulfonates prepared from oxide and glycol proved identical in melting point and mixed melting point.[4]

Active *trans*-1,2-Cyclohexanediol.—This substance was obtained by the resolution of *trans*-1,2-cyclohexanediol as carried out by Wilson and Read.[15] *l*-Menthoxyacetic acid was prepared by the method of Frankland and O'Sullivan[16] but the acid was distilled as Read and Grubb did.[17] The rotation of the distilled acid agreed with the report of Read and Grubb.

The *l*-menthoxyacetate from the *trans*-1,2-cyclohexanediol and *l*-menthoxyacetyl chloride in pyridine was obtained in ether solution by treatment of the reaction mixture with hydrochloric acid, extraction with ether, washing of the ether extracts with potassium carbonate solution, and drying of the ether extracts over potassium carbonate. Evaporation of the ether solvent yielded a residue of which nearly all turned solid on cooling. Washing of the residue with petroleum ether yielded a dry white solid. Several crystallizations of this solid from benzene consistently gave a small yield of the high-melting diastereomer of mono-*l*-menthoxyacetate of *trans*-1,2-cyclohexanediol, m. p. 126–127°.

The active glycol was conveniently obtained from the menthoxyacetate by saponification and then vacuum sublimation of the glycol from salts. A mixture of 1.00 g. of menthoxyacetate, 17 ml. of alcohol, and 1 ml. of 35% aqueous sodium hydroxide was refluxed for two hours. Then the solution was poured into an evaporating dish and saturated with carbon dioxide by the careful addition of dry-ice. Evaporation of the solvent left a solid, from which the glycol was sublimed at about 3 mm. A total of 3.46 g. menthoxyacetate yielded 1.11 g., 86%, of glycol, m. p. 109–110.5°, 109–111° (different preparations). This glycol was evidently not quite as pure as that of Wilson and Read,[15] m. p. 113–114°, but as pure as that of Derx,[18] m. p. 110.5°. The glycol on mixing with *dl-trans*-glycol showed a m. p. of 95–98°. A chloroform solution of 0.221 g. of the glycol in 25 ml. had α_D (2 dcm.) 0.53°, $[\alpha]_D$ 30.2°.

Qualitative Experiments on the Conversion of *dl-trans*-2-Acetoxycyclohexyl-*p*-toluenesulfonate to Glycol.—To 10 ml. of acetic acid of known melting point was added 1 g. of potassium acetate. Sometimes a slight excess of acetic anhydride was added and the mixture heated two hours to destroy the water. Three grams of acetate–tosylate was added and the solution was heated four hours under reflux. The reaction mixture was allowed to cool and then it was poured into water. The mixture was neutralized with potassium carbonate and extracted with ether. The ether extracts were dried over potassium carbonate, the ether was distilled off and then the residue was directly saponified to glycol according to the saponification procedure previously[2] used for analyzing ester mixtures.

When the conversion was carried out in the absence of potassium acetate, the procedure was similar except that 50 ml. of acetic acid was used and the reaction time was five hours at 100°.

To obtain the glycols, the saponification mixtures were at first saturated with carbon dioxide and allowed to evaporate, whereupon the glycol was extracted out of the solid with chloroform. The yields by this procedure were about 60%. Later, the glycols were extracted from the saponification mixture as in the saponification-analysis method used on the esters previously.[2] The yields by this method were in excess of 80%.

The glycols thus prepared tended to be impure and they melted at temperatures considerably lower than when the ester product could be isolated by distillation. However, by recrystallization from carbon tetrachloride, the predominant glycol could be obtained pure or still contaminated with the other glycol if the mixture was originally one with comparable amounts of the two glycols.

When sodium acetate replaced potassium acetate in dry or quite wet acetic acid, the results were quite unchanged.

When absolute alcohol was used as the solvent, 4.5 g. of acetate–tosylate, 6 g. of potassium acetate and 50 ml. of Commercial Solvents Gold Shield absolute alcohol were refluxed for thirty-six hours. At the end of the heating period, the mixture was filtered, the solid was washed with ether, the alcohol and ether were boiled off of the combined filtrate and ether washings and the residue was treated according to the saponification procedure. A 71% yield of glycol was obtained, which on recrystallization from carbon tetrachloride gave better than an 80% recovery of pure *cis*-glycol, m. p. 98.5°.

Conversion Reactions with Isolation of the Ester Products.—To a mixture of 100 ml. of glacial acetic acid (m. p. 16.0°), 5 ml. of acetic anhydride and 9.8 g. of potassium acetate, which had been refluxed one hour, was added 30 g. of acetate–tosylate and the solution was refluxed five hours. It was allowed to cool, poured into water, neutralized, extracted with ether and then the ether extracts were dried. Evaporation of the ether and distillation of the residue through a Weston[19] type column yielded 13.0 g., 68%, of diacetate, b. p. (12.5 mm.) 120.4–121.4°, $n^{25}D$ 1.4476. The saponification method yielded a glycol melting at 100°, which corresponds to 93% *trans*. The refractive index of the sample was somewhat high. On redistillation, the main fraction had b. p. (12 mm.) 119.5–119.8°, $n^{25}D$ 1.4470, the refractive index still high.

The same experiment was carried out using acetic acid of different water contents. Acetic acid, m. p. 10.3°, yielded 14.1 g., 85%, of product, b. p. (12 mm.) 114–116°, $n^{25}D$ 1.4574 and saponification equivalent,[20] 128. This product yielded *cis*-glycol, m. p. 98°, on saponification. Acetic acid, m. p. 16.0°, yielded 15.4 g., 83%, of product b. p. (12 mm.) 114–118°, $n^{25}D$ 1.4490 and saponification equivalent 105. This material yielded a glycol, m. p. 85°, predominantly *trans*.

In the absence of potassium acetate, 480 ml. of acetic acid (m. p. 16.4°) and 8 ml. of acetic anhydride were refluxed one hour, 30 g. of acetate–tosylate was added, and the mixture was held at about 100° for five hours. After the reaction mixture was cool, 0.1 mole of potassium acetate was added. Most of the acetic acid was distilled off

(15) Wilson and Read, *J. Chem. Soc.*, 1269 (1935).
(16) Frankland and O'Sullivan, *ibid.*, 2329 (1911).
(17) Read and Grubb, *J. Soc. Chem. Ind.*, **51**, 329T (1932).
(18) Derx, *Rec. trav. chim.*, **41**, 312 (1922).
(19) Weston, *Ind. Eng. Chem., Anal. Ed.*, **5**, 179 (1933).
(20) Redemann and Lucas, *ibid.*, **9**, 521 (1937).

at reduced pressure and the residue was poured into water. The mixture was neutralized with potassium carbonate and the diacetate was taken up in ether. The ether extract was dried over potassium carbonate, the ether was distilled off and the diacetate was isolated at reduced pressure; 12.9 g., 67%, of material, b. p. (12 mm.) 117.5–117.8°, $n^{25}D$ 1.4480, saponification equivalent 99 (theoretical 100). By the saponification procedure, this product appeared to be 89% *cis*. A small part of the steric result may be due to reaction of some unreacted acetate–tosylate with potassium acetate during the distillation of acetic acid.

For the reaction in absolute alcohol, the procedure was as for the qualitative experiment except that 30 g. of acetate–tosylate was used. When the ether washings and alcohol solution were concentrated, the residue was poured into water and the ester was extracted out with ether. The ether extract was dried over potassium carbonate and the ester isolated by distillation at reduced pressure; 9.2 g., 60%, of material, b. p. (12 mm.) 113–113.2°, $n^{25}D$ 1.4650, saponification equivalent 156.5, 99 mole per cent. monoacetate, was obtained. By the saponification procedure a glycol, mostly *cis*, m. p. 93°, was obtained. This result, together with the melting point of 96° obtained for the product in the absence of potassium acetate (see later) and the melting point of 96–98° reported by Criegee and Stanger[4] indicates that essentially pure *cis*-product is obtained in alcohol.

Conversion of Acetate–Tosylate of Active *trans*-1,2-Cyclohexanediol to the Diacetate of *dl-trans*-1,2-Cyclohexanediol.—1.02 g. of active glycol was tosylated as in the case of the *dl*-glycol, yielding 1.67 g., 70%, of crude monotosylate. As in the case of the *dl*-compound, the crude monotosylate was acetylated directly. The addition of water to the reaction mixture gave an oil which did not crystallize. The oil was finally extracted with 100 ml. of warm ligroin and the solution was dried over potassium carbonate. When the ligroin solution was cooled an oil came down which turned solid in a dry-ice bath and more loose solid developed on longer cooling. The solid could be filtered rapidly but it melted on the filter paper as it warmed up toward room temperature. Thus it appeared that the acetate–tosylate of the active glycol was quite low melting compared to the analogous *dl*-compound. The solid which was filtered off rapidly at low temperature was taken up in carbon tetrachloride, the carbon tetrachloride solution was washed with carbonate solution to remove any traces of acetic acid present and then dried over potassium carbonate. The volume of the solution was 34.5 ml., and the αD (2 dcm.) 1.22°. The carbon tetrachloride was pumped off at low pressure with the aid of a bath at 40–50° and the residue was refluxed four hours with a solution of potassium acetate in dry acetic acid. The reaction mixture was poured into water and treated in the usual way. The extracted diacetate was saponified in the usual way after the ether was driven off. The saponification mixture was saturated with carbon dioxide and allowed to evaporate. Vacuum sublimation yielded 0.24 g. of glycol. A much larger yield of glycol was obtained when *dl-trans*-glycol was carried through this whole procedure. One reason for the low yield was that considerable active acetate–tosylate was left in the ligroin solvent. When the ligroin solution remaining after filtration from the active acetate–tosylate was washed with carbonate solution, dried over potassium carbonate, and pumped down to a volume of 29 ml., it had αD (2 dcm.) 0.44°. Another reason for the lower yield is the loss attending the extra handling which was necessary for the liquid acetate–tosylate.

The glycol in 25 ml. of chloroform showed αD (2 dcm.) ±0.00°. It melted over a range up to 96°. Mixing with *dl-trans*, m. p. 104°, raised the melting point. Recrystallization from carbon tetrachloride yielded 0.18 g. of glycol, m. p. 103.5–104°, no change on mixing with pure *dl-trans* glycol. The glycol in 25 ml. of chloroform showed αD (2 dcm.) ±0.00°.

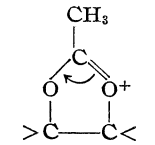
Conversion of Acetate–Tosylate to *cis*-Ester in Alcohol without Potassium Acetate.—A mixture of 1.50 g. of acetate–tosylate, 0.50 g. of calcium carbonate, 17 ml. of absolute alcohol and two drops of water was heated under reflux for thirty-nine hours, and then filtered. Saponification of the ester and sublimation of the glycol yielded 0.33 g., 59%, of product, m. p. 90–96°. Recrystallization from carbon tetrachloride gave a nearly quantitative recovery of *cis*-glycol, m. p. 98° and the same on mixing with authentic *cis*-glycol.

Tests on the Stability of Esters under Reaction Conditions.—Two-gram portions of *cis*- or *trans*-1,2-diacetoxycyclohexane were subjected to the reaction conditions prevailing in the conversion reactions. Then the reaction mixtures were worked up as for the small qualitative experiments previously described.

cis-1,2-Diacetoxycyclohexane, after refluxing four hours with 1 g. of potassium acetate in 10 ml. of dry acetic acid yielded nearly pure *cis*-glycol, m. p. 96.5°. The *trans*-diacetate on refluxing four hours with 1 g. of potassium acetate and 0.54 g. of water in 10 ml. of acetic acid yielded nearly pure *trans*-glycol, m. p. 102.5°. The *trans*-diacetate after being held five hours at 100° with 1.72 g. of *p*-toluenesulfonic acid in 50 ml. of dry acetic acid yielded nearly pure *trans*-glycol, m. p. 102°.

Summary

trans-2-Acetoxycyclohexyl *p*-toluenesulfonate is converted to diacetate with predominant retention of configuration when it is heated with potassium acetate in dry acetic acid. Also, active *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate gives rise to inactive diacetate. These results are explained by the participation of the neighboring acetoxy group in the replacement process to give rise to the intermediate



which reacts with acetate ion with a second inversion.

When *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate is heated in sufficiently wet acetic acid with or without potassium acetate, in absolute alcohol with or without potassium acetate, or in dry acetic acid without potassium acetate, there are

isolated products (mono- or diacetates or mixtures) which are entirely or very largely of the *cis*-configuration. It is considered most probable that orthoacetate intermediates are involved in these transformations.

LOS ANGELES, CALIFORNIA RECEIVED APRIL 14, 1942

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

Reversible Photochemical Processes in Rigid Media: The Dissociation of Organic Molecules into Radicals and Ions

BY GILBERT N. LEWIS AND DAVID LIPKIN

In previous papers[1] we have studied the phosphorescent state of dye molecules. This phosphorescent state returns to the initial state with light emission and is to be regarded as isomeric with the normal molecule. On the other hand, the present paper deals with the photo-dissociation of organic molecules into radicals, ions and electrons.

In a study of the absorption spectra of odd molecules we desired to investigate diphenylnitrogen, the free radical of tetraphenylhydrazine, but at any temperature at which the dissociation is appreciable the radical disappears as fast as it is formed, through processes of rearrangement or disproportionation. We therefore attempted to produce diphenylnitrogen by illuminating a solution of tetraphenylhydrazine in our EPA solvent (see experimental section) at low temperature.

The solution in a quartz tube was immersed in liquid air contained in a quartz Dewar. After a minute or two of exposure to the light from a high-pressure mercury arc the solution acquired a green color which we attributed to the formation of the diphenylnitrogen radical, although we shall see presently that other substances are also produced. The color persists for many days at the temperature of liquid air but rapidly disappears when the temperature is raised sufficiently to make the solvent fluid.[2] This rise of temperature for EPA is about 10°. That the disappearance of color is not primarily the effect of temperature but of the change in rigidity of the solvent is shown by the fact that most of the phenomena that we are going to describe are duplicated when the tetraphenylhydrazine is dissolved in glycerol or triethanolamine and illuminated at 190°K. and in a few cases similar phenomena have been obtained in glucose at room temperature.[3]

When the green solution is studied spectroscopically we find that, instead of one band, several prominent bands appear and we shall see that these belong to different substances, since their relative intensities vary greatly according to the way in which the solutions are prepared and treated. The absorption curves are shown in Fig. 1, in which the ordinates of each curve are proportional to the extinction coefficient, but with an arbitrary proportionality factor for each curve, since we have not yet determined the absolute concentration of any one of the substances.

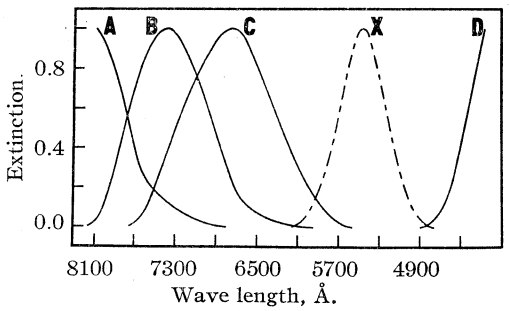


Fig. 1.—Absorption bands of tetraphenylhydrazine illuminated and measured in EPA at about 90°K. The ordinates for each curve are in arbitrary units.

In attempting to identify substances produced by illumination we are handicapped by

(1) (a) Lewis, Lipkin and Magel, THIS JOURNAL, **63**, 3005 (1941); (b) Lewis, Magel and Lipkin, *ibid.*, **64**, 1774 (1942).

(2) The production of color by illumination in the cold and its disappearance on warming may be repeated many times with the same sample, although eventually a permanent yellow color appears. Quantitative experiments show that when the initial illumination is carried to the point where all of the tetraphenylhydrazine is gone, more than 90% of it is regenerated on warming. From the fact that diphenylnitrogen is one of the chief products of the photo-dissociation and that this returns to tetraphenylhydrazine, even at very low temperatures, we have recently drawn certain conclusions regarding the heat of dissociation of the latter compound [Lewis and Lipkin, THIS JOURNAL, **63**, 3232 (1941)].

(3) The only antecedents that we have been able to find in the literature to the phenomena that are to be here described are in the inorganic field the coloration of glasses after long exposure to light and in the organic field the observations of Wieland [*Ann.*, **381**, 216 (1911)], who exposed crystalline substances such as the tetraarylhydrazines to electron bombardment at the temperature of liquid air. He obtained strong coloration which he attributed to free radicals. The color disappeared within a few minutes after the bombardment ceased.

being unable to study any of the physical properties of the new substances except their reactions with photons (absorption and luminescence).[4] On the other hand, we have the great advantage of working with isolated molecules. At the small concentrations that we use, 10^{-4} M or less, the individual molecules are on the average over 100 Å. apart and when the solution is cooled to rigidity no appreciable diffusion can occur, and therefore no bimolecular reactions. Except in cases where the solute is polymerized before the state of rigidity is attained, the simple molecule and the group of solvent molecules in its immediate neighborhood alone can participate in the photochemical process or in the reactions which occur after illumination. This restriction of all processes in the rigid solvent to the zone of a single molecule limits the number of possible structures that may be assigned to the photochemical products.

In order to investigate the several absorption bands obtained by illuminating tetraphenylhydrazine the frequency of the activating light may be varied, the effect of further illumination by light of various frequencies may be observed, and if the temperature is gradually raised we may see which substances first disappear, and whether the disappearance is accompanied by an increase in any of the other bands. Finally, we may activate with polarized light and study the molecular orientation of the products. In addition to these experiments on tetraphenylhydrazine itself we may illuminate other substances containing the diphenylnitrogen group and find whether we can reproduce any of the bands already observed.

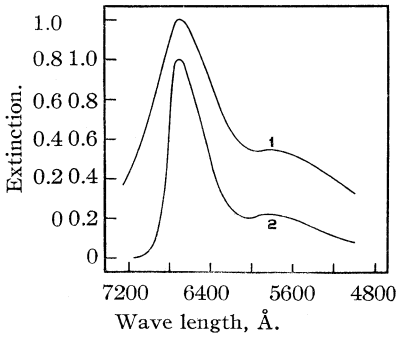


Fig. 2.—Absorption of $(p\text{-}CH_3C_6H_4)_3N^+$: Curve 1, Granick and Michaelis by chemical oxidation; Curve 2, by photo-oxidation in EPA at about 90 °K.

(4) We have not attempted to study the magnetic susceptibility of our solutions. Such an investigation, while difficult, would be profitable.

We shall find three types of photochemical reaction. The first is the one already mentioned, namely, splitting into two uncharged radicals, and this for brevity will be called *photo-dissociation*. Second, a molecule may be split by light into a positive and a negative ion. This *photo-ionization* is also observed under ordinary conditions in such substances as the leucocyanides of crystal violet and malachite green.[5] Since these positive ions behave as secondary acids[6] the recombination of the ions in the dark is observably slow at room temperature. Third, the illuminated molecule may merely eject an electron. To distinguish this from the preceding type of process we shall call it *photo-oxidation*, and indeed the simplest of all oxidation processes is the loss of an electron. Since this photo-oxidation is a new and somewhat surprising phenomenon we shall first present the evidence for its existence.

Photo-oxidation by the Loss of an Electron

Upon illuminating a variety of substances in rigid media it soon became apparent that one of the commonest photochemical processes is the mere loss of an electron by the activated molecule. When triphenylamine was illuminated at liquid air temperature in EPA a blue color was obtained. The absorption curve showed a maximum at 6560 Å. and a shoulder in the neighborhood of 5700 Å. The curve was so similar to a curve obtained by Granick and Michaelis[7] (Curve 1, Fig. 2) for the ion of tri-*p*-tolylamine, $(p\text{-}CH_3\text{-}C_6H_4)_3N^+$, produced by chemical oxidation of tri-*p*-tolylamine, that it seemed very probable that our blue substance was $(C_6H_5)_3N^+$. This *odd* ion is so unstable because of the lability of the para hydrogens that it cannot readily be obtained by chemical oxidation. We were, therefore, very grateful to Drs. Granick and Michaelis for sending us a sample of the tri-*p*-tolylamine used in their investigation. When this was illuminated in the rigid solvent we obtained the substance whose absorption is given in Curve 2 of Fig. 2. There can be no question that chemical oxidation at room temperature and photo-oxidation at liquid air temperature have given the same substance, namely, the positive ion left when one electron has been removed. In order to produce photo-oxidation of triphenylamine and tri-

(5) This phenomenon has recently been carefully studied by Harris, Kaminsky and Simard [THIS JOURNAL, **57**, 1151 (1935)].

(6) Lewis, *J. Franklin Institute*, **226**, 2093 (1938); Lewis and Seaborg, THIS JOURNAL, **61**, 1886 (1939).

(7) Granick and Michaelis, *ibid.*, **62**, 2241–2242 (1940).

p-tolylamine it is necessary to illuminate with the full mercury arc through quartz, but even so it is surprising to find the energy sufficient to expel an electron according to the process

$$Ar_3N \longrightarrow Ar_3N^+ + e^-$$

As to what becomes of the electron we can only speculate. It presumably becomes attached to a solvent molecule,[8] or to a group of molecules, or even to some unique point in the solvent determined by its rigid structure. The electron must lie in a potential hole which is deep enough so that the large electrostatic field of the ion is unable to dislodge it. The color persists at liquid air temperature for several days, but at only slightly higher temperatures the color disappears. Then presumably the electron has returned to the ion.

Another case where we may compare our results with those of Michaelis and his collaborators is that of Wurster's blue, $(CH_3)_2N\langle\bigcirc\rangle N(CH_3)_2]^+$. They prepared this odd ion by chemical oxidation, and their absorption spectrum[9] obtained at room temperature in partly aqueous solutions is given in Curve 1, Fig. 3. We dissolved the colorless base of Wurster's blue in EPA and illuminated in liquid air. The absorption spectrum was then measured above rapidly boiling liquid air.[10] The results are given in Curve 2, Fig. 3. In spite of the difference in solvent and in temperature the agreement of the two curves is remarkable, and definitely proves the ejection of an electron by light.[11]

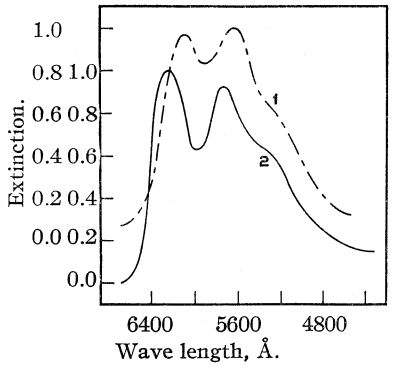


Fig. 3.—Absorption of Wurster's blue: Curve 1, Michaelis, Schubert and Granick by chemical oxidation; Curve 2, by photo-oxidation in EPA at about 90 °K.

Owing to the complete elimination of bimolecular reactions in a rigid solvent we may by this method of photo-oxidation obtain and study numerous odd ions which, under ordinary circumstances, would engage in further reactions almost as soon as formed. The triphenylamine ion is an example. As further illustrations of odd ions produced by light through the ejection of electrons, we give in Fig. 4 the very complex spectrum of tetramethylbenzidine ion, $(CH_3)_2N\langle\bigcirc\bigcirc\rangle N(CH_3)_2]^+$, and in Fig. 5 the spectrum of methyldiphenylamine ion, $(C_6H_5)_2NCH_3^+$. The spectra of several other odd ions will be given in later sections.

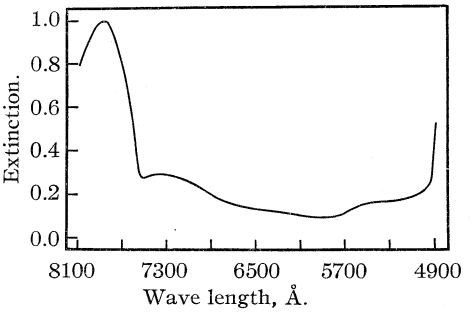


Fig. 4.—Absorption of tetramethylbenzidine ion produced by photo-oxidation in EPA at about 90 °K. The sample was not specially purified.

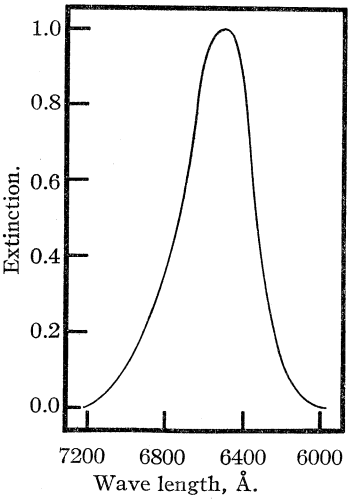


Fig. 5.—Absorption of methyldiphenylamine ion produced by photo-oxidation in EPA at about 90 °K.

(8) In a mixture of equal volumes of ether and isopentane the same results were obtained as in EPA. On the other hand, in a solvent of mixed hydrocarbons (3 vols. of isopentane to 1 vol. of methylcyclohexane) little or no blue color was produced. Whether, however, this failure was due to lack of oxygen atoms in the solvent or to a lesser rigidity of the hydrocarbon solvent, we have not as yet ascertained.

(9) Michaelis, Schubert and Granick, THIS JOURNAL, **61**, 198 (1939).

(10) Lewis, Magel and Lipkin, *ibid.*, **62**, 2973 (1940).

(11) When the ion of Wurster's blue was produced in a solvent containing air a slight blue color remained after warming. If this is due to the permanent capture of electrons by the oxygen molecules, a study of the amount of residual color as a function of the oxygen concentration might indicate how far the electron is ejected.

Further cases of presumable photo-oxidation were found in a cursory examination of the following substances which gave the colors noted, the color disappearing when the solvent became liquid. These experiments should be repeated with more carefully purified materials.

Substance	Color
Hydroquinone	Orange-yellow
α-Naphthol	Reddish-orange
p-Hydroxydiphenyl	Orange
Thiophenol	Yellow
o-Thiocresol	Yellow
Thio-β-naphthol	Orange-red
p-Hydroxythiophenol	Orange

Photo-dissociation into Free Radicals

In order to make sure that dissociation into free radicals does occur under the conditions of our experiments, we slowly cooled in a sealed quartz tube a solution of triphenylmethyl in EPA. At about $-50°$ it was so completely converted into hexaphenylethane that the free radical could no longer be detected spectroscopically. It was then placed in a quartz Dewar containing liquid air and illuminated by the mercury arc. After ten minutes of exposure the solution showed the sharp and unmistakable absorption bands of triphenylmethyl. The slow formation of the free radical, in spite of the small energy of dissociation, may indicate that the main absorption of hexaphenylethane comes at higher frequencies than are afforded by the mercury arc.

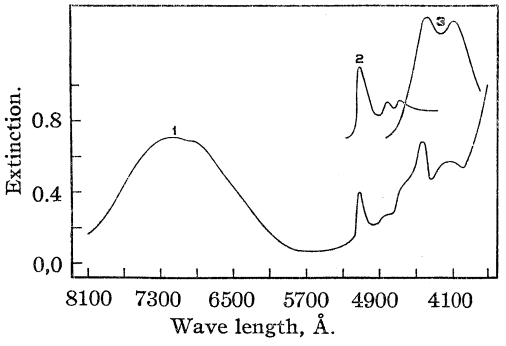


Fig. 6.—Curve 1 obtained by illuminating triphenylmethyldiphenylamine in EPA at about 90°K.: Curves 2 and 3 (with a higher base line), absorption curves of $(C_6H_5)_3C$ and $(C_6H_5)_3C^+$, respectively.

The next substance investigated was diphenyl disulfide. A solution of this substance becomes yellow on heating and nearly colorless on recooling. According to Schönberg[12] it does not obey Beer's law, so that it has been concluded that there is partial dissociation to give the free radical C_6H_5S. We have studied photographically the absorption of diphenyl disulfide in ethyl benzoate at 210°, with 1- and 5-cm. cells, and have found entirely similar but fainter absorption in ethanol with a 61-cm. cell at room temperature. While we have not yet studied the plates photometrically, the absorption band is a broad one beginning in the visible region and still rising at 3900 Å. The disulfide was next dissolved in EPA and illuminated at liquid air temperature. The resulting yellow solution showed, as was expected, the same band of C_6H_5S, but there is also a strong band with a maximum at 4600 Å. Obviously, another process besides photo-dissociation occurs and we believe that it is another case of photo-oxidation and that the new band is due to $C_6H_5SSC_6H_5^+$. As in all our experiments, except when there is an explicit statement to the contrary, the color disappeared as the solvent was warmed to fluidity. Therefore both processes are reversed at very low temperature, showing that, as in the case of diphenylnitrogen, there is no appreciable heat of activation for the dimerization of the phenylsulfur radical.

The next substance studied (EPA, liquid air) was triphenylmethyldiphenylamine, $(C_6H_5)_3CN(C_6H_5)_2$. Here we expected to find photo-dissociation into the two radicals triphenylmethyl and diphenylnitrogen, but the process proved to be more complicated, as may be seen from the absorption spectrum of Fig. 6. In addition to Curve 1, which shows the result of this experiment, we give in Curve 2 the absorption of triphenylmethyl according to our own measurements (90°K., EPA), which agree very closely with those of Anderson,[13] and in Curve 3 the absorption of $(C_6H_5)_3C^+$ as obtained by Anderson. It is evident that both of these substances are present.[14] On the other hand, the ions $(C_6H_5)_3C^-$ for which Anderson obtained an absorption maximum at 4800 Å., and $(C_6H_5)_2N^-$ whose absorption we give in Fig. 8, are not present in appreciable amount. There is, therefore, no evidence of photo-ionization into positive and negative ions. On the other hand it appears that we must write at least two

(12) Schönberg, *Trans. Faraday Soc.*, **30**, 17 (1934).

(13) Anderson, THIS JOURNAL, **57**, 1673 (1935).

(14) While the parent substance is not sensitive to air at room temperature and below, we found that the absorption band of triphenylmethyl did not appear in the low temperature illumination unless the solution had been carefully freed from oxygen. Since in the rigid solvent it seems hardly possible for the oxygen to diffuse to the triphenylmethyl that is formed, we seem forced to the conclusion that the oxygen molecule is already there; in other words, that the parent substance must form some loose complex with the oxygen on cooling.

photochemical equations, which are, presumably

$$(C_6H_5)_3CN(C_6H_5)_2 \longrightarrow (C_6H_5)_3C + (C_6H_5)_2N$$
$$(C_6H_5)_3CN(C_6H_5)_2 \longrightarrow (C_6H_5)_3CN(C_6H_5)_2^+ + e^-$$

the last substance then breaking into $(C_6H_5)_3C^+$ and $(C_6H_5)_2N$, and possibly into $(C_6H_5)_3C$ and $(C_6H_5)_2N^+$. Obviously our hope of obtaining in this way the pure spectrum of $(C_6H_5)_2N$ was a vain one and the left-hand portion of our curve is a superposition of the curves for $(C_6H_5)_2N$, $(C_6H_5)_2N^+$, and perhaps $(C_6H_5)_3CN(C_6H_5)_2^+$.

Photochemical Reactions of Other Compounds Containing the Diphenylnitrogen Group

With the object of identifying the bands obtained in the illumination of tetraphenylhydrazine we have treated by a similar procedure several substances in which the diphenylnitrogen group occurs.

Nitrosodiphenylamine, $(C_6H_5)_2NNO$, and Diphenylhydrazine, $(C_6H_5)_2NNH_2$.—The illumination of these two substances in EPA at liquid air temperatures gave green solutions of which the absorption spectra are given, respectively, in Curves 1 and 2 of Fig. 7. While we shall later discuss these curves briefly it may be noted now that their appearance is not inconsistent with the assumption that we have produced in varying amounts the two substances responsible for the B and C bands of illuminated tetraphenylhydrazine.

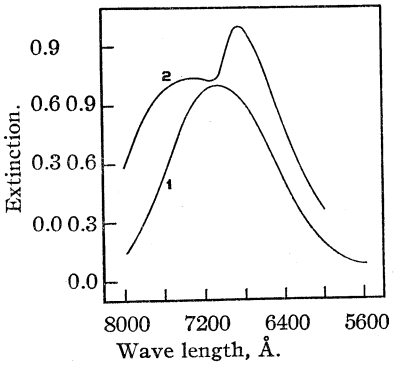


Fig. 7.—Absorption after illumination of (1) $(C_6H_5)_2NNO$ and (2) $(C_6H_5)_2NNH_2$.

Lithium Diphenylamide, $(C_6H_5)_2NLi$.—In order to study the diphenylamide ion it was necessary to use a solvent containing no alcohol, since the ion is an even stronger base than alcoholate ion. The lithium diphenylamide was found to be sufficiently soluble for our purpose in a mixture of two parts of isopentane and one part of ether. The absorption curves at this temperature before and after illumination are given in Curves 1 and 2 of Fig. 8. It appears that the second curve is identical with that of the B band of tetraphenylhydrazine.

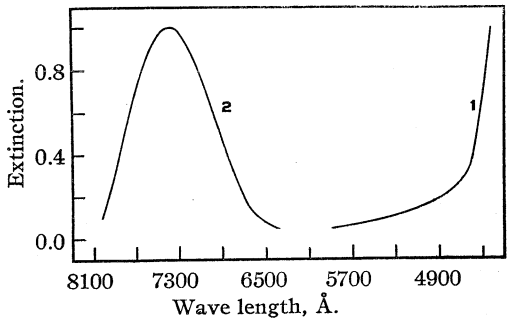


Fig. 8.—Absorption of a solution of lithium diphenylamide in ether and isopentane at about 90°K.: (1) before illumination, (2) after illumination.

Diphenylamine, $(C_6H_5)_2NH$.—While the illumination of triphenylamine and methyldiphenylamine gave simple photo-oxidation, the phenomena attending the illumination of diphenylamine proved to be of such complexity as to require a thorough investigation. When this substance in a rigid solvent is illuminated by the mercury arc, through quartz, it shows by transmitted light a purple color which takes an appreciable time, not more than a second, to rise to full intensity and disappears in about the same time after the illumination has ceased. The absorption spectrum while the sample is subjected to cross-illumination by the mercury arc is shown in Curve 3, Fig. 9. Since the half-life of the purple substance seems to correspond to that of the blue fluorescence of diphenylamine, it is probable that this absorption curve belongs to a phosphorescent state, such as we have previously studied in the case of fluorescein[1a] and of crystal violet.[1b]

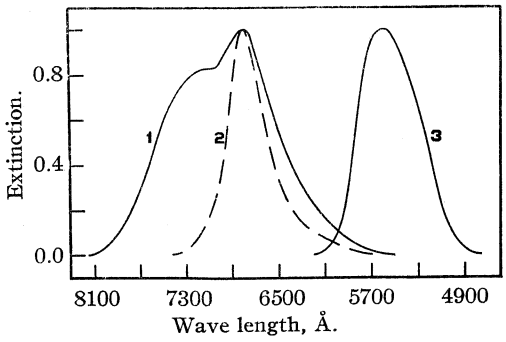


Fig. 9.—In EPA at about 90°K.: Curve 1, an example of the absorption curve obtained after prolonged illumination of diphenylamine; Curve 2, after brief illumination; Curve 3, absorption of the phosphorescent state of diphenylamine obtained while it is being illuminated.

As the illumination is prolonged the purple color disappears and is replaced by a green color which persists indefinitely after illumination has ceased. Ordinarily the absorption curve of the solution so obtained is not simple. One such curve is reproduced in Curve 1 of Fig. 9. If, however, we use only a brief illumination we obtain Curve 2 of Fig. 9. This so strongly resembles the curve of the positive ion of methyldiphenylamine (Fig. 5) that we have little hesitation in ascribing it to the corresponding ion, $(C_6H_5)_2NH^+$.

Numerous curves obtained on longer illumination, the analysis of which we shall not describe in detail, indicated the presence, in addition to $(C_6H_5)_2NH^+$, of the two substances responsible for the B and C bands of tetraphenylhydrazine. More recent experiments of Mr. J. Bigeleisen have shown that in the absence of air the C band does not appear, and the only bands are that of $(C_6H_5)_2NH^+$ and the B band of tetraphenylhydrazine, in amount depending on the length of illumination. Both of these bands disappear gradually as the temperature is raised, that of the $(C_6H_5)_2NH^+$ going more rapidly.

Interpretation of the Several Bands Obtained with Tetraphenylhydrazine

The X and D Bands.—Before considering the three main bands of Fig. 1 we shall say what we can of the elusive X band which sometimes is nearly one-third as strong as the B band, but sometimes does not appear at all. It never appeared when the illumination was by the full mercury arc through quartz. It appeared at its strongest when the illumination was with light lying between 3600 and 3800 Å. The difference proved to be due to the fact that the X substance is destroyed by all ultraviolet light as well as by the visible, in the range of absorption. Only when the frequency is in the neighborhood of 3700 Å. is the rate of its formation large compared with the rate of its destruction. On the other hand, the X substance is not very sensitive to temperature and persisted on warming as long as any color remained in the solution. Suspecting that the X band might be due to an impurity, a new preparation of tetraphenylhydrazine was made which gave under similar conditions the same curves as the preceding preparation but the X band was never more than one-half as intense. Until further preparations are tested we must doubt that the X band belongs to tetraphenylhydrazine.

The D band lay nearly outside the scope of our measuring apparatus and has therefore been little studied. It presumably does not represent an additional substance, but is part of a second band system of substance B, or substance C, or both.

The A Band.—This band, lying altogether in the infrared and with a maximum beyond the limits of our experiments, probably at about 8200 Å., might not have been discovered except for the short life of the A substance. We found that in the course of our absorption measurements over boiling liquid air that the absorption at the lowest frequencies fell off rapidly with time. It seemed, therefore, that the A absorption might readily be obtained by subtracting the curve obtained after the disappearance of A. The problem, however, was not so simple as this, for sometimes, as the A absorption diminished, that in the B and C regions substantially increased. It was finally found that A disappears by two processes, the first of which produces no change in the amounts of B and C, and the second of which produces both B and C. Fortunately at low temperatures (*ca.* 90°K.) the first process occurs almost alone and under these circumstances our method of subtracting the curves obtained before and after standing, enable us to obtain the curve for the A band given in Fig. 1.

We are going to identify the A substance with the positive ion of tetraphenylhydrazine, $(C_6H_5)_2NN(C_6H_5)_2^+$. This is the one band that does not appear when other compounds containing the diphenylnitrogen group are illuminated, and its absorption maximum in the infrared is about that which would be expected for an odd ion possessing such great possibilities of resonance.[15]

The B and C Bands.—We have seen that at higher temperatures the disappearance of A is accompanied by the production of B and C. By studying the light absorption at 8100 Å. and its change with time we have followed the kinetics of this reaction at about 90°K. The process proved to be strictly unimolecular with a half-life of twenty minutes. Concurrently the change of absorption in other parts of the spectrum were followed and it was seen that the B and C bands increased as they would if B and C were being

(15) In arriving at this conclusion it has been necessary to disregard the work of Weitz and Schwechten [*Ber.*, **60**, 1203 (1927)] and of Weitz and Müller [*ibid.*, **68**, 2306 (1935)] who by a variety of methods obtained violet substances which they believed to be the positive ions of tetraarylhydrazines. Some experiments similar to theirs but leading to a quite different interpretation will be discussed in the immediately following paper by Lewis and Bigeleisen.

produced from A. It is to be assumed that this thermal reaction is

$$(C_6H_5)_2NN(C_6H_5)_2^+ \longrightarrow (C_6H_5)_2N + (C_6H_5)_2N^+$$

These observations, together with the appearance of the B and C bands in illumination of other compounds containing the diphenylnitrogen group, lead us to identify these bands with the substances $(C_6H_5)_2N$ and $(C_6H_5)_2N^+$. It remains to decide which substance should be assigned to which curve. The first evidence came from the observation that upon brief illumination only the A and B bands appeared. The two most likely reactions in a primary illumination, that is, an illumination which is not long enough to excite further the first products of illumination, are

$$(C_6H_5)_2NN(C_6H_5)_2 \longrightarrow (C_6H_5)_2NN(C_6H_5)_2^+ + e^-$$
$$(C_6H_5)_2NN(C_6H_5)_2 \longrightarrow 2(C_6H_5)_2N$$

We believe that these two photochemical reactions occur in about equal amount and conclude that the B band is due to $(C_6H_5)_2N$ and therefore that the C band is due to $(C_6H_5)_2N^+$. By illuminating briefly and allowing the sample to stand at not too high a temperature, we were able to obtain the very satisfactory B band given in Fig. 1. On the other hand, the C band, which was obtained by a rough analysis of various compound curves, cannot be considered very accurate.

The assignment of the B and C bands enabled us to interpret satisfactorily the results obtained with other substances containing diphenylnitrogen. The illumination of triphenylmethyldiphenylamine gave $(C_6H_5)_2N$, $(C_6H_5)_3C$, $(C_6H_5)_2N^+$ and $(C_6H_5)_3C^+$, all of which can be recognized in Fig. 6. The illumination of $(C_6H_5)_2NNH_2$ seems from Fig. 7 to give largely photo-ionization according to the reaction

$$(C_6H_5)_2NNH_2 \longrightarrow (C_6H_5)_2N^+ + NH_2^-$$

The illumination of $(C_6H_5)_2NNO$ apparently gives both $(C_6H_5)_2N$ and $(C_6H_5)_2N^+$, but we should like to study this case more carefully before attempting to write the photochemical reactions.

The case of diphenylamine is interesting. We have seen that the primary illumination produces only photo-oxidation to give $(C_6H_5)_2NH^+$, but then on further illumination there is a second reaction which must be written

$$(C_6H_5)_2NH^+ \longrightarrow (C_6H_5)_2N + H^+$$

and thus the B band is obtained.[16]

(16) It is to be presumed that the proton attaches itself to the basic oxygen of the ether or alcohol of the solvent. It is probable also that in some of our other reactions the neighboring solvent molecules may take part to the extent of forming loose addition compounds presumably without causing appreciable change in the absorption spectra.

Perhaps the least ambiguous evidence for our assignment of the B band to the diphenylnitrogen radical is obtained in the experiment with diphenylamide ion. It seemed unlikely in this case that the primary illumination would cause anything except simple photo-oxidation

$$(C_6H_5)_2N^- \longrightarrow (C_6H_5)_2N + e^-$$

and the appearance in Fig. 8 of the pure B band seems almost by itself sufficient to identify this band with $(C_6H_5)_2N$.

Illumination by Polarized Light and the Production of Permanent Dichroism in Homogeneous Media.—We planned to resolve the complicated band system obtained by the illumination of tetraphenylhydrazine by using polarized light, and thus obtain an orientation of the resulting molecules which would be permanent as long as the medium remained rigid, but otherwise would be entirely similar to the orientation in the phosphorescent state that we previously studied.[1a] We have not been able to carry out this program but have nevertheless, with one or two simpler substances, shown that the method is practical. In these cases colored solutions were obtained which when studied with polarized light showed a notable variation of the absorption with the direction of polarization.

Experimental

In several cases (hexaphenylethane and the several di- and triarylamines) light between 2500 and 3000 Å. proved to be necessary for rapid photochemical action, and direct light from the high-pressure mercury arc was employed. In other cases the light passed first through a large quartz cell containing aqueous copper sulfate in order to use a high intensity of light without overheating the samples. Such overheating may easily occur even when the samples are immersed in liquid air. Various color filters were occasionally used to give selected spectral regions. The cells of quartz, or of "Pyrex" glass when permissible, were ordinarily about 1 cm. in thickness. Sometimes the color obtained was nearly uniform throughout the cell, but sometimes it all appeared near the face, in which case both faces were illuminated in turn. The depth of penetration of color depends upon the concentration and also upon the position and intensities of the ultraviolet absorption bands of the initial and final substances. Occasionally, a very dilute solution was illuminated in a tube 10 cm. long and 3 cm. in diameter, the illumination being across, and the absorption measurements along, the tube. The absorption measurements were made by methods that we have previously described.[1a]

Materials.—Tetraphenylhydrazine was prepared by the oxidation of diphenylamine with potassium permanganate, as described by Gattermann and Wieland.[17] It was not

(17) Gattermann and Wieland, "Laboratory Methods of Organic Chemistry," The Macmillan Co., New York, N. Y., 1934.

easy to determine the purity of the product since the substance decomposes before melting. We have mentioned that the X band shown in Fig. 1 may be due to impurity.

The hexaphenylethane was prepared *in vacuo* by the action of silver amalgam on triphenylchloromethane by a method that we shall describe more fully in another place. The triphenylmethyldiphenylamine was also made *in vacuo* by the method of Wieland.[18] Tetraphenylhydrazine was added to a solution of hexaphenylethane in toluene and heated two hours at 100°. When once formed the product can be filtered and recrystallized in the air, although after some months it deteriorates on standing in air.

Lithium diphenylamide was prepared as follows. A small amount of lithium and a slight excess of diphenylamine were placed in a tube on the vacuum line and ethylamine was distilled into the tube. After the completion of the reaction the ethylamine was pumped off and the mixture of ether and isopentane was distilled in. The tube was then sealed off. *unsym*-Diphenylhydrazine was prepared from the hydrochloride by adding alkali and shaking out with benzene. It was purified by vacuum distillation, as were also diphenylamine and methyldiphenylamine. Diphenyl disulfide was purified by recrystallizing from toluene at −80°.

Rigid Solvents.—At room temperature transparent glasses of boric acid or of glucose may be used. At −60 to −80° glycerol, triethanolamine, sulfuric and phosphoric acids make good rigid solvents. At the temperature of liquid air most supercooled liquids crack. Others have too little solvent power. We have found[10] that for most purposes the best solvent is a mixture of 5 parts of ether, 5 parts of isopentane,[19] and 2 parts of alcohol by volume. This we designate as EPA or more explicitly $E_5P_5A_2$. We have used higher alcoholic contents up to EPA_4, but the chance of the solvent cracking in the midst of an experiment increases with the alcoholic content. In the experiment with lithium diphenylamide the solvent was EP_2. In other cases triethylamine may replace the alcohol in EPA. If a rigid solvent containing only hydrocarbons is desired, a mixture of 3 parts isopentane and 1 part methylcyclohexane is useful.

(18) Wieland, *Ann.*, **381**, 214 (1911).

(19) We are indebted to the Shell Development Company for a liberal donation of isopentane of high purity.

Summary

When tetraphenylhydrazine in a rigid solvent is illuminated by ultraviolet light, the solution becomes colored and shows three main absorption bands, each of which is shown to be due to a separate substance. In order to identify these substances and to find what types of photochemical reaction are possible under these circumstances, various substances have been similarly studied. It is found that a molecule may be dissociated by light into two radicals, into positive and negative ions, and into a positive ion and an electron. In two cases the last type of dissociation, which may be called photo-oxidation, gives substances identical with those obtained by Michaelis and associates by chemical oxidation. From the illumination of several substances containing the diphenylnitrogen group it has been possible to find the absorption bands of $(C_6H_5)_2N$ and $(C_6H_5)_2N^+$. These are two of the main substances produced in the illumination of tetraphenylhydrazine. The third is $(C_6H_5)_2NN(C_6H_5)_2^+$, which disappears by two processes: one is the return of the electron, the other is dissociation into $(C_6H_5)_2N$ and $(C_6H_5)_2N^+$. The latter process is shown to be unimolecular.

BERKELEY, CALIFORNIA RECEIVED JUNE 27, 1942

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

The Initial Step in the Action of Acids on Tetraarylhydrazines

BY GILBERT N. LEWIS AND JACOB BIGELEISEN

Wieland[1] observed that tetraarylhydrazines react with acids to give colored substances which according to circumstances are green, violet or blue. In fact, a single preparation passes, sometimes rapidly, through a succession of color changes. If the solution has not aged much, Wieland showed that neutralization by alkali restores a large part of the original hydrazine and therefore concluded that the acid produces a mere addition complex without splitting the hydrazine. However, it has not been found possible to suggest any such addition compound that would have any of the observed colors. Weitz and others[2] have assumed a more or less reversible reaction which in the case of tetraphenylhydrazine may be written

$$3(C_6H_5)_2NN(C_6H_5)_2 + 2H^+ = 2(C_6H_5)_2NH + 2(C_6H_5)_2NN(C_6H_5)_2^+ \quad (1)$$

It is to such odd ions as the one appearing in this equation that Weitz ascribes the violet color obtained by the action either of acids or of oxi-

(1) Wieland, "Die Hydrazine," Ferdinand Enke, Stuttgart, 1913.

(2) Weitz and Schwechten, *Ber.*, **60**, 1203 (1927); Weitz and Müller, **68**, 2306 (1935).

dizing agents on tetraarylhydrazines. However, it has been shown in the adjoining paper of Lewis and Lipkin[3] that this ion, which is produced from tetraphenylhydrazine by the loss of an electron, is certainly not violet, for its chief absorption is in the infra-red. In fact, the violet color as described by Wieland and by Weitz must be the resultant of a complicated series of reactions; we have never observed the violet color in non-hydroxylic solvents in the absence of air.

Another objection to regarding equation (1) as the primary step in the process is that such a reaction would presumably have a considerable heat of activation, but we find that the production of color upon acidifying tetraphenylhydrazine is extremely rapid nearly down to the temperature of liquid air.[4] It is possible that on the way to some of the end-products that have been identified by Wieland, reaction (1) may play a part, but here we are concerned only in finding what the first step in the reaction is.

Considering the various possible initial reactions the only one that seems reasonable is the one that assumes that tetraphenylhydrazine is in rapid equilibrium with a small amount of its two ions according to the equation

$$(C_6H_5)_2NN(C_6H_5)_2 \rightleftarrows (C_6H_5)_2N^+ + (C_6H_5)_2N^- \quad (2)$$

and that upon addition of acid the negative ion is removed[5] allowing the positive ion to accumulate to such extent as to show its green color. We should expect, therefore, to obtain initially, in the absorption spectrum, the band designated as the "C" band in the preceding paper.

Our first experiments were made between 200°K. and room temperature. Solutions of tetraphenylhydrazine in various solvents such as acetone, ether, isopropyl chloride, β-*n*-amylene, and several mixtures of these, sometimes including isopentane, were exhausted on the vacuum bench after cooling with liquid air, and dry hydrogen chloride gas was allowed to enter. Then either the containing tubes were sealed off or the solution was gradually warmed and stirred by a simple magnetic stirrer. All the solutions showed apparently the same green color. However, on spectrophotometric examination the absorption curves varied greatly from sample to sample, depending upon the solvents and the temperature attained before making the measurements; none showed the expected pronounced maximum at the position of the "C" band (about 6800 Å.). It is evident that even under the conditions of these experiments numerous colored substances have been produced.

The first indication of the "C" band appeared in a solution in ether, isopentane and isopropyl chloride (1,1,2 by volume). After freezing the solution in liquid air, passing in hydrogen chloride (in moles about equal to the amount of tetraphenylhydrazine used) and warming to about 160°K., the solution was stirred, and once again cooled. The absorption measurements were made just above rapidly boiling liquid air. The experiment was unsatisfactory because of the clouding of the solvent, but there appeared to be definite evidence of an absorption maximum in the neighborhood of the "C" band.

A more conclusive experiment was then performed using our EPA solvent, ether, isopentane and ethanol (5,5,2 by volume). The procedure was that just described except that the solution was treated with hydrogen chloride at about 130° K., was stirred about half a minute and then cooled to 90°K., where the absorption measurements were made. The absorption curve obtained is shown as curve 1 in Fig. 1. In the same figure curve 2 taken from the preceding paper of Lewis and Lipkin[3] shows roughly the "C" band attributed to $(C_6H_5)_2N^+$. There seems little doubt that the positive ion of diphenylnitrogen is one of the first substances produced in the action of an acid on tetraphenylhydrazine. That it is this ion, and not the accompanying substance with an absorption chiefly in the infra-red, that is actually the first colored product of the reaction, is shown by the fact that when the solution is warmed to a little higher temperature the "C" band disappears and only the infra-red band remains.[6]

(3) Lewis and Lipkin, THIS JOURNAL, **64**, 2801 (1942).

(4) As far as we can judge the reaction may still be instantaneous at temperatures below that of liquid air, but at these low temperatures even the most fluid solvents, such as isopentane, become very viscous and the reaction time is the time required for mixing.

(5) We shall not attempt to decide whether hydrogen ion adding to $(C_6H_5)_2N^-$ forms diphenylamine immediately or whether possibly the nitrogen acts as a secondary base, and therefore the hydrogen ion attaches itself at a para position in one of the rings. When dry hydrogen chloride is added to a solution of tetraphenylhydrazine in isopentane at low temperatures a typical green solution is formed, but further addition of acid produces a red precipitate. This phenomenon, which is evidently due in some way to the addition of a second hydrogen ion or acid molecule, may be avoided by buffering the solvent with any base such as ether, acetone or alcohol to keep down the acid strength. The use of such buffers in solvents which are not sources of hydrogen ion will be obvious to those familiar with the theory of generalized acids and bases (see Lewis, *J. Franklin Institute*, **226**, 293 (1938)).

(6) It seems likely that the substance responsible for the infra-red band is formed from the positive diphenyl nitrogen ion by a disproportionation involving the para hydrogen. Our experiments, therefore, should be repeated with tetra-*p*-tolylhydrazine so as to exclude this type of side-reaction.

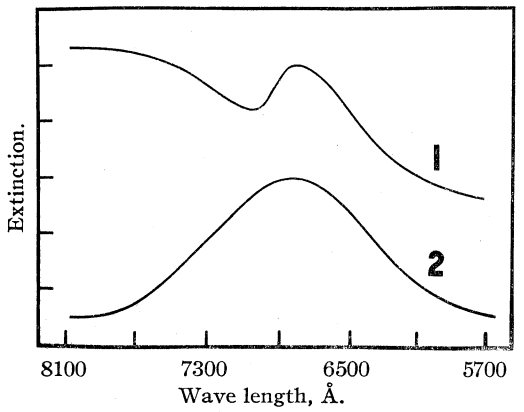


Fig. 1.—1, Absorption curve of the products of reaction of HCl and $(C_6H_5)_2NN(C_6H_5)_2$ in EPA at low temperature; 2, absorption curve of $(C_6H_5)_2N^+$. In both cases the vertical scale is arbitrary.

The difficulties encountered in establishing the presence of $(C_6H_5)_2N^+$ seem to be attributable not merely to its remarkable instability but also to the small contribution that it makes to the total absorption. This is not due to a small absorption coefficient; presumably this ion and the chloride ion are in equilibrium with diphenylchloramine according to the equation

$$(C_6H_5)_2NCl \rightleftharpoons (C_6H_5)_2N^+ + Cl^- \quad (3)$$

the diphenylchloramine being ionized only to a small extent. The situation is quite analogous to that of triphenylchloromethane in such a solvent as chlorobenzene.

Summary

Of the many reactions that are ordinarily observed when acid is added to tetraphenylhydrazine, none is the initial reaction. The first process, which occurs rapidly even near the temperature of liquid air, is the formation of $(C_6H_5)_2N^+$, which we have identified by its absorption spectrum. If tetraphenylhydrazine is assumed to be in rapid equilibrium with the positive and negative diphenylnitrogen ions, the effect of an acid is to remove the negative ion and thus cause accumulation of the colored positive ion, a considerable part of which, however, presumably combines with chloride ion to form colorless diphenylchloramine. The chloramine and its positive ion are too unstable to be observable except at extremely low temperatures.

BERKELEY, CALIFORNIA RECEIVED AUGUST 3, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

A Study of Heterogeneous Equilibria in Aqueous Solutions of the Sulfates of Tetravalent Vanadium at 30°

BY CHARLES S. ROHRER, OSCAR E. LANFORD AND SAMUEL J. KIEHL

Introduction

The hydrates of the sulfates of tetravalent vanadium reported in the literature by previous investigators are divided into two series by Mellor[1]: the one, $VO_2 \cdot SO_3 \cdot xH_2O$ and the other $2VO_2 \cdot 3SO_3 \cdot xH_2O$. However, we believe that he entertains some doubt as to the number of hydrates in each, for he states: "... some of them may be mixtures representing arbitrary states in the process of dehydration." This uncertainty is more clearly substantiated if one considers the water ratio of each series. There are reported[2–5] for the first series the following molecular ratios of $H_2O/VO_2 \cdot SO_3$: 0, 1, 1.5, 2, 2.5, 3, 3.5, 5, 6.5, and for the second series, the molecular ratios of $H_2O/2VO_2 \cdot 3SO_3$: 0, 1, 1.5, 2, 3, 4, 6, 14 and 16.

Doubtless in many of the preparations, since the products depended upon drying at various temperatures up to 360°, it is quite possible that intermediate states of incomplete hydration were reached. For, at 360° insoluble $VO_2 \cdot SO_3$ is invariably precipitated from concentrated sulfuric acid. Then, too, Gerland[3] dried the pentahydrate at 100° and reported not only $VO_2 \cdot SO_3 \cdot 2.5H_2O$, but also $VO_2 \cdot SO_3 \cdot 1.5H_2O$ by prolonged heating at that temperature.

By the same procedure Koppel and Behrendt[5] reported $VO_2 \cdot SO_3 \cdot 2.5H_2O$ and $VO_2 \cdot SO_3 \cdot 2H_2O$. If, however, the heating was done at 125°, they obtained $VO_2 \cdot SO_3 \cdot 1.5H_2O$ and $VO_2 \cdot SO_3 \cdot H_2O$ at 150°. Moreover, by heating $2VO_2 \cdot 3SO_3 \cdot 4H_2O$ in the second series at from 140 to 160° they obtained

(1) J. W. Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Vol. IX, Longmans, Green and Company, New York, N. Y., 1929.

(2) J. J. Berzelius, *Phil. Mag.*, **10**, 321 (1831); **11**, 7 (1832).

(3) B. W. Gerland, *Chem. News*, **34**, 2 (1876); *Ber.*, **9**, 869 (1876); **10**, 2109 (1877); **11**, 104 (1878).

(4) J. W. Crow, *J. Chem. Soc.*, **30**, 453 (1876).

(5) I. Koppel and E. C. Behrendt, *Z. anorg. Chem.*, **35**, 154 (1903).

$2VO_2 \cdot 3SO_3 \cdot 3H_2O$; upon further heating, however, at 175° $2VO_2 \cdot 3SO_3 \cdot 1.5H_2O$ was obtained, which finally, by continued heating to 200°, changed to the anhydrous salt $2VO_2 \cdot 3SO_3$.

Furthermore, there is little information given as to the ratios of vanadium dioxide to sulfur trioxide or to water in the reported preparations of the salts. Other authors,[3-5] besides, have reported failure in attempts to prepare hydrates by methods previously described.

From the above considerations and since nothing more than qualitative statements have been made as to the solubility of the various hydrates, it appears that a study of the system VO_2–SO_3–H_2O would not only provide solubility data for the various hydrated sulfates of tetravalent vanadium, but also tend to clarify the available data. The results of such a study at 30° and under ordinary atmospheric pressure are given below.

Preparation of Materials

Vanadium Dioxide.—The vanadium dioxide was prepared from a very good commercial product which by analysis gave 99.92% of vanadium pentoxide and showed no measurable loss of weight upon ignition. The material was very finely divided and quite insoluble in water. However, a suspension of it was slowly reduced to a solution of tetravalent vanadium by sulfur dioxide, the excess of which was removed by heating the solution for about twenty-four hours on a water-bath while a stream of nitrogen passed through it. During this process a lilac to orchid precipitate was formed which Gain and Dritte[6] identify as $V_2O_4 \cdot 2H_2O$. The expulsion of the sulfur dioxide by boiling, recommended in their procedure, was found to be impractical with more than a few grams of the vanadium pentoxide, because the very finely powdered oxide attached itself so firmly to the sides of the vessel that severe bumping approaching explosive violence at times, occurred. This difficulty was overcome by passing a stream of nitrogen through the solution while it was being heated on the water-bath.

The resulting precipitate was filtered on a fritted glass funnel and washed twenty times with hot water. In order to eliminate from our experiments any of the traces of soluble impurities which may have been in the anhydrous pentoxide, this washed precipitate only was used in preparing mixtures which were to be brought to equilibrium. By analysis this prepared dioxide was free from sulfur dioxide and was shown to have undergone no oxidation during exposure to the atmosphere in its preparation. The analysis, however, showed the compound to contain 1.3 ± 0.7% by weight of sulfur trioxide as an impurity which really was no impurity in the preparation of the vanadyl sulfates. In preparing the mixtures for solubility measurements of the solid phase $VO_2 \cdot H_2O$, however, it was an impurity. In this case the sulfur trioxide content was reduced to 0.3 ± 0.2% by agitating the finely ground material in an atmosphere of nitrogen for one month in pure water which was changed twice each week. The dioxide was reground in a mortar each time the water was changed.

The sulfuric acid, the potassium permanganate and the barium chloride, have been discussed heretofore.[7]

Apparatus.—All apparatus and their standardizations for temperature control, for stirring, for analytical work and for other purposes have been described previously.[8,9]

The containers were 250-ml. "non-sol" bottles tested for water tightness. The stoppers were sealed to the bottles with paraffin, as an added precaution, to prevent leakage while the samples were being agitated.

Analytical Determinations

Vanadium.—Since the vanadium to be determined was in the pure tetravalent state, the procedure was simple. The sample was dissolved and made up to a volume, aliquot portions of which were titrated directly with a standard solution of potassium permanganate in the presence of sulfuric acid. As an assurance that no oxidation had occurred, frequent checks were made by treating one of the aliquot parts with sulfur dioxide and titrating after removal of the excess. In no case was oxidation of the tetravalent vanadium observed.

In order to get the moist residue of the solid phase $VO_2 \cdot H_2O$, which is quite insoluble, into solution, the addition of an acid was necessary. Since the chloride ion did not interfere with the sulfate determinations, hydrochloric acid was used. Nevertheless, it was necessary to remove it from the aliquot by evaporation almost to dryness with sulfuric acid before titrating with permanganate. The sulfate thus formed, however, is the insoluble form of the normal vanadyl sulfate identified by Gerland[3] as $VO_2 \cdot SO_3$ which is not to be confused with the $VO_2 \cdot SO_3$ discussed later in this investigation, a form quite soluble. This insoluble form was dissolved by boiling in a quite concentrated solution of sulfuric acid. The solutions so obtained were reduced with sulfur dioxide, prepared and titrated with a standard solution of potassium permanganate in the usual manner.

An alternate method for the analysis in the hydrochloric acid solution was used. In this procedure the tetravalent vanadium was oxidized to the pentavalent state with chlorine, and the determinations made, after the removal of the excess, according to a method developed by Walden, Hammett and Edmonds.[10] The results obtained by the two methods were in close agreement.

Sulfate Determinations.—Sulfur trioxide determinations were made according to the standard method for sulfates.[11] Moreover, in our analytical procedure the removal of the vanadyl ion was deemed unnecessary because no serious interference due to coprecipitation occurred. This fact was confirmed by taking aliquot portions of a concentrated solution of the vanadyl ion and determining the sulfur trioxide content first in the presence of the ion and, second,

(6) G. Gain and M. A. Dritte, *Compt. rend.*, **143**, 873 (1906).

(7) O. E. Lanford and S. J. Kiehl, THIS JOURNAL, **62**, 1660 (1940).

(8) S. J. Kiehl and E. J. Manfredo, *ibid.*, **59**, 2118 (1937).

(9) E. J. Manfredo, "A Study of Heterogeneous Equilibria in Aqueous Solutions of the Sodium Salts of the Vanadic Acids at 30°, C.," Ph.D. Dissertation, Columbia University, 1936.

(10) G. H. Walden, L. P. Hammett and S. M. Edmonds, THIS JOURNAL, **56**, 57 (1934).

(11) H. A. Fales, "Inorganic Quantitative Analysis," Century Company, New York, N. Y., 1925.

after its removal from the aliquot portion by precipitation with ammonium hydroxide. The results from these experiments were in agreement within experimental error. The samples were filtered in a porous bottom Gooch type crucible, and dried in a muffle furnace at 600 to 700°.

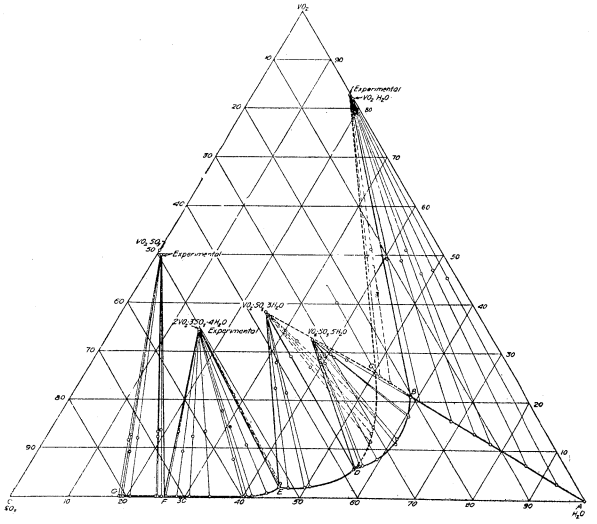
Experimental Procedure

Individual mixtures were prepared by adding the moist vanadium dioxide monohydrate to solutions of water and sulfuric acid of definite ratio ranging from pure water to pure sulfuric acid. For mixtures with higher concentrations of sulfur trioxide, it was necessary to use fuming sulfuric acid. As a precautionary measure against oxidation all samples were placed under an atmosphere of nitrogen and hermetically sealed with paraffin. These mixtures were stirred by end over end rotation for a period of time which exceeded that necessary for the attainment of equilibrium.

In order to determine the time necessary for the attainment of equilibrium, duplicate samples were prepared by taking one of the mixtures, as prepared above, at apparent equilibrium, and dividing it into two parts: one of these was maintained at 0° for twenty-four hours with frequent stirring; the other was treated likewise at 70 to 100°; they were then agitated again at 30 ± 0.01° until equilibrium, with identical phases, was reached in both.

Three criteria were used to determine the establishment of equilibrium: first, the densities of the mother liquors remained constant at the same value for both of the duplicates; this served as preliminary criterion before analyses were made; second, the analyses of the mother liquors agreed within experimental error; third, microscopic examinations revealed a single identical solid phase of definite crystalline form in both samples.

The time necessary to establish equilibrium ranged from three days, approximately, with $VO_2 \cdot SO_3 \cdot 5H_2O$, where the crystals grew rapidly in the less viscous solutions, to a year or more for the $2VO_2 \cdot 3SO_3 \cdot 4H_2O$ and $VO_2 \cdot SO_3$ in the highly viscous solutions of concentrated sulfuric acid.



Percentage by weight of H_2O.

Fig. 1.—System $VO_2 \cdot SO_3 \cdot H_2O$, 30° isotherm, data in weight percentage.

The attainment of equilibrium by approach from both higher and lower temperatures was employed, because it afforded an opportunity for formation of all possible hydrates. While temperatures of 0 and 70° or above were not the most satisfactory for economy of time, they nevertheless gave further opportunity during a period of several weeks for the crystallization of any other possible hydrates from the various concentrated solutions. During this time, moreover, they were repeatedly subjected to alternate changes from high to low temperatures as well as to stirring. No matter what compound separated at lower temperatures or higher temperatures, the mixtures obtained finally at equilibrium by stirring at 30° were the hydrates represented in Fig. 1.

After equilibrium was attained, rotation of the solutions was halted, and the solid phase was allowed to settle. Samples for density determinations and for analyses of the mother liquor were taken by the use of the pycnometer and

TABLE I

Density	Liquid phase Percentages VO_2	Liquid phase Percentages SO_3	Moist solid phase Percentages VO_2	Moist solid phase Percentages SO_3	Solid phase	
0.996	0.0068				a	
1.048	3.45	3.33	45.58	1.64	a	
1.096	7.21	6.83	47.22	3.31	a	
1.231	11.51	10.93	46.52	5.68	a	
1.278	13.41	12.78	51.20	5.97	a	
1.361	16.19	15.40	49.15	7.80	a	
1.468	20.21	19.02	49.53	10.15	a	
1.595	24.10	22.22	51.47	12.13	a	m
1.639	25.41	23.38	49.92	13.36	a	m
1.663	25.90	23.83	40.39	23.58	a	m
1.508	21.14	20.09	28.67	27.58	b	
1.473	17.24	22.35	29.08	29.27	b	
1.461	17.28	22.50	29.84	29.88	b	
1.427	12.40	26.77	29.48	30.70	b	
1.422	11.24	27.40	29.40	31.12	b	
1.416	8.11	32.35	27.85	31.82	b	
1.436	6.70	35.44	29.05	32.16	b	
1.441	6.52	36.11	28.51	32.37	b	
1.535	17.35	28.09	32.51	34.32	c	m
	17.36	28.09	34.43	35.25	c	m
1.506	14.77	29.71	34.10	35.66	c	m
1.496	13.52	30.72	33.77	35.78	c	m
	11.73	31.64	28.96	34.67	c	m
1.448	6.04	37.50	29.28	36.82	c	
1.506	2.27	46.96	21.77	41.51	c	
1.517	2.11	48.17	27.85	40.04	c	
1.662	2.05	50.96	22.58	42.95	c	
1.578	2.19	52.45	26.03	43.42	c	
1.583	2.80	51.91	21.31	50.95	d	m
1.589	2.51	52.27	17.82	51.49	d	m
1.593	0.96	55.24	11.95	53.65	d	m
1.622	.37	58.06	10.73	55.84	d	
1.582	.275	58.89	17.87	54.60	d	
1.717	.245	59.58	7.84	57.52	d	
1.754	.072	65.52	13.61	59.59	d	
1.783	.080	69.09	12.42	62.39	d	
1.787	.080	71.16	9.40	65.52	d	
1.795	.088	72.97	13.34	64.30	d	
1.801	.097	73.67	13.84	66.89	e	
1.844	.086	74.46	13.45	67.68	e	
1.811	.081	74.56	12.27	68.40	e	
1.827	.062	79.17	12.01	71.95	e	
1.827	.041	80.18	9.16	74.52	e	
1.835	.035	80.58	12.84	72.53	e	
1.825	.036	81.02	11.73	73.59	e	

a = $VO_2 \cdot H_2O$. b = $VO_2 \cdot SO_3 \cdot 5H_2O$. c = $VO_2 \cdot SO_3 \cdot 3H_2O$.
d = $2VO_2 \cdot 3SO_3 \cdot 4H_2O$. e = $VO_2 \cdot SO_3$. m = metastable.

TABLE II

	Percentage		
	VO_2	SO_3	H_2O
	$VO_2 \cdot H_2O$		
Most probable calculated value	82.78 ± 0.86	0.19 ± 0.26	17.03 ± 0.84
Value by analysis of purified compound	81.51	.30	18.2
Theoretical composition	82.16	.00	17.84
Deviation from the theoretical value	0.62	+ .19	−0.81
	$VO_2 \cdot SO_3 \cdot 5H_2O$		
Most probable calculated value	32.81 ± 0.17	31.60 ± 0.23	35.58 ± 0.29
Value by analysis of purified compound	32.96	31.46	35.58
Theoretical composition	32.78	31.63	35.59
Deviation from the theoretical value	+0.03	−0.03	−0.01
	$VO_2 \cdot SO_3 \cdot 3H_2O$		
Most probable calculated value	38.25 ± 0.20	36.83 ± 0.14	24.92 ± 0.24
Value by analysis of purified compound	38.41	36.67	24.92
Theoretical composition	38.22	36.88	24.90
Deviation from the theoretical value	+0.03	−0.05	+0.02
	$2VO_2 \cdot 3SO_3 \cdot 4H_2O$		
Most probable calculated value	34.36 ± 0.86	50.49 ± 0.42	15.14 ± 0.75
Value by analysis of purified compound	32.84	51.26	15.90
Theoretical composition	34.69	50.23	15.07
Deviation from the theoretical value	−0.33	+0.26	+0.07
	$VO_2 \cdot SO_3$		
Most probable calculated value	49.81 ± 2.80	49.28 ± 2.37	0.91 ± 1.50
Theoretical composition	50.89	49.11	0.00
Deviation from the theoretical value	−1.08	+0.17	+ .91

sampling tube described by Kiehl and Manfredo.[8] The solid phase was sampled by placing some of the mixture at equilibrium in a glass porous bottom Gooch type crucible which permitted a rapid and more complete withdrawal of the mother liquor. Thus, in turn the accuracy of the extrapolation in the determination of the solid phase was increased. These samples of mother liquors and precipitates were in due course diluted and dissolved, respectively, with water in a volumetric flask and aliquot parts taken for the determinations of both vanadium dioxide and sulfur trioxide. The water was determined by difference.

Experimental Results

Table I gives the results of the analysis for the mother liquor and for the moist solid phase expressed in percentage by weight of vanadium dioxide, sulfur trioxide. The percentage of water may be obtained by difference. In order to be consistent throughout the paper, all reference to tables, solubility, etc., will, likewise, be expressed in percentage by weight of the respective components. The results plotted on triangular coördinate paper are shown in the accompanying figure.

Calculations

The composition of the solid phase at equilibrium was determined by the method of Schreinemakers.[12] But because the errors in plotting do not permit a sufficiently accurate determination of the composition of the pure solid phase, the tie-lines were expressed by algebraic equations as described by Roozeboom.[13]

As a more objective and a more highly satisfactory procedure for the evaluation of the composition of the pure compounds by the algebraic method, the method of least squares was used, because it affords a comprehensive solution of all the equations for the tie-lines for each respective compound. For example, there were in one case ten equations which would give forty-five possibly different intersections, representing forty-five possibly different values for each of the components. By the use of the method of least squares the one most probable value for each of the components within the limits of the analytical results was obtained. The values listed below for each of the pure compounds were determined by the method of least squares.

The values of the most probable compositions of the various compounds together with the deviation from theoretical composition are listed in Table II. Moreover, these values for the composition of the pure compound as finally determined are burdened with the errors which accumulated from all sources in the course of the work. The

(12) Schreinemakers, *Z. physik. Chem.*, **11**, 76 (1893).

(13) Bakhuis Roozeboom, "Die heterogene Gleichgewichte vom Standpunkte der Phasenlehre," 1911, Vol. 3, Part I, p. 149.

method of computation of the errors has been described.[9,14]

There is more consistency in some of the most probable values for composition than the errors would indicate. For example, if one determines the deviation from the most probable value in each equation by substituting the value for one component (the one most probable value) and solving for the other, one obtains for the composition of $VO_2 \cdot SO_3$: 49.81% ± 0.99 vanadium dioxide, 49.28% ± 0.96 sulfur trioxide, and 0.91% ± 0.25 water. The larger deviations listed for this compound in the table are, of course, due to the acute angles of intersection of the tie-lines on the one hand and to the closely located points which represent the composition of the saturated solution and that of the moist solid phase, respectively, on the other.

Discussion of Results

The isothermal diagram Fig. 1 shows five solid phases: $VO_2 \cdot H_2O$, $VO_2 \cdot SO_3 \cdot 5H_2O$, $VO_2 \cdot SO_3 \cdot 3H_2O$, $2VO_2 \cdot 3SO_3 \cdot 4H_2O$, and $VO_2 \cdot SO_3$, at equilibrium, with their isothermally univariant liquid phase, respectively, in contact. Sufficient determinations were made to follow the course of the solubilities from pure water to 81.02% sulfur trioxide. No higher concentrations of sulfur trioxide were practicable since tetravalent vanadium was oxidized in the more concentrated solutions.

The Solubility Curve A-B-C for the Solid Phase $VO_2 \cdot H_2O$.—The stable portion of the curve A-B has a range of solubility from 0.0068% of the unhydrated oxide in pure water to 21.2% VO_2 at 20.1% SO_3, the invariant point B. This is the invariant point for the solid phases $VO_2 \cdot H_2O$ and $VO_2 \cdot SO_3 \cdot 5H_2O$ in contact with the solution. It was determined by intersection. The portion B-C is a metastable range in which the solubility extends to a maximum value of 25.90% vanadium dioxide at the metastable invariant point C where the percentage of sulfur trioxide is 23.83. The invariant point C was established by direct analysis of the solution at equilibrium with the two solid phases $VO_2 \cdot H_2O$ and $VO_2 \cdot SO_3 \cdot 3H_2O$. The solutions of this hydrate vary in color from an almost clear solution at point A to a solution which is so blue that it is almost opaque at the invariant point C. This hydrated oxide was described and identified by Gain and Dritte.[6] A comparison of the calculated value with one obtained by analyzing the purified compound as well as with the theoretical composition is given in Table II.

The Solubility Curve B-D for the Solid Phase $VO_2 \cdot SO_3 \cdot 5H_2O$.—The stable range of solubility for the solid $VO_2 \cdot SO_3 \cdot 5H_2O$ in this system is from invariant point B in Fig. 1 to the invariant point D. This point is the intersection of the two solubility curves B-D and C-D-E. At this point the percentage of vanadium dioxide is approximately 6.2 and that of sulfur trioxide about 37.3. No metastable equilibrium of this hydrate was observed. The color of the solutions of the compound in this region ranges from a very dark blue translucent solution at point B, 21.1% vanadium dioxide, to a blue of medium intensity at point D which contains about 6.2% vanadium dioxide.

Moreover, it was necessary to seed all the solutions in order to prepare this hydrate. After the crystals were once obtained, no difficulty was encountered in preparing the samples, as equilibrium was reached within three days or less after the seeding. The hydrate first appeared from a metastable saturated solution of the trihydrate which had been standing for a year or more.

On account of its stability, the slight viscosity of the solutions, and the larger size of the crystals, the removal of almost all of the mother liquor was accomplished quite easily. This made possible a much greater distance between the points representing the composition of mother liquor and that of the moist solid which determine the tie-lines on the diagram. For this reason the determination of the composition of this pure solid phase was made with greater precision.

In Table II a comparison of the most probable composition with the analytically determined composition and that of the theoretical will be found.

Gerland[3] prepared the pentahydrate by heating the insoluble anhydrous $VO_2 \cdot SO_3$ with a little water in a sealed tube to 150°. The resulting oily solution was boiled with alcohol to a gummy mass and dried over sulfuric acid. This remaining hard transparent mass when moistened with alcohol and left under a loose cover gradually assumed a crystalline form. The formula for it, he established by analysis. Koppel and Behrendt[5] by allowing one of the lower hydrates to deliquesce on standing in air prepared small well-defined crystals from the resulting dark blue solution. These

(14) O. E. Lanford, "A Study of Heterogeneous Equilibria in Aqueous Solutions of the Sulfates of Pentavalent Vanadium at 30° C.," Ph.D. Dissertation, Columbia University, 1939.

crystals when washed with alcohol and ether gave analyses corresponding to $VO_2 \cdot SO_3 \cdot 5H_2O$.

The Solubility Curve C-D-E for the Solid Phase $VO_2 \cdot SO_3 \cdot 3H_2O$.—The solid phase $VO_2 \cdot SO_3 \cdot 3H_2O$ has a stable solubility range from the invariant point D to the invariant point E, 2.19% vanadium dioxide in 52.45% sulfur trioxide, in Fig. 1, which was established by direct analysis of a solution at equilibrium with the solid phases $VO_2 \cdot SO_3 \cdot 3H_2O$ and $2VO \cdot 3SO_3 \cdot 4H_2O$. A metastable range extends from the invariant point D to the metastable invariant point C for this solid phase and vanadium dioxide monohydrate. It is of interest to note that there are two complete metastable solubility curves B-C and D-C above B-D, the curve for the pentahydrate in the diagram. The color of the saturated solutions of this solid varies from a very dark blue, almost opaque, solution at point C to a very clear, light blue solution at point E.

The trihydrate of the normal vanadyl sulfate may be isolated and purified without decomposition. It crystallizes readily into large, clear light blue crystals which permit removal of practically all of the mother liquor. A close agreement of the experimental with the theoretical value of the composition was therefore obtained, Table II.

In this study the hydrate was easily prepared at room temperature or slightly above by slowly adding concentrated sulfuric acid to the oxide suspended in a concentrated solution of vanadyl sulfate. These crystals of normal vanadyl sulfate trihydrate are reported by Koppel and Behrendt[5] to appear when an acid solution is evaporated at 90°.

The Solubility Curve E-F for the Solid Phase $2VO_2 \cdot 3SO_3 \cdot 4H_2O$.—The solid phase of $2VO_2 \cdot 3SO_3 \cdot 4H_2O$ has a stable range of solubility from the invariant point E to the invariant point F. Invariant point F is somewhat indefinitely located at 0.10%, approximately, vanadium dioxide in about 73.0% sulfur trioxide. The difficulty in locating the percentage of sulfur trioxide for this point is apparent if one notes in Fig. 1 how nearly the curves E-F and G-F approach each other as an almost continuous line. However, in Table I it may be observed that there is a slight but definite tendency for increased solubility which would give an intersection at point F. A metastable range extends from point E to 2.80% vanadium dioxide in 51.91% sulfur trioxide.

The solutions of this solid phase vary in color from a very light blue in solutions of minimum sulfur trioxide to an almost clear solution in higher concentrations of sulfur trioxide.

Due to increased viscosity of the solutions and to the decreasing solubility of the solid phase, equilibrium was slowly attained. One to two months for the attainment of equilibrium was required in solutions of minimum sulfur trioxide while even longer times were required in the more concentrated solutions.

In Table II a comparison of the most probable calculated value with the analytical value and that of the theoretical value may be made.

While hydrates have been reported in this series carrying 16, 14, 6, 4, 3, 2, 1.5, and no molecules of water of hydration, the tetrahydrate alone appeared as a compound at equilibrium in this study. Throughout the course of this investigation it was found that if an insufficient time was permitted for attainment of equilibrium, intermediate stages were encountered. In these cases the tie-lines would fall at random between those for this solid phase and those for $VO_2 \cdot SO_3$. This behavior would tend to support Mellor's[1] suggestion that some of the hydrates reported were intermediate stages in the process of dehydration.

The compound was found to be readily soluble in water and more slowly but quite soluble in absolute alcohol. Partial purification, nevertheless, was secured by first washing with ether–alcohol mixtures and finally with pure ether. It was reported by Gerland[3] that this compound may be purified by washing with water or alcohol. Koppel and Behrendt[5] also prepared it.

The Solubility Curve F-G for the Solid Phase $VO_2 \cdot SO_3$.—The anhydrous vanadyl sulfate has a short range of stability in concentrated solutions of sulfur trioxide. In concentrations higher than about 83 or 84% sulfur trioxide, the tetravalent vanadium is oxidized to the pentavalent state. The solubility at 81.02% sulfur trioxide is 0.036%, expressed as vanadium dioxide, which increases to 0.097% in 73.67% sulfur trioxide. These solutions are almost clear.

The time necessary for attainment of equilibrium for this compound was not determined exactly, but a year or more was required. The samples described were agitated for several months and then allowed to stand for two years before consistent analytical results were obtained. The

crystals are white with a slight tint of blue. Direct analysis of the crystals was not successful since but a small amount was available. The crystals were very small and were contaminated always with the mother liquor of highly concentrated sulfur trioxide. They are very soluble in ether–alcohol or water solutions.

In Table II a comparison of the most probable calculated value with the theoretical value of the composition is shown.

Gerland[3] identified an anhydrous normal vanadyl sulfate which he prepared by boiling the soluble hydrated sulfates in concentrated sulfuric acid. His resulting gray compound is very insoluble even in boiling water. While Gerland's insoluble compound was encountered in the course of this work, as previously mentioned, our anhydrous sulfate is quite soluble in water and dilute acid as well as in alcohol.

Summary

Solubility measurements are given for the ternary system VO_2–SO_3–H_2O at 30° and an isothermal ternary diagram has been constructed.

Over the total range of solubilities these five compounds only, $VO_2 \cdot H_2O$, $VO_2 \cdot SO_3 \cdot 5H_2O$, $VO_2 \cdot SO_3 \cdot 3H_2O$, $2VO_2 \cdot 3SO_3 \cdot 4H_2O$, and VO_2SO_3, were found to exist as stable solid phases at equilibrium with the various solutions.

For purposes of inoculation, attempts were made to prepare other compounds prepared previously by methods described in the literature in order to establish equilibrium relationships for the other reported hydrates. But no evidence was found for their existence.

A soluble form of the anhydrous normal vanadyl sulfate found in our study has not previously been reported.

NEW YORK, N. Y. RECEIVED AUGUST 13, 1942

[CONTRIBUTION OF THE LABORATORY OF PHYSICAL CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Second Virial Coefficients of Gaseous Mixtures[1]

BY A. E. EDWARDS[1a] AND W. E. ROSEVEARE[2]

Introduction.—Accurate p–V–T data at low pressures are few for pure gases and are almost non-existent for gaseous mixtures. This paper reports on the theory and experimental techniques of an indirect method of determining the second virial coefficients of gaseous mixtures. The method consists of measuring the change in volume on mixing two different gases at constant temperature and pressure and does not require determinations of absolute densities of gaseous mixtures.

Theoretical.—In this paper the virial equation of state is used in the form[3]

$$PV = RT + BP + CP^2 + DP^3 + \ldots \quad (1)$$

where B, C, D . . . are the second, third, fourth . . . virial coefficients. Pressures are expressed in mm. of mercury and volumes are expressed either in cc. or in Amagat units. The Amagat unit is considered to be 2.24×10^4 cc. for all gases used.

If two different gases are mixed at constant temperature and pressure, there is usually a change in total volume. The magnitude of this volume change depends upon the intermolecular forces between the molecular species making up the mixture and may be interpreted in terms of the virial coefficients of the pure gases and of the gaseous mixture in the following manner.

If n_1 moles of gas 1 and n_2 moles of gas 2, occupying volumes v_1 and v_2, respectively, are mixed at constant pressure P and constant temperature T and if we neglect the effect of virial coefficients higher than the second,[4] we may write

$$P(v_1/n_1) = RT + B_1P \quad (2)$$

$$P(v_2/n_2) = RT + B_2P \quad (3)$$

$$P(v_m(n_1 + n_2)) = RT + B_mP \quad (4)$$

where v_m is the volume occupied by the mixture and B_m is the second virial coefficient of the mixture. By combining these equations, we have for the volume change on mixing at constant temperature and pressure

$$\Delta v = v_m - (v_1 + v_2) = (n_1 + n_2)B_m - n_1B_1 - n_2B_2 \quad (5)$$

or in terms of the mole fractions in the mixture

$$\Delta v/n = B_m - N_1B_1 - N_2B_2 \quad (6)$$

(1) Original manuscript received February 25, 1942.

(1a) du Pont Fellow in Chemistry, University of Wisconsin, 1940–41.

(2) Present address: E. I. du Pont de Nemours and Co., Richmond, Va.

(3) For a discussion of the various forms of the virial equation of state, see Hirschfelder, Ewell and Roebuck, *J. Chem. Phys.*, **6**, 205 (1938).

(4) The contribution of virial coefficients higher than the second is very small at low pressures. It will be shown that no significant error is introduced in this work by neglecting these terms.

where n denotes the total number of moles of gas. By combining this equation with that derived by Lennard-Jones and Cook[5] for molecules having symmetrical fields, *i. e.*

$$B_m = N_1^2B_1 + 2N_1N_2B_{12} + N_2^2B_2 \qquad (7)$$

we have

$$\Delta v/nN_1N_2 = 2B_{12} - (B_1 + B_2) \qquad (8)$$

where B_{12} may be interpreted as the second virial coefficient representing only the interaction between the unlike molecules in the mixture.

Therefore, if known volumes of two gases are mixed at constant temperature and pressure and the resulting volume change measured, the value of B_{12} may be calculated providing the second virial coefficients of the pure gases are known.

Experimental.—The apparatus is shown in Fig. 1. The gases were first contained in the Pyrex bulbs A and B, each bulb having a capacity of approximately 3 liters. Bulb C, which was used to maintain gas at a constant reference pressure, had a volume of approximately one liter. Bulbs A and B were separated by magnetically operated mercury sealed glass valves V_1 and V_2 and by the diaphragm gage G. The gage consisted of a thin Pyrex diaphragm on which was mounted a small mirror M_1. Minute movement of the diaphragm could be detected by means of the optical lever, shown in Fig. 1, used in conjunction with a reference mirror M_2, the position of which was fixed with respect to the equilibrium position of M_1, a straight filament lamp L and a scale. The diaphragm gage used in this work would withstand pressure differentials of 10 cm. in either direction without rupture. Since the gage was used only as a null indicator it was unnecessary to calibrate it in terms of pressure differential.

Stopcocks S_1 and S_2 were similar in design to those described by Roper[6] and were lubricated with sirupy phosphoric acid. The consistency of the lubricant made it advantageous to maintain a pressure of 200 mm. of nitrogen in the space within the stopcock below the plug rather than to evacuate this space completely. The other stopcocks were of the ordinary type and were lubricated by stopcock grease. This made it necessary to fill bulbs B and C only with those gases which were not affected by stopcock grease and to interpose a 20-cm. length of 1-mm. capillary tubing between bulb B and stopcock S_3 in order to prevent diffusion of the gas mixture to the stopcock.

After evacuation, bulbs B and C were filled with one gas simultaneously with the filling of bulb A with the other gas. The pressures were balanced to within 0.01 mm. by means of the gage, and stopcocks S_3 and S_6 were closed, thus isolating the gas in bulb C. The valves V_1 and V_2 were opened and the contents of A and B mixed by the all glass pump P. This pump was a modification of that described by Funnell and Hoover[7] and circulated an estimated 2 to 4 liters per hour. After thorough mixing of the two gases the pressure was returned to the original value (the pressure in bulb C being used as a reference) by adding or removing mercury by means of the calibrated buret Bu. The volume change could then be determined from the initial and final mercury levels in the buret.

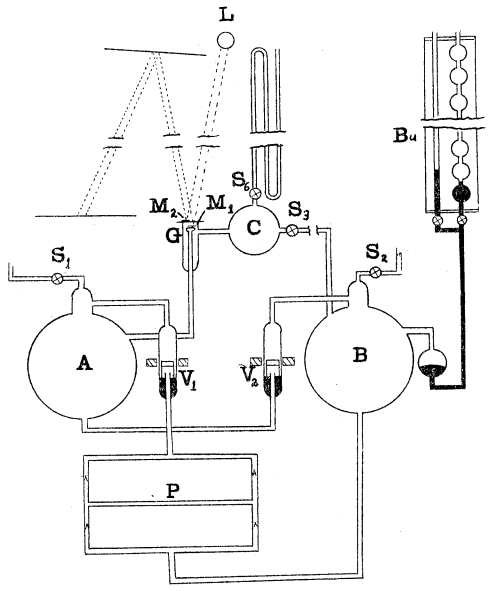


Fig. 1.

The apparatus, except for the buret and the manometer was held on a frame of brass and transite in a water thermostat which was maintained at 25 ± 0.01° throughout all experiments. The buret was held at 25 ± 0.1° by pumping thermostated water through the outer tube. The apparatus was arranged in such a manner that all stopcocks and valves could be operated from outside the thermostat.

Materials.—The hydrogen, oxygen and nitrogen used were 99.7% pure, the carbon dioxide was 99.5% pure and the helium and ethylene had a minimum purity of 99%. Further purification of the gases used in a number of runs had no observable effect upon the experimental results. Care was taken in all runs to sweep out all inlet tubes thoroughly and the bulbs were flushed several times before each run with the gases with which they were to be filled.

Experimental Results.—The data obtained for nine pairs of gases are given in Table I. Two runs were made at 760 mm. and two at 380 mm. for each pair of gases. The absolute error in the values of Δv is constant throughout the data. The percentage error in values of the function $2B_{12} - (B_1 + B_2)$, which are calculated by use of the relationship derived above, vary inversely with the magnitude of the function. It is estimated to be not more than 2% in the case of the H_2–C_2H_4 mixture but may be as much as 12 to 15% at most, *i. e.*, for the CO_2–C_2H_4 mixture.

It will be noted that values obtained for the function $2B_{12} - (B_1 + B_2)$ at 760 and 380 mm. are the same within the limits of the experimental error. Hence, omission of the virial coefficients

(5) Lennard-Jones and Cook, *Proc. Roy. Soc.* (London), **115A**, 334 (1927).

(6) Roper, *J. Phys. Chem.*, **44**, 836 (1940).

(7) Funnell and Hoover, *ibid.*, **31**, 1099 (1927).

TABLE I

Temperature = 25±0.01°; mole fraction of gas A = 0.5187; mole fraction of gas B = 0.4183; total volume = 6595 cc.

Gas A	Gas B	Pressure, mm.	Volume change, cc.	$[2B_{12} - (B_1 + B_2)]10^4$ Amagat units Exp.	Average
H_2	N_2	760	1.21	8.07	
		760	1.23	8.15	
		380	0.60	7.96	
		380	0.59	7.82	8.02
H_2	CO_2	760	2.11	13.99	
		760	2.16	14.32	
		380	1.05	13.92	
		380	1.06	14.05	14.07
N_2	CO_2	760	1.83	12.13	
		760	1.85	12.27	
		380	0.91	12.07	
		380	0.93	12.33	12.20
O_2	CO_2	760	1.69	11.20	
		760	0.82	11.34	
		380	0.82	10.87	
		380	0.87	11.54	11.12
H_2	C_2H_4	760	2.95	19.62	
		760	2.92	19.36	
		380	1.50	18.89	
		380	1.46	19.23	19.53
CO_2	C_2H_4	760	0.49	3.25	
		760	0.50	3.32	
		380	0.22	2.92	
		380	0.26	3.45	3.24
N_2	C_2H_4	760	2.40	15.91	
		760	2.37	15.71	
		380	1.14	15.12	
		380	1.20	15.91	15.66
He	N_2	760	1.23	8.15	
		760	1.18	7.82	
		380	0.58	7.69	
		380	0.61	8.09	7.94
He	CO_2	760	2.10	13.92	
		760	2.12	14.06	
		380	1.06	14.06	
		380	1.05	13.92	13.99

higher than the second appears to be justified in work of this accuracy at pressures near one atmosphere.

Discussion.—For a number of gases, p–V–T data have been expressed in terms of the virial equation of state, the range of pressures covered being determined by the number of virial coefficients used. Such equations, calculated by Newitt[8] from the data of Holborn and collaborators,[9,10,11] over a pressure range 0–200 atm. yield for the second virial coefficient of hydrogen 6.60×10^{-4}; of nitrogen -2.0×10^{-4}; and of helium 5.26×10^{-4}. These values are considered to be the best available for these gases at the present time.

If we consider the virial equation

$$PV = RT + BP \qquad (9)$$

or, rearranged

$$B = (PV - RT)/P \qquad (10)$$

the value of B as expressed by this equation may be termed the *apparent* second virial coefficient and it must approach the true second virial coefficient as the pressure approaches zero. Hence if values of B apparent are plotted against pressure the intercept of the extrapolated curve and the axis $P = 0$ will be the true second virial coefficient. This procedure has been followed for carbon dioxide, oxygen and ethylene, using the data of Masson and Dolley[12] and Michels[13] for carbon dioxide. The best curves through these data yield for the second virial coefficient of oxygen -9.2×10^{-4}; of ethylene -62.5×10^{-4}; and of carbon dioxide -52.5×10^{-4}. Roper's data[14] give B for ethylene as -65.9×10^{-4} which agrees with the above value within Roper's maximum experimental error. Schafer's data[15] give B for carbon dioxide as -56×10^{-4} by extrapolating B from data at 0 to −70°.

These values of the second virial coefficients of the pure gases and the values of B_{12} calculated by substitution of them into the function $2B_{12} - (B_1 + B_2)$ are collected in Table II.

TABLE II

SECOND VIRIAL COEFFICIENT OF GASES AND OF GASEOUS MIXTURES AT 25°

Gas	$B \times 10^4$ (Amagat units)	Gas mixture	$B_{12} \times 10^4$ (Amagat units)
H_2	6.60	H_2-N_2	6.31
N_2	− 2.0	H_2-CO_2	−14.7
He	5.26	N_2-CO_2	−21.2
O_2	− 9.2	O_2-CO_2	−25.2
CO_2	−52.5	H_2-C_2H_4	−17.7
C_2H_4	−62.5	$N_2C_2H_4$	−24.4
		CO_2-C_2H_4	−55.9
		He-N_2	5.60
		He-CO_2	−16.1

The values of B_m for mixtures of various compositions have been calculated for each of the nine pairs of gases by substituting the values of B and B_{12} from Table II into the equation of Len-

(8) Newitt, "High Pressure Plant and Fluids at High Pressures," Chapter VIII, Oxford University Press, New York, N. Y., 1940.
(9) Holborn, *Ann. Physik*, **63**, 674 (1920).
(10) Holborn and Schultze, *ibid.*, **47**, 1089 (1915).
(11) Holborn and Otto, *Z. Physik*, **10**, 367 (1922).
(12) Masson and Dolley, *Proc. Roy. Soc.* (London), **103A**, 524 (1923).
(13) Michels and Michels, *ibid.*, **153A**, 201 (1936).
(14) Roper, *J. Phys. Chem.*, **44**, 835 (1940).
(15) Schafer, *Z. physik. Chem.*, **B36**, 93 (1937).

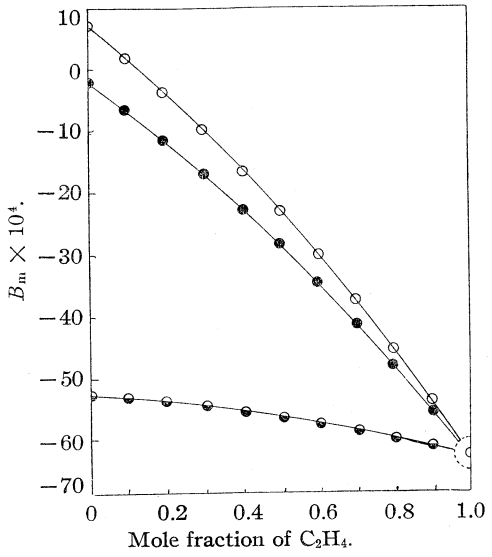


Fig. 2.—Second virial coefficients of mixtures: O, H_2–C_2H_4; ●, N_2–C_2H_4; ◒, CO_2–C_2H_4.

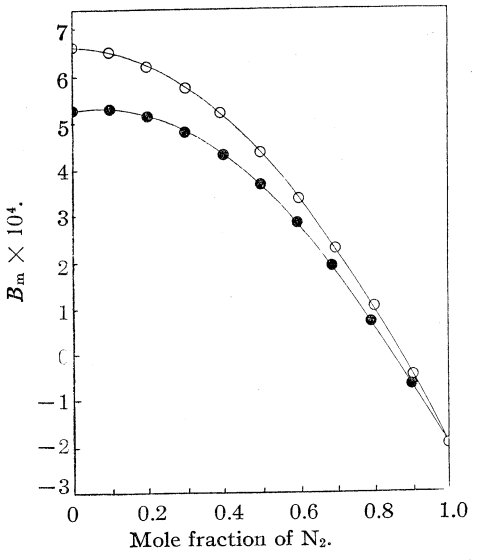


Fig. 3.—Second virial coefficient of mixtures: O, H_2–N_2; ●, He–N_2.

nard-Jones and Cook. This equation, derived on the assumption of symmetrical fields about the molecules, has been introduced into the derivations above and has been shown elsewhere[16] to be valid in similar cases.

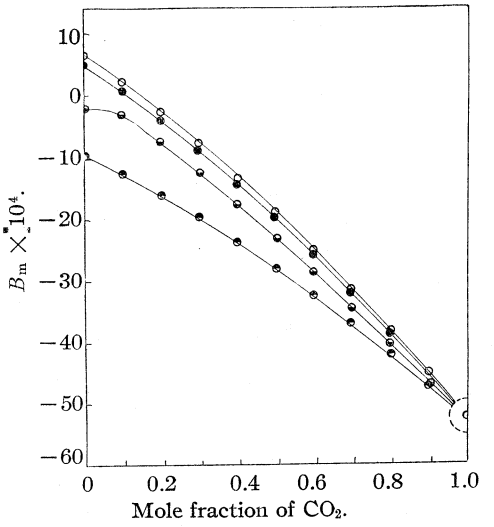


Fig. 4.—Second virial coefficients of mixtures: O, H_2–CO_2; ●, He–CO_2; ◒, N_2–CO_2; ◓, O_2–CO_2.

The values of B_m thus obtained have been plotted against mole fractions in Figs. 2, 3, and 4.

Summary

The theory and practice of a method for determining the second virial coefficients of gaseous mixtures has been described. The method gives data for mixtures corresponding in accuracy to those obtained by gas density measurements to approximately 0.002%.

Values for the second virial coefficients B_{12} for nine pairs of gases at 25° have been reported.

Values of B_m for each of the nine pairs of gases have been plotted as functions of the compositions of the mixtures.

MADISON, WISCONSIN RECEIVED SEPTEMBER 28, 1942

(16) Fowler and Guggenheim, "Statistical Thermodynamics," The Macmillan Co., New York, N. Y., 1939. p. 298.

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

Adsorption of Simple and Complex Cobalt Ions on Titanium Dioxide

BY DOUGLAS G. NICHOLSON[1]

It is a well-known fact that the addition of small amounts of certain metallic soaps to drying oils accelerates the rate of gelation of these substances. A recent report[2] has indicated that pigmented drying oil films containing drier metal ions coördinated with ortho-phenanthroline tend to absorb oxygen more rapidly and at a more uniform rate than did similarly pigmented films containing uncoördinated metal ions. In this respect the films pigmented with titanium dioxide showed the greatest differences, while those containing zinc oxide or zinc sulfide exhibited slight differences.

Authorities in the drying field agree on the fact that cobalt ions are adsorbed on the surface of titanium dioxide particles suspended in a drying oil. This adsorption has been thought to be a rather slow process involving rather long periods of time. A recent study[3] has indicated that the adsorption of a monomolecular film of cobalt ions on the surface of the titanium dioxide particles would account for the loss in catalytic drying properties of such materials.

In an effort to show that these ion adsorptions progress to a considerable extent in the early stages of the aging of suspensions of titanium dioxide and cobalt materials, as well as to account for the reported rapid oxygen absorption of drying oils containing coördinated cobalt ortho-phenanthroline materials and titanium dioxide, a conductometric study of the subject was undertaken. As the work progressed, it was decided that spectrophotometric data obtained from the experimental solutions would also yield interesting related data.

Conductometric Measurements.—To 10 ml. of conductivity water in a Freas type conductivity cell maintained in a thermostat at 25 ± 0.1°, ten successive additions of 0.1 ml. of 0.002 *M* solutions of cobaltous acetate were made. The cell was shaken after each addition and allowed to come to the temperature of the thermostat. This experiment was then repeated except that instead of the cobaltous acetate, an equivalent solution of cobaltous ortho-phenanthroline acetate was added.

This pair of experiments was then repeated, except that in each experiment 5 g. of commercial, rutile type, titanium dioxide was first added to the conductivity water.

Another pair of similar experiments was carried out identical to the above except that the conductivity water was replaced in the first by glacial acetic acid, and in the second by glacial acetic acid 0.0005 *M* in cobaltous acetate. Small, but accurately measured, quantities of solid ortho-phenanthroline were added to each of these solutions and the resistance of the cell determined after each.

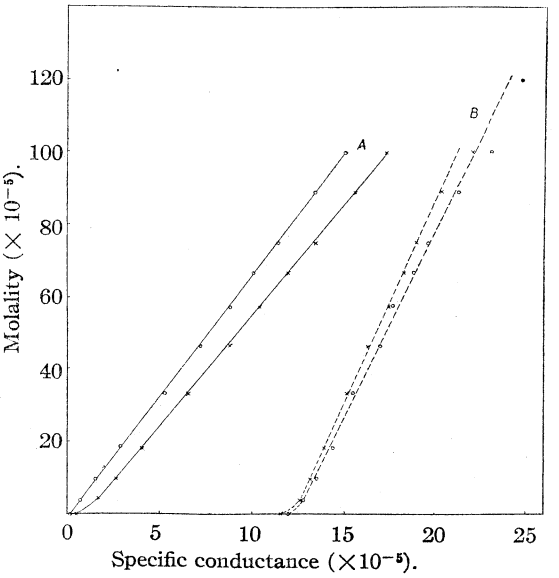


Fig. 1.—Graphical representation of conductometric data obtained by the addition of cobalt acetate and cobalt *o*-phenanthroline acetate to (A) conductivity water and (B) conductivity water containing a known quantity of commercial rutile type titanium dioxide: o—o, $Co(o\text{-}A)_3Ac_2$; x—x, $CoAc_2$; o---o, $Co(o\text{-}A)_3Ac_2 + TiO_2$; x---x, $CoAc_2 + TiO_2$.

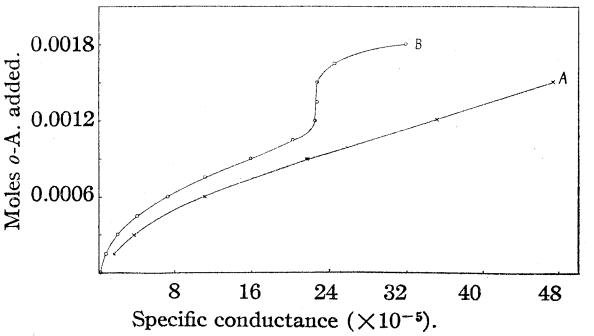


Fig. 2.—Graphical representation of conductance data obtained from the addition of *o*-phenanthroline to (A) glacial acetic acid and (B) to a 0.0005 *M* solution of cobalt acetate in glacial acetate acid: o—o, HAc + 10 cc. of 0.05 *M* $CoAc_2$; x—x, HAc.

(1) Present address: Chemical Warfare School, United States Army, Edgewood Arsenal, Md.

(2) Douglas G. Nicholson, paper presented before The Paint and Varnish Group of The American Chemical Society, 103rd meeting, Memphis, Tenn., April, 1942.

(3) *Am. Paint J.*, **26**, 4-B, October, 29, 1941.

The results of these experiments are shown in graphical form in Figs. 1 and 2.

Spectrophotometric Measurements.—Samples of cobaltous acetate and of cobaltous ortho-phenanthroline acetate, 0.025 *M* in cobalt ion, were prepared and spectrophotographic transmittancy curves obtained for each by means of a General Electric Recording Spectrophotometer. Additional portions of each of these solutions were shaken with commercial, rutile type, titanium dioxide and after allowing approximately twelve hours of standing and filtering off the pigment, transmittancy curves were again obtained from the resulting solutions.

These data appear in graphical form in Figs. 3 and 4.

Discussion.—Figure 1 shows that the solutions containing the coördinated cobalt ions are poorer conductors than are uncoördinated solutions of equal ion concentration. When titanium dioxide is present in the solution, the reverse effect is true. Thus it appears that the loss of conductivity of the uncoördinated ions may be due to adsorption of some on the surface of the pigment particles. The presence of the large coördinating molecules surrounding the cobalt ions, apparently reduces the tendency for this adsorption, with the result that the coördinated ions are better conductors when the pigment is present.

Figure 2 shows quite conclusively that cobalt acetate does form a coördination compound with ortho-phenanthroline in glacial acetic acid. The break in the curve occurs at approximately three molecules of the coördination agent per ion of cobalt. The data appearing in this graph also indicate that ortho-phenanthroline also reacts with the glacial acetic acid, with the probable formation of ortho-phenanthroline acetate.

Figures 3 and 4 show, respectively, the transmissivity curves obtained from the uncoördinated and the coördinated cobalt acetate–glacial acetic acid solutions, before and after the suspension of titanium dioxide pigment. It is to be noted (Fig. 3) that there is an increased transmissivity after the titanium dioxide contact with the solution. This tends to indicate that some of the coloring material (cobalt ions) had been removed by the treatment. This point supports the adsorption idea. In Figure 4, there is actually a slight loss of transmissivity after the contact with the titanium dioxide. No explanation is offered to justify this anomalous behavior. However, there is little doubt regarding the fact that the pigment reacts differently toward the simple and the coördinated cobalt ions of equal concentration. These spectrophotometric data support the information obtained from the conductometric portion of this work.

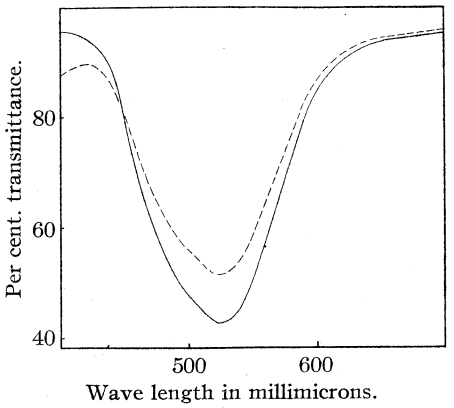


Fig. 3.—Spectrophotometric transmittancy curves obtained from 0.025 *M* cobalt acetate dissolved in glacial acetic acid: (a) solid line is control material; (b) dotted line is same material after having titanium dioxide suspended and filtered.

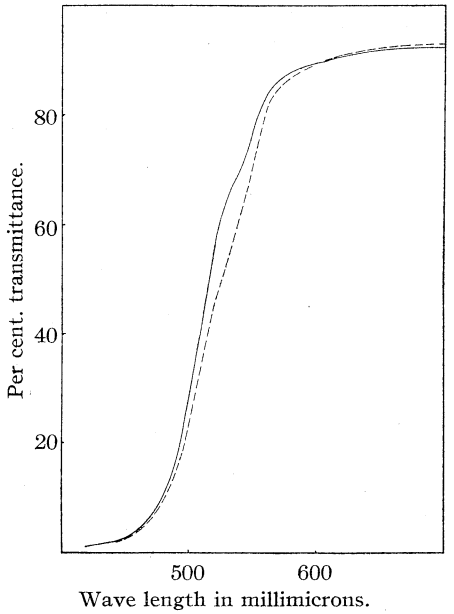


Fig. 4.—Spectrophotometric curves obtained from 0.025 *M* cobalt *o*-phenanthroline acetate dissolved in glacial acetic acid: (a) solid line is control solution; (b) dotted line is same solution after exposure to titanium dioxide.

Summary

Titanium dioxide suspended in water or glacial acetic acid solutions of cobalt acetate adsorbs cobalt ions in a relatively short time.

Coördination of cobalt ions with ortho-phenanthroline materially reduces this adsorption tendency. Ortho-phenanthroline forms a coördination compound with cobalt acetate in glacial

acetic acid. The shortened induction period, which is characteristic of titanium dioxide-pigmented drying oils containing metal-ortho-phenanthroline complex driers can be attributed to this reduction in the adsorption tendency.

URBANA, ILLINOIS RECEIVED APRIL 27, 1942

[CONTRIBUTION FROM THE HAYDEN MEMORIAL LABORATORIES OF NORTHEASTERN UNIVERSITY]

The Solubility Effect in Solvents of Low Dielectric Constant. II. A Study of the Solubility Effect in Benzene[1]

BY ARTHUR A. VERNON AND JOHN P. MASTERSON[2]

I. Introduction

In continuation of the work of Vernon, Luder and Giella[3] this paper reports the results of further solubility measurements of quaternary ammonium salts in benzene. In addition to the literature references cited in the earlier paper by these authors it should be noted that Partington[4] and co-workers have reported results using alcohols as solvent. Also Geer[5] studied some solubility effects in acetic acid, Gross, Kuzmany and Wald[6] in ethyl alcohol and Anhorn and Hunt[7] in liquid ammonia.

II. Experimental

Materials.—C. P. thiophene-free benzene, after standing for several days over anhydrous calcium chloride, was distilled from anhydrous aluminum oxide, the first and last fifth portions being discarded. It was collected and stored in five-pint, ground glass stoppered bottles.

Tetraisoamylammonium iodide was prepared by heating an equimolar mixture of Eastman Kodak Co. tri-isoamylamine and isoamyl iodide to 70° in a constant temperature oven. The crude yield was washed with petroleum ether and dissolved in hot ethyl acetate and treated while hot with alcoholic potassium hydroxide until pink to phenolphthalein. On decanting and cooling in an ice-bath, amine free iodide crystals separated out. The final leafy product was obtained after several recrystallizations from ethyl acetate (m. p. 146.5°).

Tetraamylammonium iodide was prepared similarly except that the crude yield was dissolved in 95% ethyl alcohol before treatment with potassium hydroxide. The iodide was precipitated in water and recrystallized from ethyl acetate (m. p. 134°).

The corresponding picrates were prepared by the method of Cox, Kraus and Fuoss[8] except that the recrystallizations were from 95% ethyl alcohol. They were tetraisoamylammonium picrate (m. p. 86°) and tetraamylammonium picrate (m. p. 73°).

Tributylammonium picrate was prepared by the method of Mead, Fuoss and Kraus.[9]

Procedure.—The method was essentially the same as described by Vernon, Luder and Giella[3] with the modifications that only 600 cc. of benzene was used and a water solution of silver nitrate was substituted for the alcoholic solution. It was found that using alcoholic silver nitrate, the iodide was precipitated colloidally and on aging it settled and adhered to the bottom of the beakers. Transfer of this type of solid to a Gooch crucible was very difficult and relatively inaccurate.

On using a water solution of silver nitrate, however, the precipitated silver iodide came down immediately in flocculent form and on standing settled out at the interface of the benzene and water layers. In this form it was readily transferred to a Gooch crucible since it rode along with the interface and any small particles that adhered to the beaker wall were easily transferred using a rubber policeman and a wash bottle stream. The reproducibility of results was very good, often being within one part in five hundred. Analysis of a known weight of quaternary iodide showed this technique subject to about one per cent. error. The Gooch crucible containing the transferred silver iodide was dried for twenty-four hours over phosphorus pentoxide in a desiccator to consistent weight.

Results.—The results of the determinations are recorded in Tables I and II. All concentrations are in moles per liter and are the averages of duplicate measurements. Since these data are of most value when combined with

TABLE I

SOLUBILITY OF TETRAISOAMYLAMMONIUM IODIDE IN THE PRESENCE OF EITHER (a) TETRAISOAMYLAMMONIUM PICRATE OR (b) TRIBUTYLAMMONIUM PICRATE IN BENZENE AT 25°

Concn. of (a) × 10⁴	Solubility of iodide × 10⁴	Concn. of (b) × 10⁴	Solubility of iodide × 10⁴
0.00	1.13	0.00	1.13
1.28	1.32		
2.53	1.48	3.48	3.28
5.06	1.94	6.95	4.74
10.13	2.95		
15.00	3.97	13.90	7.30
20.00	5.19		
25.33	6.89	27.78	11.24

(1) Condensed from a thesis presented by John P. Masterson to the faculty of Northeastern University in partial fulfillment of the requirements for the degree of M.S. in chemistry.

(2) Present address: Fremont, Nebraska.

(3) Vernon, Luder and Giella, THIS JOURNAL, **63**, 862 (1941).

(4) King and Partington, *Trans. Faraday Soc.*, **23**, 522 (1927); Hawkins and Partington, *ibid.*, **24**, 518 (1928); Partington and Winterton, *ibid.*, **30**, 619 (1934).

(5) Geer, Thesis, University of Kansas, 1935.

(6) Gross, Kuzmany and Wald, THIS JOURNAL, **59**, 2692 (1937).

(7) Anhorn and Hunt, *J. Phys. Chem.*, **45**, 351 (1941).

(8) Cox, Kraus and Fuoss, *Trans. Faraday Soc.*, **31**, 749 (1935).

(9) Mead, Fuoss and Kraus, THIS JOURNAL, **61**, 3257 (1939).

TABLE II

SOLUBILITY OF TETRAAMYLAMMONIUM IODIDE IN THE PRESENCE OF EITHER (a) TETRAAMYLAMMONIUM PICRATE OR (b) TRIBUTYLAMMONIUM PICRATE IN BENZENE AT 25°

Concn. of (a) × 10^4	Solubility of iodide × 10^4	Concn. of (b) × 10^4	Solubility of iodide × 10^4
0.00	0.539	0.00	0.539
1.00	0.583	1.00	1.07
5.00	0.992	3.00	2.04
10.00	1.43	10.00	3.85
20.00	2.50	30.00	7.39
		50.00	10.65

previous results, they are plotted in Fig. 1 with the curves previously obtained by Vernon, Luder and Giella.[3]

III. Discussion

A usual treatment of solubility data is to compare the curve of variation of activity coefficient *versus* the square root of salt concentration with that predicted by the Gronwall, LaMer and Sandved equations using arbitrary values of "ionic diameters." If the experimental and theoretical curves can be made to agree closely by assigning "reasonable" values to the "ionic diameter" then the theoretical equation is considered applicable in the region investigated.

To apply such calculations to the solutions investigated in benzene is fruitless. In such a low dielectric solvent, conductivity and freezing point measurements indicate that association becomes very manifest and the electrolytes behave as if incompletely dissociated. Obviously the value of an "ionic diameter" of a supposed single ion would have little meaning under such conditions.

An approach such as that of Gronwall, Sandved and LaMer might be possible if there were some means of calculating the number of charged ion aggregates in the solution. At present this is not the case.

The increase in solubility in every case on the addition of an electrolyte whether with or without a common ion seems to be further proof of other than single ion phenomena. If the predominant effect were that of single ions we should expect a decrease in solubility on adding a common ion. The fact that the tri-salt gives a greater solubility increase than the tetra-salt with tetraisoamylammonium iodide may be due to a greater interionic attraction.

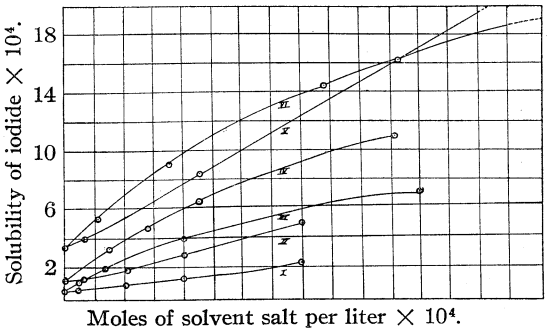


Fig. 1.—I, $(Am)_4NI$ in presence of $(Am)_4N$ picrate; II, $(Isoamyl)_4NI$ in presence of $(isoamyl)_4N$ picrate; III, $(Am_4)NI$ in presence of $(Bu)_3HN$ picrate; IV, $(Isoamyl)_4NI$ in presence of $(Bu)_3HN$ picrate; V, $(Bu)_4NI$ in presence of $(Bu)_4N$ picrate; VII, $(Bu)_4NI$ in presence of $(Bu)_4NNO_3$.

IV. Summary

1. The solubility of tetraisoamylammonium iodide in benzene solutions of tetraisoamylammonium picrate and tributylammonium picrate was determined.

2. The solubility of tetraamylammonium iodide in benzene solutions of tetraamylammonium picrate and tributylammonium picrate was determined.

3. An increase in solubility of the saturating salt was found in both cases and the relation of this to multiple ion phenomena is indicated.

BOSTON, MASSACHUSETTS RECEIVED AUGUST 20, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

Studies on High Molecular Weight Aliphatic Amines and Their Salts. IX. The Behavior of Various Salts of Dodecylamine in Water, Ethanol and Benzene

BY C. W. HOERR AND A. W. RALSTON

Previous papers in this series have presented various aspects of the behavior of the normal primary aliphatic amine hydrochlorides and hydroacetates in water,[1-4] and in ethanol and benzene.[5] These studies have shown that in water these salts are colloidal electrolytes, similar in their behavior to compounds in which the paraffin chain is in the anionic portion of the molecule. In dilute solution they act as simple, completely dissociated, uni-univalent electrolytes, while at certain concentrations dependent upon the length of the paraffin chain, a colloidal transformation results from the formation of micelles. With ethanol and with benzene, the amine salts form simple eutectic systems in which the eutectic composition is located in the region of very small concentration of amine salt.

This investigation is carried further by the preparation of a wide variety of salts of dodecylamine. While this paper is primarily a report of the solubilities of these salts in water, ethanol and benzene, a study of the phase changes of several of the salt–water systems has been included, together with a study of the state of some of the salts in solution, as indicated by their effects in depressing the freezing point of water and that of benzene.

Preparation of Materials.—The dodecylammonium chloride and the acetate were of the same lots which were used in previous experiments, and their preparations and constants have been reported.[1,2,5] The preparations of the following salts have not been reported elsewhere. These salts were prepared by adding equimolar portions of the appropriate acids to dodecylamine in the most satisfactory solvent, as noted below.

Dodecylammonium *n*-propionate and dodecylammonium *n*-butyrate were prepared in the manner of the acetate,[2] the propionate by repeated recrystallizations from ethyl ether and benzene, alternately, and the butyrate from petroleum ether (Skellysolve "F," b. p. 30–60°), until their melting points were constant. The melting point of the propionate was 56.7–56.9° and that of the butyrate was 41.0–41.2°.

Dodecylammonium formate, bromide and iodide were prepared by the method used for the chloride[1] with benzene as the solvent to facilitate the removal of the water introduced by the addition of the acids. No melting points could be obtained for these salts since they decompose at temperatures above 160°. Dodecylammonium formate transforms above 63° to a firm semi-solid liquid crystalline state.

Dodecylammonium acid sulfate and primary dodecylammonium phosphate were crystallized from 95% ethanol. Since dodecylammonium normal sulfate and secondary dodecylammonium phosphate are not appreciably soluble in any of the usual solvents, these salts were refluxed with ethanol for several hours, washed repeatedly with hot water and with ethanol, and finally with hot benzene. No melting points could be obtained for either of the sulfates or the phosphates since they decompose on heating above 250°. Attempts to prepare *t*-dodecylammonium phosphate were unsuccessful.

Dodecylammonium dodecylcarbamate was prepared in this Laboratory by Dr. F. M. Garland. Pure, dry carbon dioxide was passed into liquid dodecylamine at about 30°. Measurement by means of a gas buret of the quantity of carbon dioxide which reacted indicated that two moles of amine combine with one mole of carbon dioxide. This compound was purified by repeated crystallization from 95% ethanol. It melts at 92–93°, and decomposes at 98° to dodecylamine and carbon dioxide.

The secondary and tertiary amine salts were prepared in this Laboratory by Dr. W. O. Pool. Primary dodecyl alcohol (133 g.) was refluxed with resublimed iodine (97 g.) and red phosphorus (7.2 g.) for one hour at 170°. The dodecyl iodide (b. p. 118–120° at 0.7 mm.) was removed from the mixture by solution in ethyl ether and purified by fractional distillation under reduced pressure. The iodide (184 g.) was then heated with methylamine (635 g. of methanol solution containing 13.6 g. methylamine per 100 ml.) in a bomb for eight hours at 135 ± 5°. Excess methanol and methylamine were removed by distillation, and the N-methyldodecylamine was purified by fractionation *in vacuo*. Its boiling point was 88–89° at 1 mm. The hydrochloride of this amine was prepared in the manner of the corresponding primary salt. It melts with decomposition at about 180°, which agrees with a recent observation.[6]

N-Dimethyldodecylamine was prepared by the same method as was used for the corresponding secondary amine, except that a methanol solution of dimethylamine was used. The boiling point of the tertiary amine was 87–88° at 0.9 mm. The hydrochloride and hydroacetate of this amine were prepared by the methods used for the corresponding primary salts, the hydrochloride melting at 170–171° and the hydroacetate at 38.8–39.0°.

The water used in these experiments was freshly distilled conductivity water. The ethanol was commercial "absolute" (99.4% by weight) diluted to 95.0% by weight, ex-

(1) Ralston, Hoffman, Hoerr and Selby, THIS JOURNAL, **63**, 1598 (1941).
(2) Ralston, Hoerr and Hoffman, *ibid.*, **63**, 2576 (1941).
(3) Ralston, Hoerr and Hoffman, *ibid.*, **64**, 97 (1942).
(4) Ralston and Hoerr, *ibid.*, **64**, 772 (1942).
(5) Harwood, Ralston and Selby, *ibid.*, **63**, 1916 (1941).
(6) Westphal and Jerchel, *Ber.*, **73B**, 1002 (1940).

cept where other dilutions are noted below. The ethanol concentration was determined by measurement of its density at each dilution with a 25-ml. pycnometer, and interpolation of these values with those from the "International Critical Tables."[7] The benzene was Baker C. P. thiophene-free grade and was dried over sodium wire.

Apparatus and Procedure.—The experimental procedures were essentially those used in the previous investigations of this series. Visual observations were made by the synthetic method first proposed by Alexejew.[8] The samples were prepared in small glass tubes and rotated in a water-bath with the apparatus and by the procedure described elsewhere.[1,5] Temperatures were measured with a calibrated thermometer which was graduated in 0.1° intervals. The temperatures of solution of the amine salts investigated were reproducible to ±0.1°, and are, in general, considered accurate within ±0.2°.

Transition temperatures of the system dodecylammonium acetate–water below approximately 80° were determined by analysis of cooling curves. These were obtained by carefully controlled cooling of 5–7 g. samples contained in test-tubes (1.5 × 15 cm.) immersed in a bath (800 ml.) of light mineral oil (acetone was used as the bath for sub-zero temperatures). After preliminary heating to homogeneity, the acetate–water samples were allowed to cool slowly while being agitated with a small "Chromel" wire stirrer. The temperature of the bath was at no time more than 2° below that of the sample. Undercooling, in general, did not occur. Temperatures of the samples were read with the calibrated thermometer. The transition temperatures of this system are considered to be accurate to ±0.5° above 80°, while below this temperature they are probably accurate within ±0.2°.

The depression of the freezing points of water and of benzene by several of the salts was measured by means of a Beckmann thermometer which had been calibrated by the National Bureau of Standards, and the temperatures obtained were considered accurate to ±0.001°.

Various compositions of dodecylammonium acetate in water were examined microscopically with polarized light to confirm the preliminary gross visual observations of the nature of the phases which were present.

Results

The Acetate–Water Systems.—A preliminary study of the system dodecylammonium acetate–water has been reported previously.[2] In the light of recent investigation of the higher amine–water systems,[9] this acetate–water system was studied further, and the complete temperature-concentration diagram is shown in Fig. 1. On this diagram, A represents the freezing point of dodecylammonium acetate (69.3°) and K that of water. Area 1 is clear, isotropic solution. Two hydrates are found, a tetrahydrate (m. p. 129.0°) and an eicosahydrate (m. p. 86.0°).

The eutectic between dodecylammonium acetate and its tetrahydrate is represented by B. Areas 2 and 3 are two phase mixtures. Area 5 is a region of microscopically homogeneous material in a mesomorphic state. This region is analogous to the solid solutions of metallic systems and is physically identical with the corresponding phases of the amine–water systems,[9] with reference to which a sufficiently thorough discussion has been presented. Area 4 consists of a mixture of acetate crystals and the solid solution phase of concentration on curve EN. A eutectoid between the acetate and water is represented by N. Area 6 consists of a mixture of crystals of these components. F represents a eutectic between the tetrahydrate and the eicosahydrate. After passing through a narrow two phase region upon cooling, samples containing mixtures of these two hydrates become physically identical with other samples in area 5. J represents a eutectic between the eicosahydrate and water.

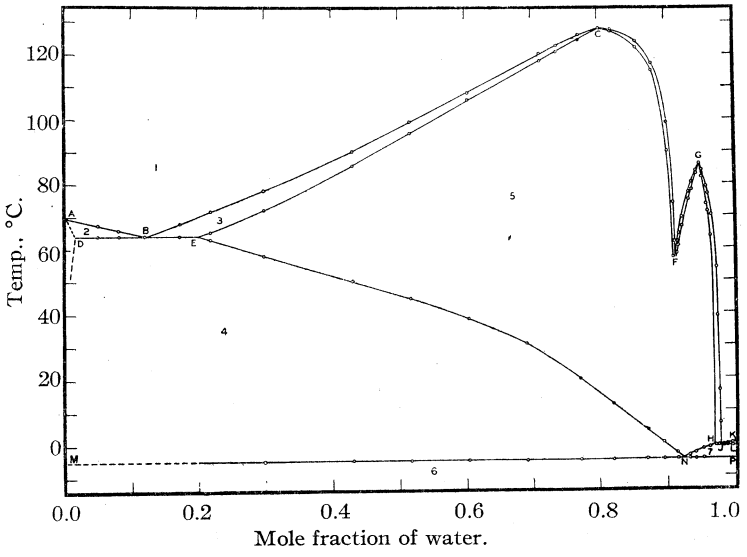


Fig. 1.—The system dodecylammonium acetate–water.

The broken lines at the left of Fig. 1 represent the existence of a region of solid solution, which was indicated by observation, though not verified by direct measurement.

Other Solubilities in Water.—Dodecylammonium formate and *n*-propionate and N-dimethyldodecylammonium acetate exhibit be-

(7) "International Critical Tables," 1929, Vol. III, p. 117.

(8) Alexejew, *J. prakt. Chem.*, **133**, 518 (1882); *Bull. soc. chim.*, **38**, 145 (1882).

(9) Ralston, Hoerr and Hoffman, THIS JOURNAL, **64**, 1516 (1942).

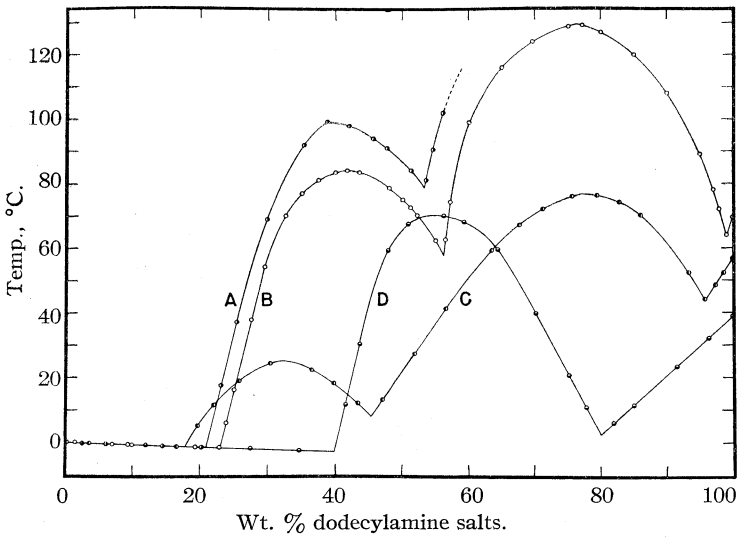


Fig. 2.—Liquidus curves of dodecylamine salts in water: dodecylammonium formate, A; acetate, B; propionate, C; N-dimethylammonium acetate, D.

havior with water similar to that of the acetate. Since the latter system has been described sufficiently, only the liquidus curves of these salts are shown graphically in Fig. 2. Due to thermal instability of the formate, this system was not investigated beyond approximately 60%.

Study of these systems shows the presence of the following hydrates. The formate forms at least one hydrate, an eicosahydrate (m. p. 99.6°). The propionate, like the acetate, forms two hydrates, a tetrahydrate (m. p. 77.0°) and a triacontahydrate (m. p. 24.8°). N-Dimethyldodecylammonium acetate forms one hydrate, a dodecahydrate (m. p. 70.0°).

While it has not been thoroughly investigated, the butyrate-water system is qualitatively similar to the system octadecylammonium acetate–water.[2] Above 33°, the butyrate system exists as two conjugate solutions over practically the entire range of concentration, similar to the behavior of the octadecylamine salt. In the case of dodecylammonium butyrate, the region of isotropic solution exists over a much smaller range of concentration than does the corresponding region of the octadecylamine salt system.

Figure 3 shows the solubilities of dodecylammonium bromide and iodide, primary dodecylammonium phosphate, N-methyldodecylammonium chloride and N-dimethyldodecylammonium chloride, together with the curve which has been reported for dodecylammonium chloride.[1] All of these salts pass through the same phase changes as does the chloride. In all cases, except that of N-dimethyldodecylammonium chloride, there is an abrupt change in the solution temperature at approximately 0.39%. In the case of the bromide, a metastable form precipitates from solution upon cooling, as indicated by the broken line in Fig. 3. This behavior recalls that of dodecylammonium chloride.[1] No metastable compound formation by the other salts was observed.

From the freezing point data, the osmotic coefficient g was calculated for dodecylammonium formate, acetate and propionate, and for the hydroacetate and hydrochloride of N-dimethyldodecylamine. These values are plotted against the square root of the molality ($\sqrt{N_w}$) in Fig. 4.

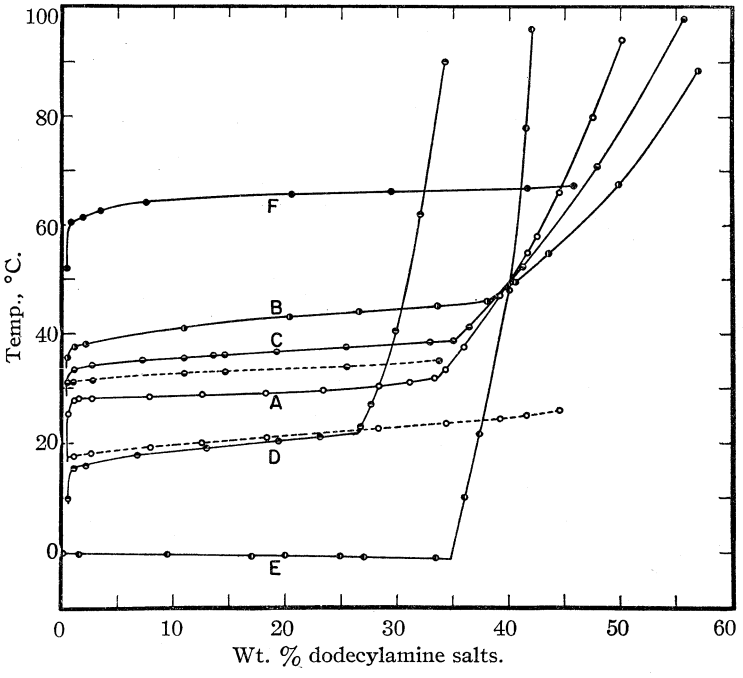


Fig. 3.—Solution temperatures of dodecylamine salts in water: dodecylammonium chloride, A; iodide, B; bromide, C; N-methylammonium chloride, D; N-dimethylammonium chloride, E; primary dodecylammonium phosphate, F. The broken lines refer to the corresponding metastable modifications.

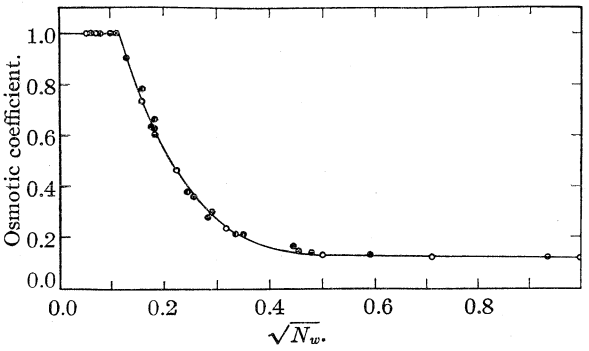


Fig. 4.—Osmotic coefficients of dodecylamine salts in water: ⊗ formate, O acetate, ● propionate, ◐ N-dimethylammonium chloride, ◒ N-dimethylammonium acetate.

It can be seen from Fig. 4 that the values for the osmotic coefficients of all of the salts investigated fall on the same curve, within experimental error. Up to approximately 0.013 molal these salts behave as simple, completely dissociated, uni-univalent salts, as shown by the fact that their osmotic coefficients are 1.0 in this range. At 0.013 molal, the values of g decrease abruptly, indicating the formation of micelles in these solutions. This molality agrees with the value of the critical concentration for the formation of micelles which has been reported[3,4] for the dodecylammonium ion.[10] The interesting fact to be noted in this connection is that the values of the osmotic coefficients of the N-dimethyldodecylamine salts fall on the same curve as the primary dodecylamine salts. Evidently, in the case of these salts at least, N-substitution by methyl groups has no apparent effect upon the concentration at which micelles are formed.

Solubilities in Ethanol.—In Figs. 5 and 6 are shown the solubilities of the dodecylammonium halides, the acetate series, the dodecylcarbamate, the primary phosphate and the acid sulfate in 95.0% ethanol.

In preliminary study of dodecylammonium acetate it was observed that the solubility of this salt was increased by the dilution of ethanol with water. To investigate this further, a number of samples containing 50.0% dodecylammonium acetate were prepared in various dilutions of ethanol in small sealed glass tubes, and the temperatures at which solution occurred were determined by visual observation. The results of this experiment are shown graphically in Fig. 7; 41% aqueous ethanol gave the lowest solution temperature observed for a 50.0% mixture of dodecylammonium acetate–solvent. Minimum solution temperatures of other concentrations of this salt occur at approximately 45 ± 5% ethanol.

Solubilities in Benzene.—The solubilities of the dodecylammonium halides in anhydrous benzene are shown in Fig. 6, and Fig. 8 shows those of dodecylammonium formate, acetate, propionate, butyrate and dodecylcarbamate in the same solvent. The propionate and butyrate (and no doubt the other salts also) form simple eutectics with benzene. In the case of the butyrate, the eutectic is located at 3.6%, and that of the propionate occurs at 0.75%, while those of the acetate and formate occur at considerably greater dilutions.

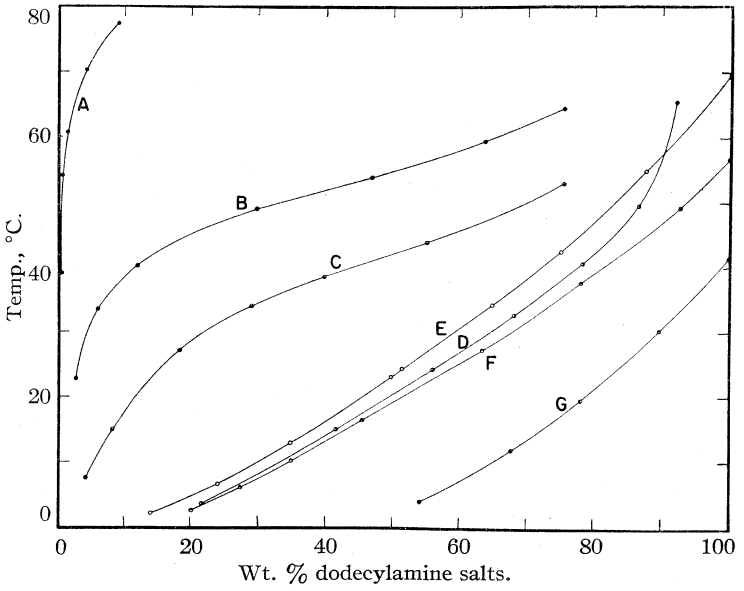


Fig. 5.—Solution temperatures of dodecylamine salts in 95.0% ethanol: primary dodecylammonium phosphate, A; dodecylammonium dodecylcarbamate, B; dodecylammonium acid sulfate, C; dodecylammonium formate, D; acetate, E; propionate, F; butyrate, G.

The lowering of the freezing point of benzene by dodecylammonium butyrate was measured accurately up to the concentration of the eutectic (3.6%). The apparent molecular weight of the butyrate was calculated from the amount of the freezing point depression at each concentration measured. The results are shown graphically in

(10) While this value was reported in terms of molarity, the values of molality and molarity are, for all practical purposes, equal in these dilutions.

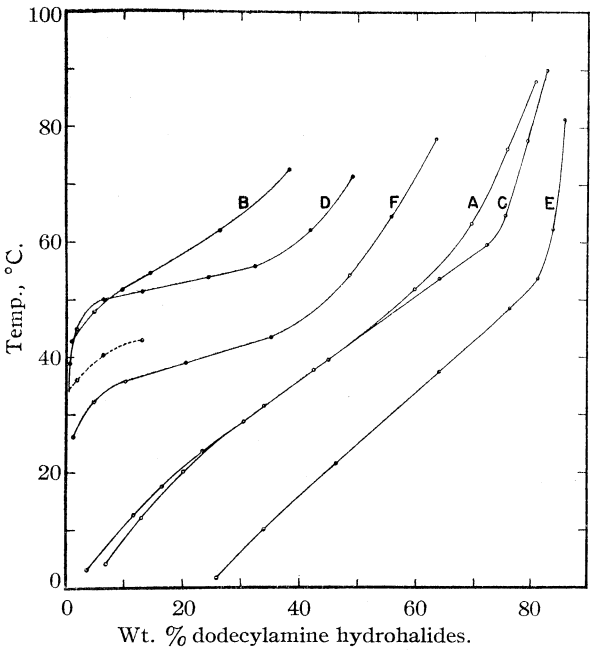


Fig. 6.—Solution temperatures of dodecylamine hydrohalides in 95.0% ethanol and in anhydrous benzene: dodecylammonium chloride in ethanol, A, and in benzene, B; bromide in ethanol, C, and in benzene, D; iodide in ethanol, E, and in benzene, F. The broken line refers to the metastable modification of the bromide in benzene.

phase.[11] However, it can be assumed safely that if associated molecules exist in the vapor, they also occur in the solution which is in equilibrium with it, though the extent of the association in the latter case is problematical. At any rate, molecu-

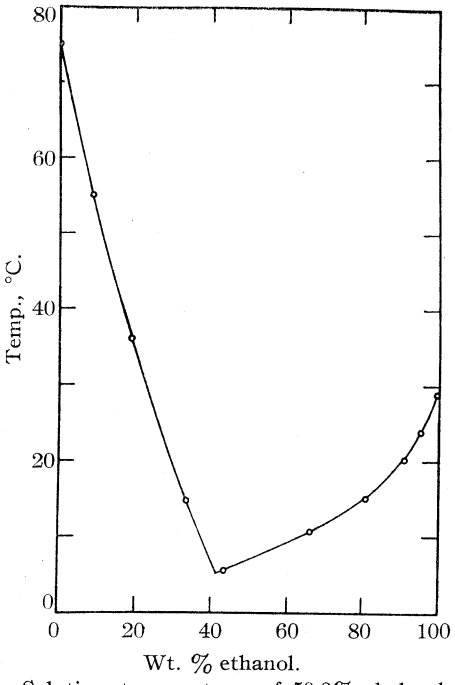


Fig. 7.—Solution temperatures of 50.0% dodecylammonium acetate in aqueous ethanol.

Fig. 9 as the ratio of apparent to true molecular weight (M/M_0) against the square root of the molality ($\sqrt{N_w}$). At approximately 0.1 molal, M/M_0 approaches a value of 2.0. A few measurements of the effects of the propionate upon the freezing point of benzene showed that its M/M_0 values fall on the curve for the butyrate.

The increase of the apparent molecular weight of dodecylammonium butyrate in benzene indicates that there is probably some degree of molecular association. Figure 9, however, cannot be interpreted literally to demonstrate that double molecules exist in solution, even though the M/M_0 values approach a value of 2.0 in higher concentrations, since, in the derivation of the equations involved, the solutions were assumed to be ideal, and certain pertinent factors have been omitted. Moreover, it has been proved with reasonable certainty that the values obtained by this method are actually the molecular weight of the solute in the vapor

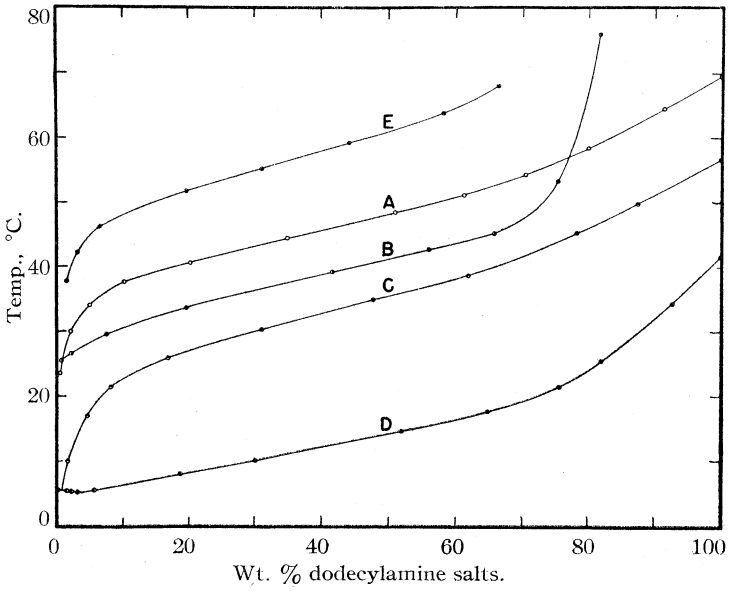


Fig. 8.—Solution temperatures of dodecylamine salts in anhydrous benzene: dodecylammonium acetate, A; formate, B; propionate, C; butyrate, D; dodecyl carbamate, E

(11) Peterson and Rodebush, *J. Phys. Chem.*, **32**, 709 (1928).

lar association of dodecylammonium butyrate to some extent in benzene is evidenced by the data presented.

Further evidence of molecular association is indicated by the rather irregular displacement of the solubility curves of dodecylamine salts toward the ethanol and benzene axes. Similar behavior of the higher fatty acids in benzene has been attributed[12] to molecular association in solution.

Summary

1. The solubilities of dodecylammonium formate, acetate, *n*-propionate, *n*-butyrate, chloride, bromide, iodide, dodecylcarbamate, primary and secondary phosphates and acid and normal sulfates, N-methyldodecylammonium chloride and N-dimethyldodecylammonium chloride and acetate in water, ethanol and benzene have been determined.

2. The phase changes of the water systems of dodecylammonium formate, acetate, propionate and N-dimethyldodecylammonium acetate have been investigated, and the hydrates formed by these salts are reported.

3. The colloidal nature of aqueous solutions of these salts has been demonstrated by a study of their osmotic coefficients.

4. Molecular association of dodecylammonium butyrate in benzene has been discussed.

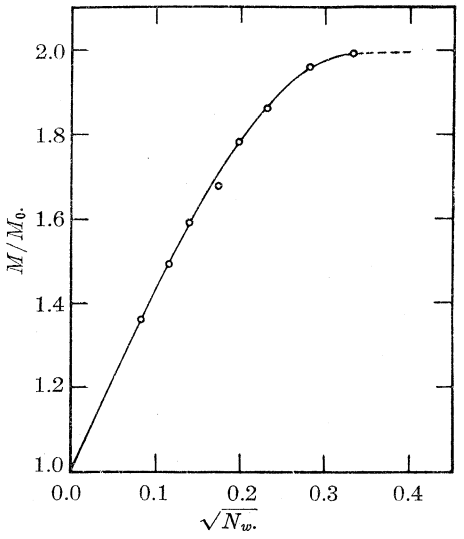


Fig. 9.—Molecular weight of dodecylammonium butyrate in benzene solutions.

(12) Powney and Addison, *Trans. Faraday Soc.*, **34**, 625 (1938).

CHICAGO, ILLINOIS RECEIVED JUNE 24, 1942

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Dipole Moment, Induction and Resonance in Nitroethane and Some Chloronitroparaffins

BY EVERETT C. HURDIS AND CHARLES P. SMYTH

Recent investigations[1] have shown an increase of moment of 0.21–0.23 from nitromethane to α- and β-nitropropane and 2-methyl-2-nitropropane, presumably because of the effect of induction upon the α- and β-carbons, since branching of the carbon chain did not increase the moment appreciably above that of the straight-chain nitropropane. One would, therefore, expect the moment of nitroethane to be close to those of the nitropropanes and nitrobutanes. This appeared to be true in the earlier measurements of Groves and Sugden,[2] who found 3.58, 3.57 and 3.55 for nitroethane, α-nitropropane and α-nitrobutane, values barely distinguishable from their value 3.54 for nitromethane. As this discrepancy between the two sets of investigations left a slight possibility of further increase of moment and, hence, of inductive effect, from nitroethane to the propanes, it seemed desirable to make a careful redetermination of the moment of nitroethane. This has been done, together with measurements upon three chloronitroparaffins, from which conclusions as to induction effects may be drawn. At the same time, measurements upon certain previously measured substances have been carried out as a check upon the absolute accuracy of the determinations.

(1) Wiswall and Smyth, *J. Chem. Phys.*, **9**, 356 (1941).
(2) Groves and Sugden, *J. Chem. Soc.*, 158 (1937).

Preparation and Purification of Materials

Carbon Dioxide.—The gas was taken from a cylinder of commercial material, passed through a tube containing eight-mesh calcium chloride and used without further purification.

Benzene.—The material used had been purified by Dr. P. F. Oesper for use in solution measurements and had been dried over sodium wire.

***n*-Octane.**—This hydrocarbon was supplied as a part of the American Petroleum Institute Pure Hydrocarbon Program. It was prepared and/or purified at the Pure Hydro-

carbon Laboratory, Department of Chemistry, operating as project No. 31 of the Ohio State University Research Foundation. A full description of this product will be published at a later date.

Water.—Ordinary distilled water was used for this measurement.

Nitroethane, Sample I.—Material kindly furnished by the Commercial Solvents Corporation was dried over calcium chloride and fractionally distilled under low pressure. The fraction used for measurements had a boiling point of 65.6° (153 mm.), $n^{20}D$ 1.3917.

Nitroethane, Sample II.—Material prepared by the reaction of silver nitrite with ethyl bromide[3] was fractionally distilled under low pressure. The fraction used for measurements had a boiling point of 81.5–82.0° (263 mm.), $n^{20}D$ 1.3912.

Monochloronitromethane.—Material kindly furnished by Professor R. H. Ewell of Purdue University was fractionally distilled under vacuum in an all glass trap system connected to the gas apparatus.

1-Chloro-1-nitroethane.—Material kindly furnished by Professor Ewell was fractionally distilled under low pressure in an all glass system. The fraction used for measurements had a boiling point of 55° (60 mm.), $n^{20}D$ 1.4224.

1-Chloro-1-nitropropane.—Material kindly furnished by Professor Ewell was fractionally distilled under low pressure in an all glass system. The fraction used for measurements had a boiling point of 67° (56 mm.), $n^{20}D$ 1.4251.

Experimental Method

The dielectric constants of the vapors were measured with the apparatus and much the same technique as that previously described.[4] A polarization value, P, was usually obtained at an absolute temperature, T, by plotting the results over a wide range of pressure and thus eliminating the error caused by possible deviations from the ideal gas law. This method, which we have generally employed, will be referred to as the "extrapolation method." However, in some cases, such as those of substances undergoing slight thermal decomposition with the passage of time, better results could be obtained by making one measurement at 10–30 millimeters pressure and another at a pressure, generally about 200 millimeters, for which experience showed the gas law deviation to be within the experimental error. These pressures were about twice those for which Brockway and Coop[5] calculated a possible error of 0.002×10^{-18} in dipole moment due to gas law deviation. In general, successive measurements by the "two-point method" showed considerable variation, but, if the results of four to six such measurements were averaged at each temperature studied, the averages showed excellent agreement over a wide temperature range.

The oil-bath in which the dielectric constant cell was immersed was altered so that it could be kept constant to within 0.02° at any temperature from room temperature to 250°. A very sensitive mercury-bulb temperature regulator was made by bending ten feet of 1-cm. "Pyrex" tubing into a coil. The fixed contact was a tungsten rod sealed into the glass and the movable contact was steel piano wire, which was much more resistant than platinum to the mercury at the higher temperatures.

The calibration of the apparatus was carried out by an absolute method, for the use of which it was not necessary to rely on the purity of any compound. A system of parallel compensating and measuring condensers was so constructed that a small precision measuring condenser with a scale 2500 divisions and a variable capacity of only 7 $\mu\mu f$ could be balanced against a large precision condenser, 1000 units on the small condenser having to be successively added 128.09 times to cover 400 units on the large condenser. The large condenser was thus calibrated by comparison with the small condenser, which, in turn, was calibrated in the manner previously described[4] by successive insertions of a small unit of about 0.05 $\mu\mu f$ capacity equal to about 25 scale divisions on the small condenser. The capacity of the gas cell was measured on the large condenser and its lead capacity determined from that of a set of dummy leads. Subtraction of this fixed capacity from the total capacity of the cell gave the geometrical capacity used in calculating the dielectric constant. The total cell capacity of about 200 $\mu\mu f$ was measured frequently on the large condenser and converted into units of the small condenser by multiplying by the conversion factor 320.2. It was remeasured whenever the temperature of the oil-bath was changed more than about 10°. The cell showed a temperature coefficient of capacity of about 0.0015% per degree, superimposed on a slow continuous downward drift of capacity. As the cell had been taken apart, cleaned, and reassembled before the measurements were begun, this downward drift in capacity may have been due to the opportunity afforded by thermal expansion and contraction for the relief of strains. During twelve months of operation, the capacity of the cell decreased by 5%, showing the importance of frequent checking. Care was taken to carry out both calibration and measurements at a constant frequency of 780 ± 3 kilocycles. Under these conditions, the effects introduced by lead and condenser inductances were constant and cancelled out in the measurements.

The platinum resistance thermometer in the cell was calibrated by comparison with a Bureau of Standards calibrated platinum resistance thermometer. As the platinum wire was exposed to the vapor in the cell, it was occasionally necessary to bake out the cell at 250° for a few days to avoid adsorption effects which lowered the apparent temperature reading. Temperatures as measured are believed accurate to within 0.2°.

Three compounds were measured as calibration checks: carbon dioxide, benzene and water. Carbon dioxide was measured by the two-point method, the pressures used being about 35 and 950 millimeters. The effect of frequency drift was corrected for by repeating each measurement in the reverse direction and averaging the two figures obtained. The observed pressures were corrected by the use of van der Waals constants. The average of six successive measurements on carbon dioxide was $(\epsilon_{760} - 1) \times 10^6 = 988 \pm 2$, reduced to 0°, in excellent agreement with the values of McAlpine and Smyth,[6] 989, and Stuart,[7] 987.

Benzene was measured at 140° by the extrapolation

(3) Kissel, *Ber.*, **15**, 1574 (1882); Gotting, *Ann.*, **243**, 115 (1888).
(4) Wiswall and Smyth, *J. Chem. Phys.*, **9**, 352 (1941).
(5) Brockway and Coop, *Trans. Faraday Soc.*, **34**, 1434 (1938).
(6) McAlpine and Smyth, THIS JOURNAL, **55**, 453 (1933).
(7) Stuart, *Z. Physik*, **47**, 457 (1928).

method. The average of four measurements gave a polarization of 27.1 cc., in agreement with the previously determined[6] value of 27.0 cc.

The polarization of a sample of pure *n*-octane, kindly given us by Dr. C. E. Boord, was also measured. This served in a sense as a calibration check, as the expected small increase in polarization over the liquid value was observed. The average of four measurements at 160° gave a polarization of 40.1 cc. The polarization of the same material in the liquid phase was 39.7 cc., as measured by Dr. P. F. Oesper in this Laboratory.

The dipole moment of water vapor was measured, using the two-point method, over the temperature range 111 to 250°, the average moment value obtained being 1.844 Debye units. This figure is in good agreement with those reported by Sänger, Steiger and Gachter,[8] 1.852 ± 0.008, and by Groves and Sugden,[9] 1.850 ± 0.01, values which have been recalculated with the currently accepted factor, 0.01281, in the Debye equation.

Experimental Results

The results of individual runs are given in Table I for the dielectric constant ϵ minus 1 for

TABLE I

POLARIZATIONS AND DIPOLE MOMENTS

Carbon dioxide (measured at 299°K., reduced to 0° and 760 mm.)		Benzene	*n*-Octane
$(\epsilon - 1) \times 10^6$	*P*	*P* (413.1°K.)	*P* (433.1°K.)
985	7.36	27.6	40.7
984	7.35	26.9	40.1
995	7.43	27.0	40.2
990	7.40	27.0	39.6
984	7.35	Av. 27.1	40.2
992	7.41		
Av. 988	7.38		

Water

T, °K.	*P*	μ ($\times 10^{18}$)
384.3	57.5	1.84
	57.3	1.84
420.1	53.6	1.85
	53.6	1.85
	53.4	1.85
444.7	50.1	1.84
484.1	46.9	1.85
	46.7	1.85
522.0	43.4	1.84
	42.4	1.82
	43.4	1.84

Nitroethane (Sample I)

415.6	217.3	3.70
442.0	205.3	3.70
	206.8	3.71
	206.4	3.71
484.3	186.4	3.68
	188.6	3.70
	188.1	3.69
	188.9	3.70

Nitroethane (Sample II)

397.5	225.9	3.69
413.6	218.4	3.70
418.1	215.0	3.69
421.1	214.7	3.70

Monochloronitromethane

411.5	144.2	2.93
424.4	138.1	2.89
434.8	138.4	2.94
447.6	131.1	2.89
459.4	131.5	2.93
466.7	128.2	2.91
484.0	122.7	2.89

1-Chloro-1-nitroethane

T, °K.	*P*	$P_{av.}$	μ($\times 10^{18}$)
414.5	182.4	184.5	3.33
	186.2		
	185.1		
	184.0		
	185.0		
432.3	176.9	177.6	3.32
	178.1		
	177.1		
	178.2		
442.7	175.3	175.0	3.34
	174.5		
	178.0		
	172.8		
	176.6		
	173.1		
467.5	169.3	166.5	3.33
	166.7		
	166.1		
	163.9		

1-Chloro-1-nitropropane

416.3	205	206.6	3.51
	208		
	212		
	207		
436.2	198.8	200.7	3.53
	202.8		
	199.0		
	202.6		
	199.2		
451.9	189.9	193.4	3.52
	191.0		
	193.9		
	198.0		
	194.0		
472.9	190	187.5	3.54
	186		
	185.4		
	188.0		
493.1	180.7	178.9	3.51
	178.1		
	175.0		
	179.5		
	181.0		

(8) Sänger, Steiger and Gachter, *Helv. Phys. Acta*, **5**, 200 (1932).
(9) Groves and Sugden, *J. Chem. Soc.*, 971 (1935).

carbon dioxide, for the polarization P for all the substances, and for the dipole moment μ for the polar substances except the last two. For these two, a tendency toward decomposition and the consequent use of the two-point method of measurement increased the error in individual P values and made desirable an increased number of runs and the use of an average of the results, $P_{av.}$, to calculate the moment. The molar refraction for the sodium D line, MR_D, is listed in Table II for each nitro compound, together with the average of the moment values for the substance in Table I.

TABLE II

MOLAR REFRACTIONS AND MOMENT VALUES

	MR_D	μ ($\times 10^{18}$)
Nitroethane	17.0[a]	3.70
Monochloronitromethane	17.4[b]	2.91
1-Chloro-1-nitroethane	21.9[b]	3.33
1-Chloro-1-nitropropane	26.3[b]	3.52

[a] Landolt–Börnstein (fifth edition). [b] Calculated from refractions in Landolt–Börnstein (fifth edition).

Discussion of Results

The results obtained for the substances measured as a test of the accuracy of the apparatus agree so well with previously published data as to indicate an absolute accuracy almost as great as the relative accuracy, about 0.01×10^{-18} in moment. The slight elevation of the polarization value found for *n*-octane vapor over that of the liquid at 25° parallels that previously observed for benzene[6] and noted again in the present measurements and similar behavior on the part of other non-polar substances previously discussed.[10] It is to be noted that Sample I of nitroethane, a material prepared commercially by vapor phase nitration of hydrocarbons, gives a moment value identical with that for Sample II, prepared by the reaction of silver nitrite with ethyl bromide, which, taken in conjunction with the accuracy established for the apparatus, seems to establish definitely the correctness of the value. The average moment, 3.70×10^{-18}, may be compared with the value of Smyth and McAlpine[11] for nitromethane, 3.50 (recalculated on the basis of MR_D) and with the value of Wiswall and Smyth[1] for 1-nitropropane, 3.72×10^{-18}. From these results it appears that the inductive effect of the nitro group is barely, if at all, detectable by dipole moments beyond the first two carbons in the chain. This conclusion is consistent with the indications of the previous measurements and the accuracy of the previously reported[1] 0.2 rise in moment caused by lengthening of the carbon chain is confirmed.

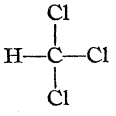
Monochloronitromethane was measured by the extrapolation method over a range of 73°. As there was some evidence of decomposition, however, it was thought best to use the two-point method for 1-chloro-1-nitroethane and 1-chloro-1-nitropropane. In this way low pressures (200 mm.) could be used, and the vapor remained in the cell at this pressure for no longer than fifteen minutes for each determination of dielectric constant. The possibility of appreciable decomposition was further minimized by limiting the temperatures used to 220° or lower.

Calculation of the moment of monochloronitromethane by vector addition of the moments of methyl chloride (1.87×10^{-18}) and nitromethane (3.50×10^{-18}), assuming tetrahedral carbon, gives a resultant moment of 3.40×10^{-18}. The observed moment, 2.91, may, for the time being, be taken to indicate that the lowering due to mutual induction between the chloro and nitro groups is 0.49. This is comparable in magnitude to the lowering observed in methylene chloride, where the moment calculated is 2.16 and the observed is 1.58,[12] so that the apparent inductive lowering is 0.58. Since the inductive lowering observed for the dichloro compound is slightly larger than that for the chloronitro compound, while the moment of nitromethane is nearly twice that of methyl chloride, it appears that the nitro group is considerably less susceptible to inductive lowering of its moment than the chlorine atom. This conclusion is consistent with the previous interpretation[13] of the moment of nitroform in carbon tetrachloride solution, which is only 0.49 lower than the solution moment of nitromethane. This lowering may be compared with that for chloroform, which has a moment 0.85 lower than that of methyl chloride.

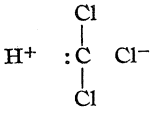
The moment of 1-chloro-1-nitroethane, calculated by vector addition of the moments of ethyl chloride and nitroethane is 3.60×10^{-18}. The observed moment, 3.33, indicates that the apparent inductive lowering is 0.27 as compared with 0.49 for monochloronitromethane. The moment rise expected between monochloronitromethane and 1-chloro-1-nitroethane is 3.60 —

(10) Smyth and McAlpine, *J. Chem. Phys.*, **2**, 571 (1934).
(11) Smyth and McAlpine, THIS JOURNAL, **56**, 1697 (1934).
(12) Maryott, Hobbs and Gross, *ibid.*, **63**, 659 (1941).
(13) Lewis and Smyth, *ibid.*, **61**, 3067 (1939).

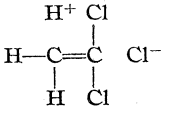
3.40 = 0.20, while the observed rise is 0.42. For the moment of 1-chloro-1-nitropropane we have: moment calculated—3.62, moment observed—3.52, apparent inductive lowering—0.10; expected rise from 1-chloro-1-nitroethane—0.02, observed rise from 1-chloro-1-nitroethane—0.19. Analogous rises are found in the values for 1,1-dichloroethane and 2,2-dichloropropane[12] and the solution value for 1,1-dichloropropane,[14] the increases again being larger than estimated. A large elevation of an apparent inductive rise was found in the difference between chloroform and methyl chloroform, which was found to be 0.77 higher.[1,12] Maryott, Hobbs and Gross[12] attribute this elevation in methyl chloroform, and, analogously, in ethylidene chloride and 2,2-dichloropropane, to "first, the transfer of charge that takes place from the methyl carbon to the other carbon atom, and second, the transfer of some of this new charge from the chloroform carbon to the chlorine atoms." A more specific mechanism may be proposed to account for the effect by assigning ionic character to the hydrogen-carbon bonds and considering the possible resonating structures. The normal covalent structure of chloroform would be

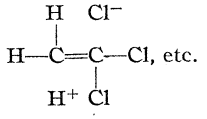


but three ionic structures of the type



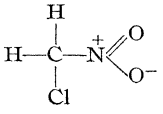
could make small contributions. Contributions from these three structures would increase the positive character of the hydrogen and probably account for its apparent ability to take part in hydrogen bonding and for its slightly tighter binding to the carbon as evidenced by Raman spectra. In methyl chloroform, instead of three such polar structures, nine can be written



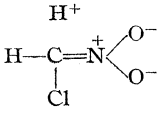


The result of small contributions from these nine structures would be an increase of moment considerably in excess of what would be expected merely from the forces exerted on the methyl group electrons by the three C–Cl dipoles. Analogous structures would contribute to the moment of ethyl chloride, but the presence of only one, instead of three, chlorines would involve a smaller accumulation of negative charge and a correspondingly smaller influence in increasing the moment. Similar considerations account for the smaller moment elevations of 1,1-dichloroethane and 2,2-dichloropropane.

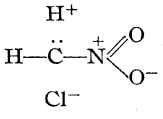
In the discussion of the chloronitroparaffins the difference between observed and calculated values, which has been referred to as the apparent inductive lowering of the moment, contains a rather large negative contribution from resonance effects similar to those just considered. The lowering of moment by mutual induction between the chlorine and the nitro group should be approximately the same in each of these three chloronitroparaffins, and the inductive effect of each of the two dipoles upon the carbon chain was taken care of approximately in calculating the moment of the chloronitro compound by using the moments of methyl chloride and nitromethane in calculating that of the disubstituted methane, of ethyl chloride and nitroethane for the disubstituted ethane, and of propyl chloride and 1-nitropropane for the disubstituted propane. The moment observed for the methane was, as previously stated, 0.49 lower than the calculated, that for the ethane, 0.27 lower than the calculated, and that for the propane 0.10 lower than the calculated. In other words, the moment of the chloronitroethane is 0.22 higher, and that of the propane 0.39 higher than would be expected on the basis of the moment of chloronitromethane and those of the monosubstituted compounds. In addition to a normal structure for chloronitromethane such as



one may write two polar structures such as



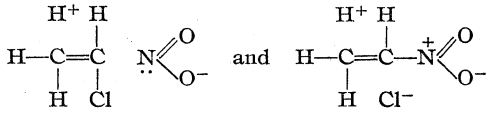
and two such as



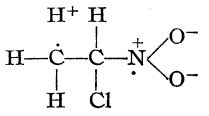
which would, by their contributions, raise the moment as in the case of analogous structures for

(14) Gross, *Physik. Z.*, **32**, 587 (1930).

chloroform. In chloronitroethane, a further increase in moment should result from contributions from structures such as



and



in addition to those from structures like those just written for the methane. For the substituted propane, analogous structures can be written, the number of possible polar structures being increased by the presence of the additional methylene group. The smallness of the increase in moment from the monosubstituted ethane to the monosubstituted propane shows that the contributions from these additional polar structures are extremely small in the monosubstituted compounds, where the concentration of negative charge on a single group would lessen the stabilities of the polar structures. In the disubstituted compounds, the distribution of negative charge between the chlorine and the nitro group would tend to stabilize the polar forms and thus increase the molecular moment. That this stabilizing effect extends, at least to a small extent, to the structures with maximum charge separation in 1-chloro-1-nitropropane is indicated by its considerable increase in moment over 1-chloro-1-nitroethane. It is to be noted that the resonance which has been proposed for these molecules gives rise to hyperconjugation.

It may be pointed out that the previously examined[11] moment of chloropicrin, 1.88, which must lie in the axis of symmetry of the Cl_3CNO_2 molecule, the C–N line, is very close to the difference between the moment of $(CH_3)_3CNO_2$ and that of Cl_3CCH_3, $3.71-1.77 = 1.94$, as it should be, while if the moment of nitromethane, 3.50, is used in the calculation, the result is 0.15 lower than the observed instead of 0.06 higher. In view of the several effects involved, neither calculated value can be regarded as far from the observed.

Summary

The dielectric constants of the vapors of nitroethane, chloronitromethane, 1-chloro-1-nitroethane and 1-chloro-1-nitropropane have been measured and used to calculate the dipole moments of the molecules. As a check on the absolute accuracy of the determination, measurements have been made upon carbon dioxide, benzene, *n*-octane and water vapor, the results obtained being in excellent agreement with those already in the literature.

The moment of nitroethane is 0.20 higher than that of nitromethane and very close to those of α- and β-nitropropane and 2-methyl-2-nitropropane, confirming the indications of their values that the inductive effect is inappreciable beyond the first two carbon atoms of the molecular chain.

The considerable increases in moment from chloronitromethane to the ethane and from the ethane to the propane are attributed to increased stabilization of resonating polar forms by the distribution of the negative charge over two groups in the disubstituted compounds instead of its localization on one group as in the monosubstituted compounds.

PRINCETON, NEW JERSEY RECEIVED SEPTEMBER 15, 1942

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

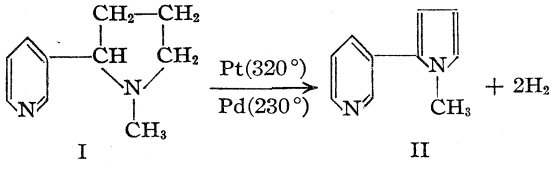
3,2′-Nicotyrine. Insecticidal Properties of Certain Azo Derivatives[1]

BY ROBERT L. FRANK, ROBERT W. HOLLEY AND DONALD M. WIKHOLM

3,2′-Nicotyrine (II)[2] can now be obtained readily from nicotine (I) by catalytic dehydrogenation. Since both of these bases possess insecticidal properties,[3] it seemed possible that dyes derived from them might also have this property and be useful as insect-proofing agents. In the present work a number of such dyes from 3,2′-nicotyrine have been prepared and tested.

The preparation of 3,2′-nicotyrine from nicotine has been accomplished by several methods. It was first carried out by Cahours and Étard[4] by oxidation of natural nicotine with calcium ferricyanide in alkaline solution. Other methods which have been used since that time are oxidation of nicotine by means of silver oxide,[5] silver acetate[6] and electrolysis,[7] but these are all unsatisfactory as preparative methods.

Wibaut and Overhoff[7] have reported yields up to 92% by means of catalytic dehydrogenation of nicotine with platinum-on-asbestos catalyst at 320° in a heated tube. The catalytic dehydrogenation of nicotine by means of palladium-on-asbestos is reported in the present communication and has been found to provide a convenient method for the preparation of 3,2′-nicotyrine. It can be carried out either in the vapor phase in an electrically heated reaction tube (Procedure 1) or more simply by refluxing nicotine containing a suspension of palladium-on-asbestos (Procedure 2). These two procedures give approximately the same yields, but the latter is the more convenient.



I II

The vapor phase dehydrogenation (Procedure 1) gives best yields, up to 41% of the nicotine which reacts, at 305–325°. Lowering the temperature lowers the yields.

In Procedure 2, on the other hand, dehydrogenation begins to take place at much lower temperatures, as evidenced by the evolution of hydrogen. Best results were obtained when nicotine and palladium-on-asbestos were heated to about 230° and the temperature was then allowed to rise gradually to 270–280°. When the reaction was carried out in this way, the yields were 30–35% and were almost as high after thirty minutes as after three hours. Very little nicotine was recovered. Several experiments were also made by this method in which lower temperatures were maintained by the addition of varying amounts of xylene to the reaction mixture. The yields were somewhat lower at temperatures varying from 185 to 230°, and the conversions were considerably lower. The yield was lowered sharply by carrying out Procedure 2 at temperatures higher than 250°.

The yields, ranging from 20 to 41% of the nicotine which reacted, are much lower than those reported by Wibaut and Overhoff, but the method should nevertheless be of value because of the rapidity of the reaction, the simplicity of the apparatus, the ready availability of nicotine, and the lower cost of palladium as compared to platinum.

In addition to 3,2′-nicotyrine and recovered nicotine, two other fractions were isolated, one boiling at 48–70° (1 mm.) and the other, approximately as large as the yield of 3,2′-nicotyrine, boiling at 210–230° (1 mm.). This is interesting in view of the fact that Wibaut and Overhoff reported that there were no side products at all in the dehydrogenation with platinum. These fractions are being further investigated.

3,2′-Nicotyrine has been found to couple readily with diazonium salts and a number of the resulting azo dyes have been prepared (III, R equals p-$C_6H_4SO_3Na$, m-$C_6H_4NO_2$, p-$C_6H_4NO_2$, p-$C_6H_4CO_2H$, β-$C_{10}H_7$). These compounds are crystalline solids ranging in color from orange to purple. They are stable in acid solution and dissolve in boiling concentrated hydrochloric acid with no apparent decomposition.

(1) Presented before the Organic Division at the Buffalo meeting of the American Chemical Society, September 7–11, 1942.

(2) This is the name adopted by Wibaut and Overhoff for *N*-methyl-(3-pyridyl)-2-pyrrole.[7] The compound is also referred to simply as nicotyrine, since it was the first of the N-methylpyridylpyrroles to be described.[5]

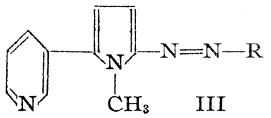
(3) LaForge, THIS JOURNAL, **50**, 2477 (1928); Richardson and Shepard, *J. Agr. Research*, **40**, 1007 (1930).

(4) Cahours and Étard, *Bull. soc. chim.*, **34**, 449 (1880).

(5) Blau, *Ber.*, **27**, 2535 (1894).

(6) Tafel, *ibid.*, **25**, 1619 (1892).

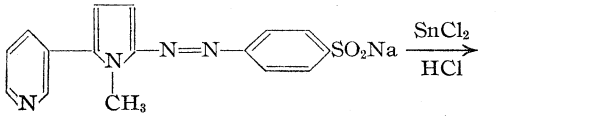
(7) Wibaut and Overhoff, *Rec. trav. chim.*, **47**, 935 (1928).



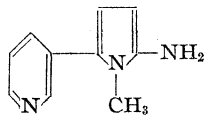
III

The coupling reaction is believed to occur at the free alpha position of the 3,2′-nicotyrine rather than at one of the beta positions since Fischer and Hepp[8] and Plancher and Soncini[9] have found that substituted pyrroles undergo coupling in one of the alpha positions unless these are blocked.

One of these azo dyes was reduced to the corresponding aminonicotyrine, which, on the basis of the above evidence, probably has the structure IV. Sodium 5′-(3,2′-nicotyrine)-azo-*p*-benzenesulfonate (IIIa) was reduced to 5′-amino-3,2′-nicotyrine (IV) in 46% yield by means of stannous chloride and hydrochloric acid. The



IIIa



IV

product, a crystalline solid melting at 86–87°, could be purified only by distillation under reduced pressure. It is stable when kept out of contact with air, but gradually becomes dark and sticky when exposed. When heated in water, alcohol, ether or chloroform, it decomposes and a dark tar separates. It was possible to form a white hydrochloride by treating the amine with gaseous hydrogen chloride in anhydrous ether, but this decomposed rapidly when isolated. The picrate was found to be a stable derivative, however, although it could not be recrystallized.

The instability of this amine parallels the findings of Fischer and Rothweiler,[10] who were unable to recrystallize 2,4,5-trimethyl-3-aminopyrrole.

Samples of wool cloth dyed with four of the compounds gave fast colors ranging from yellow to brown. These were subjected to the attack of the larvae of the black carpet beetle (*Attagenus Piceus*), and all were affected much less than a sample of undyed wool. Details are included in the experimental part.[11]

Experimental

Purification of Nicotine.—The technical product "Nicofume" of the Tobacco By-Products and Chemical Corporation of Louisville, Ky., containing 95% nicotine, was diluted with an equal volume of ethanol and refluxed over Raney nickel for three hours. The nickel was then removed by filtration and the filtrate was fractionally distilled, yielding a nicotine fraction boiling at 118–121° (18 mm.); $n^{20}D$ 1.5252.

Palladium-on-Asbestos Catalyst.—A catalyst containing 5 g. of palladium on 11 g. of asbestos wool was prepared from chloropalladic acid according to the directions of Linstead and Thomas.[12]

Dehydrogenation of Nicotine.—The dehydrogenation was carried out in two ways.

Procedure 1.—The vapor phase dehydrogenation was carried out by a procedure similar to that employed by Wibaut and Overhoff.[7] The apparatus consisted of a vertical "Pyrex" glass catalyst tube equipped with an electrically heated jacket. A thermometer was inserted in the jacket next to the tube and the open ends of the jacket were then packed with asbestos wadding. A cold-finger condenser was attached by means of a ground-glass joint to the top of the catalyst tube and a side-arm at the top of this was connected by means of glass tubing to a buret. Nicotine was allowed to drop from this buret at a rate of 0.5–0.8 cc. per hour.

The brown-colored product was collected in a filter flask attached to the bottom of the reaction tube.

It was found necessary in filling the reaction tube with catalyst to take precautions to prevent spontaneous ignition of the catalyst. A slow stream of nitrogen was passed through the tube while it was being filled; it was then put into place immediately and the nitrogen was replaced by hydrogen, which was passed in from the top by means of a three-way stopcock between the condenser and the buret. Hydrogen was passed in slowly until the tube reached the desired temperature, after which the hydrogen was shut off and the nicotine passed in.

Procedure 2.—Nicotine and palladium-on-asbestos were heated over a hot-plate in a round-bottomed flask equipped with a glass-jointed condenser and a side arm through which a thermometer was inserted. Dehydrogenation began somewhat below 230°, but became vigorous at this temperature. The evolution of hydrogen and the boiling of the liquid served to agitate the contents of the flask.

The mixture became dark in color as soon as the reaction began, and the refluxing temperature rose gradually to 270–280° (with the formation of higher-boiling products).

The reaction products were separated by slow fractional distillation in a modified Widmer column (those obtained by Procedure 2 were first filtered to remove the catalyst). A typical example using 28 g. of nicotine gave the following fractions: 2.2 g. boiling at 48–70° (1 mm.), 2.5 g. at 74–99° (1 mm.), 7.7 g. at 104–107° (1 mm.), and 7.6 g. at

(8) Fischer and Hepp, *Ber.*, **19**, 2251 (1886).

(9) Plancher and Soncini, *Atti Accad. Lincei*, **10**, 299 (1901); *Chem. Zentr.*, **72**, I, 1323 (1901).

(10) Fischer and Rothweiler, *Ber.*, **56**, 512 (1923).

(11) We are indebted to Dr. C. W. Kearns and Mr. Leroy Parker of the Department of Entomology of this University for testing the insecticidal activity of the dyed cloth.

(12) Linstead and Thomas, *J. Chem. Soc.*, 1127 (1940).

210–220° (1 mm.). Considerable residue was left in the distilling flask.

The fraction boiling at 74–99° (1 mm.) was mainly nicotine and that boiling at 104–107° (1 mm.) was 3,2′-nicotyrine, a colorless liquid, darkening somewhat on standing, very slightly soluble in water, soluble in alcohol and in acids, b. p. 150–152° (16 mm.); $n^{20}D$ 1.6057; d^{20}_4 1.241. A picrate melted at 168.5–169° (Wibaut and Overhoff reported 168–169°).

Sodium 5′-(3,2′-Nicotyrine)-azo-*p*-benzenesulfonate (IIIa).—Eleven grams (0.058 mole) of sulfanilic acid and 2.5 g. of sodium carbonate were dissolved in 100 cc. of water. Three and five-tenths grams (0.051 mole) of sodium nitrite dissolved in 20 cc. of water was added to the solution. After cooling to 3°, 7 cc. of concentrated hydrochloric acid was added with stirring. To the diazotized solution was added 7.8 g. (0.049 mole) of 3,2′-nicotyrine dissolved in 3 cc. of glacial acetic acid. After stirring for ten minutes, the solution was made alkaline by adding a solution of 7 g. of sodium hydroxide in 20 cc. of water. Some orange solid settled out, but the precipitation was made more nearly complete by the addition of 20 g. of sodium chloride. The orange-red solid was removed by filtration and allowed to dry. A yield of 15.0 g. (84%) was obtained.

The compound was crystallized from hot water, in which it was fairly soluble, and washed with alcohol and ether. It did not melt below 300°.

Anal. Calcd. for $C_{16}H_{13}O_3N_4SNa$: N, 15.38. Found: N, 15.35.

5′-(3,2′-Nicotyrine)-azo-*p*-nitrobenzene.—One and two-tenths grams (0.0087 mole) of *p*-nitroaniline was dissolved in 20 cc. of hot water and 3 cc. of concentrated hydrochloric acid. Twenty grams of ice was added and the solution cooled to 0°. To this was added 0.69 g. (0.01 mole) of sodium nitrite dissolved in 20 cc. of water.

One and four-tenths grams (0.0089 mole) of 3,2′-nicotyrine was dissolved in 25 cc. of alcohol and 3.0 g. of sodium acetate in 20 cc. of water was added to the alcoholic solution. The combined solution was added slowly with stirring to that of the diazonium salt. A red solid precipitated immediately. After standing thirty minutes, the solid was removed by filtration and recrystallized from hot alcohol. Two and four-tenths grams (90%) of beautiful purple-red needles was obtained. After two recrystallizations, these melted at 200–201°.

Anal. Calcd. for $C_{16}H_{13}O_2N_5$: N, 22.80. Found: N, 22.79.

Three other dyes were prepared in the same manner as 5′-(3,2′-nicotyrine)-azo-*p*-nitrobenzene from the corresponding aromatic amines. These are described as follows.

5′-(3,2′-Nicotyrine)-azo-*m*-nitrobenzene.—The same amounts were used as in the preparation of 5′-(3,2′-nicotyrine)-azo-*p*-nitrobenzene. The yield was 2.1 g. of orange-red solid (79%), which melted at 156–157° after two recrystallizations from alcohol.

Anal. Calcd. for $C_{16}H_{13}O_2N_5$: N, 22.80. Found: N, 22.95.

5′-(3,2′-Nicotyrine)-azo-*p*-benzoic Acid.—One and two-tenths grams (0.0088 mole) of *p*-aminobenzoic acid was used. The yield was 1.9 g. (71%) of orange needles. After five recrystallizations from hot alcohol, these melted with decomposition at 245–246°.

Anal. Calcd. for $C_{17}H_{14}O_2N_4$: N, 18.29. Found: N, 18.48.

β-Naphthaleneazo-5′-(3,2′-nicotyrine).—The amount of β-naphthylamine used was 2.86 g. (0.020 mole). The product crystallized from alcohol as red plates and weighed 5.2 g. (83%). After two recrystallizations, the crystals melted sharply at 148°.

Anal. Calcd. for $C_{20}H_{16}N_4$: N, 17.94. Found: N, 17.90.

5′-Amino-3,2′-nicotyrine (IV).—The reduction of sodium 5′-(3,2′-nicotyrine)-azo-*p*-benzenesulfonate was carried out according to the method of Smith, Opie, Wawzonek and Prichard.[13] Twenty grams (0.055 mole) of the azo compound was dissolved in 200 cc. of 20% hydrochloric acid and warmed on a steam-cone. To this was added a solution of 24 g. (0.127 mole) of stannous chloride in 30 cc. of concentrated hydrochloric acid. The mixture was stirred and within one minute became light tan in color. After three minutes it was poured into a cooled solution of 100 g. of sodium hydroxide in 100 cc. of water and this mixture was further cooled. The alkaline mixture was extracted with eight 50-cc. portions of ether and the extract dried with solid potassium hydroxide. The ether was then removed and the black oil remaining was distilled at 166–167° (3 mm.). The light yellow distillate (4.4 g.; 46.2%) crystallized in the receiver with the evolution of much heat of crystallization, m. p. 86–87°. It was a light yellow solid which darkened on exposure, and was soluble (with decomposition when heated) in water, alcohol, chloroform and ether. It was insoluble in benzene.

Anal. Calcd. for $C_{10}H_{11}N_3$: N, 24.28. Found: N, 24.30.

A golden-yellow picrate of 5′-nicotyrineamine was formed by the method of Shriner and Fuson,[14] with the exception that the solutions were not heated. It melted with decomposition at 173–174°.

Anal. Calcd. for $C_{22}H_{17}N_9O_{14}$: C, 41.84; H, 2.71; N, 19.97. Found: C, 42.21; H, 2.85; N, 19.89.

Azonicotyrine Dyes as Insect-Proofing Agents.—Four of the azo dyes prepared from 3,2′-nicotyrine were used for testing and the procedure with each was the same. Five-tenths of a gram of the dye was dissolved in 10 cc. of acetic acid and 25 cc. of warm water. To this solution was added 5 g. of sodium sulfate and 0.5 cc. of concentrated sulfuric acid and the combined solution was heated to 60°. A 1 × 3-inch strip of white wool cloth was then immersed in the dye solution and heated for one hour on a steam-bath. The cloth was then removed and rinsed with cold water.

The dyed strips were washed in boiling water and also in hot soapy water with no loss in color.

The wool strips, along with an undyed sample, were weighed and placed in separate cages, each containing ten larvae of the black beetle. After sixty-two days the samples were again weighed to determine the loss in weight

(13) Smith, Opie, Wawzonek and Prichard, *J. Org. Chem.*, **4**, 318 (1939).

(14) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., second edition, 1940, p. 149.

due to attack by the larvae, and the number of larvae still alive was also recorded, as shown in Table I.

TABLE I

ACTION OF BLACK CARPET BEETLE LARVAE ON DYED WOOL SAMPLES

Dye	Color of cloth	Mg. loss in wt. per 200 mg. cloth	% Larvae still alive
III, R = *p*-$C_6H_4SO_3Na$	Light yellow	21.2	80
III, R = *p*-$C_6H_4NO_2$	Brown	18.4	100
III, R = *p*-$C_6H_4CO_2H$	Tan	14.2	60
III, R = β-$C_{10}H_7$	Golden-yellow	12.2	40
Untreated sample	White	67.0	100

Summary

1. A convenient method for the preparation of 3,2′-nicotyrine from nicotine by means of palladium-on-asbestos catalyst is described.

2. 3,2′-Nicotyrine couples readily with diazonium salts to form azo dyes which show activity as insect-proofing agents.

3. Sodium 5′-(3,2′-nicotyrine)-azo-*p*-benzenesulfonate has been reduced to 5′-amino-3,2′-nicotyrine.

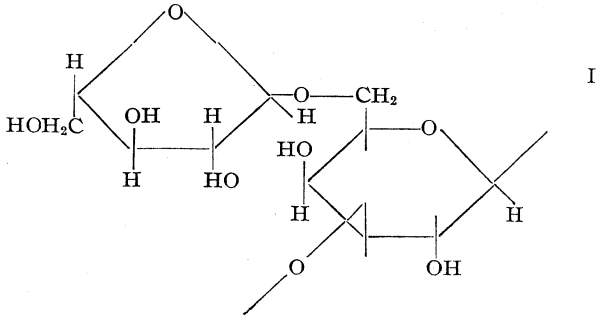
URBANA, ILLINOIS RECEIVED AUGUST 21, 1942

[CONTRIBUTION FROM THE WOOD CONVERSION LABORATORY OF THE UNIVERSITY OF IDAHO]

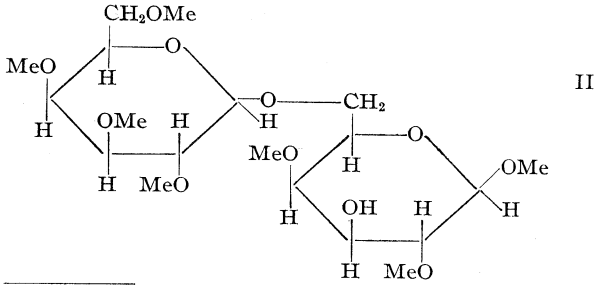
The Constitution of Arabo-galactan. IV. The Structure of the Repeating Unit

BY E. V. WHITE

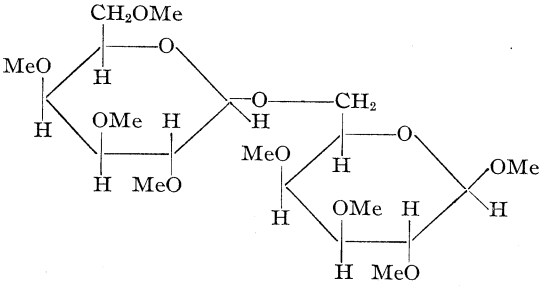
In the previous papers of this series[1a,b,c] it has been shown that the water-soluble gum extracted from western larch, *Larix occidentalis*, yields the glycosides of 2,4-dimethyl-*d*-galactose (3 parts), 2,3,4-trimethyl-*d*-galactose (1 part), 2,3,4,6-tetramethyl-*d*-galactose (2 parts), and 2,3,5-trimethyl-*l*-arabinose (1 part) upon methanolysis of the methyl ether derivative[1a]). The furanopentose unit is joined by oxygen linkage through the reducing carbon to the 6-position of an adjacent galactose residue as an arabofuranosido-galactan I[1c] and this, together with the separation of two crystalline disaccharides, heptamethyl-6-*d*-galactosidogalactose II and octamethyl-6-*d*-galactosidogalactose III from the partial methanolysis



I



II



III

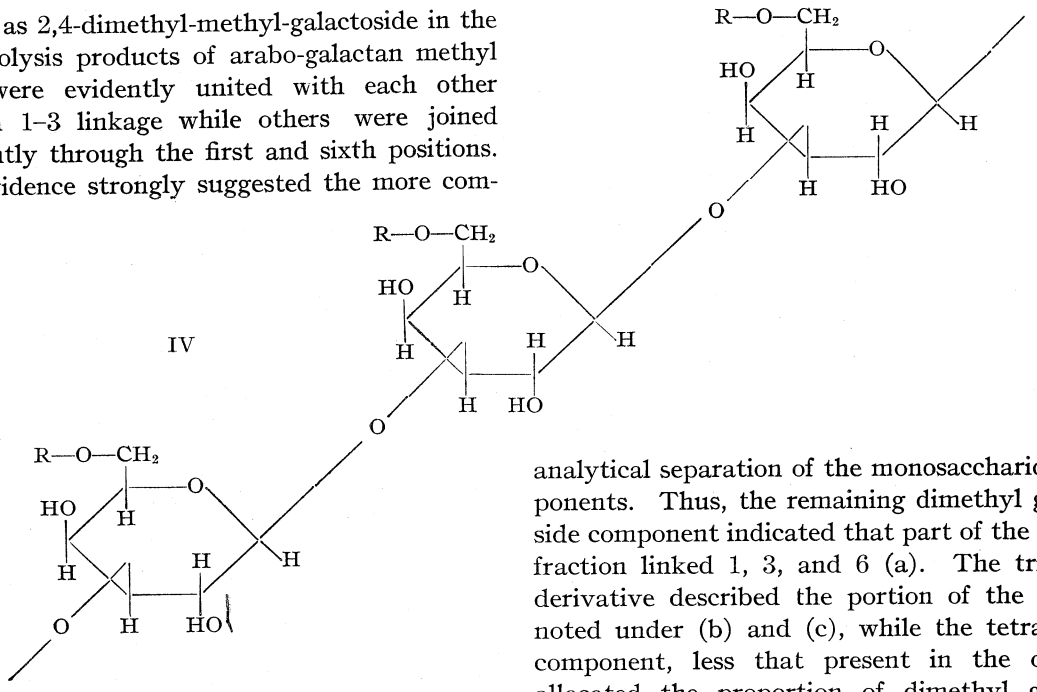
products of methylated arabogalactan[1b] establishes the position of linkage of the terminal units of the polysaccharide. It is also apparent, since two of the three 2,4-dimethyl-methyl-galactoside residues found in the complete methanolysis products are united through position 6 to terminal units in I and II, that these residues are joined by 1–3 linkage to dimethyl substituted units in the original methyl ether.

In the event that the third dimethylated residue is joined in a similar manner the repeating unit structure IV would be suggested wherein each unit of the 1–3 linked main chain galactose anhydrides is substituted in position 6 by the radicals R, respectively, *l*-arabinose, *d*-galactose, and 6-*d*-galactosidogalactose. However, if the above third residue is not part of the main chain but is located rather in a side-chain the radicals R become of polysaccharide character and the nature of the main chain linkage is open to question.

Preliminary experiments, reported in Part II, showed that some of the galactose residues oc-

(1) (a) White, THIS JOURNAL, **63**, 2871 (1941); (b) **64**, 302 (1942); (c) **64**, 1507 (1942).

curring as 2,4-dimethyl-methyl-galactoside in the methanolysis products of arabo-galactan methyl ether were evidently united with each other through 1–3 linkage while others were joined apparently through the first and sixth positions. This evidence strongly suggested the more com-



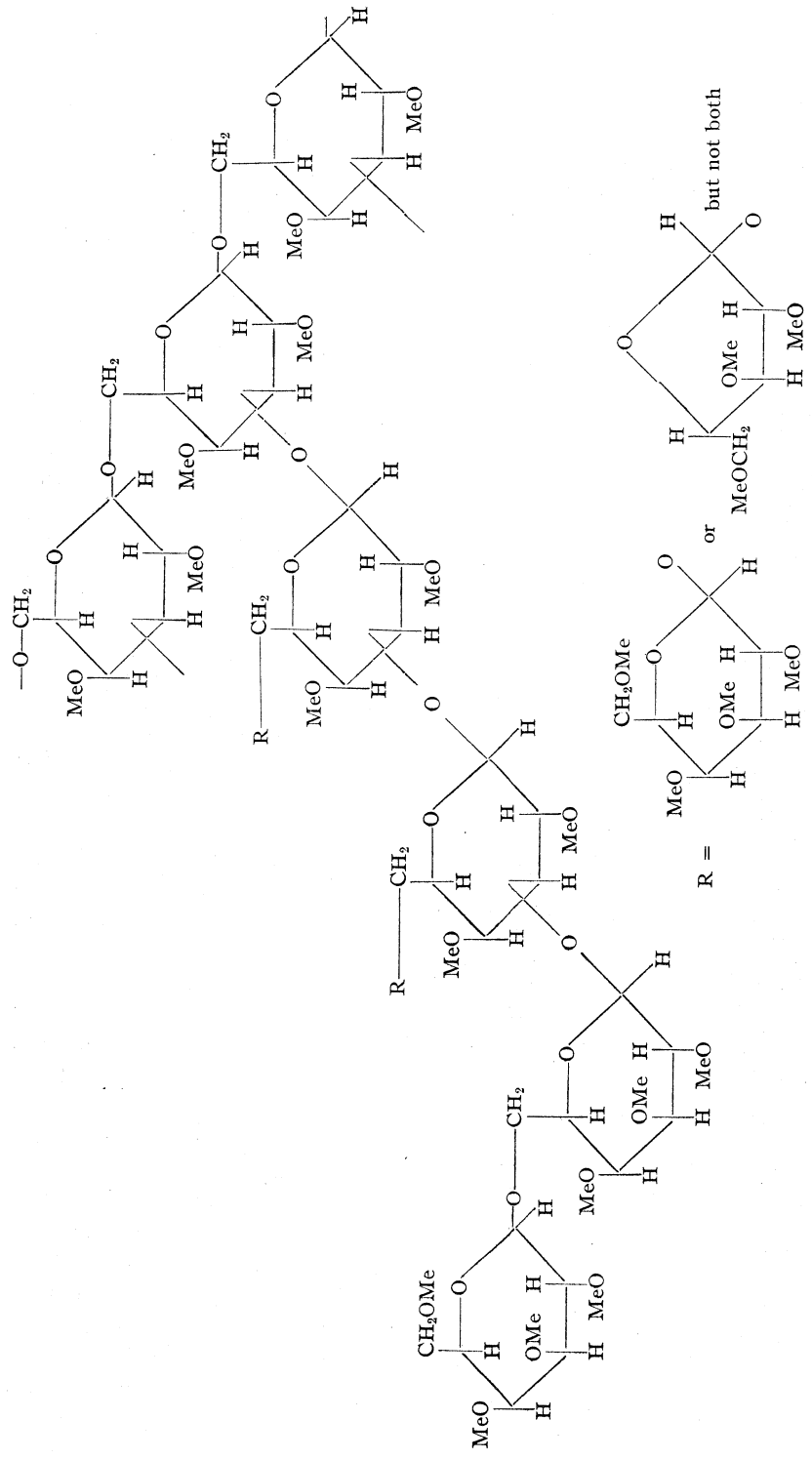
IV

plicated structure and an extension of the problem has substantiated previous indications.

The methyl ether derivative of arabo-galactan was prepared by the previously described method[1b] and subjected to partial methanolysis using anhydrous methanolic hydrogen chloride. The hydrolyzing solution contained a slightly higher concentration of hydrochloric acid than was used formerly, and a similar partition of the hydrolyzate was obtained as petroleum ether-soluble and -insoluble fractions. The latter product was separated into two components by extraction with ethyl ether. The ether-soluble portion represented approximately a methylated arabo-galactan freed from the arabinose component by hydrolysis. The ether-insoluble fraction was found to consist of dimethyl galactose anhydride residues together with a small portion of terminal tetramethyl galactose.

A theoretical analysis of the ether insoluble fraction, regardless of homogeneity, reveals that the dimethyl galactose residues can be united by oxygen linkage (a) at the 1, 3, and 6 positions, (b) at the 1 and 3 positions, a hydroxyl group occupying position 6, (c) at the 1 and 6 positions with free hydroxyl at position 3, and (d) at the 1 position only, both positions 3 and 6 being hydroxylated. A differentiation among this variety of linkage was furnished upon complete methylation of the fraction followed by methanolysis and analytical separation of the monosaccharide components. Thus, the remaining dimethyl galactoside component indicated that part of the original fraction linked 1, 3, and 6 (a). The trimethyl derivative described the portion of the original noted under (b) and (c), while the tetramethyl component, less that present in the original, allocated the proportion of dimethyl galactan hydroxylated at the 3 and 6 positions, respectively (d). A separation of the trimethyl galactoside fraction into its 2,4,6- and 2,3,4-trimethyl components furnished the ratio of 1–3 linked dimethyl galactose residues (b) to that of the 1–6 linked variety (c). On a molecular basis the decrease in dimethyl galactose anhydride resulting from etherification and, correspondingly, the sum of the tri- and corrected tetramethyl units described the over-all effect of methylation.

As a result of these experiments it was found that only a small proportion of the dimethyl galactose anhydride units present in the ether-insoluble products of partial methanolysis are united with each other through 1–3 oxygen linkage. The 1–6 linked variety, on the other hand, is relatively common and far in excess of that possibly due to the unknown character of linkage of the small tetramethylgalactose component of the fraction. Thus, since two of the three dimethyl galactose residues are known to be joined by 1–3 linkage to similar anhydrides, the conclusion is reached that the third dimethylated unit of the complete methanolysis products is joined in the original ether to other dimethyl substituted residues by 1–6 linkage. Apparently hydrolysis of arabo-galactan proceeds with removal of the labile furanopentose residue concomitant with galactan fission wherein the 1–3 linkage is somewhat more readily hydrolyzed than the 1–6 variety.



The rates of hydrolysis of the 3- and 6-galactosido-galactoses have not been evaluated for either the alpha- or beta-configurations, although the beta-methyl galactosides are known to hydrolyze more rapidly than the corresponding alpha-modifications.[2] During methanolysis of the methyl derivative there is progressively formed in the hydrolyzate 2,3,5-trimethylmethylarabinoside, octamethyl- and heptamethyl-6-*d*-galactosidogalactose and apparently a chain of 1–6 linked dimethyl galactose residues together with other intermediate products eventually leading to the previously described components of complete hydrolysis.[1a] The process is not in any sense stepwise in character but is controlled rather by the relative rates of hydrolysis of the variety of linkage involved.

The repeating unit of arabogalactan, which has been shown to comprise an association of six galactose residues with one unit of arabinose[3] must provide for the intermediate formation of the above products during methanolysis and must furnish upon complete reaction the glycosides of 2,4-dimethyl-*d*-galactose, 2,3,4-trimethyl-*d*-galactose, 2,3,4,6-tetramethyl-*d*-galactose and 2,3,5-trimethyl-*l*-arabinose in 3:1:2:1 molecular ratio. The difficulties involved in the investigation and correct representation of the complex polysaccharides are well known although in the present instance the evidence strongly supports a main chain structure of 1–6 linked galactose anhydride units as proposed by Hirst and co-workers.[4] Each unit of the primary chain is apparently substituted in position 3 by a secondary chain of three 1–3 linked galactose residues each in turn substituted at the 6 position by termi-

(2) Isbell and Frush, *J. Research Natl. Bur. Standards*, **24**, 125 (1940).

(3) Wise and Peterson, *Ind. Eng. Chem.*, **22**, 362 (1930).

(4) Hirst, Jones and Campbell, *Nature*, **147**, 25 (1941).

nal units. The latter are, respectively, *d*-galactose and the radicals R, *d*-galactose and *l*-arabinose, whose relative position is, of course, not known. The tentative structure proposed for the repeating unit is represented as the methyl ether derivative V and illustrates the highly branched structure of the polysaccharide. In all phases of the problem thus far investigated no evidence has been obtained relative to heterogeneity of the repeating unit. However, the number of such units comprising arabogalactan is not known and, in common with many natural polymers, the polysaccharide may prove to be polymolecular in this respect. On the basis of viscosity studies Husemann[5] limits the chain length between 180 and 280 monosaccharide units.

Experimental

Preparation of Methylated Arabo-galactan.—Larch sawdust was extracted with the minimum quantity of water and the extract purified, after filtering through norite and Super-Cel, by fractional precipitation using ethyl alcohol.[1a] The precipitate was then dissolved in water, evaporated at 50° under reduced pressure to remove residual alcohol, and methylated at 25° under nitrogen using dimethyl sulfate and 30% sodium hydroxide. After complete methylation the derivative was separated from the inorganic reaction products with chloroform. The chloroform extract, dried over magnesium sulfate and filtered, was evaporated to a sirup and extracted with petroleum ether. The residue, taken up in ethyl ether, filtered and evaporated to a sirup, was finally obtained as a light-yellow friable, glassy solid upon removal of residual solvent under reduced pressure; (Found: MeO, 44.4. Calcd. for $(C_6H_{10}O_5)_6(C_5H_8O_4)$-$(CH_2)_{20}$: MeO, 44.8). This procedure has been refined so that a relatively large quantity of uniform product can be prepared without difficulty.

Partial Methanolysis of Arabo-galactan Methyl Ether.—Ninety grams of methylated arabo-galactan was dissolved in anhydrous methyl alcohol and methanolic hydrogen chloride added together with fresh alcohol such that the total volume was 900 cc., 0.140 *N* in hydrochloric acid. The reacting solution was heated under reflux on a water-bath for twelve hours and cooled to room temperature. Excess acidity (0.076 *N*) was neutralized with silver carbonate and the solution treated with norite, filtered and evaporated to a sirup; yield, 93 g.

Separation and Analysis of the Products of Partial Methanolysis.—The sirup (93 g.) obtained upon partial methanolysis of methylated arabo-galactan was extracted thoroughly with hot ligroin. After removal of solvent by evaporation, the extract (26.0 g.) was distilled fractionally under high vacuum (0.2 mm.) yielding the portions given in Table I.

The products of Table I have been characterized previously and were not investigated further.

The residue remaining after removal of the ligroin-soluble components was extracted with ethyl ether. Upon removal of solvent the extract gave a sirup (54.2 g.). A sample of the latter in chloroform solution was precipitated into petroleum ether, dried, and analyzed; (Found: MeO, 42.0. Calcd. for methylated arabo-galactan arabinose-free MeO, 42.6). A second sample (17.0 g.) was subjected to complete methanolysis with methanolic hydrogen chloride. The product was isolated in the usual manner, distilled fractionally, and analyzed for monosaccharide components. The results are given in Table II.

TABLE I

FRACTIONATION OF LIGROIN-SOLUBLE EXTRACT

Fraction	Temp., °C.	Yield, g.	MeO, %
1	70– 90	16.15	60.5
2	90–180	3.15	51.1
3	180–200	3.20	53.1
4	200–250	1.00	48.9
Residue	...	2.10	44.4

TABLE II

ANALYSIS OF METHANOLYSIS PRODUCTS FROM ETHER-SOLUBLE EXTRACT

Fraction	Temp., °C.	Yield, g.	MeO	"Tetra"	"Tri"	"Di"
1	80– 90	5.30	61.2	5.30		
2	90–105	1.15	54.7	0.27	0.88	
3	105–120	4.70	47.8		2.62	2.08
4	120–140	7.35	41.8			7.35
Total grams				5.57	3.50	9.43
Molar ratio found				1.70	1.12	3.20
Molar ratio calcd.				2.00	1.00	3.00

The ether-soluble component of the methanolysis sirup thus appears to be a methylated arabo-galactan freed from the arabinose component by hydrolysis and having simultaneously undergone a small amount of terminal galactose fission. The fraction is obviously non-homogeneous.

The final residue remaining after extraction of the methanolysis sirup with ligroin and ethyl ether was taken up in chloroform, filtered from a small amount of inorganic material, and washed thoroughly by dropping the solution into an excess of rapidly stirred ether. The residue, taken up in acetone, was obtained as a light-yellow, friable, glassy solid upon evaporation of excess solvent under reduced pressure; yield, 13 g. (Found: MeO, 34.7). A sample (3.2 g.) subjected to complete methanolysis in the usual manner gave a sirup; yield, 3.64 g. (Found: MeO, 45.0). Fractional distillation of the sirup gave only tetramethyl-methyl-galactoside, 13.9 molar per cent., and 2,4-dimethyl-methyl-galactoside, 86.1 molar per cent.

Methylation and Alcoholysis of the Ether-Insoluble Residue.—The remainder of the ether-insoluble residue (9.0 g.) dissolved in 25 cc. of acetone was methylated at 30° under nitrogen using 50 cc. of methyl sulfate and 150 cc. of 30% sodium hydroxide for each methylation. The reagents were added dropwise and simultaneously over a period of three hours and the methylation was complete after three such treatments. The product was separated from the reaction mixture with chloroform, purified and isolated as a friable solid by the procedure described for the methylation of arabo-galactan; yield, 8.0 g. (Found: MeO, 44.8).

The methylated product was subjected to methanolysis in a sealed tube using 2% methanolic hydrogen chloride at

(5) Husemann, *J. prakt. Chem.*, **155**, 13 (1940).

105° for five hours. The reaction products were separated in the usual manner and distilled fractionally under high vacuum (0.2 mm.). The results are given in Table III.

TABLE III

ANALYSIS OF METHANOLYSIS PRODUCTS FROM THE ETHER-INSOLUBLE RESIDUE AFTER METHYLATION

Fraction	Temp., °C.	Yield, g.	MeO	"Tetra"	"Tri"	"Di"
1	80- 90	3.50	61.5	3.50		
2	90–105	1.25	52.9	0.05	1.20	
3	105–115	1.60	46.5		0.94	0.56
4	115–130	1.85	41.9			1.85
Total grams				3.55	2.14	2.41
Molar per cent.				41.5	26.5	31.8

Analysis of Trimethyl-methyl-galactoside Sirup and Identification of the Components.—The combined intermediate fractions (2.85 g.) from the above distillation were dissolved in 25 cc. of *N* sulfuric acid and heated on a boiling water-bath for twelve hours. The hydrolysis product was separated in the usual manner, extracted with chloroform, and fractionally distilled under high vacuum. The trimethyl-galactose portion, 1.60 g. (Found: MeO, 41.8), was dissolved in 10 cc. of pyridine and treated with 2.1 g. of trityl chloride. After two days at room temperature a small quantity of water was added to dissolve pyridine hydrochloride and the reaction poured into rapidly stirred ice water. Following two days in the ice box and occasional stirring, the flocculent precipitate was removed by filtration, washed with ice water, and dissolved in acetone. After drying and removal of solvent, a sirup was obtained from which triphenylcarbinol crystallized slowly in the presence of acetone. The non-crystallizable residue, Fraction I, (2.09 g.) comprising triphenylcarbinol and the tritylated galactose derivative, upon treatment with aniline (0.75 g.) in the usual manner gave the anilide of 2,3,4-trimethyl-6-trityl galactose after removal of solvent; m. p. 152°, recrystallized from ethyl alcohol. By calculation on the basis of yield and methoxyl content the 2,3,4-trimethyl-galactose equivalent of Fraction I was determined.

The filtrate from the tritylation reaction was neutralized with silver carbonate and filtered. Silver ion was removed as sulfide and the filtered solution, after treatment with norite, evaporated to dryness. The sirup was taken up in chloroform, filtered, and excess solvent evaporated yielding Fraction II (0.45 g.). Upon treatment with aniline in the usual manner Fraction II gave the crystalline anilide of 2,4,6-trimethyl-galactose; m. p. 178°, recrystallized from ether–ethanol.

The results of the separation are given in Table IV.

TABLE IV

ANALYSIS OF TRIMETHYL-METHYL-GALACTOSIDE SIRUP

Fraction	Yield	MeO	2,3,4-Trimethyl-galactose, g.	2,4,6-Trimethyl-galactose, g.
I	2.90	15.6	1.08	
II	0.45	41.8		0.45
Per cent.			70.6	29.4

Summary

1. Partial hydrolysis of arabo-galactan methyl ether yields a variety of fission fragments including 2,3,5-trimethyl-methyl-*l*-arabinoside, octamethyl- and heptamethyl-6-*d*-galactosidogalactose, and a residue comprising mainly 2,4-dimethyl galactose anhydride units.

2. The individual dimethylated residues are shown to be united with each other through the first position, through the first and third positions, through the first and sixth positions, and through the first, third, and sixth positions, respectively.

3. The proportion of 2,4-dimethyl galactose anhydride linked through the first and sixth positions is considerably in excess of that joined at the first and third positions.

4. A tentative structure is presented to represent the repeating unit of arabo-galactan.

MOSCOW, IDAHO RECEIVED AUGUST 3, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Attempted Asymmetric Syntheses Involving the Grignard Reagent in Optically Active Solvents

BY D. S. TARBELL AND MARK C. PAULSON

In a recent article, it was reported[1] that the Grignard reaction between methylmagnesium iodide and benzaldehyde in dimethylbornylamine as solvent gave optically active methylphenylcarbinol. The same result was obtained using phenylmagnesium bromide and acetaldehyde. This reaction interested us as an example of a new type of asymmetric synthesis,[2] and it suggested the possibility of obtaining optically active secondary and tertiary alcohols by a synthetic method. We have been unable, however, to obtain optically active carbinols by this reaction under a variety of conditions, using dimethylbornylamine, *d*-methyl *s*-butyl ether, or methyl menthyl ether as solvent for the Grignard reagent.

Attempts to duplicate the preparation of methylmagnesium iodide using dimethylbornylamine as a solvent, as reported by Betti and Lucchi,[1] failed. In all cases the quaternary am-

(1) Betti and Lucchi, *Boll. sci. facoltà chim. ind. Bologna*, No. 1–2, 2 (1940) (*C. A.*, **34**, 2354 (1940)).

(2) *Cf.* Ritchie, "Asymmetric Synthesis and Asymmetric Induction," Oxford University Press, London, 1933.

monium salt precipitated almost immediately and the magnesium remained unattacked even after days of standing in the reaction mixture.[3] When methylmagnesium iodide was prepared in ethyl ether, the displaceable ether removed by heating with benzene, and dimethylbornylamine and benzaldehyde added, a poor yield of inactive methylphenylcarbinol was produced. A similar run, (one-tenth mole) in which benzene was omitted and the ether was removed by a water pump, yielded 4 g. of inactive carbinol and 1.4 g. of a heavy straw-colored oil, b. p. 200–210° (20 mm.), m. p. 60–62° after solidification. The oil gave an observed reading of +0.75° at 25° in a polarimeter (0.44 g. diluted to 10 cc. with ethyl alcohol, 1-dm. tube). Later experiments revealed oxidation and reduction occurring in Grignard runs in the absence of ether and led to the identification of this substance as benzalacetophenone, which was doubtless formed by condensation of acetophenone (from the oxidation of methylphenylcarbinol) and benzaldehyde. The rotation of the benzalacetophenone is undoubtedly due to the by-product described in the following paragraph.

In some runs, the methylphenylcarbinol obtained showed a slight positive rotation. That this was due to an optically active by-product from the dimethylbornylamine was shown by blank runs carried out as before, except that the benzaldehyde was omitted; a neutral substance, an amorphous, soft, white solid with a marked terpene-like odor, m. p. *ca.* 110–120°, was isolated. The small quantity obtained from a one-tenth molar blank run produced a reading of +2.39° (diluted to 10 cc. with ether, 1-dm. tube). The amount isolated was so small that identification was not attempted.

Phenylmagnesium bromide was successfully prepared by heating a flask containing magnesium turnings, dimethylbornylamine and bromobenzene in an oil-bath at 130–140° for four hours, as described by Betti and Lucchi.[1] This was treated with paraldehyde and heated to 110–120° for one hour; fair yields of methylphenylcarbinol (45–60%) were obtained. Optical activity was not consistently produced; in some runs a positive rotation (as high as +0.26°, 4 g. dil. to 10 cc. with 50–50 alcohol–benzene, 1-dm. tube), in others, no rotation was observed. Since careful purification of the product appeared to eliminate the activity, it is believed that the by-product above caused the rotation.

A much more straight-forward reaction was obtained when *d*-methyl *s*-butyl ether (which does not seem to have been reported in the active form previously) was used as the solvent for the Grignard reaction. Completely inactive methylphenylcarbinol was obtained in 60–68% yield, using either methylmagnesium iodide or phenylmagnesium bromide with the proper aldehyde. The product in each case was checked by preparation of the 3,5-dinitrobenzoate, m. p. 90°, and mixed melting point of this derivative with that of an authentic sample.

It seemed desirable to try another optically active ether with a higher rotation than the *s*-butyl ether, and methyl menthyl ether, $[\alpha]^{25}D$ −95.6°, was prepared and studied. In this connection, it is interesting to note that Wegler and Ruber[4] found that in the preferential esterification of *d,l*-methylphenylcarbinol by acetic anhydride in the presence of optically active bases, the activity of the ester mixture varied greatly with the base used.

Methyl menthyl ether proved to be an unsuitable solvent for the Grignard reaction. When magnesium was treated with methyl or ethyl iodide in this ether, the magnesium quickly became coated with an insoluble white material which prevented further reaction. The coating formed by ethyl iodide gave a positive Gilman Grignard color test with Michler ketone. The Grignard reagents were better prepared in diethyl ether, which was then removed *in vacuo* in a nitrogen atmosphere with a capillary to prevent bumping. When most of the ether had been removed, methyl menthyl ether was added (75 to 100 cc. for tenth-molar runs) and the vacuum (water pump) again applied for several hours. Usually after the first half-hour, the entire contents of the flask solidified to a white solid. This was probably the Grignard etherate involving the optically active ether. Methylmagnesium iodide prepared in this manner reacted with *n*-butyraldehyde to produce, instead of the expected *s*-amyl alcohol, *n*-butyl alcohol and methyl *n*-propyl ketone. The alcohol was identified by preparation of its 3,5-dinitrobenzoate and a mixed melting point with the corresponding derivative of an authentic sample; the ketone in like fashion through its

(3) This agrees with the observations of Stadnikoff and Weizmann, *J. prakt. Chem.*, **112**, 177 (1926), who attempted to prepare Grignard reagents in dimethylaniline solution.

(4) Wegler and Ruber, *Ber.*, **68**, 1055 (1935).

2,4-dinitrophenylhydrazone. The *n*-butyraldehyde is evidently reduced by the magnesium halide alkoxide of *s*-amyl alcohol which is formed by primary addition of the Grignard.

The failure to get an asymmetric synthesis in the reaction with *d*-methyl *s*-butyl ether, at least, is rather surprising. A possible explanation is that the organomagnesium compound is coordinated with two molecules of the ether in such a way that the complex has a plane of symmetry.[5]

Preparation of Materials

Bornylamine (a mixture of the diastereoisomers, bornylamine and neobornylamine, hereafter referred to as the former) was prepared from *d*-camphor in 83% yield (crude) using Ingersoll's modification[6] of the Leuckart method. The crude product was used in the preparation of dimethylbornylamine, since the latter product is much easier to purify.

Dimethylbornylamine was prepared by adding dimethyl sulfate to a vigorously stirred mixture of the crude bornylamine, aqueous sodium hydroxide and benzene. A Schotten-Baumann reaction employing benzoyl chloride effectively separated the mixture of secondary and tertiary amines; the organic material was isolated in ether and the tertiary amine extracted from the benzamide by dilute hydrochloric acid; yield 44.5% (purified amine); b. p. 92° (13 mm.). *Rotation.* α −1.01° (0.525 g. dil. to 25 cc. with dry benzene, 1-dm. tube), $[\alpha]^{24}D$ −48.1°. No gas was evolved when this product was treated with methylmagnesium iodide.

Hydrolysis of the N-methyl-N-bornylbenzamide proved too difficult to make the recovery of the secondary amine practicable.

Optically Active Methyl *s*-Butyl Ether.—*s*-Butyl alcohol was partially resolved by the method of Pickard and Kenyon,[7] using the modification of Sprung and Wallis and of Viditz.[8] The ether[9] was prepared by the Williamson synthesis, treating the alkoxide (prepared from 42 g. of *s*-butyl alcohol and 8 g. of sodium) with 52 g. of methyl iodide; yield, 83%, b. p. 59–60°, alcohol of rotation α_D +7.5° (homogeneous, 1-dm. tube) produced an ether of α_D +12.19° (homogeneous, 1-dm. tube).

Methyl Menthyl Ether.—Sodium (24 g.) was added in approximately 1-g. portions to 172 g. of *l*-menthol dissolved in 175 cc. of dry toluene. The mixture was heated on a steam-bath for twenty-seven hours. At the end of this time, 4.1 g. of unreacted sodium was removed from the flask. The solution was cooled and 128 g. of methyl iodide was added dropwise. After the initial reaction had subsided the flask was warmed in an oil-bath at 75° for four hours. Most of the toluene was then removed under diminished pressure; the residue of sodium iodide was filtered off and was washed with ether to remove any reaction product. The product was fractionated twice under diminished pressure. Thirty-seven grams of menthol was recovered from the first fractionation. The second fractionation was carried out in the presence of a few small pieces of sodium to aid in removal of traces of menthol; yield, 109.5 g. (74%); b. p. 83° (12 mm.); b. p. 197° (uncor. 736.5 mm.); $n^{23}D$ 1.4427; $[\alpha]^{25}D$ −95.6°; d^{25}_{25} 0.8584; homogeneous rotation, −82.06°, 1-dm. tube. *Anal.*[10] Calcd. for $C_{11}H_{22}O$: C, 77.56; H, 13.03. Found: C, 77.56; H, 12.91.

Summary

1. Methylphenylcarbinol prepared by the Grignard reaction in optically active methyl *s*-butyl ether is optically inactive. The carbinol prepared in dimethylbornylamine is also inactive, although a neutral optically active impurity is formed in the reaction.

2. Methyl menthyl ether is not a suitable solvent for the Grignard reaction; *n*-butyl alcohol and methyl *n*-propyl ketone were obtained when methylmagnesium iodide was treated with *n*-butyraldehyde.

ROCHESTER, NEW YORK RECEIVED AUGUST 10, 1942

(5) *Cf.* Whitmore and George, abstracts of papers presented at Atlantic City, September, 1941.

(6) Ingersoll, Browns, Beauchamp and Jennings, THIS JOURNAL, **58**, 1808 (1936); Leuckart and Bach, *Ber.*, **20**, 104 (1887).

(7) Pickard and Kenyon, *J. Chem. Soc.*, **99**, 45 (1911); **103**, 1923 (1913).

(8) Sprung and Wallis, THIS JOURNAL, **56**, 1715 (1934); Viditz, *Biochem. Z.*, **259**, 294 (1933).

(9) This compound was prepared in the inactive form by Bennett, *J. Chem. Soc.*, 1930 (1928).

(10) Analysis by R. W. King. Tschugaeff, *J. Russ. Phys.-Chem. Ges.*, **34**, 606 (1902); *Chem. Zentr.*, **73**, II, 1238 (1902), reported d^{20}_4 0.8607 and $[\alpha]D$ −95.67°, but gave no other constants.

[CONTRIBUTION NO. 273 FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

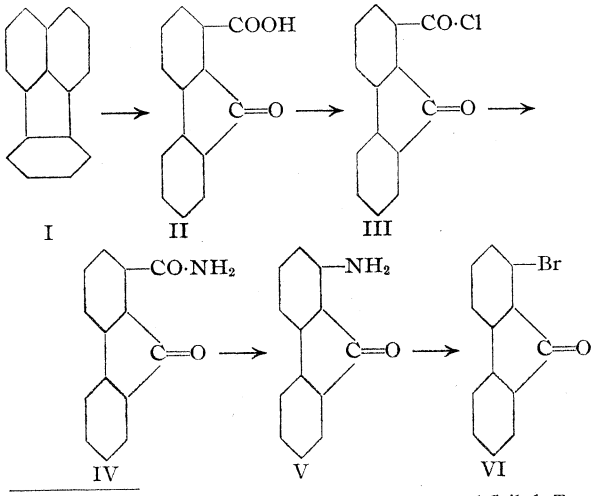
Fluorenones and Diphenic Acids. IX.[1] Establishment of Authentic 1-Bromo- and 4-Bromofluorenones

BY ERNEST H. HUNTRESS, KARL PFISTER, 3RD,[2] AND K. H. T. PFISTER

Of the four isomeric monobromofluorenones predicted by the structure theory, the 2-bromofluorenone[3] and 3-bromofluorenone[3b,4] have been well established. Data regarding the other two isomers, however, are inadequate for 1-bromofluorenone and contradictory for the 4-bromofluorenone. The present paper confirms and expands our knowledge of the first, and resolves the prior contradictions for the second.

Previous to this work, 1-bromofluorenone had been reported only once.[4a] It had been obtained by dehydrobromination of 2,6-dibromobenzophenone under conditions so drastic (heating at its boiling point for several days) as to leave some doubt as to the ultimate location of the residual bromine atom, particularly in view of previously unsuccessful attempts in this Laboratory to repeat this method of preparation and of the alleged existence of two 4-bromofluorenones discussed later in this paper.

We have, therefore, prepared authentic 1-bromofluorenone by an independent sequence of conventional reactions not involving drastic conditions. This sequence is diagrammed as follows

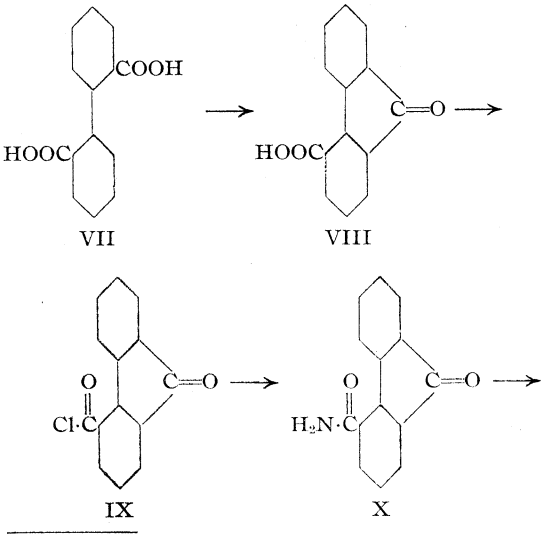


The properties of the resultant 1-bromofluorenone are in excellent agreement with those described for the original method[4a] and this result provides for the first time not only convincing evidence of the stability of the bromoketone toward heat but also a much improved method of preparation.

The structure of our product is supported not only by analysis, but also by conversion of its precursor (1-aminofluorenone) to 1-cyanofluorenone and thence to fluorenone-1-carboxylic acid whose structure has already been definitely established.[5]

Two distinctly different compounds both claimed to be 4-bromofluorenones are recorded. The higher melting compound was reported[4b,c] as the product of three independent processes. The lower melting substance was independently obtained[6] by a fourth method. Despite the marked difference of their product from that originally described by Miller and Bachman[4b,c] these authors made no reference in their paper to any of the preceding work.

We have prepared 4-bromofluorenone by a different series of reactions as follows



(1) For Article VIII of this series see Huntress and Seikel, THIS JOURNAL, **61**, 1358–1364 (1939).

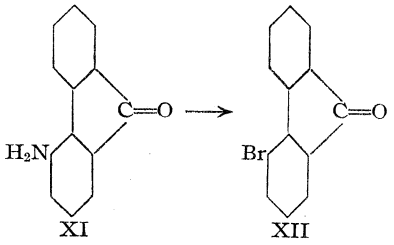
(2) This paper is in part constructed from a thesis submitted in May, 1940, by K. Pfister to the Faculty of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Bachelor of Science.

(3) (a) Courtot, *Ann. chim.*, [10] **14**, 59–62 (1930); (b) Heilbron, Hey and Wilkinson, *J. Chem. Soc.*, 113 (1938).

(4) (a) Montagne and van Charante, *Rec. trav. chim.*, **32**, 164–173 (1913); (b) Miller and G. B. Bachman, THIS JOURNAL, **57**, 2443–2446 (1935); (c) **57**, 2447–2450 (1935).

(5) (a) Mayer and Freitag, *Ber.*, **54**, 347 (1921); (b) Sieglitz, *ibid.*, **57**, 316 (1924); (c) von Braun and Anton, *ibid.*, **62**, 145 (1929).

(6) France, Heilbron and Hey, *J. Chem. Soc.*, 1364 (1938).



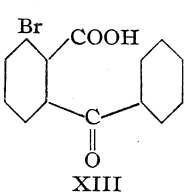
XI XII

By this sequence the position of the bromine in the ultimate ketone is unequivocally established since there can be no ambiguity regarding the structure of fluorenone-4-carboxylic acid (VIII). The melting point of our 4-bromofluorenone so prepared proved to be in accord with that observed by France, Heilbron and Hey[6] and confirms the identity of their product. Since the numerical magnitude of this melting point is not very different from that of 1-bromofluorenone we have also shown that the melting point of a mixture of authentic 1-bromofluorenone with authentic 4-bromofluorenone is substantially depressed.

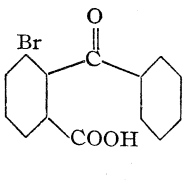
The results described above left seriously in doubt the identity of the bromofluorenone originally reported by Miller and Bachman as the 4-bromo isomer. We have, therefore, attempted to repeat their three syntheses. We were unable, however, to duplicate their results by the method starting with methyl *o*-iodobenzoate and made several unsuccessful efforts to employ their oxidation[4c] of supposed 4-bromofluorene from the mercuration of fluorene. Extensive experimentation with their method from 3-bromophthalic anhydride, however, led to the discovery that it yielded to us 1-bromofluorenone identical with our authentic material described above and definitely depressing the melting point of the true 4-bromofluorenone.

The error into which the American workers fell in this last case is attributable to their acceptance without further corroboration of the structure assigned by Stephens[7] to an acid resulting from the interaction of 3-bromophthalic anhydride with benzene in the presence of aluminum chloride.

From its method of preparation Stephens' acid could have had only one or the other of two structures (XIII or XIV).



XIII

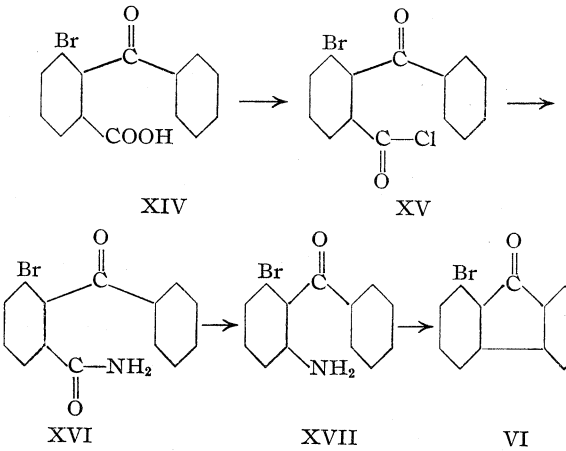


XIV

(7) Stephens, THIS JOURNAL, **43**, 1950–1956 (1921).

Upon what now seems like extremely meager evidence Stephens assigned to his product structure XIII. This evidence consisted of the observation that when his product was subjected to fusion with potassium hydroxide benzoic acid and *o*-bromobenzoic acid were isolated. Stephens appears not to have considered the possibility that both of these products might equally well have resulted from structure XIV by loss of carbon dioxide and fission of the resultant *o*-bromobenzophenone in both possible senses.

We have prepared Stephens' acid and carried it through the Miller and Bachman series of reactions to the resultant bromofluorenone. Contrary



XIV XV XVI XVII VI

to the results of Miller and Bachman this turned out to be 1-bromofluorenone identical with the authentic product prepared by us by a series of reactions starting with fluoranthene. This work thus serves not only to correct the errors of Miller and Bachman, but also establishes the structure of Stephens' acid and represents a third and independent preparation of 1-bromofluorenone.

Experimental Work

The melting points reported below were taken with a 360° rod form melting point thermometer by the Berl-Kullmann copper block method and are uncorrected.

Fluorenone-1-carboxylic Acid (II).—Pure fluoranthene (m. p. 109–110°) was oxidized to fluorenone-1-carboxylic acid substantially according to the directions of Fieser and Seligman[8]; yield 55%, m. p. 188.5–190.5°. Repeated recrystallization from dilute alcohol gave long orange-red needles, m. p. 191–192°.

Fluorenone-1-carboxylic Acid Amide (IV).—The acid was converted to the acid chloride by brief boiling with twice its weight of thionyl chloride. After cooling the clear light-red solution the precipitated yellow solid was filtered off and washed with petroleum ether (b. p. 35–60°). The finely powdered acid chloride was then allowed to

(8) Fieser and Seligman, *ibid.*, **57**, 2175 (1935).

stand overnight with excess concentrated ammonium hydroxide, the resultant amide filtered off, washed with water and dried; yield 95%, m. p. 222.5–225°. Recrystallization of the acid chloride from petrolum ether prior to ammonia treatment gave a crude amide of m. p. 224.5–227°. Recrystallization of the amide from 95% alcohol yielded long deep yellow needles, m. p. 226.5–227°.

Fluorenoneanil-1-carboxylic Acid Anilide.—This product was obtained from fluorenone-1-carboxylic acid chloride by warming for a few minutes with aniline. Evaporation of excess amine left a brown residue which upon recrystallization from 95% alcohol gave long yellow needles, m. p. 184.7–185°.

Anal. Calcd. for the anil-anilide ($C_{26}H_{18}ON_2$): N, 7.50. Found: N, 7.62. (Calcd. for fluorenone-1-carboxylic acid anilide ($C_{20}H_{13}O_2N$): N, 4.68.)

1-Aminofluorenone (V).—To fluorenone-1-carboxylic acid amide (2.0 g. = 0.009 mole) finely powdered in water (3 ml.) was added in one batch the hypobromite solution prepared by adding bromine (1.4 g. = 0.009 mole) to water (15 ml.) and then adding dropwise an ice-cold solution of potassium hydroxide (3.0 g. = 0.054 mole) in water (25 ml.). The resultant mixture was warmed gently for a few minutes until a homogeneous brown gel had formed, then allowed to stand for two hours. Finally the mixture was heated for half an hour at 100°, a solution of potassium hydroxide (4.5 g. = 0.08 mole) in water (4.5 ml.) added and heating at 100° continued for forty-five more minutes. After cooling, the resultant yellow-brown solid was filtered off and extracted four successive times with 25-ml. portions of boiling 6 *N* hydrochloric acid, refluxing fifteen minutes with each portion before filtration. The amine hydrochloride which separated from these extracts on cooling was collected, washed with 6 *N* hydrochloric acid and converted to 1-aminofluorenone with concentrated ammonium hydroxide. The resultant 1-aminofluorenone, m. p. 114.5–116.5°, was obtained in 56% yield. After vacuum sublimation (140–150° at 2 mm. bath temperature) and several recrystallizations from dilute alcohol the aminoketone formed beautiful long yellow needles, m. p. 118–118.5° (only previously recorded[9] m. p. 110°).

1-Acetylaminofluorenone.—1-Aminofluorenone boiled for one minute with acetic anhydride and a trace of concd. sulfuric acid gave on cooling a solid, which after recrystallization from 95% alcohol and from ligroin (b. p. 90–100°) separated as yellow needles (75% yield) m. p. 138–138.3°.

Anal. Calcd. for $C_{15}H_{11}O_2N$: N, 5.90. Found: N, 6.13, 6.28.

1-Benzoylaminofluorenone.—1-Aminofluorenone dissolved in pyridine and shaken with equivalent benzoyl chloride, then diluted with water gave a yellow precipitate of benzoyl derivative. After washing with water, dilute aqueous sodium carbonate and recrystallization from 95% alcohol and from ligroin, it was obtained (75% yield) as long silky yellow needles, m. p. 149–149.8°.

Anal. Calcd. for $C_{20}H_{13}O_2N$: N, 4.68. Found: N, 4.75.

1-Chlorofluorenone.—To 1-aminofluorenone (0.976 g. = 0.005 mole) was added concentrated hydrochloric acid (2.92 ml. = 0.035 mole) and from the resultant solution the free base was reprecipitated in finely divided form by addition of water (25 ml.) and cooling to 10–15°. The resulting suspension was diazotized by addition of sodium nitrite (0.35 g. = 0.005 mole) in water (10 ml.), stirring for ten minutes. After removing excess nitrous acid by addition of urea, the filtered solution was added in a fine stream to a boiling solution of cuprous chloride (0.6 g. = 0.006 mole) in 6 *N* hydrochloric acid (30 ml.). Five minutes at 100° served to coagulate the yellow precipitate which was filtered off after standing for several hours. This crude product was washed with 1 *N* sodium hydroxide, then extracted with hot glacial acetic acid (15 ml.) and the crude 1-chlorofluorenone precipitated from the filtrate by addition of water. Distillation under reduced pressure (2 mm. at 175–185° bath temperature) gave 40% yield, m. p. 134.0–135.5°; two recrystallizations from 95% alcohol raised the melting point of the yellow needles to 137–137.8°.

Anal. Calcd. for $C_{13}H_7OCl$: Cl, 16.52; Found: Cl, 16.5, 16.3.

1-Bromofluorenone (from 1-Aminofluorenone).—To 1-aminofluorenone (0.976 g. = 0.005 mole) was added 40% hydrobromic acid (5.13 ml. = 0.035 mole) and the diazotization carried through as for the preceding case. The cold diazonium solution was added in a thin stream to a gently boiling solution of cuprous bromide (0.86 g. = 0.006 mole) in 40% hydrobromic acid (50 ml.). After ten minutes digestion at 100° the reaction product was cooled, the solid filtered off and washed with 1 *N* sodium hydroxide, extracted with hot alcohol, and reprecipitated by dilution. After being dried and vacuum distilled (2 mm. at 170–180° bath temperature) the yield of 1-bromofluorenone was 42%. Two recrystallizations from 95% alcohol gave stubby yellow needles, m. p. 134–134.3°. (The only other recorded value is 135°.[4a])

Anal. Calcd. for $C_{13}H_7OBr$: C, 60.26; H, 2.73; Br, 30.84. Found: C, 60.1, 60.2; H, 2.85, 2.92; Br, 29.8, 30.0.

1-Iodofluorenone.—1-Aminofluorenone hydrochloride (1.16 g. = 0.005 mole) in a mixture of concentrated hydrochloric acid (2.5 ml. = 0.030 mole) with water (25 ml.) was diazotized as above. Particular care that every trace of excess nitrous acid should be removed by the urea treatment was found essential. To the cold filtered diazonium solution was added potassium iodide (1.0 g. = 0.006 mole) in water (15 ml.) and after heating at 100° for five minutes, the resulting suspension stood several hours. After the usual alkali washing and vacuum distillation (2 mm. at 180–190° bath temperature) the 1-iodofluorenone was obtained (48% yield) as yellow needles, m. p. 144–145°. Two recrystallizations from 95% alcohol raised the value to 146.5–147°.

Anal. Calcd. for $C_{13}H_7OI$: I, 41.46. Found: I, 41.4, 41.2.

1-Cyanofluorenone.—The diazotized solution prepared from 1-aminofluorenone exactly as for 1-chlorofluorenone (above) was added in a fine stream to the hot solution from copper sulfate crystals (1.25 g. = 0.005 mole) and potassium cyanide (1.40 g. = 0.020 mole) in water (15 ml.). After standing several hours, the solid was filtered off, washed with alkali, dried and distilled (2 mm. at bath temperature of 220°). After recrystallization from alco-

(9) Goldschmiedt, *Monatsh.*, **23**, 893–895 (1902).

hol, the resulting 1-cyanofluorenone (14% yield) melted at 174–175.5°.

This nitrile was also obtained from fluorenone-1-carboxylic acid amide (0.25 g. = 0.0011 mole) by warming with phosphorus pentachloride (0.23 g. = 0.0011 mole). After the initial rapid reaction the mixture was heated at 200° for one and one-half hours (48% yield). One recrystallization from dilute acetic acid gave a product of m. p. 172–173.2°. Since this material did not depress the melting point of the product from the Sandmeyer method, all the corresponding materials were combined and several times recrystallized from dilute acetic acid. The 1-cyanofluorenone was then obtained in short deep yellow rods, m. p. 177.2–177.8°.

Anal. Calcd. for $C_{14}H_7ON$: N, 6.83. Found: N, 6.74.

Further confirmation of the identity of this nitrile was obtained by its hydrolysis with hot 50% sulfuric acid to fluorenone-1-carboxylic acid. After crystallization from 95% alcohol the small orange-red needles (80% yield) showed m. p. 190–192° and did not depress the melting point of an authentic sample (m. p. 191–192°) from the oxidation of fluoranthene.

Fluorenone-4-carboxylic Acid (VIII).—Diphenic acid (5 g. = 0.021 mole) was added to concentrated sulfuric acid (23 g. = 0.45 mole) during the two minutes required to bring the mixture to 140 ± 5°. The red solution was held at this temperature with constant shaking for twelve minutes, then poured into water (150 ml.). The yellow precipitate was boiled gently for an hour, then filtered hot and washed with a large volume of hot water. The yield of crude keto acid was 82%; m. p. 216–218°. After recrystallization from 50% alcohol it was obtained in yellow needles, m. p. 220–221°.

Fluorenone-4-carboxylic Acid Amide (X).—The keto acid (1.0 g.) was added slowly to thionyl chloride (5 ml.). After refluxing the clear but dark colored solution for a few minutes, the excess thionyl chloride was evaporated in a dry air blast and the crude dry keto acid chloride allowed to stand for an hour in excess (5 ml.) concentrated ammonium hydroxide. The solid was then filtered, washed with water and recrystallized from 95% alcohol from which on cooling beautiful cream-colored needles, m. p. 223–224°, separated in 82% yield.

4-Aminofluorenone (XI).—Fluorenone-4-carboxylic acid amide (1 g. = 0.0045 mole) ground to a fine slurry with water (15 ml.) was added to an alkaline hypobromite solution prepared by adding to bromine (0.7 g. = 0.0045 mole) in water (5 ml.) at 0° a solution of potassium hydroxide (1.5 g. = 0.027 mole) in water (10 ml.). The amide dissolved almost immediately and the resultant orange solution was left at room temperature for two hours. After removing a dark colored high melting residue by suction filtration, the filtrate was heated at 100° for seventy-five minutes to cause precipitation of the aminoketone. After cooling the orange needles were filtered, washed with ice water and dried, yield 74%, m. p. 138–139°.

4-Bromofluorenone (XII).—The above 4-aminofluorenone (1 g. = 0.005 mole) was diazotized in the usual way using 40% hydrobromic acid (5.25 ml. = 0.036 mole), sodium nitrite (0.36 g. = 0.005 mole) and a total of 35 ml. of water. The resultant filtered solution was poured in a fine stream into a boiling solution of cuprous bromide (0.88 g. = 0.06 mole) in 40% hydrobromic acid (50 ml.). After heating at 100° for five to ten minutes the resultant light orange precipitate was filtered off, ground up with excess 1 *N* sodium hydroxide solution, filtered and washed. The undissolved bromoketone was then distilled at reduced pressure (2 mm. at bath temperature of 105–115°) giving 45% yield, m. p. 124.5–125.5°. Recrystallization from dilute acetic acid and from 95% alcohol gave 4-bromofluorenone as small yellow needles, m. p. 125–126°.

Anal. Calcd. for $C_{13}H_7OBr$: Br, 30.84. Found: Br, 30.7, 30.8.

The melting point of a mixture of this 4-bromofluorenone with authentic 1-bromofluorenone was depressed more than 25°.

2-Benzoyl-3-bromobenzoic Acid (XIV) (Stephens' Acid).—This compound was prepared from 3-bromophthalic anhydride, benzene and aluminum chloride precisely according to Stephens' directions; yield 83%, m. p. 226–227°. After recrystallization from 50% aqueous acetone our melting point was 227–228° (Stephens gave 231.5° but did not state whether this value was corrected or not).

Anal. Calcd. for $C_{14}H_9O_3Br$: neut. eq., 305.1; C, 55.11; H, 2.97; Br, 26.19. Found: neut. eq., 304.0, 304.7; C, 55.1, 54.9; H, 3.00, 3.12; Br, 26.0, 26.0.

Methyl 2-Benzoyl-3-bromobenzoate.—This ester (not previously recorded) was prepared via the diazomethane method. It formed colorless flat rectangular prisms, m. p. 136.7–137.5°.

Anal. Calcd. for $C_{15}H_{11}O_3Br$: Br, 25.04. Found: Br, 25.0, 24.9.

2-Benzoyl-3-bromobenzoyl Chloride (XV).—The above acid (Stephens') was converted to the acid chloride with phosphorus pentachloride in benzene precisely according to Miller and Bachman,[4c] except that not until the amount of benzene had been reduced to one-half their quantity and petroleum ether substituted for their ligroin did we obtain their yield. They described their acid chloride as light brown prisms, m. p. 119–120°. Our product, however, was perfectly white and showed m. p. 121–122°.

2-Benzoyl-3-bromobenzamide (XVI).—Many attempts to follow the Miller and Bachman procedure for conversion of the acid chloride from Stephens' acid to the corresponding amide gave only mixtures of compounds which obstinately resisted separation. By the following modification, however, we obtained the amide easily and in good yields.

A citrate of magnesia bottle was charged with two dozen small quartz pebbles and concentrated ammonium hydroxide (120 ml.) and chilled in an icebox overnight. To it was then added freshly prepared 2-benzoyl-3-bromobenzoyl chloride (14.5 g. = 0.045 mole) and the mixture tumbled for six hours. The flask contents were then diluted with water, the pebbles screened out, the solid filtered off with suction, washed thoroughly with dilute ammonium hydroxide (1 volume concd. NH_4OH: 2 water), and dried. The yield was 12.7 g. (93%). Recrystallization from toluene gave m. p. 202–202.5° (somewhat higher melting points were, however, sometimes obtained).

Anal. Calcd. for $C_{14}H_{10}O_2NBr$: N, 4.61; Br, 26.28. Found: N, 4.64, 4.66; Br, 26.2, 26.3.

In one experiment where the flask containing both crystals and mother liquor was allowed to stand for several

days the bulky needles were replaced by an entirely different appearing mass of intensely glittering prisms. These, however, showed the same melting point as the usual needles, and reverted to the latter upon recrystallization.

2-Benzoyl-3-bromoaniline (XVII).—The above amide (7.5 g. = 0.025 mole) was added to an alkaline hypobromite solution prepared from bromine (1.3 ml.) and potassium hydroxide solution (12.5 ml. of 1:1 solution plus 20 ml. water) and the mixture kept at 0° for half an hour with occasional stirring. The resulting white pulp was dissolved in water (60 ml.) and poured into a boiling mixture of water (400 ml.) and alcohol (50 ml.). After refluxing for an hour most of the alcohol was distilled off.

A heavy brown oil which had then separated was solidified by transferring it to a mortar, washing with a little 5% potassium hydroxide solution and then triturating with 5% hydrochloric acid (50 ml.). The resultant brown powder was filtered off, washed, dried, dissolved in ether (50 ml.), the ether solution filtered and treated with 72% perchloric acid (2.5 ml.). The amine perchlorate precipitated leaving the colored impurities behind in the mother liquor. After washing the perchlorate salt with ether it was decomposed with dilute ammonium hydroxide and the free amine washed and dried. The yield was 3.2 g. (46%). For further purification it was dissolved in ligroin (250 ml. of b. p. 60–90°), boiled with Norit, filtered and cooled. The amine separated as clusters of yellowish prisms, m. p. 84.5–85.5°.

Anal. Calcd. for $C_{13}H_{10}ONBr$: N, 5.07; Br, 28.94. Found: N, 5.45, 5.51; Br, 28.9, 29.1.

The aqueous alkaline solution decanted from the above amine (original crude oil) gave upon acidification an ample white precipitate indicating considerable hydrolysis of the original amine back to its acid as is often the case in Hofmann reactions.

1-Bromofluorenone (VI) from 2-Benzoyl-3-bromoaniline (XVII).—Preliminary experiments showed that this very weakly basic aminoketone does not readily lend itself to ring closure by elimination of the amino group *via* decomposition of the diazonium salt. The reaction tends to take a more complicated course leading largely to mixtures of resinous matter and amorphous dark-colored pigments. There is also formed a considerable amount of an alkali soluble product. However, a satisfactory result was finally obtained by the following procedure.

The aminoketone (3.5 g. = 0.0127 mole) dissolved in concentrated sulfuric acid (28 ml.) at 0° was treated at one time with finely powdered 97% sodium nitrite (0.014 mole) with constant shaking. As soon as a clear solution resulted, it was mixed with anhydrous sodium sulfate (100 g.), transferred to a large porcelain dish resting on a boiling water-bath, and constantly stirred for twenty minutes. After treatment with alkali (80 ml. 40° Baumé sodium hydroxide plus 1000 ml. water) the undissolved residue was filtered, washed and dried: weight 1.5 g.

This greyish-brown solid was mixed with Norit (3 g.), then refluxed with ligroin (400 ml., b. p. 60–90°) for one hour. After cooling and filtering, evaporation of the solvent yielded 0.4 g. of long lemon-yellow spears, m. p. 134.5–135°. From the Norit a second lot (0.4 g.) of equally pure material was obtained. The total yield was approximately 25% of the theoretical.

Anal. Calcd. for $C_{13}H_7OBr$: C, 60.26; H, 2.73; Br, 30.84. Found: C, 60.3, 60.0; H, 2.90, 3.15; Br, 30.8, 31.1.

This product (m. p. 134.5–135°) did not depress the melting point (134.0–134.3°) of 1-bromofluorenone prepared from fluorenone-1-carboxylic acid, but did depress that (125–126°) of 4-bromofluorenone obtained from fluorenone-4-carboxylic acid.

Summary

1. 1-Bromofluorenone has been prepared from fluorenone-1-carboxylic acid by a series of reactions leaving no doubt as to its structure. Our results confirm the work of Montagne and van Charante, who prepared it by another method.

2. 4-Bromofluorenone has been prepared from fluorenone-4-carboxylic acid by a series of reactions leaving no doubt as to its structure. Our product confirms the properties previously reported by France, Heilbron and Hey.

3. The series of reactions by which Miller and Bachman reported to have obtained from 3-bromophthalic anhydride a product claimed to be 4-bromofluorenone yielded in our hands only authentic 1-bromofluorenone. This discovery resolves the serious contradictions in the previous literature of this compound.

4. As a result of the establishment of the true 1-bromo- and 4-bromofluorenone it was found that the bromobenzoylbenzoic acid resulting from the reaction of 3-bromophthalic anhydride with benzene in the presence of aluminum chloride is in fact 2-benzoyl-3-bromobenzoic acid and not the alternative 2-benzoyl-6-bromobenzoic acid erroneously inferred by previous workers.

5. The above discoveries bring in question the true nature of the Miller and Bachman supposed "4-bromofluorenol" and "4-bromofluorene," the mercuration of fluorene in the 4-position, and their supposed "4-bromo-9-chlorofluorene" and "4,9-dibromofluorene." They also render very doubtful the structure proposed by Stephens for the diphenyl bromophthalide prepared from 3-bromophthalic anhydride.

6. During the course of the above work the following previously unreported compounds were characterized: 1-chloro-, 1-iodo-, 1-cyano-, 1-acetamino-, and 1-benzoylamino fluorenones; 2-benzoyl-3-bromobenzoic acid, methyl 2-benzoyl-3-bromobenzoate, 2-benzoyl-3-bromobenzoyl chloride, 2-benzoyl-3-bromobenzamide, 2-benzoyl-3-bromoaniline, and fluorenone-anil-1-carboxylic acid anilide.

CAMBRIDGE, MASSACHUSETTS RECEIVED JUNE 12, 1942

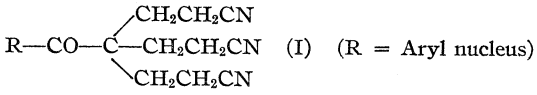
[CONTRIBUTION FROM RÖHM AND HAAS CO., INC., AND RESINOUS PRODUCTS & CHEM. CO.]

The Chemistry of Acrylonitrile. II. Reactions with Ketones

BY HERMAN ALEXANDER BRUSON AND THOMAS W. RIENER

The powerful cyanoethylating action of acrylonitrile in the presence of strong bases upon organic compounds possessing labile hydrogen atoms[1] is strikingly evident with various types of ketones.

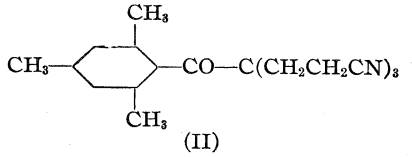
Aromatic methyl ketones of the type R—CO—CH_3 as exemplified by acetophenone, *p*-methylacetophenone, *p*-methoxyacetophenone, *p*-chloroacetophenone, *p*-bromoacetophenone, *p*-acetyldiphenyl, and 2-acetylnaphthalene readily took up three molecular equivalents of acrylonitrile in the presence of strong alkali catalysts such as trimethylbenzylammonium hydroxide or potassium hydroxide to form crystalline *tri*-cyanoethylation products (I).



(I) (R = Aryl nucleus)

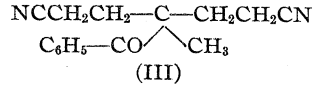
These are listed in Table I together with their physical and analytical data. Upon hydrolysis with aqueous sodium hydroxide or potassium hydroxide these tri-(cyanoethyl)-methyl aryl ketones yielded the corresponding aryl keto tricarboxylic acids R—CO—$C(CH_2CH_2COOH)_3$. These are listed in Table II.

Even acetomesitylene which because of steric hindrance reacts sluggishly, gave a small yield (30%) of the *tri*-cyanoethylation product (II).

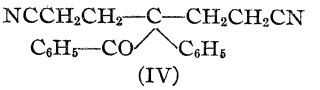


(II)

Propiophenone and desoxybenzoin which possess only two active hydrogen atoms contiguous to the carbonyl group, each took up two molecular equivalents of acrylonitrile to form γ-benzoyl-γ-methylpimelonitrile (III) and γ-benzoyl-γ-phenylpimelonitrile (IV), respectively.



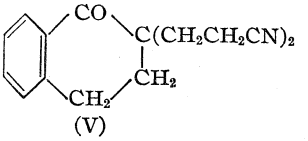
(III)



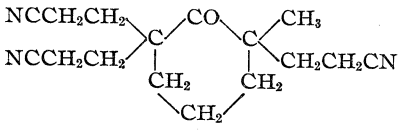
(IV)

Upon hydrolysis with aqueous sodium hydroxide, compounds III and IV yielded γ-benzoyl-γ-methylpimelic acid and γ-benzoyl-γ-phenylpimelic acid, respectively.

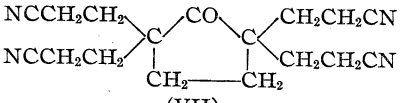
In a similar manner acrylonitrile reacted with α-tetralone, *o*-methylcyclohexanone and cyclopentanone to form compounds V, VI and VII, respectively.



(V)

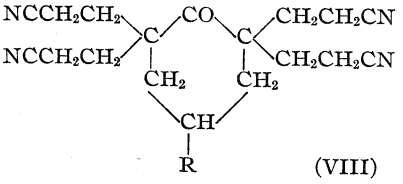


(VI)



(VII)

Cyclohexanone itself as well as *p*-methylcyclohexanone, *p*-*t*-amyl cyclohexanone, *p*-(α,α,γ,γ-tetramethylbutyl)-cyclohexanone and *p*-cyclohexylcyclohexanone each took up four moles of acrylonitrile to yield crystalline 2,2,6,6-tetracyanoethylation products of the general type (VIII) in 80–95% yields (Table III).



(R = H, alkyl, or cycloalkyl)

(VIII)

Upon alkaline hydrolysis compounds VI, VII, and VIII were converted into the corresponding ketonic polycarboxylic acids. The tetra-carboxylic acids derived from (VIII) are listed in Table IV.

When cyclohexanone reacted with only one or two molecular equivalents of acrylonitrile, it was possible to isolate a mono-cyanoethylation product, 2-(β-cyanoethyl)-cyclohexanone, and a di-cyanoethylation product, very probably 2,2-di-(β-cyanoethyl)-cyclohexanone, from the reaction mixture in addition to considerable tetra-cyanoethylation product.

(1) Bruson, THIS JOURNAL, **64**, 2457 (1942); U. S. Patent 2,287,510.

TABLE I

TRICYANOETHYLATION PRODUCTS R—CO—C(CH_2CH_2CN)$_3$, R = Aryl

Value of R	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Phenyl	128–129[a]	$C_{17}H_{17}N_3O$	73.08	6.14	15.04	73.10	6.29	15.13
2-Naphthyl	122[b]	$C_{21}H_{19}N_3O$	76.59	5.82	12.76	77.03	5.58	12.71
p-Phenylphenyl	178[d]	$C_{23}H_{21}N_3O$	77.70	5.96	11.83	77.80	6.23	11.86
p-Methoxyphenyl	133[c]	$C_{18}H_{19}N_3O_2$	69.87	6.19	13.59	69.40	6.04	13.72
p-Methylphenyl	161–162[b]	$C_{18}H_{19}N_3O$	73.68	6.53	14.33	73.12	6.42	14.63
2,4,6-Trimethylphenyl	126[b]	$C_{20}H_{23}N_3O$	74.72	7.22	13.08	75.20	7.10	13.49
p-Chlorophenyl	141–142[c]	$C_{17}H_{16}N_3OCl$	Cl, 11.30		13.39	Cl, 10.87		13.12
p-Bromophenyl	151–152[b]	$C_{17}H_{16}N_3OBr$	Br, 22.32		11.73	Br, 21.98		11.67

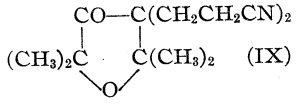
[a] Recrystallized from "Cellosolve." [b] From ethanol. [c] From methanol. [d] From dioxane.

TABLE II

R—CO—C(CH_2CH_2COOH)$_3$, R = Aryl

Value of R	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Phenyl	143–145	$C_{17}H_{20}O_7$	60.69	6.00	60.50	6.39
2-Naphthyl	173–174	$C_{21}H_{22}O_7$	65.25	5.74	65.21	5.81
p-Phenylphenyl	236–238	$C_{23}H_{24}O_7$	66.95	5.87	67.01	5.77
p-Methoxyphenyl	219	$C_{18}H_{22}O_8$	58.99	6.06	58.70	5.94
p-Methylphenyl	226	$C_{18}H_{22}O_7$	61.68	6.33	61.80	6.25
p-Chlorophenyl	225–227	$C_{17}H_{19}O_7Cl$	55.04	5.17	55.20	5.00
p-Bromophenyl	241–243	$C_{17}H_{19}O_7Br$	49.15	4.61	49.19	4.63

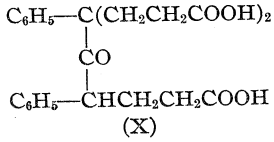
In an analogous manner, the heterocyclic ketone 2,2,5,5-tetramethyltetrahydrofuranone-3 reacted with acrylonitrile to yield the crystalline dicyanoethylation product (IX).



(IX)

Upon alkaline hydrolysis it formed the corresponding 4,4-di-(β-carboxy-ethyl)-2,2,5,5-tetramethyltetrahydrofuranone-3.

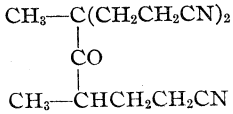
An attempt was made to *tetra*-cyanoethylate dibenzyl ketone but the only product that could be isolated after saponification, from the resinous mixture obtained, was a crystalline tricarboxylic acid (X).



(X)

instead of the expected tetra-carboxylic acid.

In a similar manner, an attempt to *tetra*-cyanoethylate diethyl ketone gave a resinous product from which a crystalline *tri*-cyanoethylation product (XI) could be isolated by vacuum distillation.



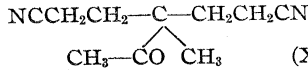
(XI)

Upon alkaline saponification (XI) yielded the corresponding 2,4,4-tri-(β-carboxyethyl)-pentanone-3.

In all of the above examples, the positions occupied by the entering cyanoethyl groups can hardly be other than those indicated since these are established by the only available active hydrogen atoms in the ketones employed.

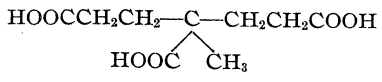
However, in the case of the saturated aliphatic methyl ketones of the type CH_3—CO—CH_2—alkyl, such as methyl ethyl ketone, methyl propyl ketone, methyl iso-butyl ketone, methyl *n*-amyl ketone, and methyl *n*-hexyl ketone, which could presumably react on either the —CH_2— group, or the CH_3—group, or both, it was of interest to determine the exact location of the entering cyanoethyl groups and also the maximum number that could be introduced.

Methyl ethyl ketone reacted with acrylonitrile to first take up two cyanoethyl radicals on the methylene group and give 4-acetyl-4-methylpimelonitrile (XII) in yields up to 90%.



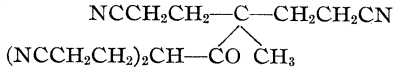
(XII)

The structure of this compound was established by saponifying it to the corresponding γ-acetyl-γ-methylpimelic acid, and subjecting the latter in alkaline hypochlorite solution to the haloform reaction, whereby chloroform was evolved and the new tricarboxylic acid XIII isolated.



(XIII)

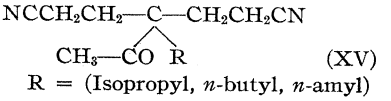
Upon treating 4-acetyl-4-methylpimelonitrile with one molecular equivalent of acrylonitrile in an attempt to cyanoethylate one of the hydrogen atoms of the remaining active methyl group, a resin was obtained from which a crystalline tetra-cyanoethylation product (XIV) could be distilled under high vacuum.



(XIV)

Acrylonitrile also combined with methyl propyl ketone to give a crystalline di-cyanoethylation product, which by conversion to the corresponding dicarboxylic acid and subjection of the latter to the haloform reaction, was shown to have both cyanoethyl groups on the methylene group. It was also possible to isolate a crystalline *tri*-cyanoethylation product, namely, 1,3,3-tri-(β-cyanoethyl)-pentanone-2 from the original di-cyanoethylation reaction mixture.

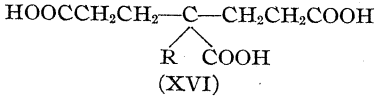
In the same manner methyl isobutyl ketone, methyl *n*-amyl ketone and methyl *n*-hexyl ketone gave crystalline γ-acetyl-γ-alkyl pimelonitriles (XV) upon treatment in alkaline solution with two moles of acrylonitrile.



(XV)

R = (Isopropyl, *n*-butyl, *n*-amyl)

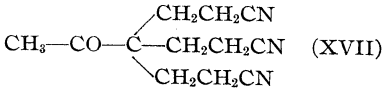
The above γ-acetyl-γ-alkyl pimelonitriles were saponified to the corresponding γ-acetyl-γ-alkyl-pimelic acids, which were isolated in the pure form. The latter in turn were each oxidized by means of alkaline hypochlorite solution to chloroform and the γ-alkyl-γ-carboxypimelic acids (XVI).



(XVI)

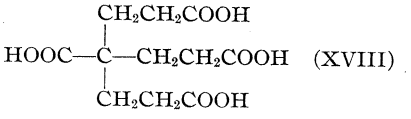
The positions taken by the two entering cyanoethyl radicals in the homologs of methyl ethyl ketone having thus been established as being on the —CH_2— group, it was of interest to study the cyanoethylation of acetone itself since this possesses two active methyl groups of equal value and might perhaps distribute the cyanoethyl radicals between both of them.

Upon treating acetone with three moles of acrylonitrile in the presence of potassium hydroxide as the catalyst, a crystalline *tri*-cyanoethylation product was obtained in 75–80% yield. This compound is 1,1,1-tri-(β-cyanoethyl)-acetone (XVII).



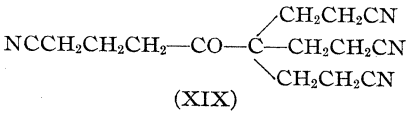
(XVII)

Upon alkaline hydrolysis it yielded the corresponding 1,1,1-tri-(β-carboxyethyl)-acetone which, upon oxidation with alkaline hypochlorite solution, gave chloroform and the tetra-carboxylic acid (XVIII).



(XVIII)

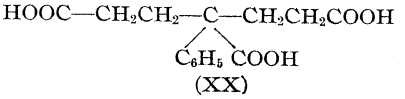
The *tri*-cyanoethylation of acetone therefore takes place first on one methyl group. Upon further cyanoethylation of the 1,1,1-tri-(β-cyanoethyl)-acetone, a crystalline *tetra*-cyanoethyl acetone could be isolated from the resinous residue, and consequently must possess formula (XIX).



(XIX)

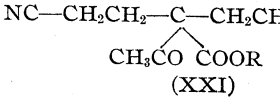
It is highly probable that the resinous residue contains a *penta*- or a *hexa*-cyanoethylation product, but the purification offers considerable difficulty.

In the case of phenylacetone, which also possesses two possible points of reaction, di-cyanoethylation took place on the methylene group to give the crystalline γ-acetyl-γ-phenylpimelonitrile in 86% yield. Upon saponification it yielded γ-acetyl-γ-phenylpimelic acid which upon oxidation with alkaline hypochlorite solution cleaved to give chloroform and γ-carboxy-γ-phenylpimelic acid (XX).



(XX)

Finally, acrylonitrile was condensed with acetoacetic esters. Both methyl acetoacetate and ethyl acetoacetate gave good yields of crystalline di-cyanoethylation products (XXI).



(XXI)

($R = CH_3, C_2H_5$)

From the foregoing it appears therefore that with aliphatic or arylaliphatic ketones possessing the reactive grouping —CH_2—CO—CH_3 cyano-

ethylation first occurs on the —CH_2— group and after this has been satisfied further cyanoethylation can occur on the remaining methyl radical.

In conclusion it may be said that certain methylene ketones were incapable of being cyanoethylated by the method here described, namely, camphor, iso-phorone, and di-isobutyl ketone. Furthermore, attempts to utilize α-methyl acrylonitrile or crotononitrile in place of acrylonitrile were unsuccessful.

Experimental

R—CO—C(CH_2CH_2CN)$_3$ (R = Aryl).—The general method of condensing aryl alkyl ketones with acrylonitrile consisted in dissolving the ketone R—CO—CH_3 (R = aryl) in dioxane or in tertiary butyl alcohol so as to form a 25–50% solution, adding a small quantity of aqueous 40% trimethylbenzylammonium hydroxide[2] corresponding to about 5–10% on the weight of the ketone, and then adding *dropwise* three molecular equivalents of acrylonitrile to the stirred reaction mixture while maintaining the temperature of the mixture between 25 and 40° by means of external water cooling and by regulating the rate of addition of the acrylonitrile. The mixture was then usually stirred for two to four hours longer at room temperature, and the tricyanoethylation product separated either by filtration or by neutralizing the alkali with dilute hydrochloric acid, evaporating off the solvent under reduced pressure on a steam-bath, and crystallizing the residue from a suitable solvent.

A typical procedure using acetophenone, for example, is as follows:

To a solution of 60 g. of acetophenone (0.50 mole) in 60 g. of dioxane and containing 5 g. of "Triton B," was added 79.5 g. of acrylonitrile (1.5 mole) dropwise during a period of two hours while the mixture was stirred and maintained between 30 and 40° by external water cooling. During the addition crystals separated. After all the acrylonitrile had been added, the mixture was stirred for one hour and then filtered by suction. The pinkish crystalline product weighed 79 g., corresponding to a 57% yield of 1,1,1-tri-(β-cyanoethyl)-acetophenone. After recrystallization from glycol monoethyl ether ("Cellosolve") it formed colorless crystals melting at 128–129°.

In Table I are given the physical and analytical data of the various homologs of acetophenone prepared in the above manner. All of the melting points given in this paper are uncorrected for stem exposure.

R—CO—C(CH_2CH_2COOH)$_3$, R = Aryl.—The general method of hydrolyzing the cyanoethylated ketones consisted in boiling the tricyanoethylation products given in Table I with an excess of sodium hydroxide or potassium hydroxide in aqueous solution for a period of from four to twelve hours until all the product had dissolved and evolution of ammonia had ceased. The solution was then clarified with charcoal, filtered, and the filtrate acidified with concentrated hydrochloric acid. The tricarboxylic acids usually precipitated first as viscous oils or dough-like masses which gradually solidified to a crystalline product. After recrystallization from hot water, or from a mixture of water–dioxane (4:1), they were obtained in pure form as colorless crystals.

A typical procedure using 1,1,1-tri-(β-cyanoethyl)-acetophenone is as follows:

A mixture consisting of 400 g. of water, 39 g. of potassium hydroxide and 55.8 g. of 1,1,1-tri-(β-cyanoethyl)-acetophenone was stirred rapidly and boiled under reflux for six hours. The solution was clarified with charcoal, filtered, and the filtrate acidified with concentrated hydrochloric acid. The 1,1,1-tri-(β-carboxyethyl)-acetophenone separated as a white, resinous mass which soon became crystalline. It was purified by recrystallization from hot water, yield 58 g. or 80%.

In Table II are given the physical and analytical data of the various 1,1,1-tri-(β-carboxyethyl)-methyl aryl ketones prepared in the above manner. The yields of pure product were between 80 and 85%.

III. γ-Benzoyl-γ-methylpimelonitrile.—To a solution of 26.9 g. of propiophenone (0.2 mole), 50 g. of dioxane and 2 g. of "Triton B" there was added dropwise 21.2 g. of acrylonitrile (0.4 mole) during the course of twenty minutes while the reaction mixture was stirred and maintained between 25 and 30° by external water cooling. The mixture was stirred for five hours longer, then neutralized with dilute hydrochloric acid and poured into 300 cc. of water. The oil layer was separated, taken up in ethylene dichloride, washed thoroughly with water, and the ethylene dichloride layer evaporated under reduced pressure on a steam-bath. The residual oil (48 g.) was mixed with an equal weight of ethanol and chilled whereupon the product crystallized. After recrystallization from ethanol the γ-benzoyl-γ-methylpimelonitrile formed colorless crystals m. p. 66°. *Anal.* Calcd. for $C_{15}H_{16}N_2O$: C, 74.96; H, 6.72; N, 11.66. Found: C, 75.10; H, 6.65; N, 11.71.

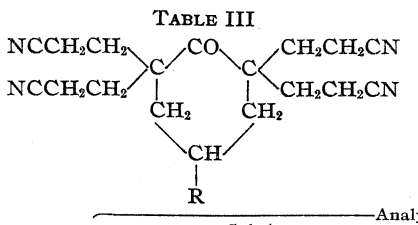
γ-Benzoyl-γ-methylpimelic Acid.—A mixture of 150 g. of water, 10 g. of sodium hydroxide, and 16.5 g. of III was boiled under reflux for six and one-half hours, treated with charcoal and the clear filtrate acidified with concentrated hydrochloric acid. The precipitated product was crystallized from hot water; m. p. 166–167°. *Anal.* Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.50; H, 6.29.

IV. γ-Benzoyl-γ-phenylpimelonitrile.—Acrylonitrile (13.5 g.) was added dropwise to a stirred solution of 50 g. of dioxane, 25 g. of desoxybenzoin and 2 g. of "Triton B" while the reaction temperature was maintained at 30–35° by external cooling. After all the acrylonitrile had been added, the mixture was stirred for three hours at 45° to complete the reaction. It was then cooled, acidified with dilute hydrochloric acid, taken up in ethylene dichloride and washed with water. The ethylene dichloride layer was evaporated to dryness under reduced pressure on a steam-bath and the residual crystalline product (38 g.) washed with a little alcohol and purified by recrystallization from ethanol. The yield of pure product melting at 149–150°, was 31 g. *Anal.* Calcd. for $C_{20}H_{18}N_2O$: N, 9.27. Found: N, 9.06.

γ-Benzoyl-γ-phenylpimelic Acid.—A mixture of 12 g. of IV, 150 g. of water and 6 g. of sodium hydroxide was boiled under reflux for twenty-one hours. The solution was treated with charcoal, filtered and the filtrate acidified with

(2) Available commercially as "Triton B."

TABLE III



Value of R	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	165	$C_{18}H_{22}N_4O$	69.64	7.15	18.05	69.80	7.08	18.20
Methyl	138	$C_{19}H_{24}N_4O$	...	..	17.27	...	..	17.26
t-Amyl	145	$C_{23}H_{32}N_4O$	...	..	14.72	...	..	14.54
t-Octyl	155–156	$C_{26}H_{38}N_4O$	73.88	9.07	13.26	74.10	9.04	13.15
Cyclohexyl	223–224	$C_{24}H_{32}N_4O$	...	..	14.27	...	..	14.28

hydrochloric acid. The product precipitated as a white solid. Upon repeated recrystallization from water and drying in an oven at 70° for twenty-four hours the analytical sample melted at 172–173°. *Anal.* Calcd. for $C_{20}H_{20}O_5$: C, 70.55; H, 5.93. Found: C, 70.21; H, 5.85.

V. 2-Di-(β-cyanoethyl)-tetralone-1.—Acrylonitrile (21.2 g.) was added at room temperature to a mixture of 29.2 g. of α-tetralone, 50 g. of dioxane, and 4 g. of "Triton B." The mixture was stirred for twenty-four hours, then neutralized with dilute hydrochloric acid, washed well with water and distilled under reduced pressure at 1 mm. The fraction boiling at 250–260° (1 mm.) formed a pale yellow oil which gradually solidified to a waxy, crystalline mass. After recrystallization from ethanol, the product formed colorless crystals melting at 80°. *Anal.* Calcd. for $C_{16}H_{16}N_2O$: C, 76.15; H, 6.39; N, 11.10. Found: C, 76.59; H, 6.05; N, 11.09.

VI. 2,2,6-Tri-(β-cyanoethyl)-6-methyl-cyclohexanone.—Acrylonitrile (63.5 g.) was added dropwise to a stirred solution of 44.8 g. of *o*-methylcyclohexanone, 200 g. of benzene, and 5 g. of "Triton B" while maintaining the reaction temperature at 30–40°. The mixture was then stirred at room temperature for eighteen hours and, after neutralization with hydrochloric acid and thorough washing with water, was filtered to remove some polyacrylonitrile which was present. The filtrate was evaporated to dryness under reduced pressure on a steam-bath and the residual oil (103 g.) distilled under high vacuum. The product (41 g.) came over at 270–285° (1–2 mm.) as a viscous, amber-colored sirup which gradually crystallized on long standing. Upon recrystallization from ice-cold methanol it was obtained in the form of colorless crystals melting at 69–70°. *Anal.* Calcd. for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.79; N, 15.49. Found: C, 71.00; H, 7.49; N, 15.86.

VII. 2,2,5,5-Tetra-(β-cyanoethyl)-cyclopentanone.—To a solution of 42 g. of cyclopentanone (0.5 mole) in 200 g. of benzene, there was added 5 g. of "Triton B." The mixture was stirred rapidly and cooled to 35–45° while 106 g. of acrylonitrile (2 moles) was added dropwise during two hours. Crystals began to separate within a few minutes after the addition was begun. As the reaction proceeded it was necessary to add 200 cc. of benzene to prevent clogging the stirrer by the crystalline mass. The mixture was allowed to stand for eighteen hours before the crystals were filtered by suction. The yield was 144 g. or 97%. The product can be recrystallized from hot methyl ethyl ketone or glycol monoethyl ether, from which it separates in colorless crystals, m. p. 175°. *Anal.* Calcd. for $C_{17}H_{20}N_4O$: N, 18.90. Found: N, 18.93.

VIII. 2,2,6,6,-Tetra-(β-cyanoethyl)-cyclohexanone.—To 935 g. of tertiary butyl alcohol there was added 15 g. of aqueous 40% potassium hydroxide solution and 294 g. of cyclohexanone (3 moles). The solution was stirred rapidly in a three-neck flask surrounded by running tap water, and 636 g. of acrylonitrile (12 moles) added dropwise thereto during one and one-half hours, while the temperature of the reaction mixture was maintained between 35 and 45°. During the addition crystals separated. The mixture was stirred for an additional fifteen hours at room temperature and the crystalline product filtered off by suction, washed with water, and dried; yield 820 g. of faintly yellow crystals, or 88%. Upon recrystallization from acetone it formed colorless fine needles, melting at 165°.

In Table III are given the physical and analytical data of the various 2,2,6,6-tetra-(β-cyanoethyl)-cyclohexanones of type VIII prepared in the above manner. The *p-t*-octylcyclohexanone used was obtained from *p*-(α,α,γ,γ-tetramethylbutyl)-phenol by catalytic hydrogenation with Raney nickel to *p*-(α,α,γ,γ-tetramethylbutyl)-cyclohexanol and oxidation of the latter with potassium dichromate–sulfuric acid mixture.[3]

Tetra-(β-carboxyethyl)-cycloalkanones.—The general method of hydrolysis used consisted in boiling the tetracyanoethylated cycloalkanones given in Table III with an excess of potassium hydroxide or sodium hydroxide in aqueous solution for a period of from four to eight hours until ammonia ceased to be evolved, then treating the hot solution with Norite decolorizing charcoal, filtering, and acidifying the filtrate with concentrated hydrochloric acid. The crude tetra-carboxylic acids precipitated in crystalline form and were then recrystallized from appropriate solvents.

The following procedures were typical:

2,2,5,5-Tetra-(β-carboxyethyl)-cyclopentanone.—A mixture of 600 g. of water, 80 g. of sodium hydroxide and 95 g. of 2,2,5,5-tetra-(β-cyanoethyl)-cyclopentanone (VII) was stirred and boiled under reflux for twenty-three hours. The clear, amber-colored solution was treated with charcoal, filtered and acidified with concentrated hydrochloric acid. The clear solution obtained was cooled in an ice-bath to 10–15° whereupon it set to a white crystalline magma, which after filtration and drying at room temperature weighed 108 g.

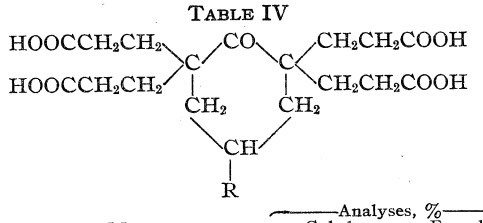
(3) Niederl, *Ind. Eng. Chem.*, **30**, 1270 (1938).

Upon recrystallization from water the product formed colorless crystals melting at 173°, containing one mole of water of crystallization. *Anal.* Calcd. for $C_{17}H_{24}O_9 \cdot H_2O$: C, 52.28; H, 6.72. Found: C, 52.20; H, 6.78.

2,2,6,6-Tetra-(β-carboxyethyl)-cyclohexanone.—A mixture consisting of 1900 g. of water, 196 g. of potassium hydroxide and 217 g. of 2,2,6,6-tetra-(β-cyanoethyl)-cyclohexanone was stirred and boiled under reflux for five hours. The clear solution was acidified with 350 g. of concentrated hydrochloric acid, and cooled to 15–20° whereupon the product crystallized. It was filtered off and washed with a little ice water; yield 199 g. of air-dried, white crystals. Upon recrystallization from water the compound formed colorless needles melting at 179–180°.

In Table IV are given the physical and analytical data of various tetra-(β-carboxy-ethyl)-cyclohexanones prepared in the above manner from the tetra-cyanoethylation products of cyclohexanone, *p*-methylcyclohexanone, *p*-*t*-amylcyclohexanone, *p*-(α,α,γ,γ-tetramethylbutyl)-cyclohexanone, and *p*-cyclohexylcyclohexanone, respectively.

TABLE IV



Value of R	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
H	179–180	$C_{18}H_{26}O_9$	55.93	6.79	56.30	6.59
Methyl	205–206	$C_{19}H_{28}O_9$	56.96	7.05	57.01	7.10
t-amyl	205	$C_{23}H_{36}O_9$	60.49	7.95	60.89	7.94
t-Octyl	185–186	$C_{26}H_{42}O_9$	62.60	8.49	61.90	8.49
Cyclohexyl	205–206	$C_{24}H_{36}O_9$	61.50	7.74	61.61	7.40

2-(β-Cyanoethyl)-cyclohexanone.—To a stirred mixture of 98 g. of cyclohexanone (1 mole) and 5 g. of "Triton B," was added dropwise 53 g. of acrylonitrile (1 mole) at 30–35° during the course of eighty minutes. The mixture was stirred at 35–40° for one hour thereafter and finally for eighteen hours at room temperature. The partially crystalline mixture was acidified with dilute hydrochloric acid and the crystalline tetracyanoethylation product (30 g.) was filtered off by suction. The filtrate was washed with water and distilled in vacuum. About 31 g. of unchanged cyclohexanone was recovered.

The 2-(β-cyanoethyl)-cyclohexanone distilled over at 138–142° (10 mm.) as a colorless oil; yield 16.5 g. *Anal.* Calcd. for $C_9H_{13}NO$: N, 9.27. Found: N, 9.03.

The fraction boiling at 195–198° (1 mm.) was a viscous yellow oil; yield 12.5 g. On standing it gradually crystallized. After recrystallization from benzene it formed colorless crystals melting at 69°, the analysis of which corresponds to a di-cyanoethylation product of cyclohexanone. *Anal.* Calcd. for $C_{12}H_{16}N_2O$: C, 70.54; H, 7.90; N, 13.71. Found: C, 70.90; H, 7.85; N, 13.78.

IX. 4,4-Di-(β-cyanoethyl)-2,2,5,5-tetramethyltetrahydrofuranone-3.—Acrylonitrile (24.4 g.) was added dropwise to a stirred solution consisting of 50 g. of dioxane, 3 g. of aqueous 40% Triton B, and 33 g. of 2,2,5,5-tetramethyltetrahydrofuranone-3 while the reaction temperature was maintained at 35–40° by external cooling. The mixture was then stirred three hours longer at 25°. During the addition crystals separated. The mixture was neutralized with dilute hydrochloric acid, the white crystalline product filtered off, and washed with a little ethanol; yield 41 g. After recrystallization from ethanol, the product formed colorless needles melting at 153°. *Anal.* Calcd. for $C_{14}H_{20}N_2O_2$: N, 11.28. Found: N, 11.16.

4,4-Di-(β-carboxy-ethyl)-2,2,5,5-tetramethyltetrahydrofuranone-3.—A mixture of 120 g. of water, 12 g. of sodium hydroxide and 27 g. of compound IX was boiled under reflux for eight hours. The solution was treated with charcoal, filtered and the filtrate acidified with concentrated hydrochloric acid. The product crystallized on cooling; yield 18 g. Upon recrystallization from water it formed colorless crystals, m. p. 170–171°. *Anal.* Calcd. for $C_{14}H_{22}O_6$: C, 58.70; H, 7.75. Found: C, 58.61; H, 7.57.

X. 1,3-Diphenyl-1,1,3-tri-(β-carboxyethyl)-propanone-2.—Acrylonitrile (21.2 g.) was added dropwise during forty minutes to a stirred mixture of 21 g. of dibenzyl ketone, 50 g. of dioxane and 2 g. of "Triton B" at 30–35°. The mixture was allowed to stand eighteen hours at room temperature. It was then acidified with dilute hydrochloric acid and taken up in ethylene dichloride. The solution was washed thoroughly with water and evaporated to dryness *in vacuo* at 30 mm. on a steam-bath. The residue was a viscous, sticky sirup weighing 42 g. which could not be made to crystallize. It was therefore saponified directly by boiling 36 g. of it with a solution of 200 g. of water and 18 g. of sodium hydroxide for eight and one-half hours under reflux. The product was treated with charcoal and filtered. Upon acidifying the clear filtrate with hydrochloric acid, the product separated as a dough-like material which solidified to a hard mass. Upon recrystallization from a mixture of dioxane–water (30:70), with Norite to remove the color, the product was obtained in colorless crystals, m. p. 205° after drying at 60° for twenty-four hours. *Anal.* Calcd. for $C_{24}H_{26}O_7$: C, 67.57; H, 6.15. Found: C, 68.18; H, 6.15.

XI. 2,4,4-Tri-(β-cyanoethyl)-pentanone-3.—To a stirred solution of 34.4 g. diethyl ketone (0.4 mole), 35 g. of tertiary butyl alcohol, and 4 g. of "Triton B," there was added dropwise 84.8 g. of acrylonitrile (1.6 mole) at 30–40° during the course of two hours. The reaction mixture was allowed to stand for twenty-four hours at room temperature. It was then acidified with dilute hydrochloric acid, taken up in ethylene dichloride, and washed thoroughly with water. The solvent was removed *in vacuo* on a steam-bath and the residual oil weighing 123 g. was distilled in high vacuum. The fraction boiling at 280–300° (2 mm.) was a viscous sirup (45 g.) which crystallized from methanol in colorless crystals melting at 90–91°; yield 30 g. pure product. *Anal.* Calcd. for $C_{14}H_{19}N_3O$: C, 68.55; H, 7.79; N, 17.14. Found: C, 68.80; H, 7.60; N, 17.38.

2,4,4-Tri-(β-carboxyethyl)-pentanone-3.—A mixture of 21 g. of compound XI, 150 g. of water and 32 g. of sodium hydroxide was boiled under reflux for fourteen and one-half hours, then treated with carbon black and filtered. Upon acidifying the clear filtrate with concentrated hydrochloric acid an oil separated on cooling. The water layer was poured off and the oil layer was dissolved in 60 cc. of warm water and allowed to crystallize in a refrigerator for

about a week. The air-dried crystalline product weighed 21 g. Upon recrystallization from nitromethane it formed colorless crystals melting at 116°. *Anal.* Calcd. for $C_{14}H_{22}O_7$: C, 55.59; H, 7.34. Found: C, 55.55; H, 7.35.

XII. 4-Acetyl-4-methylpimelonitrile.—A solution consisting of 160 g. of acrylonitrile and 100 g. of tertiary butyl alcohol was added dropwise during the course of three hours, to a rapidly stirred, ice-cold solution of 144 g. of methyl ethyl ketone, 200 g. of tertiary butyl alcohol, and 10 g. of methanolic potassium hydroxide (30% solution) care being taken that the reaction temperature did not exceed 5°. During the addition a crystalline solid separated. After all the acrylonitrile had been added, the mixture was stirred for two hours longer at 5–10°, then filtered by suction while still cold. After air-drying for twenty-four hours the product was obtained as an almost white crystalline material; yield 239 g. or 89%. Upon recrystallization from benzene it forms colorless crystals, m. p. 67°. *Anal.* Calcd. for $C_{10}H_{14}N_2O$: C, 67.37; H, 7.92; N, 15.72. Found: C, 67.80; H, 7.82; N, 15.90.

γ-Acetyl-γ-methylpimelic Acid.—A mixture of 50 g. of compound XII, 400 g. of water, and 39.2 g. of potassium hydroxide was gradually heated to boiling under reflux (exothermal reaction). Boiling was continued for three hours. The product was then evaporated to expel the ammonia and acidified with hydrochloric acid. The mixture was evaporated to dryness on a steam-bath and the powdered residue extracted with boiling ethylene dichloride. Upon chilling the extract, 38 g. of colorless crystals was obtained. After recrystallization from ethylene dichloride the product melted at 125°. *Anal.* Calcd. for $C_{10}H_{16}O_5$: C, 55.52; H, 7.46. Found: C, 55.70; H, 7.46.

XIII. γ-Carboxy-γ-methylpimelic Acid.—A solution of alkaline potassium hypochlorite was prepared by stirring at 50° a solution of 660 g. of water and 165 g. of calcium hypochlorite ("HTH" containing 70% available Cl) with a solution of 115 g. of anhydrous potassium carbonate, 33 g. of potassium hydroxide and 330 g. of water for about ten minutes and filtering off the precipitate of calcium carbonate. The clear filtrate was stirred and to it was added dropwise a solution of 71 g. of γ-acetyl-γ-methylpimelic acid in 200 g. of 20% sodium hydroxide solution, while maintaining the reaction mixture between 60 and 70° by external cooling. Chloroform was evolved. After all had been added, the mixture was stirred for one hour longer at 60–70° and any excess hypochlorite destroyed by adding a solution of sodium bisulfite. The product was then acidified with hydrochloric acid and the clear solution evaporated to dryness on a steam-bath, under reduced pressure. The solid residue was extracted with hot acetone. Upon evaporation of the acetone from the extract, 64 g. of a viscous sirup was obtained which gradually set to a solid mass. Upon recrystallization from nitromethane it separated in colorless crystals. The analytical sample was dried in a vacuum desiccator over phosphorus pentoxide for several, days. It melted at 111°. *Anal.* Calcd. for $C_9H_{14}O_6$: C, 49.51; H, 6.47. Found: C, 49.21; H, 6.33.

XIV. 1,1,3,3-Tetra-(β-cyanoethyl)-butanone-2.—To a solution of 100 g. of dioxane, 53.4 g. of compound XII (0.3 mole) and 3 g. of "Triton B," there was added 15.9 g. (0.3 mole) of acrylonitrile while stirring at 25–40°. The reaction mixture was then allowed to stand for forty-eight hours at room temperature. The product was acidified with dilute hydrochloric acid, taken up in ethylene dichloride, washed thoroughly and dried *in vacuo* at 90°. The residual oil weighing 62 g. was then distilled under high vacuum. About 40 g. of unchanged XII boiling at 180–200° (2 mm.) was recovered. The fraction boiling at 345–355° (2 mm.) distilled as a thick oil (11 g.) which crystallized when stirred with ethanol. After several recrystallizations from ethanol it was obtained as colorless crystals, m. p. 84–85°; yield 4 g. *Anal.* Calcd. for $C_{16}H_{20}N_4O$: C, 67.57; H, 7.09; N, 19.70. Found: C, 67.40; H, 6.97; N, 19.79.

4-Acetyl-4-ethylpimelonitrile.—To a stirred solution of 60 g. of methyl *n*-propyl ketone, 10 g. of tertiary butyl alcohol and 1 g. of "Triton B," there was added dropwise 74 g. of acrylonitrile during the course of one and one-half hours while maintaining the reaction temperature at 10–15° by means of an ice-bath. The mixture was stirred for one hour longer at 15° after all the acrylonitrile had been added. It was then made slightly acid with dilute hydrochloric acid, and the crystalline precipitate filtered off and washed with a little ethanol; yield 57 g. Upon recrystallization from ethanol the compound formed colorless crystals, m. p. 109°. *Anal.* Calcd. for $C_{11}H_{16}N_2O$: C, 68.70; H, 8.39; N, 14.57. Found: C, 68.50; H, 8.15; N, 14.49.

1,3,3-Tri-(β-cyanoethyl)-pentanone-2.—The filtrate from the above preparation was mixed with ethylene dichloride and washed thoroughly with water. The ethylene dichloride was evaporated off under reduced pressure on a steam-bath and the residual oil (67 g.) distilled in high vacuum. The fraction boiling at 200–270° (1 mm.) amounting to 10 g. was crystalline and consisted almost entirely of 4-acetyl-4-ethylpimelonitrile. The fraction boiling at 270–285° (1 mm.) amounted to 26 g. and consisted almost entirely of 1,3,3-tri-(β-cyanoethyl)-pentanone-2. Upon recrystallization from ethanol it melted at 90–91°. *Anal.* Calcd. for $C_{14}H_{19}N_3O$: C, 68.53; H, 7.81; N, 17.13. Found: C, 68.51; H, 7.61; N, 17.27.

γ-Acetyl-γ-ethylpimelic Acid.—A mixture of 400 g. of water, 88 g. of sodium hydroxide, and 192 g. of 4-acetyl-4-ethylpimelonitrile was boiled under reflux for five hours. The clear solution was treated with "Norite," filtered, and acidified with 210 g. of concentrated hydrochloric acid while it was cooled and stirred. The product separated as a white crystalline mass (yield 170 g.) which, upon recrystallization from hot water, melted at 112–113°. *Anal.* Calcd. for $C_{11}H_{18}O_5$: C, 57.36; H, 7.88. Found: C, 57.70; H, 7.83.

γ-Carboxy-γ-ethylpimelic Acid.—To a stirred filtered solution of potassium hypochlorite made from 250 g. of calcium hypochlorite, 1500 g. of water, 175 g. of potassium carbonate and 50 g. of potassium hydroxide, there was added gradually at 60–70°, 115 g. of γ-acetyl-γ-ethylpimelic acid in 300 g. of 20% sodium hydroxide solution. Chloroform was evolved. The product was worked up as described for compound XIII. Upon evaporation of the acetone, 105 g. of crystalline product was obtained. Upon recrystallization from water or nitromethane it melted at 172°. *Anal.* Calcd. for $C_{10}H_{16}O_6$: C, 51.69; H, 6.95. Found: C, 51.30; H, 6.51.

γ-Acetyl-γ-alkyl-pimelonitriles (Alkyl = Isopropyl, *n*-butyl, *n*-amyl).—In Table V are given the physical and

TABLE V

$$NC{-}CH_2CH_2{-}\underset{\displaystyle R \quad CO{-}CH_3}{\overset{\displaystyle |}{C}}{-}CH_2CH_2{-}CN$$

Value of R	B. p., °C.	Mm.	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Iso-propyl	200–205	2	101	$C_{12}H_{18}N_2O$	...	..	13.58	...	..	13.50
n-Butyl	205–210	2	63	$C_{13}H_{20}N_2O$	70.86	9.16	12.71	71.09	9.09	12.71
n-Amyl	195–200	1	47	$C_{14}H_{22}N_2O$	71.74	9.47	11.96	71.60	9.81	12.06

analytical data of various dicyanoethylated homologs of methyl propyl ketone, prepared, respectively, from methyl isobutyl ketone, methyl *n*-amyl ketone, and methyl *n*-hexyl ketone. These dinitriles were prepared in the same manner as compound XII, but since they did not separate as solids from the reaction mixture, they were isolated by vacuum distillation after neutralizing the alkaline catalyst with dilute hydrochloric acid. The distilled products were then crystallized from ethanol to constant melting point. The yields of dicyanoethylation product were 50 to 60% in the case of methyl *n*-amyl ketone and methyl *n*-hexyl ketone, but only about 20% in the case of methyl isobutyl ketone, which reacted very sluggishly.

γ-Acetyl-γ-alkylpimelic Acids (Alkyl = Isopropyl, *n*-butyl, *n*-amyl).—These were obtained by saponification of the dinitriles of Table V, by boiling with an excess of aqueous sodium hydroxide solution, bleaching the resulting solution with charcoal, filtering, and acidifying the filtrate with concentrated hydrochloric acid, by the method described in the preparation of γ-acetyl-γ-ethylpimelic acid. They are listed in Table VI.

TABLE VI

$$HOOC{-}CH_2CH_2{-}\underset{\displaystyle R \quad CO{-}CH_3}{\overset{\displaystyle |}{C}}{-}CH_2CH_2COOH$$

Value of R	M. p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
Isopropyl[a]	148	$C_{12}H_{20}O_5$	58.98	8.26	59.10	8.15
n-Butyl[b]	60–61	$C_{13}H_{22}O_5$	60.42	8.59	60.70	8.39
n-Amyl[b]	73–74	$C_{14}H_{24}O_5$	61.72	8.88	61.50	8.95

[a,b] Recrystallized from *a* water; *b* benzene.

γ-Alkyl-γ-carboxypimelic Acids (Alkyl = Isopropyl, *n*-butyl, *n*-amyl).—These were prepared by treating the above γ-acetyl-γ-alkylpimelic acids dissolved in aqueous sodium hydroxide solution with an excess of potassium hypochlorite solution containing free potassium hydroxide at 60–70°, destroying the excess hypochlorite after eight hours of reaction, by means of sodium bisulfite, acidifying the solution with hydrochloric acid and evaporating the mixture to dryness, by exactly the same procedure as described above in the preparation of γ-carboxy-γ-ethylpimelic acid. The dried residue was extracted with acetone, and the acetone extract evaporated to dryness in vacuum on a steam-bath. The resulting crude tri-carboxylic acids were each recrystallized from water or nitromethane and dried over phosphorus pentoxide for analysis. These are listed in Table VII.

TABLE VII

$$HOOC{-}CH_2CH_2{-}\underset{\displaystyle R \quad COOH}{\overset{\displaystyle |}{C}}{-}CH_2CH_2COOH$$

Value of R	M. p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
Isopropyl[a]	160–161	$C_{11}H_{18}O_6$	53.63	7.37	53.50	7.23
n-Butyl[b]	125	$C_{12}H_{20}O_6$	55.35	7.75	55.01	7.65
n-Amyl[b]	114–115	$C_{13}H_{22}O_6$	56.90	8.09	56.70	7.90

[a,b] Recrystallized from *a* nitromethane; *b* water.

XVII. 1,1,1-Tri-(β-cyanoethyl)-acetone.—To a solution of 29 g. of acetone, 30 g. of tertiary butyl alcohol and 2.5 g. of ethanolic 30% potassium hydroxide solution, cooled to 0° there was added dropwise, with rapid mechanical stirring, a solution consisting of 80 g. of acrylonitrile and 37 g. of tertiary butyl alcohol during a period of one and one-half hours while the reaction mixture was maintained between 0 and 5° by an ice–salt cooling bath. The mixture was stirred thereafter for two hours at 5° and the crystalline product filtered off by suction; yield 84 g. After recrystallization from hot water or from glycol monoethyl ether it formed colorless crystals; m. p. 154°. *Anal.* Calcd. for $C_{12}H_{15}N_3O$: C, 66.32; H, 6.96; N, 19.34. Found: C, 66.80; H, 6.91; N, 19.40.

1,1,1-Tri-(β-carboxyethyl)-acetone.—A mixture consisting of 140 g. of potassium hydroxide, 800 cc. of water, and 120 g. of XVII was boiled under reflux for four hours. The solution was treated with "Norite," cooled to 50° and filtered. The filtrate was acidified to congo red indicator with concentrated hydrochloric acid, and then evaporated to dryness under reduced pressure on a steam-bath. The residue was extracted with hot acetone. Upon cooling the hot filtered acetone extract, tri-(carboxyethyl)-acetone separated in colorless crystals; yield 80 g. More can be obtained from the mother liquor. The compound forms colorless needles from acetone melting at 149–150°. It is readily soluble in water or in ethanol. *Anal.* Calcd. for $C_{12}H_{18}O_7$: C, 52.53; H, 6.62. Found: C, 52.30; H, 6.68.

XVIII. Tri-(β-carboxyethyl)-acetic Acid.—To a stirred filtered solution of potassium hypochlorite prepared from 85 g. of calcium hypochlorite ("HTH" containing 70% available chlorine), 59.5 g. of anhydrous potassium carbonate, 17 g. of potassium hydroxide and 510 g. of water, there was added dropwise at 60–70° a solution of 136 g. of 20% sodium hydroxide solution and 46.5 g. of 1,1,1-tri-(β-carboxyethyl)-acetone. Chloroform was evolved. The mixture was stirred for two hours after reaction had apparently ceased. The product was worked up as described for compound XIII. The acetone extract upon evaporation yielded a white powdery residue which after several recrystallizations from water melted at 192° after softening at 182°. *Anal.* Calcd. for $C_{11}H_{16}O_8$: C, 47.80; H, 5.84. Found: C, 47.70; H, 5.67.

XIX. 1,3,3,3-Tetra-(β-cyanoethyl)-acetone.—A solution of 43.4 g. of 1,1,1-tri-(β-cyanoethyl)-acetone in 150 g. of acetonitrile was prepared by warming at 50°. To this stirred solution, 5 g. of "Triton B" was added. Acrylonitrile (31.6 g.) was then added dropwise during twenty

minutes, while stirring and maintaining the temperature at 40–42°. The mixture was stirred for two hours longer, then cooled, acidified with dilute hydrochloric acid, poured into water, and the oil taken up in ethylene dichloride. The ethylene dichloride solution was washed with water and dried in vacuum on a steam-bath. The residual oil weighed 53 g. Upon distillation in high vacuum, 27 g. of material distilled over up to 320° (1–3 mm.) This was mostly tri-(cyanoethyl)-acetone. The fraction which came over at 320–340° (1–3 mm.) weighed 7 g. Upon recrystallization from methanol it formed colorless needles, m. p. 121–122°. *Anal.* Calcd. for $C_{15}H_{18}N_4O$: C, 66.63; H, 6.71; N, 20.73. Found: C, 66.04; H, 6.63; N, 20.39.

γ-Acetyl-γ-phenylpimelonitrile.—Acrylonitrile (53 g.) was added dropwise to a stirred solution of 100 g. of tertiary butyl alcohol, 67 g. of phenylacetone, and 5 g. of "Triton B" while the reaction mixture was stirred and maintained at 20–25° by cooling. After one hour of additional stirring the almost solid mixture of crystalline product was filtered off and washed with about 50 cc. of methanol; yield 104 g. of colorless crystals. Upon recrystallization from ethanol it melted at 109–110°. *Anal.* Calcd. for $C_{15}H_{16}N_2O$: C, 74.95; H, 6.71; N, 11.66. Found: C, 74.70; H, 6.67; N, 11.63.

γ-Acetyl-γ-phenylpimelic acid.—A mixture of 40 g. of sodium hydroxide, 400 g. of water, and 87 g. of γ-acetyl-γ-phenylpimelonitrile was boiled under reflux for nine hours, treated with "Norite," filtered, and acidified with concentrated hydrochloric acid. The product separated as a thick oil which rapidly solidified. After recrystallization from water, the analytical sample melted at 171–172°. *Anal.* Calcd. for $C_{15}H_{18}O_5$: C, 64.72; H, 6.52. Found: C, 64.85; H, 6.64.

XX. γ-Carboxy-γ-phenylpimelic Acid.—To a stirred filtered potassium hypochlorite solution made from 50 g. of calcium hypochlorite ("HTH" containing 70% available Cl), 35 g. of anhydrous potassium carbonate, 10 g. of potassium hydroxide and 300 g. of water, there was added dropwise at 60–70° a solution of 27.8 g. of γ-acetyl-γ-phenylpimelic acid in 60 g. of aqueous 20% sodium hydroxide, while stirring. Chloroform was evolved. The mixture was stirred for one hour after reaction had ceased, and worked up as described for compound XIII. Upon evaporation of the acetone, 19 g. of resin-like material was obtained. Upon crystallization of the resin from nitromethane the product separated in the form of colorless crystals melting at 154°. *Anal.* Calcd. for $C_{14}H_{16}O_6$: C, 59.97; H, 5.76. Found: C, 59.67; H, 5.85.

XXI. α,α-Di-(2-cyanoethyl)-acetoacetic Methyl Ester.—(a) To a solution of 58 g. of methyl acetoacetate, 100 g. of dioxane and 7 g. of "Triton B," there was added 53 g. of acrylonitrile while the solution was stirred and cooled to 30–40°. After stirring for one hour the crystalline product was filtered off; yield 55 g. After recrystallization from acetone it formed colorless crystals melting at 154°. A further quantity can be obtained from the original filtrate on addition of water. *Anal.* Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.43; H, 6.35; N, 12.60. Found: C, 59.80; H, 6.29; N, 12.59.

(b) The ethyl ester can be obtained in the same manner by using 65 g. of ethyl acetoacetate in the above procedure. The crude reaction product was poured into one liter of ice water whereupon the compound separated in crystalline form. After recrystallization from ethanol it melts at 82°. *Anal.* Calcd. for $C_{12}H_{16}N_2O_3$: C, 60.98; H, 6.83; N, 11.85. Found: C, 61.60; H, 6.88; N, 11.84.

Acknowledgment.—The analyses of the above products were performed by the semi-micro method by Mr. C. W. Nash of these laboratories.

Summary

1. Acrylonitrile condenses in the presence of aqueous trimethylbenzylammonium hydroxide or other strong alkali as a catalyst, with reactive ketones having a —CH—, —CH_2—, or CH_3— group adjacent to the carbonyl, so as to replace one or more of the reactive hydrogen atoms thereof by β-cyanoethyl radicals. The reaction furnishes a simple method for preparing a wide variety of ketonic polynitriles and polycarboxylic acids.

2. Acetophenone and its aryl substituted derivatives gave tri-cyanoethylation products R—CO—$C(CH_2CH_2CN)_3$; cyclopentanone, cyclohexanone and para-substituted cyclohexanones gave tetra-cyanoethylation products; *o*-methylcyclohexanone gave a tri-cyanoethylation product, and α-tetralone gave a dicyanoethylation product.

3. Acetone gave a crystalline tri-cyanoethylation product, $CH_3CO—C(CH_2CH_2CN)_3$. Substituted acetones of the type R—CH_2—CO—CH_3 (R is alkyl or aryl) reacted first on the —CH_2— group to give dicyanoethylation products. These products are cyanoethylated further on the residual CH_3 group.

4. Acetoacetic esters similarly gave crystalline dicyanoethylation products.

PHILADELPHIA, PA. RECEIVED AUGUST 17, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN]

Phenethylamines. IV. Dimethoxy and Dihydroxyphenyl-*n*-propylamines (β-Methyl-β-phenethylamines)[1]

BY E. H. WOODRUFF

It was desired to have available for the purpose of pharmacological study a series of compounds possessing the phenethylamine skeleton in which all possible mono and disubstituted isomers were represented. This communication reports the preparation of all possible nuclear dimethoxy and dihydroxy-β-phenyl-*n*-propylamines. In conjunction with work already published[2] the first such complete series of isomers is available for pharmacological comparison, the results of which will appear elsewhere.

The general outline for the preparation of the amines described in the experimental section follows that previously used in this Laboratory.[3,4] The appropriately substituted cinnamic acid was reduced to the hydrocinnamic acid, the amide prepared from the acid chloride and the amine then obtained from the amide by means of sodium hypobromite.

When possible it was found to be more convenient to prepare the β-methylcinnamic acids having an ortho methoxyl group by the hydrolysis and methylation of a hydroxy-4-methylcoumarin. This method gave uniformly the *trans* or high melting form of the cinnamic acid in contrast to the mixture of isomers obtained by the dehydration and saponification of a hydroxy ester.[4,5] No satisfactory method for the preparation of 8-hydroxy-4-methylcoumarin was found so the 2,3-dimethoxy-β-methylcinnamic acid as well as those not containing an ortho methoxyl were obtained through the Reformatsky reaction on the appropriate ketone followed by dehydration and saponification.

The preparation of 2,6-dimethoxy-β-methylcinnamic acid from the 5-hydroxy-4-methylcoumarin gave an 80% yield of the *trans*-form melting at 185°.[6] None of the low melting (148–150°) form previously reported[7] as being obtained from this coumarin was found. However, when the acid was prepared through the Reformatsky reaction after repeated crystallizations an acid melting at 143–144° was obtained. These two acids on further treatment gave identical products.

In an early attempt to prepare 3,5-dihydroxyacetophenone, the alkali fusion of the supposed acetophenone 3,5-disulfonyl chloride of Riesz and Frankfurter[8] was tried. *m*-Hydroxybenzoic acid m. p. 201–202° and *m*-methoxybenzoic acid m. p. 102–108° from the methylation of the hydroxy acid were obtained. This confirms the statement of Suter and Weston[9] that only one sulfonyl group had entered the ring.

The 2,3- and 3,5-dimethoxyacetophenones were prepared from the corresponding benzoyl chlorides and dimethylcadmium.[10] This method is satisfactory for aromatic acid chlorides with dimethylcadmium to give methyl ketones but the yields are lower when used to prepare higher members of a series.

The reduction of the cinnamic acids by sodium amalgam as previously used[4] was replaced early in this investigation by electrolytic reduction using a lead anode and a mercury cathode.[11] This method is as efficient as sodium amalgam in the reduction of cinnamic acids with the possible exception of the 2,6-dimethoxy derivative and is more convenient when large amounts of the amalgam must be prepared.

Experimental

Preparation of Coumarins.—7-Hydroxy-[12,13] and 6-hydroxy[14]-4-methylcoumarins were prepared as described in the literature. For the preparation of 5-hydroxy-4-methylcoumarin the condensation of methyl β-resorcylate with acetoacetic ester by means of anhydrous aluminum chloride in nitrobenzene was carried out according to Sethna, Shah and Shah.[7] After the removal of the nitrobenzene the product was boiled twice with 200-cc. portions of methyl alcohol, filtering hot and discarding the filtrate. The intermediate crude methyl 5-hydroxy-4-methylcoumarin-6-carboxylate melting at 175–182° was obtained

(1) A part of this material was presented at the St. Louis meeting of the American Chemical Society, April, 1941.
(2) Woodruff, Lambooy and Burt, THIS JOURNAL, **62**, 922 (1940).
(3) Woodruff and Conger, *ibid.*, **60**, 465 (1938).
(4) Woodruff and Pierson, *ibid.*, **60**, 1075 (1938).
(5) Lindenbaum, *Ber.*, **50**, 1272 (1917).
(6) Limaye and Kelkar, *Rasayanam* [I], **27**, 47 (1936), through *C. A.*, **31**, 2213 (1937).
(7) Sethna, Shah and Shah, *J. Chem. Soc.*, 231 (1938).
(8) Riesz and Frankfurter, *Monatsh.*, **50**, 68 (1928).
(9) Suter and Weston, THIS JOURNAL, **61**, 233 (1939).
(10) Gilman and Nelson, *Rec. trav. chim.*, **55**, 528 (1936).
(11) Ingersoll, "Organic Syntheses," Coll. Vol. I, 2nd ed., 1941, p. 311.
(12) Russell, Frye and Mauldin, THIS JOURNAL, **62**, 1443 (1940).
(13) Russell and Frye, "Organic Syntheses," Vol. **21**, 1941, p. 23.
(14) Borche, *Ber.*, **40**, 2731 (1907).

TABLE I

ISOMERIC DIMETHOXY DERIVATIVES OF β-METHYLCINNAMIC ACID ($C_{12}H_{14}O_4$)

Isomer	Ethyl ester B. p., °C.	Mm.	Yield, %	M. p., °C.	Yield,[a] %	Analyses, % C Calcd.	C Found	H Calcd.	H Found
2,3-	165–175	8	37	121 –122	84	64.83	64.74	6.35	6.22
2,6-	136–138[b]	0.03	16[c]	143 –144[d]	83	64.83	64.51	6.35	6.51
3,4-	200–203	11	70	138 –140[e]	67				
3,5-	197–203	11	75	123.5–124.5	88	64.83	64.79	6.35	6.28

[a] From ester before crystallization. [b] *Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.17; H, 7.20. Found: C, 67.11; H, 7.09. [c] Yield 48% allowing for recovered ketone. [d] From Reformatsky reaction. An 80% yield of acid melting at 185–185.5° was obtained by hydrolysis of 6-hydroxy-4-methylcoumarin. [e] M. p. 138–140°, ref. 34.

in 47% yield. The hydrolysis of the ester was accomplished by refluxing with 73% sulfuric acid instead of heating in a sealed vessel with a mixture of hydrochloric and acetic acids. The product so obtained was heated to 300° and after decarboxylation was distilled at 10 mm. The crude 5-hydroxy-4-methylcoumarin was obtained in 57.5% yield and melted when crystallized once from alcohol at 260°.

Preparation of Ketones.—2,3-Dimethoxybenzoic acid[15,16] was prepared in 85% yield by the oxidation of 2,3-dimethoxybenzaldehyde[17] with potassium permanganate.[18] Oxalic acid was used to remove the manganese dioxide prior to the precipitation of the acid. The acid was converted to the chloride (94%)[19] using a sixfold excess of thionyl chloride. Twice the calculated amount of thionyl chloride was consumed, the remainder being recovered. 3,5-Dimethoxybenzoic acid[20] was obtained by methylating 3,5-dihydroxybenzoic acid.[21] The acid was converted to the acid chloride (90%) using phosphorus pentachloride and carbon tetrachloride.[22] The 2,3- (71%) and 3,5- (84%)-dimethoxyacetophenones[23,24] were obtained from the acid chlorides by the procedure of Gilman and Nelson.[10] The ketone so prepared was always contaminated with ester. This was removed by refluxing the crude product with alcoholic alkali. The yields given deduct for the recovered acid. 3,4-Dimethoxyacetophenone[25] was prepared by the reaction of veratrole with acetyl chloride and anhydrous aluminum chloride below +10°, using twice the quantity of solvent used in the previous preparation. After filtration from the insoluble complex (20% loss) the solvent may be reused without purification. 2,6-Dimethoxyacetophenone[26] was obtained by methylating 2,6-dihydroxyacetophenone.[13]

Preparation of Cinnamic Acids.—The cinnamic acids were prepared in two ways as previously mentioned. For a discussion of the Reformatsky reaction a recent review by Shriner[27] is recommended. In two instances the presence of *o*-methoxy groups caused a considerable lowering of the yield. This was so great in the case of the 2,6-dimethoxyacetophenone as to render this method unsuitable for the preparation of suitable quantities of the acid. The dehydration of the hydroxy esters was accomplished with a minimum of side reactions by heating to 250–300° at atmospheric pressure. The hydrolysis and methylation of a hydroxycoumarin is illustrated by the following example: 35.2 g. (0.2 mole) of 6-hydroxy-4-methylcoumarin was shaken with 25 cc. of dimethyl sulfate and 28 cc. of 33% potassium hydroxide solution. After the reaction had subsided the solution was cooled and again shaken with alkali and methyl sulfate. While hot, 50 cc. of 33% potassium hydroxide was added and the reaction refluxed one hour. The methylation treatment was repeated and after the addition of excess alkali the solution was refluxed to hydrolyze any methyl ester formed. The solution was diluted to one liter and boiled with decolorizing charcoal and filtered. When cold, hydrochloric acid was added, the precipitated acid collector on a Büchner funnel, washed with water and dried. Crystallization is best from a benzene–skelly-solve B mixture although alcohol–water may be used. The 2,5-dimethoxy-β-methylcinnamic acid (81%) so obtained melted at 119–120°.[28] In a similar manner 2,4-dimethoxy-β-methylcinnamic acid (76% yield) melting at 148° was obtained.[29]

Hydrocinnamic Acids.—The cinnamic acids were reduced electrolytically.[11] 2,6-Dimethoxy-β-methylhydrocinnamic acid was also prepared by the reduction of 5-hydroxy-4-methylcoumarin[30] followed by the hydrolysis and methylation of the dihydrocoumarin.

Seventeen and six-tenths grams (0.1 mole) of 5-hydroxy-4-methylcoumarin, 200 cc. of alcohol and 6 cc. of Raney nickel catalyst were reduced at 60° and 60 pounds hydrogen pressure in an Adams hydrogenator. After seven hours, the theoretical amount of hydrogen was absorbed. The catalyst was filtered and the solvent removed. The residue was crystallized from alcohol–water or benzene–skelly solve B.

Fourteen and six-tenths grams (82%) of 5-hydroxy-4-methyl-3,4-dihydrocoumarin b. p. 214° at 5 mm., m. p. 160° was obtained. *Anal.* Calcd. for $C_{10}H_{10}O_3$: C,

(15) Perkin and Robinson, *J. Chem. Soc.*, 2383 (1914).

(16) Perkin, Robinson and Stoyle, *ibid.*, 197 (1925).

(17) Obtained through the courtesy of the Monsanto Chemical Company.

(18) Shriner and Kleiderer, "Organic Syntheses," Vol. X, 1930, p. 82.

(19) Mauthner, *J. prakt. Chem.*, **112**, 60 (1926).

(20) Mauthner, *ibid.*, **87**, 405 (1913).

(21) Weston and Suter, "Organic Syntheses," Vol. **21**, 1941, p. 27. By the use of a countercurrent extraction column the yield of acid was 1983 g. from 6220 g. of barium salt or 82%.

(22) Fischer, Bergmann and Lipschutz, *Ber.*, **51**, 55 (1918).

(23) (a) v. Krannichfeld, *ibid.*, **46**, 4016 (1913); (b) Baker and Smith, *J. Chem. Soc.*, 347 (1936).

(24) Mauthner, *J. prakt. Chem.*, **107**, 106 (1924).

(25) Koepfli and Perkin, *J. Chem. Soc.*, 2995 (1928).

(26) Sugasawa, *ibid.*, 1483 (1934).

(27) "Organic Reactions," Roger Adams, Editor-in-Chief, John Wiley and Sons, Inc., New York, N. Y., 1942, Chapter 1.

(28) Baltzly and Buck, THIS JOURNAL, **62**, 161 (1940), obtained an acid m. p. 113° from the Reformatsky reaction.

(29) v. Pechmann and Cohen, *Ber.*, **17**, 2132 (1884).

(30) de Benneville and Connor, THIS JOURNAL, **62**, 283 (1940), report the reduction of coumarin to dihydrocoumarin in ether using Raney nickel at 100°.

TABLE II

ISOMERIC DIMETHOXY-β-METHYLHYDROCINNAMIC ACIDS ($C_{12}H_{16}O_4$)

Isomer	M. p., °C.	B. p. °C.	B. p. Mm.	Yield, %	Analyses, % C Calcd.	C Found	H Calcd.	H Found
2,3-	77	181–184	0.15	85	64.27	64.43	7.24	7.33
2,4-	104 –105			82	64.27	64.28	7.24	7.10
2,5-	78 – 79[a]	175–185	0.1	86				
2,6-	78.5– 79	190–197	3.0		64.27	64.38	7.24	7.33
3,4-	84 – 85[b]			80				
3,5-	Liquid	184–188	0.05	85	64.27	64.05	7.24	7.09

[a] M. p. 79°; ref. 5. [b] M. p. 84–85°; ref. 34.

TABLE III

ISOMERIC DIMETHOXY-β-METHYLHYDROCINNAMIDES $C_{12}H_{17}ON$

Isomer	M. p., °C.	Yield,[a] %	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
2,3-	90 – 91	52	64.55	64.33	7.68	7.44	6.27	6.01
2,4-	133 –134	61	64.55	64.35	7.68	7.48		
2,5-	122[b]	80						
2,6-	153 –155	88	64.55	64.40	7.68	7.60	6.27	6.09
3,4-	131	90	64.55	64.56	7.68	7.94		
3,5-	92.5– 93[c]	60	64.55	64.40	7.68	7.50	6.27	6.09

[a] Yield before crystallization. [b] M. p. 121°; ref. 5. [c] B. p. 210–235° at 0.15 mm. This amide is difficult to crystallize.

TABLE IV

ISOMERIC DIMETHOXY-β-PHENYL-*n*-PROPYLAMINO HYDROCHLORIDES ($C_{11}H_{18}O_2NCl$)

Isomer	B. p. °C.[a]	B. p. Mm.	Yield, %	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
2,3-	150–154	11	37	133.5–134	57.01	56.80	7.82	8.04	6.04	6.02	15.31	15.55
2,4-	158–160	14	15	146 –147	57.01	56.81	7.82	7.82				
2,5-	164–166[b]	16	80	149 –150[b]								
2,6-	155–158	5	36	143 –145	57.01	56.79	7.82	8.05	5.04	6.00	15.31	15.30
3,4-	163–166	15	62	205 –206	57.01	56.81	7.82	7.60				
3,5-	179–184	14	57	105 –107	57.01	56.79	7.82	8.07	6.04	6.18	15.31	15.11

[a] The boiling point is for the free amine. [b] B. p. 114° at 1 mm., m. p. 149–150°; ref. 5.

TABLE V

ISOMERIC DIHYDROXY-β-PHENYL-*n*-PROPYLAMINE HYDROCHLORIDES ($C_9H_{14}O_2NCl$)

Isomer	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
2,3-	191 –191.5	53.07	53.01	6.93	6.99	6.88	6.90	17.41	17.65
2,4-	222 –223	53.07	53.11	6.93	7.08				
2,5-	167.5–169.5	53.07	53.01	6.93	7.15	6.88	6.98	17.41	17.50
2,6-	93 – 95	53.07	52.99	6.93	7.14	6.88	6.72	17.41	17.26
3,4-	180 –181	53.07	52.92	6.93	7.17				
3,5-	164 –166	53.07	52.99	6.93	7.20	6.88	6.98	17.41	17.14

67.40; H, 5.66. Found: C, 67.10; H, 5.85. The hydrolysis to the hydrocinnamic acid was carried out as previously given. A yield of 91% was obtained. After two crystallizations from a dilute solution in skelly-solve B, crystals m. p. 78.5–79° were obtained identical with those obtained by the reduction of the cinnamic acid.

Dimethoxy-β-methylhydrocinnamides.—The amides were prepared as previously reported.[3] They were crystallized from alcohol–water or benzene–skelly solve B.

Dimethoxyphenyl-*n*-propylamines.—The amines were prepared by the action of sodium hypobromite on the finely divided (to pass a 40-mesh screen) amide.[3] The ease of solution of the amide appears to vary with the ring substituents. The presence of a *m*-methoxy group confers increased ease of solubility. The 2,4-dimethoxy amide was the least soluble. The hydrochlorides were best prepared by adding a weighed amount (10% over the molecular quantity) of dry hydrogen chloride to absolute ethyl alcohol. The alcoholic hydrogen chloride was added to the amine and the hot solution is diluted with anhydrous ether until a faint cloudiness just fails to persist. On cooling, the amine hydrochloride precipitates in a crystalline condition. The direct addition of dry hydrogen chloride to an anhydrous ether solution of the amine often gave a gummy precipitate which later solidified. This was more difficult to purify. Recrystallization was carried out from an absolute alcohol–ether mixture.

Dihydroxyphenyl-*n*-propylamine Hydrochloride.—Demethylation was accomplished by heating in a sealed tube with concentrated hydrochloric acid for two hours at

160°.[3,4] The dihydroxyamine hydrochlorides are more hygroscopic and difficult to crystallize than the methoxy amines. The crystalline condition of the hydrochloride has much to do with its deliquescence. When alcohol–ether cannot be used for crystallization, alcohol–benzene, alcohol–toluene, or ethyl–acetate–alcohol may be used. The usefulness of the solvent varies with the amine hydrochloride even in such a closely related group of isomers as reported here.

The author wishes to thank Dr. Earl Pierson, Dr. John P. Lambooy and Dr. William E. Burt for their assistance while holders of Kalamazoo College Fellowships and Mr. Harold Emerson and Mr. William A. Struck for the micro analyses.

Summary

All of the nuclear dimethoxy- and dihydroxy-β-phenyl-*n*-propylamines and their hydrochlorides have been prepared. The properties are reported for the cinnamic acids, hydrocinnamic acids and hydrocinnamides used in the preparation of these amines as well as the syntheses of many of the intermediates used in their preparation. The hydrolysis and methylation of an hydroxy-4-methylcoumarin always gave the *trans* form of the resulting dimethoxy-β-methylcinnamic acid.

KALAMAZOO, MICHIGAN RECEIVED AUGUST 1, 1942

[CONTRIBUTION FROM THE SANDERS LABORATORY OF CHEMISTRY, VASSAR COLLEGE]

The Reaction of *n*-Butylmagnesium Bromide with Some Aromatic Ketones[1,2]

BY H. MARJORIE CRAWFORD, MARY ELIZABETH SAEGER[3] AND FLORENCE E. WARNEKE[4]

Since *n*-butyl bromide can be prepared by students in good yield and reacts readily with magnesium to give a Grignard reagent, we had hoped to work out a series of student preparations by adding this Grignard reagent to a ketone and dehydrating the resulting tertiary alcohol to the corresponding unsaturated compound. This purpose was not achieved, but several new compounds were prepared in the course of the studies. Four ketones were selected for study: acetophenone, benzophenone, benzil and desoxybenzoin.

A. Acetophenone.—The reaction of acetophenone and *n*-butylmagnesium bromide gave good yields (72–80%) of the expected tertiary alcohol, 2-phenylhexanol-2 (I). This tertiary alcohol was very resistant to complete dehydration, but was finally transformed into the unsaturated hydrocarbon, 2-phenylhexene-2 (II), by heating with Lucas reagent. The position of the double bond was established by oxidation to acetophenone and *n*-butyric acid. The same results were obtained whether the oxidizing agent was potassium permanganate in sulfuric acid or chromium trioxide in acetic acid.

B. Benzophenone.—The reducing action of aliphatic Grignard reagents on benzophenone has been studied by several workers.[5] Schlenk and Bergmann[6] obtained impure diphenyl-*n*-butylcarbinol by the reaction of phenylmagnesium bromide on ethyl *n*-valerate. It was mixed with the dehydration product and was easily converted into the unsaturated hydrocarbon. The two reactions which we carried out gave no tertiary alcohol and no unsaturated hydrocarbon. Benzohydrol (17 and 30%) was obtained. The remaining oils were distilled under reduced pressure and a yield of 5.6% of dibenzylhydryl ether separated from the residue (above 270°, 42 mm.). Analyses of this compound agreed closely with the calculated values. Dibenzhydryl ether had previously been reported by Kharasch and Weinhouse[5] as resulting from the reaction of allylmagnesium bromide on benzophenone.

C. Benzil.—The reaction of *n*-butylmagnesium bromide on benzil gave small yields of solid products regardless of the variations in procedure. Both addition and reduction occurred. The reduction product, benzoin, was obtained in seven of the ten reactions in yields varying from 0.5 to 13.0%. The mono-addition product 1,2-diphenylhexanol-2-one-1 (II) was obtained in all ten reactions in yields varying from 0.5 to 5.6%. A solid which was possibly the di-addition product (V) was obtained twice in very small yields. Benzoic acid was obtained after the oily

(1) Presented before the Organic Division of the American Chemical Society, Buffalo, September 7, 1942.

(2) Abstracted from the theses submitted by Mary Elizabeth Saeger and Florence E. Warneke in partial fulfillment of the requirements for the degree of Master of Arts at Vassar College.

(3) Present address, American Cyanamid Company, Stamford, Conn.

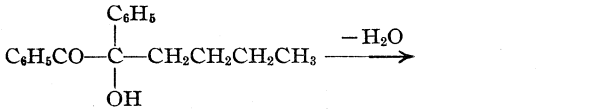
(4) Present address, U. S. Department of Agriculture, Chicago, Ill.

(5) Blicke and Powers, THIS JOURNAL, **51**, 3378 (1929); Noller and Hilmer, *ibid.*, **54**, 2503 (1932); Kharasch and Weinhouse, *J. Org. Chem.*, **1**, 209 (1936).

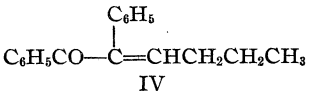
(6) Schlenk and Bergmann, *Ann.*, **479**, 42 (1930).

mixtures were exposed to the light for some time. Under these conditions benzil decomposes to form benzoic acid.[7] The only generalization which can be drawn from the results of the ten reactions is that the yield of mono-addition product (III) was smaller when a large excess of *n*-butylmagnesium bromide was used. The highest yields were obtained when 0.2 mole of benzil was added to 0.5 mole of *n*-butylmagnesium bromide.

Dehydration of the mono-addition product (III) by refluxing with Lucas reagent gave a liquid unsaturated ketone (IV) whose structure was established by oxidation to benzil and *n*-butyric acid.



III



IV

Attempts to prepare the di-addition product by the reaction of *n*-butylmagnesium bromide on the mono-addition product were not successful.

D. Desoxybenzoin.—No addition products were obtained from the reaction of *n*-butylmagnesium bromide on desoxybenzoin, but various reduction products were isolated in very small yields. The product obtained in the largest amounts was stilbene, which would result from reduction of the desoxybenzoin followed by the loss of a molecule of water. It was obtained in three of the four reactions in yields of 2.5, 5.3 and 7.4%. Desoxybenzoin pinacol (m. p. 175°) was obtained in two reactions, but the total yield was only 0.3 g. It was identified by a mixed melting point with a known sample of the pinacol. A compound thought to be the pinacolone (VI) was obtained in two reactions, the total yield being 1%. All attempts to rearrange the pinacol were unsuccessful and the amount of the compound VI available was too small to make structure proof possible. The formation of a pinacolone would be interesting, for, although the pinacol has been known since 1870, no mention of the pinacolone could be found. Orechoff[8] dehydrated the pinacol by boiling it with acetyl chloride, a treatment known to rearrange many pinacols, and recorded the formation of 1,2,3,4-tetraphenylbutadiene-1,3 and other products.

(7) Klinger, *Ber.*, **19**, 1864 (1886).
(8) Orechoff, *ibid.*, **47**, 91 (1914).

Experimental

General Procedure.—Since the variations in length of time of heating the reaction mixtures, variations in the kind and amount of solvent used to dissolve the ketones and decomposition of the magnesium complex with dilute sulfuric acid or with ammonium chloride solution seemed to have no effect on the kind or amount of resulting products, the individual experiments will not be described.

n-Butylmagnesium bromide was prepared in the usual way from 0.5 mole of *n*-butyl bromide. Slightly less than the calculated amount of the ketone was dissolved in either benzene or ether and dropped slowly into the Grignard solution. After standing or being heated for varying lengths of time the magnesium complex was decomposed, the organic material was extracted with ether, and most of the solvent was removed on the steam-bath. If solid separated on standing, it was filtered and recrystallized from appropriate solvents. When no more solid formed, the oils were distilled under reduced pressure. Solid which formed in any of the fraction was then removed and recrystallized. Many of the fractions have not solidified after standing for over a year.

2-Phenylhexanol-2, I.—One refractionation gave the pure alcohol, b. p. 123–124° (9 mm.); d^{25} 0.954. It was colorless and decomposed partially when distilled at atmospheric pressure.

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18; mol. wt., 178. Found: C, 80.67; H, 10.15; mol. wt., 178.

2-Phenylhexene-2, II.—Many attempts were made to dehydrate 2-phenylhexanol-2 and none of them were entirely successful. Distillation at atmospheric pressure resulted in the partial decomposition of the alcohol. Samples of the alcohol (20–25 g.) were refluxed for two hours with 75 ml. of 20% sulfuric acid and with 20 g. of fused potassium bisulfate, for four hours with 10 g. of fused zinc chloride and with 50 g. of acetic anhydride, and for eight hours with a trace of iodine. The alcohol was dropped on anhydrous cupric sulfate at 230°. Analyses of the products from all of these reactions showed a percentage of carbon intermediate between the values calculated for the alcohol and for the unsaturated hydrocarbon. The best results were obtained by refluxing the alcohol with an equal weight of Lucas reagent for thirty minutes. After separation, washing with water and drying, the product boiled 210–230° with the main fraction at 223–226°. It decolorized bromine readily.

Anal. Calcd. for $C_{12}H_{16}$: C, 89.94; H, 10.06; mol. wt., 160. Found: C, 87.13; H, 9.87; mol. wt., 161.

1,2-Diphenylhexanol-2-one-1, III.—This compound is a white solid melting at 124°. When crystallized from a benzene–petroleum ether mixture or from 50% alcohol it forms long fine needles. The dehydration is described below. The starting material was recovered unchanged after attempts to prepare the di-addition product by treating 0.004 mole of this mono-addition product with 0.04 mole of *n*-butylmagnesium bromide. The reaction was forced by refluxing the reactants in *n*-butyl ether for five hours.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51; mol. wt., 268. Found: C, 80.13; H, 8.44; mol. wt., 273.

1,2-Diphenylhexene-2-one-1, IV.—This compound was prepared by the dehydration of 1,2-diphenylhexanol-2-

one-1. Treatment of the alcohol with gaseous hydrochloric acid and refluxing it with a trace of iodine in glacial acetic acid failed to bring about the expected dehydration. After repeated trials had failed to produce any solid material from the products of the reaction of the alcohol with Lucas reagent, the resulting liquid was distilled at atmospheric pressure. In an actual preparation of the unsaturated compound, 2 g. of the alcohol was boiled for six hours with 30 ml. of Lucas reagent. After washing with water and drying, the yield was almost 2 g. of a liquid boiling 288–290°. It decolorized bromine readily.

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.28; H, 7.23.

5,6-Diphenyldecandiol-5,6, V.—A total of about 0.5 g. of solid thought to be this di-addition product was obtained in two of the ten reactions between *n*-butylmagnesium bromide and benzil. It was only slightly soluble in benzene but after recrystallization from alcohol it melted at 184°.

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26; mol. wt., 326. Found: C, 81.87, 81.49; H, 6.24, 5.79; mol. wt., 339, 318.

Preparation of Desoxybenzoin Pinacol.—A very small yield (5%) of the pinacol was obtained by the reduction of benzoin by the method of Ballard and Dehn,[9] and no pinacol was obtained by the method of Wislicenus and Blank.[10] Desoxybenzoin pinacol was obtained in 97% yield by exposing a solution of 6 g. of desoxybenzoin in 50 ml. of isopropyl alcohol to the sunlight for several days. This is an adaptation of the method described by Fieser[11] for the preparation of benzopinacol from benzophenone. The pinacol melted at 172° and was identical with the small amount of material obtained from the reaction of *n*-butylmagnesium bromide on desoxybenzoin. Molecular weight determinations and analyses for carbon and hydrogen agreed well with the calculated values.

Attempts to Rearrange the Pinacol to the Pinacolone.—When 2 g. of the pinacol was refluxed for five minutes with a few crystals of iodine in 15 ml. of glacial acetic acid, only starting material was recovered. Increasing the time of heating to one and one-half hours caused no rearrangement and the pinacol was recovered. When the time of heating was increased to eight hours, dark gummy material was formed which would not crystallize. Refluxing for six hours with hydriodic acid in glacial acetic acid gave dark non-crystalline material. Two grams of the pinacol was added to 70 ml. of cold, concd. sulfuric acid and the resulting bright green solution was poured over ice after standing for two hours at room temperature. The pinacol was recovered. Refluxing for two hours with dilute sulfuric acid caused no rearrangement and the pinacol was recovered. Finally, *n*-butylmagnesium bromide was prepared from 5 g. of *n*-butyl bromide and 1 g. of the pinacol was added to the Grignard reagent. The ether was refluxed for one hour, then the solvent was removed and the mixture was heated overnight on the steam-bath. After decomposition with ice and ammonium chloride solution, the pinacol was recovered.

Desoxybenzoin Pinacolone, VI.—The compound thought to be the pinacolone was obtained in one reaction from a fraction boiling 242–252° (53 mm.) and from the residue, above 226° (64 mm.), in another reaction. It was crystallized from alcohol and melted at 133°. The amount available was too small to determine whether the phenyl or the benzyl group had migrated.

Anal. Calcd. for $C_{26}H_{24}O$: C, 89.32; H, 6.42; mol. wt., 377. Found: C, 89.23, 89.21; H, 6.07, 6.19; mol. wt., 376.

Summary

1. The reaction of *n*-butylmagnesium bromide on acetophenone resulted in addition to form a new tertiary alcohol. This alcohol was dehydrated to form the corresponding new olefin.

2. Benzophenone was reduced by *n*-butylmagnesium bromide to form benzohydrol and dibenzhydryl ether.

3. The reaction of *n*-butylmagnesium bromide on benzil resulted in reduction to benzoin and addition to form a new hydroxy ketone. The hydroxy ketone was dehydrated to form the corresponding unsaturated ketone.

4. Desoxybenzoin was reduced by *n*-butylmagnesium bromide to form stilbene, desoxybenzoin pinacol and a compound thought to be desoxybenzoin pinacolone.

POUGHKEEPSIE, N. Y. RECEIVED AUGUST 6, 1942

(9) Ballard and Dehn, THIS JOURNAL, **54**, 3970 (1932).

(10) Wislicenus and Blank, *Ann.*, **248**, 9 (1888).

(11) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Company, Boston, Mass., 1935, p. 202.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Ionic Nature of the Grignard Reagent

BY WARD V. EVANS AND RALPH PEARSON[1]

Work has been done in this Laboratory for the past nine years on various phases of the electrolysis of organo-magnesium halides, in ethyl ether.[2] The products of electrolysis are magnesium metal at the cathode, various hydrocarbons at the anode and magnesium halide formed in solution. Since the magnesium halide was believed to form at the anode,[3] several equations were suggested to represent the electrode reactions[4]

(a) at the cathode: $Mg^{++} + 2e^- \longrightarrow Mg$
at the anode: $R_2MgX_2^= - 2e^- \longrightarrow 2R\cdot + MgX_2$

(b) at the cathode: $2RMg^+ + 2e^- \longrightarrow Mg + R_2Mg$
at the anode: $2RMgX_2^- - 2e^- \longrightarrow 2R\cdot + 2MgX_2$

The symbol R· stands for an alkyl or aryl free radical that immediately underwent coupling, disproportionation or other reactions.

Because of the very great interest in the Grignard reagent in synthetic work and the need to understand its method of operation, it was thought desirable to do further work to prove or disprove the suggested electrode reactions and to investigate more fully the ionic equilibria involved in ether solutions of the Grignard reagent. This was done by means of transference studies, conductance data and chemical evidence. New light is also thrown upon the equilibrium

$$2RMgX \longrightarrow R_2Mg + MgX_2$$

known to be present in solutions of the Grignard reagent.[5]

Transference Studies

Experimental.—An H-tube transference cell with large internal bore in order to reduce resistance was used. Three glass stopcocks were provided for draining out the anode, cathode and middle portions. Circular platinum electrodes mounted horizontally so that no potential drop existed along their length were used. Rubber stoppers freed from sulfur, one of which was fitted with a glass tube connected to two mercury traps to allow for expansion and contraction, supported the glass tubing holding the electrodes. The whole cell was immersed almost completely in a large jar and surrounded by a mixture of ice and water. Voltages used were from 90 to 180, current was from 0.03 to 0.04 ampere filtered through a no. 80 Radiotron tube. A copper coulometer in series was used to measure the total number of coulombs. Runs were from eight to twelve hours. Sampling before and after electrolysis was by means of 25-cc. washout pipets in a hood of nitrogen to prevent decomposition by air and moisture. The anode, cathode and middle portions were weighed to the closest 0.01 g., cooled in an ice-bath, samples withdrawn, and then reweighed to get weight of sample. In this way the loss of ether by evaporation was at a minimum. Each sample was hydrolyzed with excess standard nitric acid and then back-titrated using sodium hydroxide and methyl orange indicator. This gave the equivalents of R present. Then eosin and dextrin were added to the neutral or slightly basic sample and the total halogen was titrated with standard silver nitrate. The equivalents of magnesium were then equal to the sum of R and X, where R is the alkyl group and X the halogen. In many cases this was confirmed by determining the magnesium separately as the pyrophosphate.

Results.—The only Grignards tried were ethylmagnesium bromide, *n*-butylmagnesium bromide and phenylmagnesium bromide. The ethylmagnesium bromide was found to be unsuitable for transference study as the tabulated results of Table I show. There was a considerable transport of matter to the anode portion, indicating a large, mobile anion. Since the cathode portion did not gain by transport, it became more dilute and solute diffused from the middle portion into the cathode portion. Hence a true middle portion could not be obtained. This difficulty could have been avoided by using a vertical transference cell with the cathode on top and the anode on the bottom so that diffusion to the cathode would be prevented by gravity. However, instead of changing the cell, the Grignard reagent was changed, one being chosen that would possess a larger, heavier alkyl radical both to slow down the anion and to decrease its coördinating power by virtue of its

TABLE I

TRANSFERENCE STUDY OF ETHYLMAGNESIUM BROMIDE

$T = 0°$, v. = 90, $I = 0.03$, R = 1.44 molar, X = 1.63 molar, total current = 17.4 milli-faradays. Changes in each portion expressed in milliequivalents.

	Anode	Cathode	Middle
R	+36.0	−22.3	−32.1
X	+ 5.0	+ 1.3	− 5.6
Mg	+41.0	−21.0	−37.7

This is one run out of a dozen that were made. It is selected as representative of all of them.

(1) Universal Oil Products Fellow.

(2) See THIS JOURNAL, **63**, 2574 (1941), for complete references.

(3) (a) Gaddum and French, *ibid.*, **49**, 1295 (1927); (b) Lee, Ph.D. Thesis, Northwestern University, 1931.

(4) (a) Evans and Lee, THIS JOURNAL, **56**, 654 (1934); (b) Evans and Field, *ibid.*, **58**, 720 (1936).

(5) Schlenk and Schlenk, *Ber.*, **54**, 1665 (1921).

TABLE II

TRANSFERENCE STUDIES OF *n*-BUTYLMAGNESIUM BROMIDE

(a) $T = 0°$, v. = 90, $I = 0.03$, R = 1.57 molar, X = 1.78 molar, total current = 11.6 milli-faradays.

	Anode	Cathode	Middle
R	+4.2	−15.5	−0.5
X	−0.3	+ 0.8	− .4
Mg	+3.9	−14.7	− .9

(b) $T = 0°$, v. = 180, $I = 0.035$, R = 1.89 molar, X = 2.69 molar, total current = 11.0 milli-faradays.

	Anode	Cathode	Middle
R	+1.2	−14.3	+0.7
X	+8.0	− 8.2	+ .2
Mg	+9.2	−22.5	+ .9

(c) $T = 0°$, v. = 180, $I = 0.035$, R = 1.29 molar, X = 1.48 molar, total current = 12.6 milli-faradays.

	Anode	Cathode	Middle
R	+4.6	−16.8	−0.4
X	−1.1	+ 1.6	− .3
Mg	+2.9	−15.2	− .7

These runs were taken as representative from about two dozen that were made.

bulk. *n*-Butylmagnesium bromide was selected and as the data of Table II show, fairly good results were obtained. The total loss of R agreed with the number of faradays passed through the cell to within one or two milliequivalents, excellent agreement considering the great reactivity of the RMgX compounds and the volatility of the solvent. Other workers have previously shown that for the aliphatic Grignards one equivalent of magnesium is plated out per faraday of electricity.[6] It was also known that the amount of gaseous hydrocarbons formed in the electrolysis of simple aliphatic Grignards corresponds closely to 100% current efficiency.[7] All calculations were made on a weight basis making due allowance for the weight of solution due to the solute.

Although the data of Table II are not suitable for quantitative calculations, a number of interesting observations can be made from them:

1. All of the losses occur in the cathode portion. The anode portion shows a gain in solute at all times even after losing an equivalent amount of R by electrolysis.

2. The relative amounts of R and X gained by the anode portion are not constant but depend upon the ratio of R to X in the original solution, that is, upon the concentration of MgX_2 present. When the MgX_2 concentration is low, R_2Mg or RMgX is transported to the anode so that the anode gains in R. When the MgX_2 concentration is high, MgX_2 is transported to the anode and the anode gains in X.

(6) Konduirev, *J. Russ. Phys.-Chem. Soc.*, **60**, 545 (1928).

(7) Braithwaite, Ph.D. Thesis, Northwestern University, 1940.

3. The net migration of magnesium to the anode shows that it is present in the anion as well as in the cation.

4. The cathode losses show that MgX_2 is always gained since the loss of R is always greater than the loss of X. However, this gain is probably due to two factors, a real gain in MgX_2 as a product of electrolysis and an apparent gain in MgX_2 because of the loss of R_2Mg from the cathode portion by transference.

The behavior of phenylmagnesium bromide in a transference cell is unusual. After several hours of running all of the Grignard reagent settles out at the anode and the cathode, leaving a clear supernatant liquid that has no RMgX in it and only a little MgX_2. This appears to be an electrophoretic effect. The colloidal nature of the aromatic Grignards is further shown by the dark color of their ether solutions and their pronounced Tyndall effect. The aliphatic C_2H_5MgBr and *n*-C_4H_9-MgBr solutions were water white, optically clear liquids after settling and filtering through glass wool. The conclusion is that while the aliphatic Grignards form true solutions, the aromatic Grignards are in part colloidal. The difference may be due to the greater coördinating power of the benzene ring. Benzene, for example, forms complexes with aluminum chloride.[8] With ions for nuclei, large complexes could be formed in ether, so large as to be of colloidal dimensions. This colloidal nature does not affect the reactivity of the aromatic Grignards, which behave in general like the aliphatic Grignards in synthesis. Nor is the molecular weight as measured by boiling point rise any different from the aliphatics, both C_6H_5-MgBr and C_2H_5MgBr being approximately $(RMgX)_2$ in half molar solution.[9] Presumably because of the low ionic concentration only a small percentage of the Grignard molecules are involved in the colloidal complexes. In an electrolysis, however, as the ions were continuously discharged leaving the rest of the particle neutral and free to settle out, more ions would form and new complexes build up until the solution was exhausted of ArMgX.

Conductance Data

The conductances of several Grignards in ethyl ether have been reported.[10] The form of

(8) Gustavson, *Chem. Zentr.*, **14**, 344 (1883).

(9) Meisenheimer and Schlichenmaier, *Ber.*, **61**, 720 (1928).

(10) (a) Evans and Lee, THIS JOURNAL, **55**, 1474 (1933); (b) Konduirev and Ssusi, *Ber.*, **62B**, 1856 (1929); (c) Konduirev, *J. Gen. Chem. U. S. S. R.*, **4**, 203 (1934).

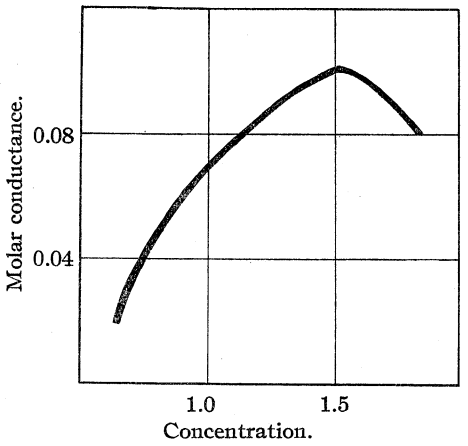


Fig. 1.—Molar conductance of ethylmagnesium iodide plotted against molar concentration.

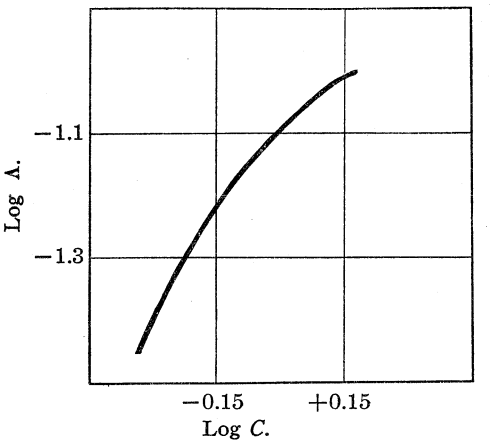


Fig. 2.—Log molar conductance of ethylmagnesium iodide plotted against log molar concentration.

the conductance–concentration curves for ethyl magnesium iodide is shown in Fig. 1. The molar conductance increases rapidly with the concentration, a general phenomenon in solvents of low dielectric constant. A maximum is reached at about 1.5 molar concentration, then the molar conductance falls off rapidly. This decrease in conductance is not surprising since the solvent is no longer ether but is 30% MgX_2 and RMgX by weight. In addition to changes in the dielectric constant and nature of the medium, the viscosity has changed from that of a mobile liquid to a sirupy solution. The great decrease in conductance could be explained by the change in viscosity alone. If the log of the molar conductance is plotted against the log of the concentration up to 1.5 molar, a curve is obtained (Fig. 2) that is not a straight line but falls off as log c increases. The slope of the straightest portion of the curve varies from 0.75 to 1.5. The interpretation of this according to the Kraus–Fuoss theory of multiple ions[11] is that the over-all formula for the ionization involves not one molecule of RMgX but from three to five. Accordingly, the ions formed are not simple but complex. This is in accordance with the size of the ions as indicated by the transference studies of ethylmagnesium bromide, where several times as many equivalents of R and X are transported as faradays of electricity are used.

Measurement of the gross conductance of RMgX does not give any information as to the contribution to the total of the conductances of R_2Mg, MgX_2, and RMgX. Consequently the conductances of several organometallic compounds in ether have been measured and compared with the conductance of ethylmagnesium bromide and magnesium bromide in ether. The results are included in Table III and for comparison the amounts of ionic character in the various bonds as calculated from the electronegativities of the elements according to the method of Pauling[12] are also presented. There is good agreement between the specific conductance and the amount of ionic character expected for each bond. The prediction of almost as much ionic character in the C-Mg bond as in the Mg-Br bond as predicted by Pauling's table of electronegativities is confirmed by the fair conductance of magnesium diethyl, prepared by the method of Noller.[13]

TABLE III

SPECIFIC CONDUCTANCE OF HALF MOLAR SOLUTIONS IN ETHYL ETHER AT 20°

		Bond	% Ionic character
$MgBr_2$	2.0×10^{-5}		
C_2H_5MgBr	1.6×10^{-5}	Mg-Br	47
$(C_2H_5)_2Mg$	1.0×10^{-5}	Mg-C	34
$(C_2H_5)_2Zn$	5×10^{-6}	Zn-C	24
$(C_2H_5)_2Hg$	0	Hg-C	10

A specific conductance of zinc diethyl in ether was reported as 10^{-4} by Rodebush.[14] The conductance of a half molar solution is somewhat less than this. The conductance of magnesium bromide at half molar concentration was extrapolated from lower concentrations since the limiting solubility of $MgBr_2$ in ether alone is only 0.15 molar.[10a] The presence of RMgX greatly increases the solubility of MgX_2 in ether as was

(11) Fuoss and Kraus, THIS JOURNAL, **55**, 2387 (1933).

(12) Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940, p. 64.

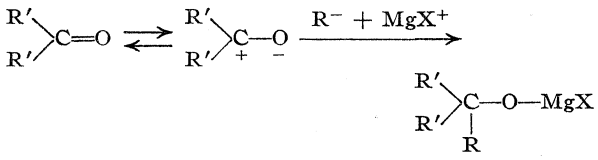
(13) Noller, THIS JOURNAL, **53**, 635 (1931).

(14) Rodebush and Peterson, *ibid.*, **51**, 638 (1929).

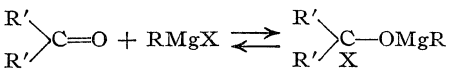
shown by Doering and Noller.[15] The actual concentration of MgX_2 in the Grignard solution may easily be half molar or above depending on the total concentration of RMgX. The total conductance of a Grignard is then due to the ionization of R_2Mg, MgX_2, and RMgX, with the R_2Mg contributing almost as much as the MgX_2. The conductance of RMgX alone cannot be measured since disproportionation to R_2Mg and MgX_2 always occurs. However, it seems reasonable to believe that the molar conductance of RMgX lies between those of R_2Mg and MgX_2 and that the ionic character of one bond does not greatly affect the ionic character of another bond in the same molecule.

Chemical Evidence

In the majority of its reactions the Grignard reagent behaves as an R^- anion and a MgX^+ cation. The anion with its unshared pair of electrons goes on an atom with an open sextet and the cation adds on to an atom with an unshared pair of electrons. The reaction with a ketone may be taken as illustrative



Instead of an atom with an open sextet, an ionizable hydrogen may furnish the necessary orbital for the unshared pair of the anion which in this sense acts as a base. The hydrogen ion may come from OH, NH, SH, or activated CH. The behavior of the Grignard reagent in enolization and condensation is due to this reaction. The reducing effect of Grignard reagents is particularly noticed in the case of highly branched R^- anions and branched chain carbonyl compounds.[16] Here, due to steric factors, a hydride ion, H^-, adds to the carbonyl group, giving a reduction product and an olefin. In other cases, as in the reaction with allyl bromide, the R^- behaves like any other anion, pushing out the Br^- by the usual displacement reaction. In all of these cases the reaction is carried to completion by the irreversibility of the formation of the carbon–carbon or carbon–hydrogen bond. Because of this only the R^- seems to react. Actually the X^- must be undergoing the same reactions but to a lesser degree because of the lower basicity of the halide ion as compared with an alkide ion



But in such cases the reaction is readily reversible because of the lability of the carbon halogen bond alpha to an oxygen atom. Similarly, if HX were formed from an ionizable hydrogen, it would react further to give RH. In cases where the carbon–halogen bond is not easily broken, stable halogenated products can be formed from the Grignard reagents or simply magnesium halide in ether. For example, ethylene oxide reacts with RMgX to give both RCH_2CH_2OH and XCH_2CH_2OH.[17]

The nature and extent of the reaction $2RMgX \rightarrow R_2Mg + MgX_2$ has been the subject of numerous papers.[18] It has been shown that the dioxane precipitation of the halogen compounds does not give true values for the position of equilibrium nor for the time necessary to reach equilibrium.[19] Some speculation can be made on the subject with the aid of a study on a related reaction, the exchange between anhydrous zinc chloride and ethylmagnesium bromide in ether. When equal volumes of molar solutions of these two substances were mixed, white fumes of zinc oxide were given off immediately and a precipitate of magnesium chloride and ethylmagnesium chloride was formed. The fuming is typical of organo-zinc compounds. The mixture was treated with dioxane at once to precipitate all the halogen and then centrifuged. The clear solution, free from halogen, was analyzed for zinc and magnesium. It was found that 95% of the ethyl radical present was zinc diethyl and less than 5% was magnesium diethyl. Allowing the solution to stand overnight before precipitating with dioxane did not change the per cent. conversion from RMgX to R_2Zn. The exchange was evidently instantaneous. Reasoning by analogy, if MgX_2 were added to a solution containing R_2Mg the exchange would be instantaneous and equilibrium reached in a very short time. Such rapid reaction in a solution of as low dielectric constant as ether cannot proceed by a purely ionic mechanism since the concentration of ions is

(15) Doering and Noller, THIS JOURNAL, **61**, 3436 (1939).

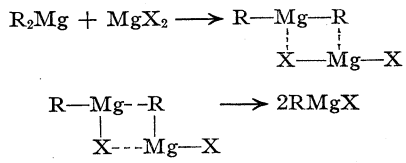
(16) Kharasch and Weinhouse, *J. Org. Chem.*, **1**, 209 (1936).

(17) (a) Blaise, *Compt. rend.*, **134**, 552 (1902); (b) Magrane and Cottle, THIS JOURNAL, **64**, 484 (1942).

(18) (a) Noller, *ibid.*, **53**, 635 (1931); (b) Cope, **57**, 2238 (1935); (c) Gilman and Brown, **52**, 4480 (1930); (d) Noller and Raney, **62**, 1749 (1940).

(19) Noller and White, *ibid.*, **59**, 1354 (1937).

probably too small. The most likely method is a collision leading to an association of these highly polar molecules and a dissociation with the groups interchanged.



The ease with which the groups are lost by one atom and gained by another suggests strongly that primarily ionic linkages are involved and that the molecules can be considered to a first approximation as being simply ion pairs held together by coulombic forces. This is not strictly true, of course, since the physical properties, especially of R_2Mg, suggest a considerable amount of covalent character in the bonds. There is, unfortunately, no direct evidence as to the position of equilibrium above, but if the undissociated molecules are considered as ion pairs, it seems likely that only statistical factors will determine the relative numbers of R_2Mg, MgX_2 and RMgX molecules. In such case the equilibrium constant $K = [R_2Mg][MgX_2]/[RMgX]^2$ should be unity. Actually the constants calculated by the dioxane method are of this order of magnitude for most Grignards. The dioxane constants cannot be regarded as more accurate than an order of magnitude since undoubtedly as the least soluble component, presumably MgX_2, is precipitated first the reaction is dragged to the direction that causes the formation of more MgX_2. The chloride always gives a greater percentage of R_2Mg than the bromide, and the bromide gives a greater percentage of R_2Mg than the iodide.[18b] This is the same order as increasing solubility of the magnesium halides. The iodide should give the most nearly correct results, though even here the values are doubtful because the concentration of R_2Mg changes with rate of addition of the dioxane and the time and intimacy of contact of the mother liquor with the precipitate.[19] That the yields of R_2Mg are increased by shaking the precipitate with the mother liquor indicates that R_2Mg is coprecipitated with the halogenated compounds to a considerable extent. Since the Grignard reagents are undoubtedly associated, such coprecipitation is not surprising and invalidates the quantitative value of the dioxane precipitation as a means of comparing various Grignard reagents.

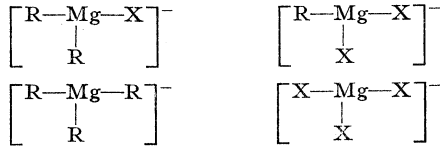
Discussion

Taking into account the foregoing evidence, a fairly lucid picture of the ionization and electrode reactions of the aliphatic Grignard reagents in ethyl ether can now be given. The specific properties of the four types of molecules present must be first taken into account. The ether molecule is strictly an electron donor molecule by virtue of the unshared pairs on the oxygen atom. The R_2Mg, RMgX and MgX_2 molecules are all acceptor molecules because of the two stable unfilled orbitals of the magnesium atom. The RMgX and MgX_2 molecules are also donor molecules because of the unshared pairs of the halogen atoms, but the donor power of a halogen atom is much less than that of oxygen atoms. The following ionic ruptures undoubtedly all occur

$$RMgX \rightleftharpoons R^- + MgX^+ \text{ or } X^- + RMg^+$$
$$R_2Mg \rightleftharpoons R^- + RMg^+$$
$$MgX_2 \rightleftharpoons X^- + MgX^+$$

The presence of Mg^{++} is unlikely in view of the low dielectric constant of the medium. As is true in any solution, ionization only occurs because the energy of solvation is great enough to overcome the coulombic attraction. The positively charged cation must be strongly solvated by the ether molecules. Since the cation MgX^+ has at least three stable orbitals, more than one molecule of ether is coördinated with it. This is of importance in determining the mobility of the cation since it eliminates the possibility of its jumping from one ether molecule to the next and possessing a high mobility analogous to the proton in water solution.

The anion having an unshared pair of electrons is but weakly attracted to the ether molecules, or repelled, and is coördinated instead with an acceptor molecule containing a magnesium atom



It is unlikely that the process stops at this point since the negative charge makes the anion a stronger base than the ether molecule. Consequently the ether molecules are displaced from other magnesium atoms and an anion involving several molecules of RMgX or R_2Mg or MgX_2 may be built up. This is in accordance with the conductance data in that several molecules of Grignard are necessary for the ionization re-

action to occur. We have then a small, highly solvated cation which is not mobile because of its attraction for the solvent and a large anion which is mobile because it has little attraction for the electron donating solvent. This is in accordance with the transference data where, especially with ethylmagnesium bromide, there is a large transference of matter to the anode. Even with the butylmagnesium bromide there are more equivalents of R plus X transferred to the anode than faradays of electricity used. More R is transferred to the anode than X, probably because R_2Mg is a better electron acceptor than MgX_2 and coördinates with the anion more readily. If the MgX_2 concentration is high, however, more of it is carried to the anode in place of R_2Mg, since the concentration of the latter must be small and the difference in concentration balances the difference in acceptor power.

The cation upon reaching the electrode is discharged to give an RMg· or MgX· free radical which reacts in pairs to give magnesium plus MgX_2 or R_2Mg

$$2RMg^+ + 2e^- \longrightarrow Mg + R_2Mg$$
$$2MgX^+ + 2e^- \longrightarrow Mg + MgX_2$$

The anion upon reaching the electrode is discharged in such a way that the R or X group having the lowest discharge potential is liberated as a free atom or radical. In the case of the aliphatic Grignards, and the aromatic Grignards at low current density, the R group is most easily discharged[2]

$$R_2MgX^- \longrightarrow R\cdot + RMgX + e^-$$
or $$R_3Mg^- \longrightarrow R\cdot + R_2Mg + e^-$$
or $$RMgX_2^- \longrightarrow R\cdot + MgX_2 + e^-$$

However, under certain circumstances the halide ion may be discharged

$$R_2MgX^- \longrightarrow X\cdot + R_2Mg + e^-$$
or $$MgX_3^- \longrightarrow X\cdot + MgX_2 + e^-$$
or $$RMgX_2^- \longrightarrow X\cdot + RMgX + e^-$$

The following series of reactions would then occur

$$2X\cdot \longrightarrow X_2$$
$$X_2 + RMgX \longrightarrow RX + MgX_2$$
$$RX + Mg \longrightarrow RMgX$$

In the electrolysis of phenylmagnesium bromide, for example, it was shown that bromobenzene formed at the anode and, unless prevented from diffusion, would migrate to the cathode and react with the magnesium plated out there.[2] That the halogen molecule is an intermediate is shown by the electrolysis of phenethinylmagnesium iodide, $C_6H_5C\equiv C—MgI$. In this electrolysis the $C_6H_5—C\equiv C^-$ ion is not discharged but the iodide ion is. Since iodine reacts only slowly with this particular Grignard, a mass of crystalline iodine collects upon the anode and can be readily identified.

The discharge of halogen instead of the alkyl or aryl radical is favored by several factors: high electronegativity of the radical, low electronegativity of the halogen, and high voltages. Aryl radicals are more electronegative than alkyl radicals and the electrolysis of aromatic Grignards gives current efficiencies, based upon the amount of hydrocarbons formed, that are very much lower than for the aliphatic Grignards.[2] Among the several halogens the order of increasing current efficiency is iodide, bromide, and chloride in accordance with increasing decomposition potentials for these ions.[20] High voltages favor the release of halogen and lower the current efficiency because a saturation current due to anions containing the alkyl or aryl group is reached. Anions such as MgX_3^- are then discharged because the source of more easily discharged ions is momentarily exhausted.

The necessity for having both electron donors and electron acceptors present to promote ionization in solutions of low dielectric constant is shown by several other organo-metallic compounds in solution. Zinc diethyl and magnesium diethyl etherate are non-conductors in benzene, while magnesium bromide etherate and ethylmagnesium bromide etherate in benzene conduct fairly well.[21] The explanation is in the low electron donating power of benzene compared to ether which leaves the zinc and magnesium diethyl with no means of solvating the cation. Magnesium bromide and ethylmagnesium bromide have the halogen atom to serve as electron donor and coordinate the cation. Zinc diethyl by itself is known to be a non-conductor, but in ether it conducts because the ether solvates the RZn^+ cation. Sodium ethyl conducts in zinc diethyl and Hein showed that the anion was $Zn(C_2H_5)_3^-$ with the zinc atom acting as the acceptor molecule.[22] There is no molecule present to solvate the sodium ion, but solvation other than that furnished by the negative end of the zinc–carbon dipole is not necessary for the sodium ion, which has a low coördinating power at all times. The organolithium compounds, C_2H_5Li, C_6H_5Li and n-C_4H_9Li in ethyl ether solution have been tested in this

(20) Evans and Field, THIS JOURNAL, **58**, 2284 (1936).
(21) Unpublished work in this Laboratory.
(22) Hein, *Z. Elektrochem.*, **28**, 469 (1922).

Laboratory and found to be non-conductors.[21] This non-conductance is due in part to a high amount of covalent character in the lithium–carbon bond as shown by the much lower conductance of lithium ethyl in zinc diethyl than the corresponding sodium and potassium compounds.[22] It is probably due more to the inability of the lithium atom to serve as an acceptor atom for the unshared pair of the alkide ion in comparison with the high coördinating power of the zinc and magnesium atoms.

Summary

Transference studies of *n*-butylmagnesium bromide and ethylmagnesium bromide in ether are reported.

The conductances of magnesium diethyl and zinc diethyl in ether have been measured.

The exchange reaction between zinc chloride and ethylmagnesium bromide in ether has been found to be instantaneous.

From a consideration of all available data a theory is proposed for the ionization of the aliphatic Grignard reagents and for the electrode reactions in their electrolysis.

Both the halogen and the alkyl group can ionize. The cation is coördinated with ether and is small and slow. The anion is coördinated with RMgX, MgX_2 and R_2Mg and is large and mobile.

The importance of having both molecules with electron donor properties and molecules with electron acceptor properties to promote ionization in solvents of low dielectric strength is brought out.

EVANSTON, ILLINOIS RECEIVED AUGUST 17, 1942

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE, AND FROM THE CORN PRODUCTS REFINING COMPANY]

The Stability of β-Methylmaltoside toward Hot Alkali

BY THOMAS JOHN SCHOCH, E. JUSTIN WILSON, JR., AND C. S. HUDSON

In connection with studies on the decomposition of starch in alkaline medium, it was desirable to establish whether the 1,4-α-glucosidic linkage is susceptible to direct hydrolytic scission by hot aqueous alkali. Evans and Benoy[1] have shown that the action of hot alkali upon maltose results primarily in a rapid enediol splitting. If this reaction could be prevented by blocking the aldehyde group against enolization, as in β-methylmaltoside, then any acids developed during hot alkali digestion could be attributed to direct hydrolysis of the disaccharide linkage, and subsequent enolic splitting of the former glucosido portion of the maltoside molecule. β-Methylglucoside is known to be fully resistant to hot aqueous alkali.

β-Methylmaltoside and calcium maltobionate have been so tested, by dissolving 0.5 g. in 100 ml. of 0.1 *N* sodium hydroxide, heating at 100° for one, two and five hour periods, and then back-titrating the unconsumed alkali. Except for the use of longer heating periods, the technique is identical with that described by Schoch and Jensen[2] for alkali number evaluation of starches; in their method the time of heating is one hour. Production of acidity is similarly expressed, as the number of milliliters of 0.1 *N* sodium hydroxide consumed per gram of carbohydrate. Each value in Table I represents the average of three to five determinations; blank runs (without carbohydrate) showed negligible loss of alkali. As an additional check on the results obtained, beta-methylcellobioside was tested in the same manner.

TABLE I

ALKALI CONSUMPTION AT 100°

Digestion time, hr.	β-Methyl-maltoside	β-Methyl-cellobioside	Calcium maltobionate	Calcium gluconate
1[a]	0.32 ± 0.04	0.10 ± 0.05	0.72 ± 0.06	0.76 ± 0.03
2	.24 ± .04	.13 ± .05	.99 ± .06	.93 ± .08
5	.16 ± .04	.08 ± .05	1.60 ± .09	1.78 ± .11

[a] Starches give alkali numbers of about 4 (waxy maize), 7 (potato) and 11 (corn).

Since the alkaline decomposition of 1 g. of anhydrous glucose consumes 85.2 ml. of 0.1 *N* sodium hydroxide,[2] it may be calculated that β-methylmaltoside hydrate and calcium maltobionate would consume 41.0 ml. and 40.7 ml., respectively, if the disaccharide bond were completely hydrolyzed. The very slight consumption by the two glycosides is barely detectable and is not progressive, which leads us to believe that it is caused by traces of impurities which recrys-

(1) Evans and Benoy, THIS JOURNAL, **52**, 294 (1930).
(2) Schoch and Jensen, *Ind. Eng. Chem., Anal. Ed.*, **12**, 531 (1940).

tallization failed to remove. From the experimental data we conclude that β-methylmaltoside may be regarded as stable against hot alkali; a similar conclusion applies to β-methylcellobioside, containing the 1,4-β-glucosido linkage. While calcium maltobionate undergoes a slight progressive decomposition, this is of the same order of magnitude as for calcium gluconate, and therefore cannot be attributed to glycosidic hydrolysis. In all probability this decomposition follows the mechanism previously given by Upson and co-workers[3] as accounting for the action of 4 *N* barium hydroxide at 140° upon the aldonic acids. The results are in agreement with the theory of alkaline oxidation of carbohydrates, as developed by Evans and his co-workers.

We assume from the present data, in agreement with Evans' views, that alkali attacks starch only at a terminal aldehydo glucose, and this must undergo enolic splitting before the second glucose can in turn be attacked. Admittedly, this does not take into account the possibility of linkages other than 1,4-α-glucosidic bonds, which might be susceptible to direct alkaline hydrolysis since definite data to the contrary are not known.

It seems worthy of mention that what is commonly called the 1,4-α-glycosidic linkage that is present in maltose is not precisely the 1,4-linkage that is postulated as the main linkage in the starch structure or in the Schardinger dextrins. If the linkage in maltose be used as a definition of the true 1,4-α-linkage, the attachment of a substituent glucose molecule to carbon atom 4 changes the type of this linkage in chains made up of glucose units. The change may have great effect upon the character of enzyme actions on starch, and an alteration of the speed of acid hydrolysis is a possibility.

Experimental Part

Calcium Maltobionate.—The calcium maltobionate here employed was prepared by the method of Glattfeld and Hanke,[4] with subsequent purification through the basic lime compound.[5] The product contained 7.53% calcium oxide; theory 7.43%.

β-Methylcellobioside.—The heptaacetate of this substance was prepared according to the directions of Pacsu.[6] The β-methylcellobioside was obtained by deacetylation, using the method of Zemplén and Pacsu[7]; the substance melted at 190–193° (cor.) and rotated $[\alpha]^{20}D$ −19.7° in water (*c* = 3), in agreement with recorded values.[8]

Improved Preparation of β-Methylmaltoside.—Previously, β-methylmaltoside has been obtained in pure form only with considerable difficulty and in low yields.[9] The following procedure has been found to give readily excellent yields of the pure crystalline substance. Thirty grams of β-octaacetylmaltose (m. p. 157–159°) was converted to acetobromomaltose by the method of Brauns.[10] The resulting sirup was dissolved with gentle warming in 400 ml. of absolute methanol and the solution shaken with 20 g. of silver carbonate. It was then heated under reflux for one hour, filtered through Darco, and concentrated *in vacuo*. Fine needles separated on cooling; one recrystallization from absolute ethanol gave 20.6 g. of nearly pure heptaacetyl-β-methylmaltoside, melting at 126–128.5° as compared with the recorded value of 128–129° for the pure substance.[9] Deacetylation was effected by the procedure of Zemplén and Pacsu.[7] Twenty grams of the heptaacetate was dissolved in 120 ml. of absolute methanol, and the solution was boiled for one hour with 5 ml. of 0.2 *N* sodium methylate. The slight yellow color was removed by filtration with Darco, and the filtrate evaporated to dryness *in vacuo*. The resulting sirup was taken up in hot 95% ethanol, and the product crystallized as long needles on cooling. The yield was 10.8 g. (94%), melting at 111–113° (cor.), with $[\alpha]^{20}D$ +84.6° in water (*c* = 1.7) as compared with the recorded m. p. of 110–111° and $[\alpha]_D$ of +83.9° in water (*c* = 1).[9] Recrystallization gave no further change in the constants. The product was isolated as the monohydrate.

One of the authors (E. J. W., Jr.) expresses his thanks to the Corn Industries Research Foundation for a fellowship.

Summary

The 1,4-α-glucosidic linkages in β-methylmaltoside and calcium maltobionate do not undergo direct hydrolysis in hot alkali. The 1,4-β-glucosidic linkage in β-methylcellobioside is likewise stable to alkali.

It appears probable that alkali can attack starch only at the terminal aldehydo glucose, which must undergo enolic splitting before the second glucose can in turn be attacked. The present results agree with Evans' views on the degradation of starch by alkali.

BETHESDA, MARYLAND
ARGO, ILLINOIS RECEIVED SEPTEMBER 30, 1942

(3) Upson, Noyce and Albert, THIS JOURNAL, **61**, 779 (1939).
(4) Glattfeld and Hanke, *ibid.*, **40**, 989 (1918).
(5) Hudson and Isbell, *Bur. Standards J. Research*, **3**, 57 (1929).
(6) Pacsu, THIS JOURNAL, **52**, 2571 (1930).
(7) Zemplén and Pacsu, *Ber.*, **62**, 1613 (1929).
(8) Helferich, Löwa, Nippe and Riedel, *Z. physiol. Chem.*, **128**, 141 (1923).
(9) Irvine and Black, *J. Chem. Soc.*, 862 (1926).
(10) Brauns, THIS JOURNAL, **51**, 1820 (1929).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF GEORGIA]

Some Allyl Nitrophenyl Thiosemicarbazides and their Analytical Properties

BY ALFRED W. SCOTT AND J. T. ANDREWS[1]

Thiosemicarbazide and allyl groups have been present in a number of organic compounds which gave precipitates or color reactions with aqueous solutions of certain inorganic cations. While these groups together would appear to be the reactive part of the compound, both the selectivity and sensitivity of the reagent would seem to be affected by the constitution of the remainder of the molecule.

The purpose of this investigation was to study the effect on the selectivity and sensitivity of a related series of reagents which contained both the thiosemicarbazide and allyl groups. For this purpose 1-allyl-4-phenyl thiosemicarbazide[2,3] was selected as the reference compound and a nitro group was successively introduced into the phenyl group in the ortho, meta and para positions. In addition to the selectivity and sensitivity possibilities mentioned above, the results of a study of this series of compounds might add to our information upon the effect of ortho, meta and para substitution in organic analytical reagents.

Distilled water solutions (0.1 *N*) of the metallic nitrates of most of the cations usually encountered in elementary qualitative analysis were tested. Each of the four reagents gave tests with silver, mercurous, mercuric and copper ions. Therefore, the nitro group had no effect upon the selectivity of the reactive group. The sensitivity of the four reagents, however, varied widely. The para nitro compound was by far the most sensitive in every instance, and the ortho nitro compound was next, while the meta nitro compound and the reagent without any nitro group present, were found to be the least sensitive and about equally poor.

1-Allyl-4-(*p*-nitrophenyl) thiosemicarbazide gave a red precipitate upon standing with mercuric mercury solutions of one part in a million and a slight color reaction with one part in ten million. Several attempts were made to use this reagent in a gravimetric quantitative determination of mercury, but the results obtained were unsatisfactory.

(1) Constructed from a thesis by J. T. Andrews, presented to the Graduate Faculty of the University of Georgia, in partial fulfillment of the requirements for the degree of Master of Science in Chemistry.

(2) Dixon, *J. Chem. Soc.*, **57**, 263 (1890).

(3) Avernarius, *Ber.*, **24**, 268 (1891).

Experimental

1-Allyl-4-phenyl thiosemicarbazide was prepared according to Avernarius.[2,3] It melted at 119° (uncor.) and agreed in all other respects to the compound described in the literature. An excess of the compound was added to water, heated to 90°, agitated for some time, and allowed to cool to 25°. Ten ml. of this saturated solution was pipetted into a tared dish, evaporated and dried in an oven at 90° and weighed. The result in grams times ten was taken as the water solubility of the compound in 100 ml. of water. Duplicate results gave the solubility as 0.118 g. at 25°. An alcoholic solution of the compound added to aqueous solutions of the cations gave a white precipitate with silver, a gray precipitate with mercurous mercury, a yellow precipitate with mercuric mercury, and a blue color with copper.

1-Allyl-4-(*o*-nitrophenyl) thiosemicarbazide was prepared according to Guha.[4] The purified needles melted at 166° (uncor.). There was 0.029 g. found to be soluble in 100 ml. of water at 25°. An alcoholic solution of the compound added to aqueous solutions of the cations gave orange precipitates with both mercurous and mercuric mercury, a red precipitate with silver, and a green precipitate with copper.

1-Allyl-4-(*m*-nitrophenyl) Thiosemicarbazide.—To an alcohol solution of 10 g. of *m*-nitrophenylhydrazine was added 7 g. of allyl isothiocyanate. This solution was heated for five minutes and allowed to cool. The thick oil which separated was dissolved in hot 50% alcohol and allowed to cool. The yellow crystals obtained were soluble in acetone, bases (turning orange red), and very slightly soluble in water. Their m. p. was 120° (uncor.). The yield was 90% of the theoretical.

Anal. Calcd. for $C_{10}H_{12}N_4O_2S$: N, 22.21; S, 12.71. Found: N, 22.14; S, 12.63.

The solubility in 100 ml. of water at 25° was 0.033 g. An alcoholic solution of the compound added to aqueous solutions of the cations gave a cream colored precipitate with silver, a grayish-black precipitate with both mercurous and mercuric mercury, and a blue color with copper. It was not very sensitive with any of these.

1-Allyl-4-(*p*-nitrophenyl) Thiosemicarbazide.—To a solution of 8 g. of *p*-nitrophenylhydrazine dissolved in 95% alcohol was added 4.6 g. of allyl isothiocyanate. This mixture was heated for five minutes and allowed to cool. The yellow needles obtained were recrystallized from 95% alcohol until pure. They were very soluble in acetone, soluble in alcohol, slightly soluble in water and soluble in bases (turning a red color). At 25°, 3.273 g. of the compound was soluble in 100 ml. of 95% alcohol. At 25°, 0.031 g. of the compound was soluble in 100 ml. of water. The compound melted at 188° (uncor.), with some decomposition. The yield was 76% of the theoretical.

(4) P. C. Guha and S. K. Ray, *Quart. J. Indian Chem. Soc.*, **2**, 83–94 (1925); P. C. Guha and T. N. Ghosh, *ibid.*, **4**, 561–72 (1927).

TABLE I

Concn., γ/l. (mcg.)	Reagent A	Reagent B	Reagent C
		Sensitivity for Cu^{++}	
1×10^7	Dark blue color	Black-green ppt.	Black ppt.
1×10^6	Blue color	Black-green some ppt.	Black-green ppt.
1×10^5	Blue color	Dark green colored soln.	Gray ppt.
1×10^4	Blue color	Light green color	Brown-red color, brown ppt. after standing
1×10^3	Slight blue color	No reaction	Very slight color
		Sensitivity for Ag^+	
1×10^7		Brown ppt.	Orange ppt.
1×10^6		Brown-purple ppt.	Orange-red ppt.
1×10^5		Purple ppt.	Crimson ppt.
1×10^4		No color or ppt.	Light red soln., ppt. after standing
1×10^3		No reaction	Slight color
		Sensitivity for Hg^{++}	
1×10^7		Yellow ppt.	Orange ppt.
1×10^6		Red ppt.	Red ppt.
1×10^5		Purple red ppt.	Red ppt.
1×10^4		Red color	Red ppt.
1×10^3		Slight color	Some ppt. after standing
2.5×10^2		No reaction	Red color that can be seen clearly
1×10^2		No reaction	Slight change in color

Anal. Calcd. for $C_{10}H_{12}N_4O_2S$: N, 22.21; S, 12.71. Found: N, 22.26; S, 12.66.

An alcoholic solution of the compound when added to aqueous solutions of the cations gave an orange precipitate with both mercurous and mercuric mercury, a red precipitate with silver, and a dark green precipitate with copper.

Sensitivities.—The tests for the sensitivities of the compounds were made in the following way. A solution containing 1×10^7 mcg. per liter of the ion to be tested was prepared and diluted to other concentrations in volumetric flasks. A saturated alcohol solution of each reagent was used in the tests. When eight drops of this alcohol solution of the reagent were added to five ml. of water or to five ml. of dilute nitric acid, and allowed to stand overnight, no precipitation resulted. When eight drops of the reagent were added to 5 ml. of concentrated nitric acid and allowed to stand overnight, a slight precipitation occurred. The sensitivity of 1-allyl-4-(*m*-nitrophenyl) thiosemicarbazide was not determined since it affected the mercurous, mercuric, silver and copper ions in fairly concentrated solutions only. For the same reason, the sensitivity of 1-allyl-4-phenyl thiosemicarbazide (Reagent A) was only tested for copper. The sensitivities of 1-allyl-4-(*o*-nitrophenyl) thiosemicarbazide (Reagent B) and 1-allyl-4-(*p*-nitrophenyl) thiosemicarbazide (Reagent C) are shown in the table.

Summary

1. Neither the presence of a nitro group, nor its position, affected the selectivity of the reactive group, but did materially affect the sensitivity of the compounds.

2. 1-Allyl-4-(*p*-nitrophenyl) thiosemicarbazide is a very sensitive reagent for mercuric mercury.

ATHENS, GA. RECEIVED APRIL 21, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Mechanism of the Reaction between Hindered Carbonyl Compounds and the Grignard Reagent. II[1]

BY RICHARD T. ARNOLD AND R. WINSTON LIGGETT[2]

In the first paper of this series[1] it was shown that esters of the type $R-C(=O)-O-R'$ are cleaved abnormally by the Grignard reagent if in R— there are substituents which sterically hinder additions to the carbonyl group of the ester, and if R'— is of such a nature that it has considerable thermodynamic stability as a cation (R'^+). The general reaction between such an ester and the Grignard reagent can be expressed by the equation

$$R-C(=O)-O-R' + R''MgX \longrightarrow R-C(=O)-O-MgX + R'R'' \quad (1)$$

If on the other hand, R'— has little tendency to form a cation and the group —OR' readily forms an anion (*i. e.*, Cl^-, $-OC_6H_5$, or $R_1CO_2^-$) then an entirely different reaction takes place and ketones are produced[3,4,5,6]

$$R-C(=O)-O-R' + R''MgX \longrightarrow R-C(=O)-R'' + R'O-MgX \quad (2)$$

The present paper deals with a study of the cleavage reaction (Eq. 1). As indicated earlier,[1] when the magnitude of the steric factors about the carbonyl group is small, then simple allyl esters of carboxylic acids react normally with the Grignard reagent to produce tertiary alcohols.[7]

If the steric factors in R— are sufficiently great to prevent or decidedly inhibit the addition of R''MgX to the carbonyl group, then allyl esters react entirely according to Equation (1). Obviously there must be some point between these two extremes where the rates of the normal ester-Grignard reaction and the cleavage reaction are alike. This midpoint has now been roughly determined by a systematic study in which the steric effects in group R— have been varied over a wide range of values.

R = I = triphenylmethyl
II = diphenylmethylcarbinyl
III = 2,3-dimethylnaphthyl
IV = benzylethylmethylcarbinyl
V = 3-heptyl
VI = 3-pentyl
VII = cyclohexyl
VIII = 1-ethylcyclohexyl

The element of steric hindrance is pronounced enough when R = I, II, III, or IV that the corresponding allyl esters undergo complete cleavage with phenylmagnesium bromide. When R = V or VI, the cleavage and normal reactions proceed simultaneously and at comparable rates. The marked increase in steric properties observed when one passes from a methyl to an ethyl group is usually attributed to the large effective volume swept out by the freely rotating methyl component of the ethyl group. We have found additional confirmation for this explanation in the fact that when R = VII or VIII only the normal reaction takes place between the allyl esters and phenylmagnesium bromide. In these two cases, free rotation is prevented by the rigidity of the ring structures.

A later report will discuss the effects of changes in the nature of groups R' and R'' on the allyl ester–Grignard reaction.

Experimental

1-Bromo-2,3-dimethylnaphthalene.—To a cooled solution of 200 g. of 2,3-dimethylnaphthalene in 500 cc. of chloroform in an ice-bath, 215 g. of bromine in 200 cc. of carbon tetrachloride was added over a two-hour interval with stirring. After three additional hours at room temperature the solution was thoroughly washed with dilute alkali, the solvent distilled off and the residue crystallized from 400 cc. of hot ethanol; yield, 250 g.; m. p. 62–63°; after recrystallization, m. p. 63–64°.

Anal. Calcd. for $C_{12}H_{11}Br$: C, 61.3; H, 4.72. Found: C, 60.4; H, 4.72.

2,3-Dimethyl-1-naphthoic Acid.—Fifty-seven grams of 1-bromo-2,3-dimethylnaphthalene in 150 cc. of ether was converted to the Grignard reagent with 11.8 g. of magnesium and two drops of ethylmagnesium bromide solution. Carbonation was effected by dropping the Grignard solution slowly into dry ether through which passed a vigorous stream of anhydrous carbon dioxide. After

(1) For paper I see THIS JOURNAL, **63**, 3444 (1941).
(2) DuPont Postdoctorate Fellow 1941–1942.
(3) Adams and Binder, THIS JOURNAL, **63**, 2773 (1941).
(4) Whitmore, *et al.*, *ibid.*, **64**, 1242, 1247, 1252 (1942).
(5) Fuson, Bottorff and Speck, *ibid.*, **64**, 1450 (1942).
(6) Fuson, Corse and Rabjohn, *ibid.*, **63**, 2852 (1941).
(7) The one general exception to this rule is the case in which group R' has an extreme tendency to form a cation (*i. e.*, triphenylmethyl acetate); here only cleavage occurs [Fieser and Heymann, THIS JOURNAL, **64**, 376 (1942)].

decomposition there was obtained 36–40 g. of crude acid. Recrystallization from methanol–water mixtures gave a product melting at 167–168°.

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 78.0; H, 6.04. Found: C, 77.4; H, 6.13.

Allyl 2,3-Dimethyl-1-naphthoate.—Fifty grams of 2,3-dimethyl-1-naphthoic acid was treated with a sodium ethoxide solution prepared from 6 g. of sodium and 100 cc. of ethanol. The alcohol was removed by vacuum distillation and to the residue was added 32 cc. of allyl bromide in 200 cc. of xylene. The mixture was effectively stirred at the reflux temperature for eight hours. Extraction of the xylene solution with dilute alkali followed by drying and fractionation gave 37.5 g. of ester; b. p. 155–160° (2 mm.). The distillate was taken up in low boiling petroleum ether and cooled. The ester appeared as a white solid; m. p. 33–34°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.78; H, 6.70. Found: C, 79.79; H, 6.13.

Reaction of Allyl 2,3-Dimethyl-1-naphthoate with Phenylmagnesium Bromide.—The Grignard solution was prepared from 13.0 cc. of bromobenzene and 3.2 g. of magnesium in 75 cc. of ether. To this in one portion was added 15.1 g. of the crystalline ester dissolved in 50 cc. of ether. Refluxing was continued for two hours and the solution stood at room temperature for an additional twenty-four hours. Alkali extraction of the ether layer after decomposition yielded 12.2 g. of 2,3-dimethyl-1-naphthoic acid (97%). Fractionation of the ether layer gave 6 g. of allylbenzene (82.4%); b. p. 155–157°.

Allyl Triphenylacetate.—The anhydrous salt from 6.4 g. of triphenylacetic acid was heated under reflux for ten hours with 20 cc. of allyl bromide and 50 cc. of toluene. After filtration, the toluene was removed by distillation and the oily residue taken up in ether and extracted with dilute alkali. Evaporation of the ether solution gave a solid ester which on recrystallization from alcohol melted at 85–85.5°.

Anal. Calcd. for $C_{23}H_{20}O_2$: C, 84.14; H, 6.14. Found: C, 84.18; H, 6.16.

Cleavage of Allyl Triphenylacetate.—To a solution of phenylmagnesium bromide prepared from 2.6 g. of bromobenzene was added 3.8 g. of the ester dissolved in 50 cc. of ether. After standing overnight the solution was decomposed with dilute hydrochloric acid in the usual way. There was obtained 3.1 g. (93%) of triphenylacetic acid.

Ethyl Benzylmethylethylacetate.—The enolate of ethyl methylethylacetate was formed by the use of triphenylmethylsodium according to the procedure of Hudson and Hauser.[8] Because of the unexpected violent reaction which ensued during the benzylation with benzyl bromide, a slight accident occurred and only 44.5 g. of ethyl benzylmethylethylacetate was obtained from 61 g. of the starting ester. The product boiled at 127–130° (9–10 mm.).

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.47; H, 9.12.

Allyl Benzylmethylethylacetate.—The ethyl ester (28 g.) was saponified by refluxing for ten hours with 25 g. of potassium hydroxide in 50 cc. of absolute alcohol. After adding 250 cc. of water and extracting with ether, the aqueous solution was neutralized to congo red with hydrochloric acid. The free acid was extracted with ether and purified by distillation; yield 24 g. From this acid the anhydrous sodium salt was prepared with sodium ethoxide and converted to the ester by heating with 20 cc. of allyl bromide and 150 cc. of xylene for ten hours. The allyl ester weighed 23 g. (80%) and distilled at 139–140° (8 mm.).

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.66; H, 8.51.

Cleavage of Allyl Benzylmethylethylacetate.—The ester (20 g.) was added in one portion to a Grignard solution prepared from 21 cc. of bromobenzene in the usual manner. After an induction period of a few minutes the reaction became quite violent and had to be cooled periodically. The reaction mixture was decomposed after standing two hours with dilute hydrochloric acid. There was obtained 14.5 g. (87%) of benzylmethylethylacetic acid and 7.0 g. (70%) of allylbenzene.

Allyl α,α-Diphenylpropionate.—Fifteen grams of α,α-diphenylpropionic acid[9] was converted to its sodium salt by treatment with 1.7 g. of sodium in 50 cc. of absolute ethanol. The ethanol was removed by distillation under diminished pressure, and the residual salt refluxed with allyl bromide (10 cc.) in 100 cc. of dry xylene for thirty hours. The ester (b. p. 175–177° (8 mm.)) was isolated in the usual manner.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.11; H, 6.82. Found: C, 81.19; H, 6.75.

Reaction of Phenylmagnesium Bromide with Allyl α,α-Diphenylpropionate.—To a Grignard solution prepared from 5.25 cc. of bromobenzene in 50 cc. of ether there was added 5.07 g. of the allyl ester in one portion. The solution was refluxed gently for four hours. After decomposition of the reaction mixture there was obtained 3.8 g. (88%) of α,α-diphenylpropionic acid.

Allyl 2-Ethylcaproate.—One hundred grams of commercial 2-ethylhexanal was placed in a large gas drying tower with a trace of manganese dioxide. Air was bubbled through vigorously for four hours at 90°. Basic extraction of the acid from the mixture and purification by distillation resulted in a yield of 58 g.; b. p. 118–120° (8–10 mm.). The acid was converted to the pure acid chloride; yield 56 g. To a solution of 50 g. of pyridine and 25 g. of allyl alcohol in 100 cc. of chloroform, the acid chloride dissolved in 50 cc. of chloroform was added slowly. The mixture was cooled at all times to prevent the temperature from rising above 15°. After addition, the solution was kept at 4° overnight.[10] The mixture was washed once with normal hydrochloric acid, twice with water, and then extracted with dilute sodium bicarbonate solution. The chloroform layer was dried and distilled. The allyl ester (45 g.) boiled at 79–79.5° (8 mm.).

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.67; H, 10.94. Found: C, 71.44; H, 10.87.

Phenylmagnesium Bromide Reaction with Allyl 2-Ethylcaproate.—Treatment of the allyl ester (31.5 g.) with a Grignard solution prepared from 36.6 g. of bromobenzene in 100 cc. of ether yielded after decomposition 2-

(8) Hudson and Hauser, THIS JOURNAL, **62**, 2457 (1940).

(9) Batemann and Marvel, *ibid.*, **49**, 2917 (1927).

(10) Schving and Sabetay, *Bull. soc. chim.*, **43**, 857 (1928).

ethylcaproic acid (30%), allylbenzene (26%) and a mixture recognized as carbinol (about 49%) containing the olefin as impurity.

Allyl Diethylacetate.—This ester was prepared from the dry sodium salt (from 160 g. of acid), allyl bromide and xylene as described above. The reflux time employed was forty-eight hours; yield 65 g.; b. p. 165–167°.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.3; H, 10.3. Found: C, 69.9; H, 10.3.

Reaction of Allyl Diethylacetate with Phenylmagnesium Bromide.—The Grignard solution was prepared from 45 cc. of bromobenzene in 200 cc. of ether. To this was added slowly 25.3 g. of allyl diethylacetate in 50 cc. of ether. A violent reaction ensued and the mixture was decomposed after thirty minutes. There were obtained 4.5 g. of diethylacetic acid, 9.0 g. of allylbenzene, and 10.3 g. of carbinol boiling at 170–175° (8 mm.). The carbinol was identified by dehydration with formic acid to an olefin having the correct composition for 1,1-diphenyl-2-ethylbutene-1.

Anal. Calcd. for $C_{18}H_{20}$: C, 91.5; H, 8.5. Found: C, 91.3; H, 8.5.

Allyl Hexahydrobenzoate.—This ester was prepared from 50 g. of the acid chloride, 25 g. of allyl alcohol, 100 cc. of chloroform and 40 g. of pyridine by the method described above; yield 44 g.; b. p. 103–104° (18 mm.).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.35; H, 9.58. Found: C, 71.15; H, 9.48.

Diphenylcyclohexylidenemethane.—Treatment of allyl hexahydrobenzoate with two moles of phenylmagnesium bromide in the usual manner gave a carbinol as the sole product. Dehydration of the carbinol with formic acid (85%) gave the expected olefin; m. p. 82–83°.[11]

Ethyl 1-Ethyl-2-ketocyclohexanecarboxylate.—Dry sodium ethoxide was prepared in xylene solution from sodium (13.5 g.) and ethanol. The excess ethanol was removed by distillation. To this suspension was added 100 g. of ethyl 2-ketocyclohexanecarboxylate in 100 cc. of xylene. After stirring at reflux temperature for three hours, 110 g. of ethyl benzenesulfonate was added and the mixture was refluxed for fifteen hours. The precipitate was filtered and the filtrate was carefully fractionated. The desired alkylated β-ketoester (86 g.) was obtained; b. p. 125–130° (15–18 mm.). Its semicarbazone melted at 156.5–157°.

Anal. Calcd. for $C_{12}H_{21}O_3N_3$: C, 56.44; H, 8.30. Found: C, 56.69; H, 8.05.

Allyl 1-Ethylcyclohexanecarboxylate.—As preliminary tests at each stage showed that purification of the intermediates was unnecessary and wasteful, the following series of reaction was carried out without purifying at each step. Forty-one grams of ethyl 1-ethyl-2-ketocyclohexanecarboxylate was reduced with Raney nickel at 175–200° and 2000 lb. pressure of hydrogen. The product after removing the catalyst was dissolved in dry benzene and 30 g. of phosphorus pentoxide was cautiously added. The solution was refluxed for two hours. The benzene solution was poured from the tarry residue and the solvent was removed; 25 g. of oil remained. The oil was reduced with Raney nickel at 150° and 1800 pounds pressure of hydrogen. The reduced material (12 g.) distilled at 100–110° (10–15 mm.). Saponification with methanolic potassium hydroxide yielded 7.5 g. of crude acid. This was converted through its acid chloride and allyl alcohol to the allyl ester; yield 4.7 g.; b. p. 97–98° (8 mm.).

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.4; H, 10.3. Found: C, 73.4; H, 10.7.

Reaction of Allyl 1-Ethylcyclohexanecarboxylate with Phenylmagnesium Bromide.—A Grignard solution (30 cc.) prepared from 5 cc. of bromobenzene was treated with 3 g. of the allyl ester. A rather violent reaction ensued and after standing overnight the mixture was decomposed with dilute acid. No fatty acid or allylbenzene could be detected. The highly viscous product was obviously the normally expected carbinol.

Summary

1. A number of allyl esters have been prepared which have varying degrees of steric hindrance about the carbonyl group.

2. It has been shown that the magnitude of these steric factors determines very largely whether the allyl esters are cleaved by the Grignard reagent or undergo the well-known reaction to produce tertiary alcohols.

MINNEAPOLIS, MINNESOTA RECEIVED JANUARY 26, 1942

(11) Schmidlin and Escher, *Ber.*, **45**, 893 (1912).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Preparation of Mixed, Secondary Aliphatic Amines, RR'NH[1,2]

BY HENRY R. HENZE AND DAVID D. HUMPHREYS[3]

In connection with a program of synthesis of pharmaceutical products, a number of mixed, secondary amines were needed. Compounds of the type HNRR' in which one group is aryl and the other alkyl are obtainable fairly readily by standard methods of synthesis, but those possessing two different alkyls are not so easily obtained. For production of this type three methods, perhaps, are used more commonly.

(1) The Hinsberg[4] method leads to the preparation of a pure mixed secondary amine but the procedure is somewhat involved, is not rapid and frequently the over-all yield is low.

(2) Stepwise alkylation of aniline with a subsequent nitrosation and alkaline hydrolysis[5] leads to the formation of a mixed, secondary amine in a state of purity dependent upon that of the mixed dialkyl aniline used.

(3) Interaction of a primary amine and a carbonyl compound with subsequent reduction of the imine.

(a) Reduction by means of sodium and alcohol[6] requires a separation and purification of the imine with a consequent loss of time and product.

(b) As reported by Skita and Keil,[7] reduction with colloidal platinum and hydrogen at room temperature and three atmospheres pressure for two to three hours produced, in satisfactory yield, several secondary amines of carbon content between C_9 and C_{15}.

(c) Mailhe[8] stated that catalytic reduction of the imine derived from isovaleraldehyde and ethylamine, by passing its vapors over finely divided nickel in the presence of hydrogen at a temperature of 190–200°, yielded N-ethyl-isoamylamine as the principal product together with some diethylamine and triethylamine.

In all probability the infrequency of reference in the chemical literature to the use of mixed, secondary aliphatic amines is highly indicative of the fact that these methods are neither very simple, rapid, nor productive of wholly satisfactory yields.

Because of the success in this Laboratory[9] in obtaining mixed secondary amines by reduction in the presence of Raney nickel catalyst of the Schiff bases formed by the interaction of benzaldehyde, or a derivative, with a primary amine, it was decided to study the analogous synthesis of mixed, secondary aliphatic amines in a similar manner.

It has been found that without preliminary isolation or purification, the products formed from the interaction of primary amines and simple aldehydes, except formaldehyde, or ketones in a hydrocarbon solvent can be hydrogenated in the presence of Raney nickel catalyst to produce mixed, secondary aliphatic amines in satisfactory yield.

In the preparation of seven of the mixed amines obtained during this investigation, *n*-butylamine was allowed to react with the appropriate carbonyl compound. However, in the case of N-methyl-*n*-butylamine the reactants were methylamine and *n*-butyraldehyde and here a significant amount of N-methyl-di-*n*-butylamine was formed also. The other preparations yielded various amounts of high boiling basic mixtures of indefinite composition.

In order to characterize them further and at the same time obtain substances useful for other syntheses, the amines were condensed with bromoacetone to form aminoacetones. The latter are colorless or faintly yellow, slightly viscous liquids having a characteristic odor and when impure they acquire a red color very rapidly. However, when pure they remain essentially colorless for long periods of time. They are quite soluble in the usual organic solvents, but are insoluble in water. The molecular refractions and parachors calculated from the densities, refractive indices, and surface tensions check quite closely with the sum of the atomic refractions[10] and the atomic parachors.[11] All attempts to form picrates of the aminoacetones resulted in the formation of oils which could not be solidified. Treatment of anhydrous ether

(1) Presented before the Division of Organic Chemistry at the 101st meeting of the American Chemical Society at St. Louis, Mo., April 8–10, 1941.

(2) From the Ph. D. dissertation of D. D. Humphreys, June, 1941.

(3) Present address, Sharples Chemicals Inc., Wyandotte, Mich.

(4) Hinsberg, *Ann.*, **265**, 178 (1891).

(5) Baeyer and Caro, *Ber.*, **7**, 963 (1874).

(6) Störmer and Leper, *ibid.*, **29**, 2110 (1896).

(7) Skita and Keil, *ibid.*, **61**, 1452, 1686 (1928).

(8) Mailhe, *Bull. soc. chim.*, [4] **25**, 321 (1919).

(9) Magee with Henze, THIS JOURNAL, **62**, 910 (1940).

(10) Landolt–Börnstein, "Physikalisch-chemische Tabellen," 5 Auflage, II, p. 985.

(11) Sugden, *J. Chem. Soc.*, **125**, 1180 (1924).

TABLE I

N-ALKYL-*n*-BUTYLAMINES, R—NH—C_4H_9

	Yield, %	B. p. °C. (cor.)	mm.	d^{20}_4	$n^{20}D$	Mol. refract. Calcd.	Found	γ^{20}
Methyl[a]	26	89–91	750	0.7377	1.4011	28.89	28.71	22.46
Ethyl[b]	31	111–112	747	.7398	1.4040	33.51	33.45	22.52
n-Propyl[c]	31	138–139	745	.7497	1.4127	38.13	38.30	23.30
Isopropyl	52	124–125	748	.7408	1.4050	38.13	38.12	21.92
Isobutyl	56	150–151	738	.7519	1.4120	42.75	42.74	22.85
s-Butyl	51	149–149.5	751	.7568	1.4150	42.75	42.76	23.39
n-Amyl[d]	51	180–182	743	.7667	1.4230	47.36	47.59	24.50
Isoamyl[e]	41	175–177	745	.7658	1.4200	47.36	47.34	24.17

	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found	Parachor Calcd.	Found	Free surface energy
Methyl							258.8	259.3	540.8
Ethyl	71.21	70.98	14.94	14.96	13.85	13.92	297.8	298.0	597.8
n-Propyl	72.97	72.90	14.88	15.04	12.16	11.95	336.8	337.7	668.5
Isopropyl	72.97	72.72	14.88	14.85	12.16	12.25	336.8	336.5	634.0
Isobutyl	74.34	73.90	14.82	14.79	10.84	10.49	375.8	375.8	706.4
s-Butyl	74.34	74.27	14.82	15.01	10.84	11.14	375.8	375.5	720.0
n-Amyl	75.44	75.29	14.78	14.74	9.78	10.43	414.8	415.0	816.6
Isoamyl	75.44	75.70	14.78	14.97	9.78	10.01	414.8	414.8	790.6

[a] Francimont and v. Erp, ref. 12a, reported d^{15} 0.7375; b. p. 90.5–91.5°; Löffler and Freytag, ref. 12b, recorded d^{15}_4 0.7367; b. p. 90–91°; picrate, m. p. 111–112°; we find picrate, m. p. 112.5–113.5° (cor.). [b] Brill, ref. 13, reported b. p. 108–109°. [c] v. Braun and Weismantel, ref. 14, reported b. p. 134–135°. [d] Ochiai and Tsuda, ref. 15, listed b. p. 94° (45 mm.); Lazier and Adkins, ref. 16, recorded preparation of this amine but noted no data for its physical properties. [e] Ochiai and Tsuda, ref. 15, recorded b. p. 89° (45 mm.) and 85° (40 mm.).

solutions of these ketoamines with dry hydrogen chloride yielded no solid hydrochloride.

Where high pressure hydrogenation apparatus is available it is our belief that the method to be described below represents a simpler and more rapid procedure for preparing mixed, secondary, aliphatic amines in satisfactory yields than the older methods.

Experimental

Aldimines.—Half-mole quantities of amine and aldehyde are separately dissolved in 25-cc. portions of Skellysolve. The solutions are chilled in a salt–ice mixture (except that of methylamine which is chilled to −15° with a bath of acetone chilled with solid carbon dioxide) and the solution of aldehyde is added slowly to that of the amine while shaking the mixture. Water begins to separate after approximately one-half of the aldehyde has been added. The reaction mixture is allowed to stand for one hour in the ice box and the water is separated. The hydrocarbon solution is dried over anhydrous potassium carbonate or sodium sulfate before hydrogenation.

Ketimines.—Half-mole quantities of amine and ketone are mixed with 50 cc. of Skellysolve and the clear, homogeneous solution is hydrogenated without any attempt at dehydration.

Hydrogenation.—The Skellysolve solutions as prepared above are hydrogenated at 75° in the Adkins apparatus using 10 g. of Raney nickel catalyst, and an initial hydrogen pressure of 3000 lb./sq. in. Separation of water occurs during the hydrogenation of the ketone–amine solution. The hydrogenation of the aldimines is practically complete within three hours, but that of the ketimine solutions requires three to four times that period.

Isolation of the Amines.—The hydrogenation solution is filtered from the catalyst and the amine is extracted with a slight excess of 6 *N* hydrochloric acid. After washing the acid solution with ether, it is made strongly alkaline with 40% sodium hydroxide and ether extracted. The ether solution of basic material is dried with anhydrous potassium carbonate, and after removal of the ether the crude amine is partially purified by distillation. The distillate is dried over sodium and fractionated to obtain the pure amine.

The N-alkyl-*n*-butylamines prepared by this procedure are the methyl, ethyl, *n*-propyl, isopropyl, isobutyl, sec-butyl, *n*-amyl and isoamyl compounds. In this series, synthesis of the methyl,[12] ethyl,[13] *n*-propyl,[14] *n*-amyl[15,16] and iso-amyl[15] members has been reported previously, but their characterization is incomplete.

Preparation of Aminoacetones.—The conversion of the amines to aminoacetones is accomplished by one of the methods used by Magee,[9] namely, the condensation of two-tenths mole of amine dissolved in 200 cc. of anhydrous ether with one-tenth mole of bromoacetone dissolved in 25 cc. of ether. The amine precipitated as hydrobromide is recovered and treated with another portion of bromoacetone until three reaction mixtures have been obtained. The combined ether solutions are washed with water, then the basic material is extracted with a slight excess of 6 *N* hydrochloric acid solution. The acid solution is washed with ether, then made alkaline with a considerable excess

(12) (a) Franchimont and v. Erp, *Rec. trav. chim.*, **14**, 317 (1894); (b) Löffler and Freytag, *Ber.*, **42**, 3429 (1909); (c) Graymore, *J. Chem. Soc.*, 1353 (1932).

(13) Brill, THIS JOURNAL, **54**, 2484 (1932).

(14) von Braun and Weismantel, *Ber.*, **55**, 3165 (1922).

(15) Ochiai and Tsuda, *J. Phar. Soc. Japan*, **56**, 357 (1936); through *C. A.*, **30**, 6363 (1936).

(16) Lazier and Adkins, THIS JOURNAL, **46**, 741 (1924).

TABLE II

N-ALKYL-*n*-BUTYLAMINOACETONES, $R(n\text{-}C_4H_9)NCH_2COCH_3$

—R	Yield, %	B. p. °C. (cor.)	mm.	d^{20}_4	$n^{20}D$	γ^{20}	Mol. refract. Calcd.	Found
Methyl	68	76	19	0.8551	1.4720	27.96	43.10	43.01
Ethyl	41	87–88	17	.8537	1.4305	27.72	47.71	47.63
n-Propyl	74	90–91	12	.8512	1.4321	27.90	52.33	52.19
Isopropyl	55	92–94.5	13	.8576	1.4338	27.69	52.33	51.99
Isobutyl	55	106–107	14	.8476	1.4331	27.21	56.95	56.83
s-Butyl	57	105–106	12	.8610	1.4381	28.35	56.95	56.53
n-Amyl	65	110–111	6	.8508	1.4362	28.33	61.57	61.28
Isoamyl	62	80–82	3	.8441	1.4350	27.47	61.57	61.62

—R	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found	Parachor Calcd.	Found	Free surface energy
Methyl	67.08	66.74	11.97	12.27	9.78	9.64	384.8	385.4	849.6
Ethyl	68.74	68.45	12.18	12.27	8.91	10.93	423.8	432.7	897.4
n-Propyl	70.12	70.17	12.36	12.88	8.19	8.32	462.8	462.4	958.1
Isopropyl	70.12	69.72	12.36	12.51	8.19	8.26	462.8	458.2	946.2
Isobutyl	71.29	71.34	12.51	12.84	7.56	7.71	501.8	499.3	987.5
s-Butyl	71.29	70.86	12.51	12.55	7.56	8.01	501.8	496.6	1012.2
n-Amyl	72.30	72.11	12.62	12.68	7.03	7.77	540.8	540.5	1077.5
Isoamyl	72.30	72.56	12.62	12.84	7.03	7.07	540.8	540.7	1025.4

TABLE III

SEMICARBAZONES OF N-ALKYL-*n*-BUTYLAMINOACETONES

$R(n\text{-}C_4H_9)NCH_2(CH_3)C{=}NNHCONH_2$

—R	Yield, %	M. p. °C. (cor.)	Nitrogen, % Calcd.	Found
Methyl	69	104.0–104.5	27.78	27.76
Ethyl	62	126.5–127.5	26.15	25.95
n-Propyl	51	130.5–131.0	24.54	24.82
Isopropyl		151.0–152.0	24.54	25.43
Isobutyl	27	139.0–139.5	23.12	23.74
s-Butyl	72	172.0–172.5	23.12	23.41
n-Amyl	27	107.5–108.5	21.85	21.93
Isoamyl	32	116.0–117.0	21.85	21.63

of 40% sodium hydroxide solution. The basic material is extracted with ether and after drying over anhydrous potassium carbonate or sodium sulfate the ether is removed leaving the crude aminoacetone to be purified by fractional distillation. When the aminoacetones are not to be used for synthesis immediately they should be stored in a desiccator over potassium carbonate.

In Table I are included data for certain physical properties, values derived from them by calculation, and the results of analyses of the N-alkyl-*n*-butylamines.

Data for the new aminoacetones prepared in this investigation are tabulated in Table II, and for the semicarbazones of these ketones in Table III.

Summary

1. A simple, rapid method of preparing mixed, secondary aliphatic amines in satisfactory yield has been tested by synthesizing eight examples of N-alkyl-*n*-butylamines. The method involves high pressure hydrogenation of aldimines or ketimines in the presence of Raney nickel.

2. These amines have been converted into eight new disubstituted aminoacetones of the type CH_3COCH_2NRR'.

AUSTIN, TEXAS RECEIVED SEPTEMBER 11, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

5,5-Dimethylhydantoins Containing a —NRR′ Substituent. II

BY HENRY R. HENZE AND DAVID D. HUMPHREYS[1,2]

About four years ago there was reported[3] from this Laboratory the synthesis of a series of 5,5-dimethylhydantoins containing a dialkylamino substituent in which the two alkyls were alike. More recently,[4] was recorded the preparation of another series of 5,5-dimethylhydantoins, these, however, containing a —NRR′ substituent in which R represented a normal alkyl group or phenyl and R′ phenyl or benzyl. Intermediate between these two series would be that containing a —NRR′ substituent in which R and R′ represent different alkyl groups.

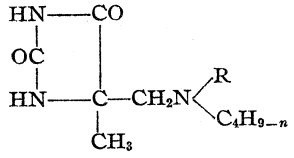
As a result of another investigation[5] there were available eight N-alkyl-*n*-butylaminoacetones. Each of these has been converted into the corresponding hydantoin derivative by reaction with ammonium carbonate and potassium cyanide. Through the courtesy of Parke, Davis and Company, six of these hydantoins have received preliminary testing on mice intraperitoneally for toxicity and possible hypnotic action. The N-methyl and N-ethyl members of the series produced slight analgesia in nearly fatal doses. None exhibited any appreciable hypnotic activity.

Experimental

The dialkylaminoacetones were readily converted into substituted hydantoins by the Bucherer[6] procedure. In general, 0.1 mole of the N-alkyl-*n*-butylaminoacetone was dissolved in 75 cc. of ethyl alcohol; then a solution of 0.11 mole of potassium cyanide dissolved in 60 cc. of water was added. Ammonium carbonate (0.3 mole) was crushed to a coarse powder and added to the ketone–cyanide mixture. Now, 60% alcohol solution was added until only one liquid phase existed in the reaction mixture at 55–60°; the ammonium carbonate was completely in solution after a few hours. The warming continued at 55–60° under a reflux condenser for ten to twelve hours. The light yellow solution was chilled causing virtually complete separation of the hydantoin. The latter was recrystallized from diluted alcohol; in some instances addition of petroleum ether to a benzene solution of the hydantoin proved to be an efficacious method for purification. Data concerning certain physical properties for and analyses of the eight hydantoins have been placed in Table I.

TABLE I

5-[N-ALKYL-*n*-BUTYLAMINOMETHYL]-5-METHYLHYDANTOINS



—R	M. p., °C. (cor.)	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	137–138	63	56.30	56.04	8.98	9.08	19.71	19.67
Ethyl	136–137	59	58.12	57.95	9.31	9.56	18.49	18.75
n-Propyl	146–147	57	59.72	59.34	9.61	9.67	17.42	17.96
Isopropyl	160–162	56	59.72	59.97	9.61	9.89	17.42	17.22
Isobutyl	177.5–178	79	61.14	61.16	9.87	10.10	16.46	16.62
s-Butyl	188–189	43	61.14	61.15	9.87	9.99	16.46	16.31
n-Amyl	165–166	46	62.41	62.44	10.11	10.13	15.60	15.81
Isoamyl	181.5–182	49	62.41	62.04	10.11	10.13	15.60	15.90

Summary

Eight new 5-[N-alkyl-*n*-butylaminomethyl]-5-methylhydantoins have been prepared. These compounds appear to be devoid of hypnotic activity but some are slightly analgesic in nearly fatal doses.

AUSTIN, TEXAS RECEIVED SEPTEMBER 11, 1942

(1) From the Ph.D. Dissertation of D. D. Humphreys, June, 1941.
(2) Present address, Sharples Chemicals Inc., Wyandotte, Mich.
(3) Magee with Henze, THIS JOURNAL, **60**, 2148 (1938).
(4) Henze and Magee, *ibid.*, **62**, 912 (1940).
(5) Henze and Humphreys, *ibid.*, **64**, 2878 (1942).
(6) Bucherer and Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Keto Ethers. X. 1-Methoxyethyl Alkyl Ketones

BY WINSTON PAUL WALLACE[1] AND HENRY R. HENZE

In connection with two other problems being investigated in this Laboratory, namely, the extension of the Pfitzinger procedure to the synthesis of alkoxyalkylquinolines[2,3] and to the preparation of hydantoin derivatives[4] possessing therapeutic activity, a number of alkyl 1-methoxyethyl ketones were needed. Methyl and ethyl members of this series had previously been prepared by Gauthier[5] who reported, however, no data other than boiling points for their physical properties. These two keto ethers, together with eight additional examples of this type, have now been prepared.

Experimental

1-Chloroethyl Methyl Ether.[6]—Henry's[7] method was utilized through condensation of methyl alcohol (10 moles) with an equivalent amount of paraldehyde by means of dry hydrogen chloride. A yield of 810 g. (95% of the theoretical) of crude material was obtained; by fractionation 485 g. was collected; b. p. 70–72° (746 mm.); d^{20}_4 0.9909; $n^{20}D$ 1.3969; *MR* calcd. 22.56; *MR* found 22.96.

α-Methoxypropionitrile.[8]—In resynthesizing this compound, because of unsatisfactory yields, various diluents were used; dry ether proved best, but with it only a 36% yield was obtained; b. p. 117–119° (740 mm.); d^{20}_4 0.8928; $n^{20}D$ 1.3818; *MR* calcd. 22.13; *MR* found 22.17.

Alkyl 1-Methoxyethyl Ketones.—After preparing the necessary alkylmagnesium bromide in the usual way, the ether solution of α-methoxypropionitrile was added slowly at such a rate that there was rapid refluxing of the solvent. Usually the reaction product stood for twelve to eighteen hours before being decomposed by addition of ice-cold dilute hydrochloric acid. The ether layer was separated and combined with the ether extract of the neutralized acidic layer. After washing with sodium bicarbonate solution and with water, the ether extract was dried over anhydrous calcium chloride and fractionally distilled; the first three members were fractionated at atmospheric pressure and the remainder under reduced pressure. The keto ethers are mobile liquids which frequently required repeated distillation in order to be obtained water white and of pleasant ester-like odor.

The data determined for physical properties of the keto ethers, together with results obtained from their analysis, are reported in Table I. Although excellent agreement between the calculated and found values for molecular refraction was obtained, and despite the fact that in all cases save one combustion analyses yielded satisfactory values for hydrogen content, the values found for percentage of carbon were uniformly high. Only a poor yield of *t*-butyl ketone was obtained using *t*-butylmagnesium chloride; no yield resulted from attempted use of the corresponding bromide or iodide.

In order to further characterize the keto ethers, they were converted into semicarbazones which could be recrystallized from benzene to sharp melting points. The data for these derivatives are recorded in Table I.

TABLE I

ALKYL 1-METHOXYETHYL KETONES, R—CO—CH(CH₃)—O—CH₃

	Ketones										Semicarbazones		
	B. p.,					Mol. refract.		Carbon, %		Hydrogen, %		M. p.,	Nitrogen, %	
—R	°C. (cor.)	mm.	Yield, %	d^{20}_4	$n^{20}D$	Calcd.	Found	Calcd.	Found	Calcd.	Found	°C. (cor.)	Calcd.	Found
Methyl[a]	115–116	739	37	0.9014	1.3936	26.94	27.08					141	26.40	26.55
Ethyl[b]	135–136	750	22	.8965	1.4019	31.56	31.54					120.5	24.26	24.11
n-Propyl	154–155	746	33	.8913	1.4091	36.18	36.12	64.58	66.3	10.84	10.50	169	22.44	22.35
Isopropyl	57–58	31	13	.8890	1.4092	36.18	36.22	64.58	65.9	10.84	10.31	146	22.42	22.48
n-Butyl	81–82	36	63	.8862	1.4160	40.80	40.82	66.63	67.5	11.18	10.88	154	20.88	20.75
Isobutyl	51–52	9	21	.8795	1.4128	40.80	40.85	66.63	67.5	11.18	10.83	145	20.88	20.76
s-Butyl	76–77	36	43	.8872	1.4158	40.80	40.75	66.63	67.3	11.18	10.95	127	20.88	20.67
t-Butyl	54–64	34	14	.8895	1.4130	40.80	40.41	66.63	68.8	11.18	9.74	121	20.88	23.59
n-Amyl	60–61	3	36	.8828	1.4207	45.42	45.40	68.31	68.9	11.47	11.17	144	19.52	19.50
Isoamyl	64–65	6	29	.8795	1.4191	45.42	45.41	68.31	68.2	11.47	11.16	154.5	19.52	19.65

[a] Gauthier, ref. 5, reported b. p. 114° (727 mm.); Diels and Pflaumer [*Ber.*, **48**, 230 (1915)] recorded b. p. 113° (759 mm.). [b] Gauthier, *ibid.*, reported b. p. 133° (729 mm.).

Summary

1. The series of alkyl 1-methoxymethyl ketones has been extended, by the synthesis of eight additional members, to include branched as well as normal groupings. The methyl and ethyl members have been resynthesized and characterized more fully.

2. Semicarbazones, useful in identification of these keto ethers, have been prepared for each member.

AUSTIN, TEXAS RECEIVED SEPTEMBER 15, 1942

(1) From the M. A. thesis of W. P. Wallace.

(2) Lesesne with Henze, THIS JOURNAL, **64**, 1897 (1942).

(3) A. F. Isbell, M. A. Thesis, August, 1941; E. J. Smith, unpublished research.

(4) Rigler with Henze, THIS JOURNAL, **58**, 474 (1936); Speer and Henze, *ibid.*, **61**, 3376 (1939).

(5) Gauthier, *Ann. chim. phys.*, [8] **16**, 289 (1909).

(6) Henze and Murchison, THIS JOURNAL, **53**, 4077 (1931).

(7) Henry, *Bull. soc. chim.*, [2] **44**, 458 (1885).

(8) Gauthier, ref. 5, reported b. p. 118° (729 mm.); d^{20}_4 0.893; $n^{20}D$ 1.382.

[CONTRIBUTION FROM DIVISION OF INSECTICIDE INVESTIGATIONS, AGRICULTURAL RESEARCH ADMINISTRATION, BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, UNITED STATES DEPARTMENT OF AGRICULTURE]

Quassin. IV. A Minor Constituent of Jamaica Quassia Wood*

BY E. P. CLARK

In the preparation of crude quassins from Jamaica quassia wood,[1] the mother liquors consistently yielded a small quantity of a fairly soluble material which, in the crude state, melted at about 150°. It was readily purified to a constant melting point of 166–167° by recrystallization from 16% methanol and as such had the physical characteristics of a pure compound. Analyses of several specimens gave fairly consistent values for carbon, hydrogen, methoxyl, and molecular weight, but they failed to harmonize with any possible formula. These facts indicated that if the material was an individual substance it was impure, but since its purification was complete as established by physical standards, the only conclusion tenable was that it was a complex of two or more substances which separated as mixed crystals.

With this as a working hypothesis, resolution was attempted by methods other than fractional crystallization. Selective adsorption upon aluminum oxide was the most successful in that the material was roughly separated into neoquassin, unchanged material, and a fraction which would not crystallize. The first two fractions could be readily purified, but all attempts to isolate the material in the last fraction failed.

The facts here recorded are presented for record in order to describe an unreported constituent of quassia wood and to call attention to the unique properties of the substance. Further work upon the material is not contemplated, because the small yield (0.015% of the wood) precludes any possible importance of the substance as an insecticide, the original object of the study.

Experimental

The aqueous-methanolic mother liquors from the crystallization of crude quassins from 200 kg. of Jamaica quassia wood were concentrated under reduced pressure until a resinous material began to separate. The liquid was then filtered through norit and set aside to crystallize. A product slowly separated as long, thin, slightly colored hexagonal plates, which melted unsharply at 150°. Reworking the mother liquors gave more material, the total quantity being 30 g. A solution of 5 g. of the crystals in 15 cc. of hot methanol was diluted with 90 cc. of hot water. The liquid was immediately filtered through norit and allowed to crystallize. The product was further purified by repeating the process three times. It then had a melting point of 166–167°, which further recrystallization failed to change. The crystals were long, colorless rods and hexagonal plates. In parallel polarized light (crossed nicols) the extinction was parallel and the elongation was negative. Many of the rods did not extinguish sharply and low polarization colors were characteristic. In convergent polarized light (crossed nicols) biaxial interference figures were rarely observable, but when they were the acute bisectrix was nearly vertical. The apparent optic axial angle in air was very small. The indices of refraction were η_α, 1.557, usually lengthwise; η_β, indeterminate; η_γ, 1.559, usually crosswise; both ± 0.002.[2]

The substance contained only carbon, hydrogen, and oxygen, and analyses of three different preparations are as follows:

Anal. Found: C, 66.14, 65.11, 65.63; H, 7.83, 7.78, 7.59; OCH_3, 11.69, 11.79, 11.79; mol. wt., 410.

Chromatographic Separation of Neoquassin.—A solution of 1 g. of the purified material in 30 cc. of ethyl acetate was passed through a 12 × 200 mm. column of aluminum oxide, and the chromatogram was developed with the same solvent. The eluate was collected to 50-cc. fractions, each evaporated under reduced pressure to dryness, and the residues were dissolved from the flask with small quantities of methanol. These liquids were evaporated to a small volume, diluted with 6 to 7 volumes of water, and allowed to crystallize. Five main fractions were obtained: I, m. p. 195–205°; II, m. p. 185–190°; III, m. p. 165°; IV, m. p. 155–160°, and V, m. p. 145–147°. The first two fractions contained most of the neoquassin, the third contained practically pure starting material, and the fourth and fifth fractions consisted of impure starting material. Fractions I and II were further purified by repeating the process with chloroform as a solvent. Impure neoquassin, m. p. about 215°, was obtained from the first fractions of this operation, and unchanged material in rather impure condition was obtained in the last fractions. Two recrystallizations of the impure neoquassin (solvent 35% methanol) gave a pure product, m. p. 226°. It was identified by its characteristic crystal habit and its failure to depress the melting point of an authentic sample of neoquassin. The last fractions from both the ethyl acetate and chloroform extractions were recrystallized from 16% methanol, which gave a preparation that melted at 166–167° and did not depress the melting point of the starting material.

The columns, after having been exhausted with either chloroform or ethyl acetate, were eluted with methanol. An appreciable quantity of sirupy, water-soluble material was thus obtained, but all efforts to crystallize it failed. It is impossible to state that this represents the material

* Not copyrighted.

(1) E. P. Clark, THIS JOURNAL, **59**, 927 (1937).

(2) The crystallographic data here recorded were determined by George L. Keenan, of the Food and Drug Administration, Federal Security Agency, Washington, D. C.

associated with neoquassin in the original substance, for it may represent a decomposition product resulting from the operation involved, or it is possible the unknown component was not eluted from the adsorbent. Both considerations seem doubtful, for a methanolic solution of the original material was rapidly and quantitatively passed through a column of aluminum oxide without separation or apparent change. However, a solution of neoquassin added to a solution of the uncrystallizable material failed to effect a synthesis of the original substance.

Summary

A hitherto unrecorded constituent of Jamaica quassia wood is described. It has the physical properties of an individual compound, but in reality consists of a complex of neoquassin and one or more unknown materials, which apparently separate as mixed crystals.

BELTSVILLE, MD. RECEIVED OCTOBER 7, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF RICHMOND]

Local Anesthetics. II. Alkoxybenzoates of 2-Monoalkylamino-2-methyl-1-propanols and 2-Monoalkylamino-1-butanols[1,2]

BY J. STANTON PIERCE, J. M. SALSBURY, WALTER W. HADEN AND L. H. WILLIS

In a recent paper from this Laboratory,[3] the preparation of β-monoalkylaminoethanol esters of alkoxybenzoic acids was described. Goldberg, Ringk and Spoerri[4] reported aminobenzoates of β-monoalkylaminoethanols in which branching occurs on the alpha carbon of the amino alcohol.

We have mono-alkylated 2-amino-2-methyl-1-propanol and 2-amino-1-butanol, which are now on the market, and have been engaged in the preparation of esters of these amino alcohols with alkoxybenzoic, alkoxycinnamic, alkoxynaphthoic, diphenylacetic, acetyltropic, acetylmandelic and *p*- and *m*-nitrobenzoic acids, with the expectation of reducing the latter to the aminobenzoate esters. The recent report of Kremer and Waldman[5] on *p*-nitrobenzoic and *p*-aminobenzoic esters of 2-monoalkylamino-2-methyl-1-propanols makes it desirable to report the results thus far obtained. This paper takes up the preparation of 2-monoalkylamino-2-methyl-1-propanols, 2-monoalkylamino-1-butanols and the alkoxybenzoates of these amino alcohols.

Alkylation of 2-amino-2-methyl-1-propanol and 2-amino-1-butanol with the lower alkyl halides usually was carried out by heating equimolar quantities of the amino alcohol and alkyl bromide in a sealed tube or under reflux at 100° for two hours. For the introduction of the amyl, hexyl, heptyl, allyl and benzyl radicals, usually the molar quantity of amino alcohol was doubled and in the introduction of the latter two groups, chlorides were used instead of bromides. The reaction product was dissolved in dilute hydrochloric acid, separated from unchanged alkyl halide, in case the reaction was not complete, and treated with excess concentrated sodium hydroxide. The alkylation product rose to the surface of the hot solution as an oil. The oil was vacuum distilled and the distillate redistilled at atmospheric pressure. The 2-monoalkylamino-2-methyl-1-propanols except the allyl, solidified on cooling. Several of the 2-monoalkylamino-1-butanols showed a tendency to crystallize, reaching a maximum in the case of 2-monobenzylamino-1-butanol. The crystals of this compound, on separation, reverted to a mixture of liquid and crystals.

In a previous paper from this Laboratory,[3] the preparation and isolation of β-monoalkylaminoethyl alkoxybenzoate hydrochlorides was described. The same general procedure, with some modifications, was used to obtain hydrochlorides of alkoxybenzoates of 2-monoalkylamino-2-methyl-1-propanols and 2-monoalkylamino-1-butanols.

Experimental

Examples are given of the preparation of 2-*n*-amylamino-2-methyl-1-propanol and of the condensation of this amino alcohol with *p*-ethoxybenzoyl chloride.

2-*n*-Amylamino-2-methyl-1-propanol.—A mixture of 113 g. (0.75 mole) of *n*-amyl bromide and 134 g. (1.5 moles) of 2-amino-2-methyl-1-propanol was heated in two sealed tubes for two hours at 100°. The contents of the tubes were combined and dissolved in 500 ml. of water and 80 ml. of concentrated hydrochloric acid. No oil remained undissolved. To the acid solution was added a solution of 100 g. of sodium hydroxide in 100 ml. of water. The oil which rose to the surface was vacuum distilled, yielding

(1) Acknowledgment is made to Dr. E. Emmet Reid, Research Adviser to the Chemistry Department of the University of Richmond, for his advice in this work.

(2) This research was made possible by a grant from Chas. C. Haskell and Co., Inc., Richmond, Va.

(3) J. Stanton Pierce, J. M. Salsbury and J. M. Fredericksen, THIS JOURNAL, **64**, 1691–1694 (1942).

(4) Goldberg, Ringk and Spoerri, *ibid.*, **61**, 3562–3564 (1939).

(5) Kremer and Waldman, *ibid.*, **64**, 1089–1090 (1942).

108 g. of product, boiling 103–135° (30 mm.). On redistillation, there was obtained 70 g. (58%) of 2-*n*-amylamino-2-methyl-1-propanol; b. p. 212–222°.

TABLE I

β-MONOALKYLAMINOALKANOLS

R	Empirical formula	B. p., °C. (cor.)	M. p.,[a] °C. (uncor.)	Nitrogen, % Calcd.	Found
(a) 2-Monoalkylamino-2-methyl-1-propanols: $RNHC(CH_3)_2CH_2OH$					
Ethyl[b]	$C_6H_{15}ON$	167–170	72–73	11.95	11.91, 11.87
n-Propyl[b]	$C_7H_{17}ON$	185–188	56–57.5	10.68	10.41, 10.43
n-Butyl[b]	$C_8H_{19}ON$	202–204	68–69	9.64	9.59, 9.61
n-Amyl[b]	$C_9H_{21}ON$	218–221	56–59	8.80	8.50, 8.55
n-Hexyl	$C_{10}H_{23}ON$	235–238	62–62.5	8.08	7.82, 7.81
n-Heptyl	$C_{11}H_{25}ON$	253–256	50–52	7.48	7.13, 7.14
Iso-butyl[b]	$C_8H_{19}ON$	184–187	48–49	9.64	9.52
Iso-amyl[b]	$C_9H_{21}ON$	214–217	73–74	8.80	8.48, 8.52
Allyl	$C_7H_{15}ON$	183–187		10.84	11.20
Benzyl	$C_{11}H_{17}ON$	277–280	53–57	7.81	7.55, 7.55
(b) 2-Monoalkylamino-1-butanols: $RNHCH(C_2H_5)CH_2OH$					
Ethyl	$C_6H_{15}ON$	177–179		11.95	11.95, 11.96
n-Propyl	$C_7H_{17}ON$	192–193		10.68	10.44, 10.43
n-Butyl	$C_8H_{19}ON$	210–213		9.64	9.40, 9.47
n-Amyl	$C_9H_{21}ON$	227–230		8.80	8.52, 8.53
n-Hexyl	$C_{10}H_{23}ON$	247–252		8.08	7.68
n-Heptyl	$C_{11}H_{25}ON$	263–266		7.48	7.13, 7.15
Iso-butyl	$C_8H_{19}ON$	195–198		9.64	10.01, 10.04
Iso-amyl	$C_9H_{21}ON$	221–224			
Allyl	$C_7H_{15}ON$	194–197		10.84	10.91, 10.87
Benzyl	$C_{11}H_{17}ON$	283–285		7.81	7.51, 7.50

[a] The melting points of the distilled amino alcohols were taken without recrystallization of the products, since it was found that recrystallization raised the melting point only slightly. [b] Also prepared by Kremer and Waldman.[5]

Hydrochloride of *p*-Ethoxybenzoate of 2-Mono-*n*-amylamino-2-methyl-1-propanol.—To 15.9 g. (0.1 mole) of 2-mono-*n*-amylamino-2-methyl-1-propanol was added 12.5 ml. (0.15 mole) of concentrated hydrochloric acid. The excess hydrochloric acid was removed by vacuum evaporation. To the solid hydrochloride of 2-mono-*n*-amylamino-1-propanol was added 18.4 g. (0.1 mole) of *p*-ethoxybenzoyl chloride. The reaction mixture was heated, with occasional shaking, in an oil-bath at 100° for thirty minutes, at 130° for thirty minutes, and at 150° for fifteen minutes. The reaction mixture was dissolved in 60 ml. of 95% ethanol, poured into 800 ml. of *N* sodium hydroxide solution, and extracted with 125 ml. of isopropyl ether. The ether solution was extracted with 1500 ml. of 0.4 *N* hydrochloric acid. The acid solution was made basic with sodium hydroxide and the free base of the amino alcohol ester was extracted with 150 ml. of isopropyl ether. The isopropyl ether solution was saturated with dry hydrogen chloride, yielding 23 g. (67%) of an oily precipitate of the hydrochloride of β-mono-*n*-amylamino-β,β-(dimethyl)-ethyl *p*-ethoxybenzoate, which solidified within a few minutes. On two crystallizations from acetone, this product melted at 127–129°.

In this study, approximately sixty alkoxybenzoates of 2-monoalkylamino-2-methyl-1-propanols and 2-monoalkylamino-1-butanols were prepared, that their anesthetic activity might be tested. In some runs in which very insoluble ester hydrochlorides were formed, the products were isolated by precipitation with a large excess of hydrochloric acid and by filtration. Table II gives the melting points and chloride analyses of the hydrochlorides of the above alkoxybenzoates which were most readily crystallized.

TABLE II

β-MONOALKYLAMINOALKYL ALKOXYBENZOATE HYDROCHLORIDES

R	R′	M. p., °C. (uncor.)	Empirical formula	Chlorine, % Calcd.	Found
(a) β-Monoalkylamino-β,β-(dimethyl)-ethyl alkoxybenzoate hydrochlorides: $ROC_6H_4COOCH_2C(CH_3)_2NHR'\cdot HCl$					
p-Methyl	*n*-Butyl	154–155	$C_{16}H_{26}O_3NCl$	11.23	11.11
p-Ethyl	*n*-Amyl	128–129	$C_{18}H_{30}O_3NCl$	10.31	10.15
p-Ethyl	*n*-Hexyl	135–136	$C_{19}H_{32}O_3NCl$	9.91	9.82
o-Ethyl	*n*-Butyl	118–120	$C_{17}H_{28}O_3NCl$	10.75	10.86
m-Ethyl	*n*-Butyl	106–108	$C_{17}H_{28}O_3NCl$	10.75	10.67
m-Ethyl	*n*-Amyl	73–76	$C_{18}H_{30}O_3NCl$	10.31	9.82
p-*n*-Propyl	*n*-Butyl	98–100	$C_{18}H_{30}O_3NCl$	10.31	10.38
p-*n*-Propyl	*n*-Amyl	103–106	$C_{19}H_{32}O_3NCl$	9.91	10.06
p-*n*-Propyl	*n*-Hexyl	118–120	$C_{20}H_{34}O_3NCl$	9.53	9.34
p-*n*-Butyl	Ethyl	136–138	$C_{17}H_{28}O_3NCl$	10.75	10.47
p-*n*-Butyl	*n*-Propyl	105–107	$C_{18}H_{30}O_3NCl$	10.31	10.24
p-*n*-Butyl	*n*-Butyl	125–127	$C_{19}H_{32}O_3NCl$	9.91	9.66
p-*n*-Butyl	*n*-Hexyl	122–123	$C_{21}H_{36}O_3NCl$	9.19	9.21
p-*n*-Butyl	Benzyl	161–162	$C_{22}H_{30}O_3NCl$	9.05	9.02
o-*n*-Butyl	*n*-Butyl	91–94	$C_{19}H_{32}O_3NCl$	9.91	9.96
p-*n*-Amyl	*n*-Propyl	112–113	$C_{19}H_{32}O_3NCl$	9.91	10.00
p-*n*-Amyl	*n*-Butyl	125–126	$C_{20}H_{34}O_3NCl$	9.53	9.64
p-*n*-Amyl	*n*-Amyl	103–104	$C_{21}H_{36}O_3NCl$	9.19	9.01
p-*n*-Amyl	Benzyl	139–140	$C_{23}H_{32}O_3NCl$	8.74	8.79
p-*n*-Hexyl	*n*-Butyl	125.5–127	$C_{21}H_{36}O_3NCl$	9.19	9.11
p-*n*-Heptyl	*n*-Propyl	108–110	$C_{21}H_{36}O_3NCl$	9.19	9.11
p-*n*-Heptyl	*n*-Butyl	117–118	$C_{22}H_{38}O_3NCl$	8.86	8.80
p-*n*-Heptyl	*n*-Amyl	105–106	$C_{23}H_{40}O_3NCl$	8.57	8.56
p-*n*-Heptyl	*n*-Hexyl	105–107	$C_{24}H_{42}O_3NCl$	8.28	8.25
(b) β-Monoalkylamino-β-ethyl-ethyl alkoxybenzoate hydrochlorides: $ROC_6H_4COOCH_2CH(C_2H_5)NHR'\cdot HCl$					
p-Ethyl	Ethyl	184–185	$C_{15}H_{24}O_3NCl$	11.75	11.42
p-Ethyl	*n*-Butyl	134–135	$C_{17}H_{28}O_3NCl$	10.75	10.82
p-Ethyl	*n*-Hexyl	135–136	$C_{19}H_{32}O_3NCl$	9.91	9.88
p-Ethyl	Benzyl	181–184	$C_{20}H_{26}O_3NCl$	9.74	9.64
p-*n*-Propyl	*n*-Butyl	129–131	$C_{18}H_{30}O_3NCl$	10.31	10.25
p-*n*-Propyl	*n*-Hexyl	112–114	$C_{20}H_{34}O_3NCl$	9.53	9.33
p-Iso-propyl	*n*-Butyl	119–121	$C_{18}H_{30}O_3NCl$	10.31	10.29
p-*n*-Butyl	*n*-Butyl	114–116	$C_{19}H_{32}O_3NCl$	9.91	9.85
p-*n*-Heptyl	*n*-Propyl	108–109	$C_{21}H_{36}O_3NCl$	9.19	8.76

The β-monoalkylaminoalkyl alkoxybenzoate hydrochlorides reported in this paper are being tested pharmacologically by Dr. C. C. Haskell. The results will be reported elsewhere.

Summary

A series of hydrochlorides of alkoxybenzoates of 2-monoalkylamino-2-methyl-1-propanols and of 2-monoalkylamino-1-butanols is described.

RICHMOND, VA. RECEIVED SEPTEMBER 1, 1942

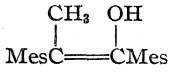
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Vinyl Alcohols. IV.[1] Oxidative Cleavage

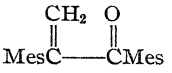
BY REYNOLD C. FUSON, D. J. BYERS,[2] A. I. RACHLIN AND P. L. SOUTHWICK[3]

The vinyl alcohol, 1,2-dimesityl-1-propen-1-ol (I),[4] was observed to undergo slow deterioration in contact with the air.[5] In the absence of air, however, it has proved to be stable. Samples of this remarkable enol, kept in sealed tubes under nitrogen, show no change after eighteen months.

The oil produced by the action of oxygen on the enol was found to contain acetomesitylene and mesitoic acid, evidently produced by oxidative cleavage. Subsequent study of this cleavage has shown acetomesitylene to occur invariably as a principal product whereas mesitoic acid is generated only in small amounts or not at all. Another product, isolated in traces, proved to be



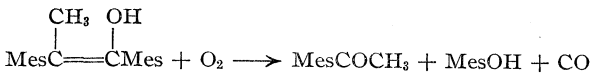
I



II

mesityl α-mesitylvinyl ketone (II). Its formation is to be ascribed to 1,4-dehydrogenation of the enol, a reaction that had been brought about earlier by the use of permanganate, chromic anhydride[6] and chloranil.

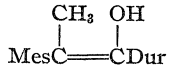
It remained to discover the moiety sheared off in the production of acetomesitylene. By suitable modification of the procedure it was an easy matter to isolate in quantity a low-melting, volatile solid, which proved to be *mesitol*. The amount corresponded roughly to that of acetomesitylene. Attempts to write an equation, however, revealed that a carbon atom was yet to be accounted for. Tests for formaldehyde and carbon dioxide showed that neither was produced in appreciable amounts. Analysis of the exit gas, however, provided the answer; carbon monoxide was present and in amounts proportional to those of acetomesitylene and mesitol. The production of a mole of carbon monoxide for every mole of oxygen absorbed explains the observation that there was no change in pressure during the reaction. The oxidative degradation can accordingly be represented by the following equation



Two additional products were detected in small amounts. One of these was hydrogen, which was found in the exit gases from the oxidation chamber. Its origin is not apparent. The other by-product was a phenolic compound melting at 169.5–171.5°. Its properties indicate that it may be made up of two mesitol residues but this surmise has not been verified.

It seems probable that a peroxide is formed which then breaks down to yield the three products shown in the equation. The peroxide could decompose in an alternative manner to yield mesitoic acid and acetomesitylene. The chief reaction, however, is that leading to the production of mesitol, carbon monoxide and acetomesitylene. It is a new type of oxidative cleavage. There is a possibility that it is related to the well-known Dakin cleavage of certain types of aromatic aldehydes and ketones to the corresponding phenols.[7]

The new reaction has been used to degrade several enols, structurally similar to I, and appears to be generally applicable to compounds of this type. For example, 1-duryl-2-mesityl-1-propen-1-ol (III)[1] yielded acetomesitylene, durenol, carbon monoxide and smaller amounts of 2,3,5,6-tetramethylbenzoic acid and duryl α-mesitylvinyl ketone. It is interesting that in this cleavage no



III

high-melting phenol was detected. Results similar to the foregoing have been obtained in structure studies of other vinyl alcohols described elsewhere.[8]

Experimental

Cleavage of 1,2-Dimesityl-1-propen-1-ol

The cleavage is readily accomplished by bubbling oxygen through a solution of the enol in an organic solvent such as acetone, or a mixture of ether and petroleum ether. However, to facilitate collection of the gaseous products of the reaction it was found convenient to make use of a Parr

(1) For the preceding communication in this series, see Fuson and Sperati, THIS JOURNAL, **63**, 2643 (1941).
(2) Du Pont Post-doctorate Fellow, 1940–1941.
(3) Abbott Fellow, 1942–1943.
(4) Mes and Dur denote mesityl and duryl, respectively.
(5) Fuson, Byers and Rabjohn, *ibid.*, **63**, 2639 (1941).
(6) Stodola, *Science*, **98**, 452 (1941).
(7) Dakin, *Am. Chem. J.*, **42**, 477 (1909).
(8) Fuson, Lindsey and Welldon, THIS JOURNAL, **64**, 2888 (1942); Fuson, Byers and Rachlin, *ibid.*, **64**, 2891 (1942).

low-pressure hydrogenation machine of the Adams type.[9] The reaction was carried out by shaking acetone solutions of the enol with oxygen in this apparatus. Various procedures for separating and identifying the products of the cleavage were tried. The following is the description of a run in which the most satisfactory procedure was used.

Treatment with Oxygen.—A solution of 8.4 g. (0.029 mole) of the enol in 250 cc. of acetone was placed in the shaker bottle and treated with oxygen for three days at a gage pressure of 14.75 lb. per sq. in. The drop in pressure during this time was negligible.

Analysis of Gases.—Gas samples were taken from the shaker bottle by means of an exit tube provided in the stopper, and from the tank through the outlet valve. The gases were passed through sulfuric acid to remove acetone vapors and samples were collected by displacement of water from sample tubes of 300 cc. capacity.

The presence of carbon monoxide was detected by the palladium chloride test.[10] Quantitative analysis[11] of the gas samples was carried out with an apparatus of the Orsat type. Carbon dioxide was determined by absorption in 33% potassium hydroxide solution, and oxygen by absorption in a 10% solution of pyrogallol in 33% potassium hydroxide. After removal of carbon dioxide and oxygen, the gases were scrubbed with 90% sulfuric acid and then passed over cupric oxide at 250°. Hydrogen was then estimated from the decrease in the volume of the sample upon condensation of the water formed. Carbon monoxide was determined by absorption of the resulting carbon dioxide in 33% potassium hydroxide solution.

The sample from the shaker bottle contained 56.1 mole per cent. of carbon monoxide, and the sample from the tank 4.8 mole per cent. An estimate based on the capacity of the bottle and of the tank indicated the formation of approximately 0.028 mole of carbon monoxide in the reaction. No carbon dioxide was found in the gases produced in this run, although minute quantities were found in another run by passing the entire gaseous mixture through a saturated barium carbonate solution. Hydrogen was found to the extent of 2.6 mole per cent. in the sample from the bottle, and 0.6 per cent. in the sample from the tank.

The solution was taken from the shaker bottle, and the acetone removed by distillation from a steam-cone. The acetone distillate was refluxed for four hours while a slow stream of carbon dioxide was bubbled through it, and the exit gases were passed through 150 cc. of water kept at 0°. At the end of that time no formaldehyde could be detected in the water by the fuchsin test. In another run a fuchsin test which could not be decolorized by sulfuric acid was obtained from the acetone distillate, but the methone test was negative.

Acidic Components

The oil remaining after removal of the acetone was taken up in a very small amount of ether and extracted repeatedly with a 10% potassium hydroxide solution. Acidification of the alkaline extracts yielded 4.2 g. of a solid precipitate. This material was dissolved in ether, and the solution was extracted twice with a 10% solution of potassium bicarbonate. Acidification of the extracts precipitated 0.2 g. of a white solid melting at 151–153°. No depression of the melting point was observed when this compound was mixed with an authentic sample of mesitoic acid.

The ether solution of the acidic components, which now contained only the phenolic fraction, was evaporated, and the residual solids were subjected to steam distillation. Two and four-tenths grams of a white solid melting at 67–69° was obtained by cooling and filtering the distillate. Crystallization from low-boiling petroleum ether gave white needles melting at 71–72° which did not depress the melting point of a known sample of mesitol.

The solid remaining in the steam-distillation flask was collected on a filter and dissolved in 10% potassium hydroxide solution. The solution was filtered free of a small amount of insoluble solid material, and acidified with hydrochloric acid. Five-tenths of a gram of a tan solid was precipitated. After repeated crystallization from glacial acetic acid, white crystals melting at 169.5–171.5° were obtained.

Anal.[12] Calcd. for $C_{18}H_{22}O_2$: C, 79.95; H, 8.28. Found: C, 79.60; H, 8.13.

Approximately 0.2 g. of the high-melting phenol was heated for a few minutes with 5 cc. of acetic anhydride and one drop of concentrated sulfuric acid. Excess acetic anhydride was decomposed by heating with water, and the resulting solid product was crystallized four times from high-boiling petroleum ether. White needles melting at 148–149° were obtained.

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.53; H, 7.40. Found: C, 74.71; H, 7.75.

Neutral Components.—After extraction with 10% potassium hydroxide, the ether solution containing the neutral components was washed with water, and the ether was removed by distillation. Distillation of the residual oil yielded 3.2 g. of a liquid boiling at 85–90° at 3 mm. A 0.5-g. portion of this oil was treated with 10 cc. of fuming nitric acid at 0°, and the nitration mixture was poured on ice. The precipitated white product melted at 135–137° after crystallization from ethanol, and did not depress the melting point of a known sample of dinitroacetomesitylene.

A small amount of methanol was added to the viscous red oil remaining in the distilling flask after removal of the acetomesitylene, and a crystalline precipitate formed immediately. About 0.3 g. of this material was obtained by cooling and filtering the solution. After crystallization from ethanol, it melted at 132–133° and was shown to be mesityl α-mesitylvinyl ketone by the mixed melting point test.

Cleavage of 1-Duryl-2-mesityl-1-propen-1-ol

The cleavage was brought about by shaking a solution of 8.5 g. of the enol in 250 cc. of acetone with oxygen for three days at a gage pressure of 10 lb. per sq. in.

A gas sample from the bottle contained 39.4 mole per cent. of carbon monoxide, no appreciable carbon dioxide and 1.2 mole per cent. of hydrogen.

(9) Adams and Voorhees, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., second edition, 1941, p. 65.

(10) Fritz Bayer, "Gasanalyse," W. Böttger and F. Enke, Stuttgart, 1938, p. 52.

(11) The gas analyses were carried out by Mr. Robert S. Hanmer.

(12) Microanalyses by Miss Theta Spoor.

Acidic Components.—The procedure was very similar to that described above for 1,2-dimesityl-1-propen-1-ol. Acidification of the bicarbonate extract yielded 0.5 g. of a white solid melting at 176.5–178.5° after crystallization from high-boiling petroleum ether. It did not depress the melting point of an authentic sample of 2,3,5,6-tetramethylbenzoic acid.

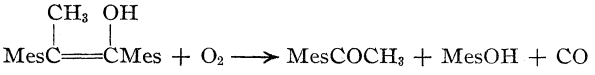
The remainder of the acidic fraction was dissolved in 10% potassium hydroxide solution, filtered free of insoluble material, and precipitated by acidification. One and four-tenths gram of a product melting at about 110° was obtained. Crystallized twice from low-boiling petroleum ether, it melted at 117–118° and did not depress the melting point of a known sample of durenol.

Neutral Components.—After extraction of the acidic components, the oil was washed with water and allowed to stand; a small amount of a crystalline product separated and was removed by filtration. Distillation of the filtrate yielded 1.5 g. of an oil boiling at 93–95° at 5 mm. Nitration of this oil as described above converted it to dinitroacetomesitylene.

Methanol was added to the viscous residue in the distilling flask, and the yellow solid which separated was filtered and crystallized from ethanol. It melted at 156.5–157.5° and did not depress the melting point of a sample of duryl α-mesitylvinyl ketone. The solid mentioned above, which crystallized from the oily mixture, was crystallized from ethanol, and likewise proved to be duryl α-mesitylvinyl ketone. A total of 0.8 g. of this compound was isolated.

Summary

It has been found that treatment with oxygen causes the vinyl alcohol, 1,2-dimesityl-1-propen-1-ol, to undergo cleavage to acetomesitylene, mesitol and carbon monoxide according to the equation



Small amounts of mesityl α-mesitylvinyl ketone, mesitoic acid, hydrogen and an unidentified phenol were also detected among the reaction products.

Similar results were obtained with 1-duryl-2-mesityl-1-propen-1-ol.

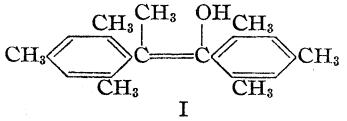
URBANA, ILLINOIS RECEIVED SEPTEMBER 8, 1942

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

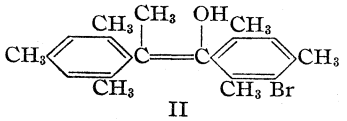
Vinyl Alcohols. V.[1] Isomeric Bromo-1,2-dimesityl-1-propen-1-ols

BY REYNOLD C. FUSON, R. V. LINDSEY, JR., AND P. BURKE WELLDON

In an effort to relate the remarkable stability of 1,2-dimesityl-1-propen-1-ol[2] (I) to structural features, a number of similar enols were prepared. The method in every case involved the corresponding desoxybenzoin as a starting material. One of the most interesting of these syntheses was that of the bromo derivative (II) of the original enol. It was made from 3′-bromodesoxymesitoin (III),

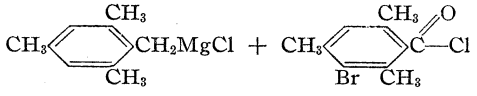


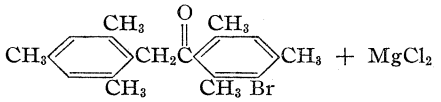
I



II

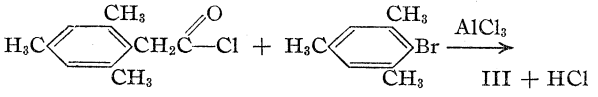
which in turn was prepared by condensing 3-bromomesitoyl chloride with α[2]-isodurylmagnesium chloride.





III

Because the yields of the bromodesoxymesitoin (III) were low, an effort was made to find a better method of synthesis. The most promising alternative appeared to be the Friedel–Crafts reaction between mesitylacetyl chloride and bromomesitylene.



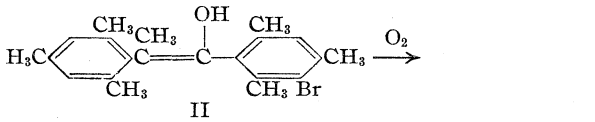
The result was, however, very surprising. The condensation proceeded smoothly to yield a compound of the expected composition and similar melting point. But a mixed melting point determination showed it to be different from the desired 3′-bromodesoxymesitoin.

(1) For the preceding article in this series, see Fuson, Byers, Rachlin and Southwick, THIS JOURNAL, **64**, 2886 (1942).

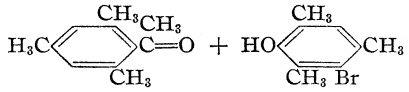
(2) (a) Fuson, Corse and McKeever, *ibid.*, **62**, 3250 (1940); (b) Fuson, Byers and Rabjohn, *ibid.*, **63**, 2639 (1941).

That we were dealing with isomeric bromodesoxymesitoins became clear when it was found that each compound, when condensed with formaldehyde, yielded an unsaturated ketone that could be converted by hydrogenation to a vinyl alcohol. Both vinyl ketones melted at 150°, but a mixed melting point determination showed a 20° lowering. The new vinyl alcohols were considerably less permanent than the parent enol, 1,2-dimesityl-1-propen-1-ol (I); they were isolated only as unstable solids. Enol II was converted to the methyl ether.

Fortunately, the newly discovered oxidative cleavage[1] of such enols offered a simple method of structure determination. The vinyl alcohol (II) derived from 3′-bromodesoxymesitoin (III) yielded acetomesitylene (IV) and 3-bromomesitol (V), as was expected.

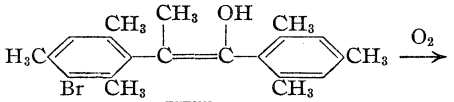


II

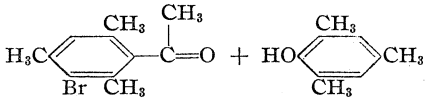


IV V

The enol from the new desoxy compound was oxidized to 3-bromoacetomesitylene (VI) and mesitol (VII).

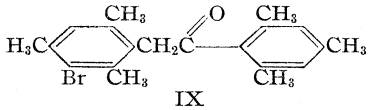


VIII



VI VII

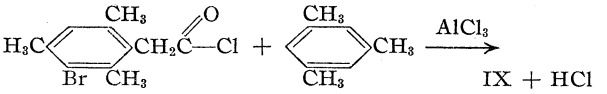
It must, therefore, have the structure, VIII. As a consequence, the desoxy compound from the Friedel–Crafts synthesis can be assigned the structure of 3-bromodesoxymesitoin (IX). Its



IX

formation involves the transfer of the bromine atom from one ring to the other. This remarkable migration must occur at some intermediate point in the condensation, for the 3′-bromodesoxymesitoin did not undergo isomerization when treated with aluminum chloride. Although halogen migrations during the Friedel–Crafts reaction are well-known,[3] this one seems noteworthy for the selectivity with which it proceeds. The yields ranged from 40 to 90%.

The structure of 3-bromodesoxymesitoin was confirmed by an independent synthesis. This compound was obtained in satisfactory yields by condensing 3-bromomesitylacetyl chloride with mesitylene.



Experimental

3-Bromomesitoic Acid.—Mesitoic acid was brominated by the method of Shildneck and Adams[4]; omission of the iron catalyst gave consistently higher yields. There was obtained 288 g. (74% yield) of 3-bromomesitoic acid, m. p. 162–165°, from 260 g. of mesitoic acid.

The acid was converted to the *acid chloride* (b. p. 175–178° (28 mm.)) in 97% yield by the action of thionyl chloride at room temperature.

Condensation of 3-Bromomesitoyl Chloride with α^2-Isodurylmagnesium Chloride.—A solution of 8.4 g. of α^2-chloroisodurene in 350 cc. of dry ether was added over one and one-half hours to 10 g. of magnesium in 150 cc. of dry ether at 0°. The temperature of the mixture was allowed to rise to room temperature; stirring was continued for thirty minutes, after which a solution of 13 g. of 3-bromomesitoyl chloride in 25 cc. of dry ether was added dropwise. Stirring was continued for one hour; the reaction mixture was then decomposed with cold, dilute hydrochloric acid. The ether layer was extracted with dilute alkali, washed with water and evaporated. The residue was crystallized from absolute alcohol; 8 g. (45% yield) of 3′-bromodesoxymesitoin was obtained as white plates melting at 91–92°.

Anal. Calcd. for $C_{20}H_{23}OBr$: C, 66.85; H, 6.40. Found: C, 67.00; H, 6.42.

Repetition of this preparation gave yields of less than 10%; the product was contaminated with large amounts of 1,2-dimesitylethane (m. p. 115–116°) from the coupling of the Grignard reagent and could be obtained pure only by repeated fractional crystallization from low-boiling petroleum ether.

Condensation of Mesitylacetyl Chloride with Bromomesitylene.—A solution of mesitylacetyl chloride (20 g.) and bromomesitylene (25 g.) in carbon disulfide (30 cc.) was added over forty-five minutes to a stirred mixture of bromomesitylene (20 g.), aluminum chloride (30 g.) and carbon disulfide (80 cc.) at 0°. Stirring was continued at 0° for three hours, and for an additional three hours at 0–17°. The reaction mixture was decomposed with ice and hydrochloric acid; the organic layer was diluted with 200 cc. of ether and washed thoroughly with 10% sodium hydroxide solution and water. Exhaustive steam distillation removed the solvents and excess bromomesitylene; the

(3) Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1941, p. 692.

(4) Shildneck and Adams, THIS JOURNAL, **53**, 349 (1931).

last portion of the distillate yielded 1 g. of a white solid mixture from which was isolated tribromomesitylene.[5] The viscous residue was crystallized from absolute alcohol; there was obtained 33.4 g. of white solid melting at 90–93°. A mixture of this solid and 3′ bromodesoxymesitoin melted at 71–75°. Recrystallization first from petroleum ether and then from methanol yielded white crystals melting at 98–99°. This compound was subsequently shown to be 3-bromodesoxymesitoin; yield, 90%.

Anal. Calcd. for $C_{20}H_{23}OBr$: C, 66.85; H, 6.40. Found: C, 66.91; H, 6.31.

3-Bromomesityl α-Mesitylvinyl Ketone.—The procedure was that described for the preparation of α-mesitylvinyl mesityl ketone.[2b] From 8 g. of 3′-bromodesoxymesitoin there was obtained 6.84 g. of the vinyl ketone, melting at 150–151°; yield, 83%.

Anal. Calcd. for $C_{21}H_{23}OBr$: C, 67.92; H, 6.24. Found: C, 68.06; H, 6.32.

Mesityl α-(3-Bromomesityl)-vinyl Ketone.—The same procedure[2b] was followed, except that the time of stirring was reduced to seventeen hours. Addition of a second portion of paraformaldehyde was unnecessary. From 12 g. of 3-bromodesoxy-mesitoin there was obtained 12.2 g. of mesityl α-(3-bromomesityl)-vinyl ketone, melting at 149–150°; yield, 98%.

Anal. Calcd. for $C_{21}H_{23}OBr$: C, 67.92; H, 6.24. Found: C, 67.82; H, 6.37.

A mixture of this compound and 3-bromomesityl α-mesitylvinyl ketone melted at 131–134°.

The Methyl Ether of 1-(3-Bromomesityl)-2-mesityl-1-propen-1-ol.—3-Bromomesityl α-mesitylvinyl ketone (15 g.) in glacial acetic acid (150 cc.) was subjected to one and one-half atmospheres pressure of hydrogen in the presence of platinum oxide catalyst. One mole of hydrogen was absorbed per mole of ketone. The solution was filtered into water; the enol was obtained as a white precipitate which became gummy after short exposure to air. It was dissolved in benzene; the solution was washed with dilute potassium bicarbonate solution and water. The benzene solution was partially distilled to dry it, and then was stirred and heated with 2.3 g. of finely divided sodium for one and one-half hours. Excess methyl sulfate was added, and the treatment continued for two hours. The benzene solution was warmed with dilute alkali, washed with water, and evaporated to dryness. Crystallization of the residue from ethanol yielded 12.5 g. of the enol ether, melting at 117.5–119°; yield, 80%.

Anal. Calcd. for $C_{22}H_{27}OBr$: C, 68.22; H, 6.98. Found: C, 68.22; H, 6.99.

Oxidative Cleavage of 1-(3-Bromomesityl)-2-mesityl-1-propen-1-ol.—3-Bromomesityl α-mesitylvinyl ketone (5.5 g.) in ether (50 cc.) was reduced to the enol. The solution was filtered, diluted with acetone and treated with oxygen for three days by the procedure of Fuson, Byers, Rachlin and Southwick.[1] Extraction of an ethereal solution of the residue with alkali followed by acidification yielded 2.24 g. of a solid which was sublimed *in vacuo* to give white needles, m. p. 81–82°. A mixture of this compound and an authentic sample of 3-bromomesitol (prepared by the method of Jacobsen[6]) melted at 81–82°.

(5) Fittig and Storer, *Ann.*, **147**, 8 (1868).

(6) Jacobsen, *ibid.*, **195**, 270 (1879).

Distillation of the neutral residue yielded 1.4 g. of acetomesitylene, which was identified by conversion to the dinitro derivative as previously described.[2b]

Oxidative Cleavage of 1-Mesityl-2-(3-bromomesityl)-1-propen-1-ol.—When mesityl α-(3-bromomesityl)-vinyl ketone was reduced in methanol by the usual procedure, the resulting enol was again a white solid which became gummy after short contact with air. Treatment of this unstable enol with cold potassium permanganate in acetone[2b] dehydrogenated it to regenerate the vinyl ketone.

A solution of the enol (formed by reduction of 5.6 g. of mesityl α-(3-bromomesityl)-vinyl ketone) in an ether–acetone mixture was treated with molecular oxygen[1] for three days. The phenolic product obtained (1.4 g.) was shown to be mesitol by a mixed melting point determination. Distillation of the neutral residue gave 2.4 g. of 3-bromoacetomesitylene, b. p. 110–115°(3 mm.). The identity of this compound was established by use of the procedure of Adams and Miller.[7] By treatment with phosphoric acid the ketone was cleaved to bromomesitylene, which was identified as the dinitro derivative.

Attempted Isomerization of 3′-Bromodesoxymesitoin.—Efforts to transform the 3′-bromo ketone to the isomeric 3-bromodesoxymesitoin by the influence of aluminum chloride were unsuccessful. Conditions of the original Friedel–Crafts reaction were duplicated. If excess bromomesitylene was added, the products were tribromomesitylene, starting material and some intractable oil.

3-Bromomesitylmethyl Chloride.—Gaseous hydrogen chloride was passed for eight hours into a violently agitated mixture of bromomesitylene (50 g.), paraformaldehyde (25 g.), zinc chloride (2 g.) and concentrated hydrochloric acid (250 cc.) at 65–70°. The cooled mixture was extracted with benzene; the benzene solution was washed with alkali and water, dried (calcium chloride) and distilled. Seven grams of unchanged bromomesitylene was recovered; the chloromethyl compound was obtained as white needles; m. p. 44–45°; b. p. 126–129° (2 mm.); weight, 45 g. (84% yield).

Anal. Calcd. for $C_{10}H_{12}BrCl$: C, 48.51; H, 4.89. Found: C, 48.72; H, 5.00.

3-Bromomesitylacetonitrile.—3-Bromomesitylmethyl chloride (24.75 g.) was added over five minutes to a mixture of sodium cyanide (8.4 g.), alcohol (28 cc.) and water (20 cc.) at 55–60°; stirring and heating were continued for three hours. The cooled mixture was extracted with benzene; the benzene solution was washed with water, dried (calcium chloride) and evaporated on the water-bath. The residue was crystallized from high-boiling petroleum ether, yielding white needles melting at 113–114°; weight, 19.6 g. (82% yield).

Anal. Calcd. for $C_{11}H_{12}NBr$: C, 55.48; H, 5.08. Found: C, 55.49; H, 4.94.

3-Bromomesitylacetic Acid.—3-Bromomesitylacetonitrile (11.9 g.) was hydrolyzed by refluxing and stirring with 104 cc. of 55% sulfuric acid for ten hours. The acid was obtained as white, fluffy needles after crystallization from benzene–high-boiling petroleum ether; m. p. 168.5–169.5°; weight, 10.06 g. (78% yield).

Anal. Calcd. for $C_{11}H_{13}O_2Br$: C, 51.36; H 5.09. Found: C, 51.43; H, 5.23.

(7) Adams and Miller, THIS JOURNAL, **62**, 53 (1940).

3-Bromomesitylacetamide (0.38 g.) was obtained as alkali-insoluble residue. After crystallization from benzene–high-boiling petroleum ether, it formed white, fluffy needles melting at 231–232°.

Anal. Calcd. for $C_{11}H_{14}ONBr$: C, 51.58; H, 5.51. Found: C, 51.78; H, 5.49.

The acid was converted to the *acid chloride* (b. p. 146–148° (4 mm.)) in 85% yield by the action of thionyl chloride at room temperature.

3-Bromodesoxymesitoin.—A solution of 3-bromomesitylacetyl chloride (3.25 g.) in mesitylene (5 cc.) was added over fifteen minutes to a stirred mixture of mesitylene (15 cc.), aluminum chloride (2 g.), and carbon disulfide (40 cc.) at 0°. Over one hour, the mixture was gradually warmed to 50°, at which temperature it refluxed gently for fifteen minutes. It was decomposed with ice and hydrochloric acid; the organic layer was diluted with 100 cc. of ether and washed with dilute alkali and water. Steam distillation removed the solvents and excess mesitylene; the residue was dried and crystallized from absolute alcohol. The white solid product melted at 97–99°; a mixture with the product of the Friedel–Crafts reaction between mesitylacetyl chloride and bromomesitylene melted at 97–99°.

Summary

Isomeric bromo 1,2-dimesityl-1-propen-1-ols have been prepared; they are very unstable compared to similar vinyl alcohols containing no halogen substituent.

The Friedel–Crafts reaction of mesitylacetyl chloride and bromomesitylene has been shown to yield 3-bromodesoxymesitoin instead of the expected 3′-bromo compound.

URBANA, ILLINOIS RECEIVED SEPTEMBER 8, 1942

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

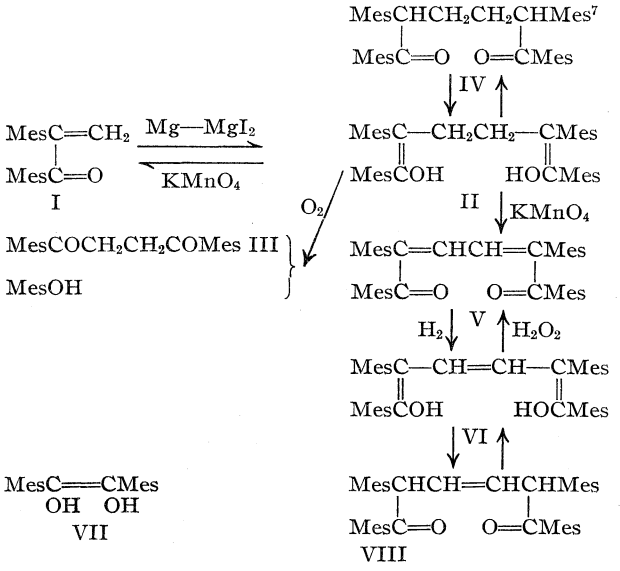
Enediols. XI.[1] Vinylogs of Ethylene and Acetylene Glycols

BY REYNOLD C. FUSON, D. J. BYERS[2] AND A. I. RACHLIN

The production of a stable vinyl alcohol by the hydrogenation of mesityl α-mesitylvinyl ketone (I)[3] suggested that the corresponding dienol (II) might be formed if the reduction could be caused to take place bimolecularly. Experiment has shown that this type of reduction can be accomplished readily and in high yield by use of the binary mixture, Mg-MgI_2.[4]

The structure of the dienol, 1,2,5,6-tetramesityl-1,5-hexadien-1,6-diol (II), was established by use of the cleavage described recently for enols of this type.[5] Treatment with oxygen converted it to mesitol and 1,2-dimesitoylethane (III).

The dienol exhibited chemical properties similar to those of the monoenol. It could be ketonized by long treatment with hot alcoholic hydrogen chloride to yield 1,2,5,6-tetramesityl-1,6-hexanedione (IV). The dienol was regenerated by use of ethylmagnesium bromide. Oxidation with permanganate brought about cleavage, giving the parent vinyl ketone (I). This remarkable reaction resembles the cleavage of 1,2-glycols by lead tetraacetate[6]; it was found that cleavage to the vinyl ketone could be effected with this reagent.



This scission of a 1,6-glycol with lead tetraacetate is in accord with the vinylogous relationship between this glycol and ethylene glycol. It is particularly interesting from a theoretical point of view, since the formation of a cyclic intermediate seems unlikely.[8]

The principal product of the oxidation, however, was not the vinyl ketone but the doubly unsaturated diketone, 1,2,5,6-tetramesityl-2,4-hexadien-

(1) For the tenth communication of this series see Fuson and Scott, THIS JOURNAL, **64**, 2152 (1942).
(2) DuPont Post-doctorate Fellow, 1940–1941.
(3) Fuson, Corse and McKeever, THIS JOURNAL, **62**, 3250 (1940).
(4) Gomberg and Bachmann, *ibid.*, **49**, 236 (1927).
(5) Fuson, Byers, Rachlin and Southwick, *ibid.*, **64**, 2886 (1942).
(6) Criegee, *Ber.*, **64B**, 200 (1931).
(7) Mes is used to represent the mesityl radical.
(8) Criegee, Kraft and Rank, *Ann.*, **507**, 159 (1933).

1,6-dione (V). This compound underwent 1,8 hydrogenation to yield what was perhaps the most remarkable compound of the entire series—the dienol, 1,2,5,6-tetramesityl-1,3,5-hexatriene-1,6-diol (VI). It is a vinylog of the enediol, 1,2-dimesitylacetylene glycol (VII). Like the acetylene glycol, it can be ketonized by treatment with alcoholic hydrogen chloride. From the resulting diketone (VIII) the dienol can be regenerated by the use of ethylmagnesium bromide.

Experimental[9]

1,2,5,6-Tetramesityl-1,5-hexadiene-1,6-diol (II).—To a well-stirred mixture of 1.92 g. of magnesium, 40 cc. of dry ether and 80 cc. of dry benzene was added 9.8 g. of iodine. When the iodine color had disappeared, 11.68 g. of solid α-mesitylvinyl mesityl ketone was added within one minute. The solution was stirred and heated at the refluxing temperature for three hours. The reaction mixture was cooled, decomposed with iced hydrochloric acid and washed once with water. The aqueous layer was extracted with ether, and the combined organic solution was dried over calcium chloride. It was then concentrated to a volume of 25 cc. and cooled in an ice-bath. The product which precipitated weighed 11 g. (94%) and melted at 203–205°. The pure compound, recrystallized from benzene, melted at 207–208°.

Anal. Calcd. for $C_{42}H_{50}O_2$: C, 85.95; H, 8.60; mol. wt., 586. Found: C, 86.08; H, 8.69; mol. wt. (ebullioscopic in chloroform), 605.

1,2,5,6-Tetramesityl-1,5-hexadiene-1,6-diol Diacetate.—A solution of 2.0 g. of the diol (II) in 15 cc. of acetic anhydride was heated at the refluxing temperature for two hours. The reaction mixture was cooled and poured into water. The white diacetate, recrystallized from benzene, weighed 1.95 g. and melted at 217.5–218.5°.

Anal. Calcd. for $C_{46}H_{54}O_4$: C, 82.34; H, 8.11. Found: C, 82.72; H, 8.23.

Ketonization of 1,2,5,6-Tetramesityl-1,5-hexadiene-1,6-diol.—A solution of 2.0 g. of the diol in 200 cc. of absolute ethanol, which had previously been saturated with dry hydrogen chloride, was refluxed for twelve hours. The solid diketone started to separate from the hot solution. The mixture was cooled and filtered. The product weighed 1.5 g., and melted at 250–255°. A second crop of crystals weighing 0.4 g. was obtained. Recrystallized from benzene, the diketone (IV) melted at 259–261°.

Anal. Calcd. for $C_{42}H_{50}O_2$: C, 85.95; H, 8.60. Found: C, 86.04; H, 8.83.

Enolization of 1,2,5,6-Tetramesityl-1,6-hexanedione (IV).—To a Grignard solution made from 11 g. of ethyl bromide, 2.4 g.of magnesium and 50 cc. of ether was added a solution of 1 g. of the diketone (IV) in 50 cc. of dry benzene. The mixture was stirred and refluxed for twelve hours, cooled and decomposed with iced ammonium chloride solution. The aqueous layer was extracted with benzene, and the benzene solution was dried over calcium chloride and concentrated to a volume of 10 cc. Cooling caused the separation of 0.8 g. of a solid, which, after recrystallization from benzene, melted at 207–208° alone or mixed with a sample of the diol obtained by the other method.

Reaction of 1,2,5,6-Tetramesityl-1,5-hexadiene-1,6-diol with Oxygen.—Oxygen was bubbled through a solution of 4 g. of the diol in 300 cc. of acetone for seventy-two hours. The solvent was removed by distillation and the residue was dissolved in ether. The ether solution was extracted three times with 10% potassium bicarbonate solution. Acidification of the combined bicarbonate solutions failed to cause the precipitation of an insoluble acid. The ether solution was then extracted with several portions of 10% sodium hydroxide solution. Acidification of the combined alkaline solutions caused the precipitation of 0.9 g. of mesitol. A sample, purified by sublimation, melted at 70° and did not depress the melting point of a known sample of mesitol.

The ether solution was washed with water and the residue, after removal of the ether, weighed 2.2 g. The crude solid was recrystallized from methanol. The first crop of crystals weighed 1.2 g. and melted at 136–137° alone or when mixed with an authentic sample of 1,2-dimesitoylethane.

Reaction of 1,2,5,6-Tetramesityl-1,5-hexadiene-1,6-diol (II) with Potassium Permanganate.—A solution of 1.9 g. of potassium permanganate in 250 cc. of acetone was added over a period of one-half hour to a well-stirred solution of 5 g. of the diol in 160 cc. of acetone. The manganese dioxide was gathered on a filter and extracted in a Soxhlet apparatus with acetone until the solvent was no longer yellow. The solutions were combined and concentrated to a volume of 150 cc. The excess permanganate was removed by filtration as manganese dioxide and the clear yellow solution was concentrated to 25 cc. Cooling caused the separation of the canary yellow diketone (V) which weighed 2.2 g. and melted at 279–282°. After recrystallization from benzene, it melted at 282–284°.

Anal. Calcd. for $C_{42}H_{46}O_2$: C, 86.53; H, 7.97. Found: C, 86.73; H, 8.13.

The mother liquor was evaporated to dryness and subjected to fractional crystallization from methanol. In this manner there was isolated 0.2 g. of the diketone and 1.1 g. of a white compound identified as α-mesitylvinyl mesityl ketone; m. p. 131–132°.

Reaction of 1,2,5,6-Tetramesityl-1,5-hexadiene-1,6-diol (II) with Lead Tetraacetate.—To a hot well-agitated solution of 5 g. of the diol in 100 cc. of benzene was added 10.5 g. of lead tetraacetate. The mixture was stirred and refluxed for fourteen hours. It was filtered and the clear solution was concentrated to a volume of 20 cc. Cooling caused the separation of 2.5 g. of the yellow diketone (V), m. p. 279–282°. Further investigation of the mother liquor resulted in the isolation of 0.3 g. of α-mesitylvinyl mesityl ketone, m. p. 129–131°. The residue was a dark tar.

When the reaction mixture was heated for five hours, there was produced 2.4 g. of the yellow diketone (V) and 0.8 g. of α-mesitylvinyl mesityl ketone.

1,2,5,6-Tetramesityl-1,3,5-hexatriene-1,6-diol (VI).—**A.** A solution of 0.2 g. of the diketone (V) in 150 cc. of

(9) Microanalyses by Miss Mary S. Kreger, Miss Margaret McCarthy, Miss Theta Spoor and Mr. L. G. Fauble.

benzene (thiophene-free) was shaken with a platinum oxide catalyst and hydrogen at atmospheric pressure until the yellow color had disappeared. The catalyst was removed by filtration and the solution was concentrated to a small volume and cooled. The resulting white diol melted to a yellow liquid at 252–253°.

Anal. Calcd. for $C_{42}H_{48}O_2$: C, 86.24; H, 8.28. Found: C, 86.14; H, 8.22.

When it was exposed to the atmosphere, the pure diol gradually assumed a brownish color. After two days it was brownish-yellow and the melting point was 235–240°.

B. To a solution of 0.5 g. of the diketone in 75 cc. of hot glacial acetic acid was added 3 g. of zinc dust. The mixture was heated on a steam-bath for one hour, after which time the zinc was removed by filtration. Cooling caused the separation of 0.45 g. of a brownish crystalline solid which melted, after washing with water, at 235–240°. Recrystallized from ethanol, the diol was white and melted to a yellow liquid at 252–253° alone or mixed with a sample of the diol obtained by method A.

1,2,5,6-Tetramesityl-1,3,5-hexatriene-1,6-diol Diacetate.—A. A solution of 0.5 g. of the diol (VI) in 25 cc. of acetic anhydride was heated at the refluxing temperature for ninety minutes. Cooling caused the separation of 0.5 g. of white needles, m. p. 271–273°. Recrystallized from glacial acetic acid, the diacetate melted at 273–274°.

Anal. Calcd. for $C_{46}H_{52}O_4$: C, 82.59; H, 7.83. Found: C, 82.63; H, 8.03.

B. To a solution of 0.18 g. of the diketone (V) in acetic anhydride was added 0.3 g. of fused zinc chloride and 3 drops of concentrated hydrochloric acid.[10] The mixture was shaken for twenty minutes with 10 mg. of platinum oxide catalyst and hydrogen at atmospheric pressure. At the end of this time the solution was colorless and the product separated as white needles. It weighed 0.15 g. Recrystallized from glacial acetic acid, it melted at 273–274° alone or mixed with the diacetate obtained by method A.

Oxidation of 1,2,5,6-Tetramesityl-1,3,5-hexatriene-1,6-diol with Hydrogen Peroxide.—A solution of 0.28 g. of the yellow diketone (V) in 60 cc. of benzene (thiophene-free) was shaken with hydrogen at atmospheric pressure over platinum until the color had disappeared. The catalyst was removed by filtration and the benzene solution was shaken for ten minutes with 5 cc. of 30% hydrogen peroxide and 25 cc. of water. The benzene solution turned yellow. After removal of the solvent the yellow residue weighed 0.19 g. Recrystallized from benzene, the product melted at 282–284° alone or when mixed with another sample of the yellow diketone.

Ketonization of 1,2,5,6-Tetramesityl-1,3,5-hexatriene-1,6-diol.—Two grams of the yellow diketone (V) was reduced by the zinc and acetic acid method. The resulting trienediol (1.8 g.) was transferred to a flask containing 500 cc. of absolute ethanol which had previously been saturated with dry hydrogen chloride. The solution was refluxed on a steam-bath for twelve hours. After cooling, this product (1.25 g.) was separated by filtration; m. p. 170–185°. The pure diketone (VIII) obtained by fractional crystallization from methanol melted at 201° and weighed 0.8 g.

Anal. Calcd. for $C_{42}H_{48}O_2$: C, 86.24; H, 8.28. Found: C, 86.00; H, 8.38.

Enolization of 1,2,5,6-Tetramesityl-3-hexene-1,6-dione (VIII).—To a Grignard solution made from 11 g. of ethyl bromide, 2.5 g. of magnesium and 25 cc. of ether was added a solution of 1.5 g. of the diketone (VIII) in 10 cc. of ether and 25 cc. of benzene. The mixture was stirred and refluxed for five hours. It was cooled and poured into iced ammonium chloride solution. The aqueous layer was extracted with 50 cc. of ether. The ether solution was dried over calcium chloride and evaporated to dryness on a steam-bath. Treatment of the residue with cold ethanol caused the separation of 0.8 g. of the diol (VI), m. p. 235–240°. Recrystallized from ethanol, it melted to a yellow liquid at 252–253° alone or mixed with a sample of the compound obtained by another method.

Summary

Bimolecular reduction of mesityl α-mesitylvinyl ketone yields 1,2,5,6-tetramesityl-1,5-hexadien-1,6-diol, a vinylog of ethylene glycol. Oxidation of the diol produces chain cleavage analogous to that of 1,2-glycols, regenerating the parent vinyl ketone.

A second product of oxidation is 1,2,5,6-tetramesityl-2,4-hexadien-1,6-dione. This ketone undergoes 1,8 addition of hydrogen to yield 1,2,5,6-tetramesityl-1,3,5-hexadien-1,6-diol, a vinylog of acetylene glycol.

The new dienols can be ketonized by long treatment with alcoholic hydrogen chloride. The dienols can be regained by treating the resulting diketones with the Grignard reagent.

(10) Thompson, THIS JOURNAL, **61**, 1281 (1939).

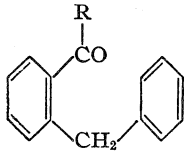
URBANA, ILLINOIS RECEIVED SEPTEMBER 8, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

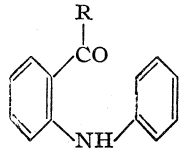
The Mechanism of Cyclization Reactions

BY ERNST BERLINER

Following the observation of E. Bergmann[1] that the acetal of *o*-benzylbenzaldehyde (I) yields a certain amount of anthracene when hydrolyzed with hydrochloric acid in acetone, Bradsher[2] worked out a convenient method of synthesizing 9-substituted anthracenes and 1,2-benzanthracenes in excellent yield by refluxing ketones of the type II with 34% hydrobromic acid and acetic acid. The synthesis of naphthalene by the cyclization of β-styrylaldehyde is considered by Bradsher[3] the simplest cyclodehydration reac-



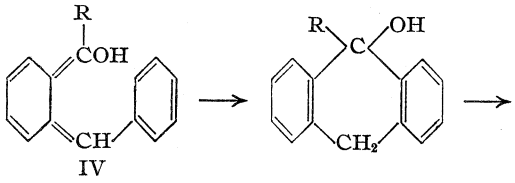
I R = hydrogen
II R = alkyl or phenyl



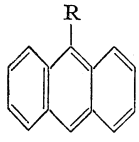
III R = alkyl or phenyl

tion of this type and similar to the formation of β-phenylnaphthalene from two molecules of phenylacetaldehyde observed by Zincke.[4]

A reaction analogous to the above hydrocarbon synthesis has been known in the acridine series for a long time and a number of acridines have been prepared[5] from the corresponding aldehydes or phenylketones (III) (in one case a methyl ketone). As far as the mechanism of the hydrocarbon synthesis is concerned, Bergmann suggested a similarity to the Elbs pyrolysis assuming enolization as the first step. Bradsher[6] pointed out

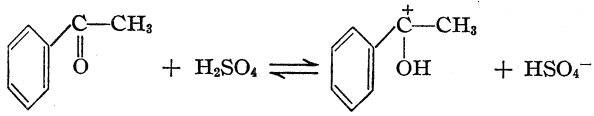


IV



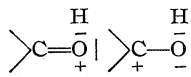
that the reaction is more like a Friedel–Crafts condensation than an Elbs pyrolysis, and proposed enolization as the first step followed by cyclization and subsequent loss of water.

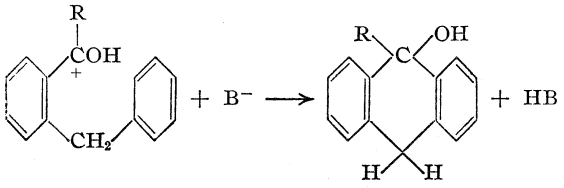
The following alternate explanation is based upon the behavior of carbonyl compounds in strongly acidic media and upon the concept of cyclodehydration as essentially an internal aromatic substitution. It is believed that the neutral enol (IV), even if it were formed by an acid-catalyzed enolization of the type proposed, would hardly undergo cyclization. It is now generally believed that ionic fragments play an important role as reaction intermediates, even in cases where the initial and final products are non-ionic in character and where the concentration of the ions is not great enough to be detected.[7] Thus in most aromatic substitution reactions, a positive fragment attacks a position of high electron density in the benzene ring, which loses a proton to the acid residue (base), after the intermediate complex is formed.[8] In order to satisfy these requirements, a mechanism is proposed on the basis of an addition of a proton to the carbonyl oxygen followed by an electrophilic substitution reaction. Addition compounds of the carbonyl group with acids and salts have long been known,[9] but their nature was not clearly understood until the work of Hantzsch, and later Hammett[10] showed that the solubility of carbonyl compounds in sulfuric acid depends on salt formation, as illustrated for the case of acetophenone



A proton is transferred from the acid to the carbonyl group and the conjugate acid of the ketone is positively charged. The first step in the cyclization reaction thus may be the formation of the conjugate acid (V), which is a hybrid of the

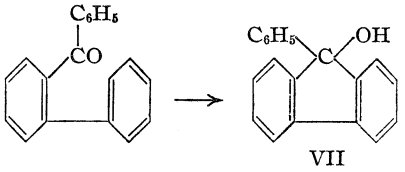
(1) E. Bergmann, *J. Org. Chem.*, **4**, 1 (1939).
(2) Bradsher, THIS JOURNAL, **62**, 486, 1077 (1940).
(3) Bradsher, *ibid.*, **64**, 1007 (1942).
(4) Zincke and Breuer, *Ann.*, **226**, 23 (1884); **240**, 137 (1887); Carter and van Loon, THIS JOURNAL, **60**, 1077 (1938).
(5) Ullmann and Ernst, *Ber.*, **39**, 298 (1906); Ullmann and Broide, *ibid.*, **39**, 356 (1906); Mayer and Stein, *ibid.*, **50**, 1306 (1917); Jensen and Rehwisch, THIS JOURNAL, **50**, 1144 (1928).
(6) References 2 and 3 and Abstracts from the 103rd meeting of The American Chemical Society, Memphis, Tenn., April, 1942.
(7) Whitmore, THIS JOURNAL, **54**, 3274 (1932); Meerwein and van Emster, *Ber.*, **55**, 2500 (1922); Arndt and Eistert, *ibid.*, **69**, 2381 (1936); Hammett, THIS JOURNAL, **59**, 1063 (1937).
(8) For general references: Ingold, *Chem. Rev.*, **15**, 225 (1934); Price, *ibid.*, **29**, 37 (1941).
(9) Houben, "Methoden der organischen Chemie," Georg Thieme, Leipzig, 1930, Vol. 3, page 470 ff.
(10) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 54 ff.

two resonant forms  , the positive charge being distributed between the oxygen and carbon atoms. The ring closure is an electrophilic attack by the carbon atom on the opposite ortho position forming the dihydroanthranol (VI), which readily suffers dehydration.



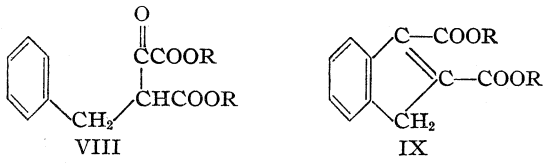
V VI

This mechanism does not require enolization as the first step and no active hydrogen is necessary. This concept is substantiated by the present observation that a similar cyclization can be accomplished with a compound which has no hydrogen available for enolization. When 2-phenylbenzophenone[11] was treated according to the procedure of Bradsher a mixture was obtained from which 9-phenylfluorenol and its acetate were isolated. Furthermore, when the same ketone was treated with sulfuric acid and acetic anhydride, a substance was obtained identical with a polymer of 9-phenylfluorenol obtained by treating the carbinol (VII) with the same reagents.[12] A reaction



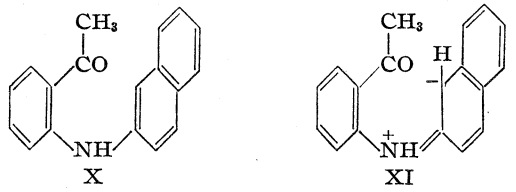
VII

very similar to the one considered was discovered by Bougault,[13] who found that the ester of the keto acid (VIII) undergoes ring closure under the



VIII IX

influence of sulfuric acid to give the indene dicarboxylic ester IX. The reaction was studied by Auwers and Moeller[14] and has proved useful in synthesis.[15] Auwers and Moeller regarded the enol form of the ketone as reaction intermediate, but here again the neutral enol, although it certainly could be present in this case, is not likely to enter into the substitution reaction for reasons given above. The first step in the proposed mechanism is the same as in the mechanism for acid-catalyzed enolization.[16] After the positively charged conjugate acid is formed, the ketone which is about to enolize, attacks the ring before the neutral enol is formed, and while it still carries the positive charge.



X XI

The cyclization proceeds with greater ease in the acridine series. If the secondary amine (X) is dissolved in glacial acetic acid and a few drops of concentrated sulfuric acid are added the reaction is completed after short heating, whereas much longer periods are necessary in the case of the hydrocarbons. The amino group (X) is much stronger ortho-directing than the methylene group, and an equivalent structure (XI) can be written with a true negative charge in the ortho position.[17]

The cyclization reaction has been utilized further for the synthesis of three higher benzologs of 9-methylacridine, namely, the 1,2-benz-, 3,4-benz- and 1,2,3,4-dibenz- derivatives. Since dibenzacridines have been shown to possess carcinogenic properties it seemed of interest to test these meso-substituted derivatives for comparison with the potent isolog 9-methyl-1,2-benzanthracene.

Another cyclodehydration reaction, where ionic fragments appear to be the intermediates, is the formation of 9-phenylfluorenes from triarylcarbinols.[18,19] The reaction proceeds with surprising ease and is accompanied by a remarkable color change. Thus when the carbinol (XII) is

(11) Schlenk and Bergmann, *Ann.*, **464**, 34 (1928).

(12) Kliegl, *Ber.*, **38**, 290 (1905); **43**, 2490 (1910).

(13) Bougault, *Compt. rend.*, **159**, 745 (1915).

(14) Auwers and Moeller, *J. prakt. Chem.*, [2] **109**, 124 (1925).

(15) Fieser and Hershberg, THIS JOURNAL, **57**, 1851 (1935), **58**, 2314 (1936); Ruzicka, *Helv. Chim. Acta*, **16**, 833 (1933); Cook and co-workers, *J. Chem. Soc.*, 667, 1319 (1935).

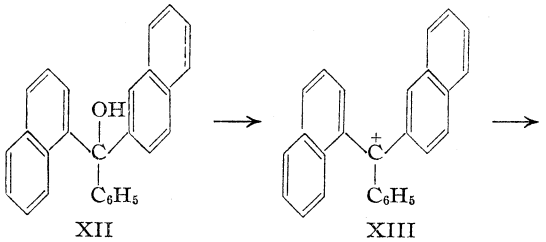
(16) Pederson, *J. Phys. Chem.*, **37**, 751 (1933); **38**, 581 (1934); Reitz, *Z. physik. Chem.*, **A179**, 119 (1937); Cohen and Urey, THIS JOURNAL, **60**, 679 (1938).

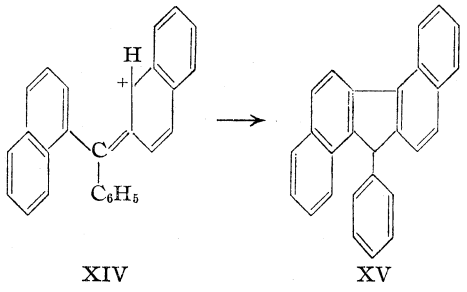
(17) The secondary amino group in this medium apparently is not basic enough to form the meta-directing ammonium ion. If, however, only sulfuric acid is used, heating to a higher temperature and for a longer time becomes necessary.

(18) Kliegl, *Ber.*, **38**, 287 (1905); Ullmann, *ibid.*, **38**, 2216, 2219 (1905); Tschitschibabin, *J. prakt. Chem.*, **84**, 760 (1911); **88**, [2] 514 (1913); **90**, [2] 168 (1914).

(19) Bachmann and Kloetzel, *J. Org. Chem.*, **2**, 356 (1937); Schoepfle, THIS JOURNAL, **44**, 192 (1922).

dissolved in acetic acid and heated to the boiling point, the solution is but slightly colored. If a few drops of hydrochloric acid are added at the boiling point a deep green color appears for a few seconds, water is given off as the green color disappears, and a reddish-brown color results. The reaction is over and another drop of hydrochloric acid does not produce any further color change. The fluorene, XV, crystallizes from the cooled solution and the whole reaction resembles those with inorganic ions. The carbinol itself dissolves in sulfuric acid with the same green color. In all observed cases the transient color was identical with the color of the carbinol in sulfuric acid. It is generally accepted that the color which is obtained when triarylcarbinols are dissolved in sulfuric acid, or when they are treated with different inorganic salts, is due to the color of the positive carbonium ion. Therefore, it seems justifiable to assume that the first step in the cyclodehydration is the formation of the carbonium ion (XIII).





The positive charge is distributed on the ortho and para postions, accounting for the stability of these ions. If the charge moves to the nearest ortho position, an equivalent structure (XIV) is obtained which allows substitution on the opposite ring. This is followed by aromatization. If the initial step consists in the formation of the carbonium ion and not in the loss of water, any electrophilic reagent other than strong mineral acids should bring about the cyclization. This was confirmed by dissolving the carbinol (XII) in an inert solvent and adding different salts which are known to effect ionization of the triarylcarbinols. In each case a complex precipitated immediately which had the color of the carbinol in sulfuric acid, and the fluorene was obtained after decomposition with water. This explains why it is so difficult to prepare stable salts or the chlorides of the higher benzologs of triphenylcarbinol.[18,19] Two fluorene derivatives, 1,2,5,6- and 1,2,7,8-dibenz-9-phenylfluorene were synthesized by the above reaction. The intermediate carbinols were prepared by the Grignard action of a naphthyl halide and a naphthyl phenyl ketone. The possibility of reaction in the phenyl instead of the naphthyl group to form the 9-naphthyl-benzfluorene is less likely because of the relative inertness of the phenyl group. Furthermore, Schoepfle[19] and Ullmann[18] prepared similar compounds by the dehydration of the carbinols, as well as by the action of phenylmagnesium bromide on the corresponding fluorenones and obtained identical compounds. It can be assumed, therefore, that the above compounds have the structure assigned to them.

Acknowledgment.—I wish to express my sincere thanks to Professor L. F. Fieser, Harvard University, under whom I have the privilege to work and without whose generous help and kind interest this work would not have been accomplished. I also thank Mrs. L. F. Fieser for her help in preparing the manuscript.

Experimental[20]

o-(α-Naphthyl)-aminoacetophenone.—A mixture of 2.4 g. of *o*-aminoacetophenone,[21] 4 g. of α-bromonaphthalene, 5 g. of potassium carbonate and 0.3 g. of copper powder was heated in refluxing nitrobenzene (50 cc.) in an all glass apparatus. The solution became dark and carbon dioxide was evolved. After three hours the reaction mixture was steam-distilled to remove the solvent and excess reagents, and the residue was taken up in ether–benzene, and dried with sodium sulfate. After evaporation, a brown oil remained which could be used for cyclization without further purification. The oil crystallized upon the addition of alcohol and 3.9 g. was obtained as small yellow prisms after several recrystallizations from alcohol and a little benzene, m. p. 96.4–97.2°.

Anal.[22] Calcd. for $C_{18}H_{15}NO$: C, 82.73; H, 5.78. Found: C, 83.00; H, 5.65.

9-Methyl-3,4-benzacridine.—Three grams of the above oil was dissolved in 25 cc. of glacial acetic acid, 3 cc. of concentrated sulfuric acid was added, and the flask was placed on the steam-bath. The yellow sulfate of the acridine precipitated immediately and was filtered after ten minutes' heating. It was suspended in water, and the base (2.5 g.) which precipitated on addition of concentrated ammonia, was filtered and dried. It formed yellow needles from alcohol, m. p. 111.6–112.2°.

(20) All melting points are corrected.
(21) Clar, *Arch. Pharm.*, **14**, 240 (1902).
(22) Microanalyses by Miss E. Werble.

Anal. Calcd. for $C_{18}H_{13}N$: C, 88.86; H, 5.38. Found: C, 88.91; H, 5.33.

The **picrate** (fine yellow needles) is sparingly soluble in the common solvents. Higher boiling solvents (toluene, dioxane) dissolve it, but with decomposition. The picrates of the other acridines show the same properties. It was crystallized from acetone; m. p. 251–255° (dec.).

Anal. Calcd. for $C_{24}H_{16}N_4O_7$: N, 11.86. Found: N, 11.83.

***o*-(β-Naphthyl)-aminoacetophenone** (X) was prepared in the same way as the other isomer from 3.1 g. of *o*-aminoacetophenone, 5.2 g. of β-bromonaphthalene, 6 g. of potassium carbonate and 0.3 g. of copper powder in 50 cc. of boiling nitrobenzene. The remaining oil was distilled at 6 mm. and 195–196°. In an attempt to prepare the picrate, a precipitate was formed after short boiling with picric acid which proved to be the picrate of the cyclized product.

Anal. Calcd. for $C_{18}H_{15}NO$: N, 5.36. Found: N, 5.4.

9-Methyl-1,2-benzacridine.—Four grams of the oil was heated on the steam-bath in 25 cc. of glacial acetic acid and 4 cc. of concentrated sulfuric acid. After fifteen minutes it was poured on ice and filtered. The filtrate was treated with ammonia and the acridine which precipitated (3.7 g.) was dried and recrystallized repeatedly from benzene–ligroin. It forms yellow, shining plates, m. p. 145–145.2°.

Anal. Calcd. for $C_{18}H_{13}N$: C, 88.86; H, 5.38. Found: C, 88.87; H, 5.1.

The **picrate** forms small yellow needles from acetone, m. p. 245–248° (dec.).

Anal. Calcd. for $C_{17}H_{16}N_4O_7$: N, 11.86. Found: N, 11.56.

9-Methyl-1,2,3,4-dibenzacridine.—A mixture of *o*-aminoacetophenone (1.5 g.), 9-bromophenanthrene (3 g.), potassium carbonate (4 g.) and copper powder (0.3 g.) was heated in 40 cc. of nitrobenzene as described for the other isomers. The remaining oil was taken up in glacial acetic acid (20 cc.) and after the addition of 3 cc. of concentrated sulfuric acid heated for twenty-five minutes on the steam-bath. Part of the sulfate precipitated and was filtered off and treated with ammonia. This was combined with the precipitate obtained after adding ammonia to the filtrate, and crystallized from a little alcohol and benzene, as straw-like needles (3 g.), m. p. 121.4–122.4°.

Anal. Calcd. for $C_{22}H_{15}N$: C, 90.07; H, 5.1. Found: C, 90.05; H, 4.9.

The picrate forms yellow needles from acetone; m. p. 206–208° (dec.).

Anal. Calcd. for $C_{18}H_{18}N_4O_7$: N, 10.72. Found: N, 10.44.

β-Benzoylnaphthalene.—A Grignard solution prepared from 18 g. of bromobenzene and 2.8 g. of magnesium turnings was treated with 12 g. of β-naphthonitrile in absolute ether; a crystalline precipitate separated after short boiling. Refluxing and stirring was maintained for five hours, after which time the mixture was decomposed with ammonium chloride solution. The ether layer was evaporated and the remainder refluxed with 50 cc. of water, 16 cc. of acetone, and 25 cc. of concentrated hydrochloric acid. After three hours the cooled solution was extracted with ether and the ketimide hydrochloride, which was not hydrolyzed, was treated once more with acid to which 30 cc. of benzene was added. The combined organic layers were dried and the solvents evaporated. The remaining solid was crystallized from alcohol: (15 g., 82.5%), m. p. 81–82°.[23]

α,β-Dinaphthylphenylcarbinol (XII).—A Grignard solution was prepared from 8 g. of α-bromonaphthalene and 0.94 g. of magnesium turnings in absolute ether. About 0.5 cc. of α-bromonaphthalene was added at the end of the reaction to take care of the unreacted magnesium. Eight grams of β-benzoylnaphthalene was added over a period of twenty-five minutes, and stirring and refluxing was maintained for two hours after which the complex was decomposed with ice-cold 25% ammonium chloride solution. The organic layer was separated, dried over sodium sulfate and the oil remaining after evaporation crystallized readily upon the addition of ether–ligroin (9 g., 72%). The carbinol crystallizes with benzene or alcohol when in contact with these solvents. The addition products are very stable and melt between 195–205° with loss of solvent. The carbinol was recrystallized from ether–ligroin as small white prisms; m. p. 168–169°. It dissolves in concentrated sulfuric acid with a dark green color and appears red in transmitted light.

Anal. Calcd. for $C_{17}H_{20}O$: C, 89.97; H, 5.59. Found: C, 90.09; H, 5.84.

1,2,5,6-Dibenz-9-phenylfluorene (XV).—Four grams of the crude carbinol was dissolved in 15 cc. of glacial acetic acid, heated to the boiling point and a few drops of hydrochloric acid added. The solution turned green and then reddish. An oil separated which solidified on cooling. It was crystallized repeatedly from acetic acid and forms white needles, m. p. 219–219.5°. It is soluble in ether, warm benzene, hot acetic acid, sparingly soluble in alcohol and ligroin.

Anal. Calcd. for $C_{27}H_{18}$: C, 94.7; H, 5.3. Found: C, 94.67; H, 5.3.

The following experiments were carried out with 100 mg. of the carbinol. It was dissolved in benzene (5 cc.) and a spatula full of aluminum chloride, aluminum bromide, iodine, phosphorus pentachloride, or a few drops of stannic chloride was added. In each case the green complex separated immediately. The mixture was heated for about five minutes on a steam-bath, and then decomposed with water until it had all dissolved. The fluorene was isolated from the benzene layer. No fluorene was obtained by heating the carbinol in refluxing xylene or acetonitrile.

β,β-Dinaphthylphenylcarbinol was prepared in the same way as the other isomer from 9 g. of β-bromonaphthalene and 1.1 g. of magnesium to which 9 g. of β-benzoylnaphthalene was added in ether and benzene. The reaction mixture was worked up as usual and a quantity of small white needles (2 g.) separated from the ether–benzene solution after drying and concentrating. A further quantity (3 g.) was obtained on concentrating the solution but about half of the carbinol remained in an oily condition and crystallized only very slowly in the ice chest. Recrystallized from benzene–ether (very little soluble in

(23) Kollarits and Merz, *Ber.*, **6**, 543 (1873), give 82°.

ether) it melts at 216.5–217.5°. A dilute solution of the compound in concentrated sulfuric acid looks green when viewed through a thin layer, but red in more concentrated solutions.

Anal. Calcd. for $C_{27}H_{20}O$: C, 89.97; H, 5.59. Found: C, 90.17; H, 5.52.

1,2,7,8-Dibenz-9-phenylfluorene.—The cyclization was carried out on the oil. Three grams in 30 cc. of glacial acetic acid and 3 cc. of hydrochloric acid were refluxed for twenty minutes. An oil and a solid separated, which were filtered off and extracted with boiling acetic acid without further drying. This removed an unidentified by-product which, when not removed, made the purification of the fluorene very difficult. The white compound which was obtained after cooling the solution was recrystallized several times by suspending it in hot ligroin and adding just enough benzene to bring it into solution, small white needles arranged in rosets resulted; m. p. 148.5–149.5°.

Anal. Calcd. for $C_{27}H_{18}$: C, 94.7; H, 5.3. Found: C, 94.6; H, 5.15.

α,α-Dinaphthylphenylcarbinol.—This compound was first made by Elbs[24] from benzoic ester and α-bromonaphthalene and later by Schoepfle who used toluene to improve the yield. We prepared it by the above general method using 11 g. of bromonaphthalene, 1.3 g. of magnesium and 11 g. of α-benzoylnaphthalene[25] (64% yield). In order to obtain crystals, the ether solution was concentrated to a small volume and ligroin was added until no more of the light oil separated. The supernatant layer which contained the by-products was disregarded. The carbinol crystallized in the desiccator after a few cc. of benzene was added, m. p. 169–170°.

3,4,5,6-Dibenz-9-phenylfluorene was prepared as above, the transient color is purple; m. p. 275° (as given by Schoepfle).

Cyclization of 2-Phenylbenzophenone, 1.—One gram of 2-phenylbenzophenone was dissolved in 10 cc. of glacial acetic acid and 10 cc. of 34% hydrobromic acid was added at the boiling point. Five more cc. of acetic acid was added to keep all in solution. After twenty-four hours a yellow oil separated and boiling was continued for two more days. The oil solidified on cooling and crystallized on rubbing. The crude product softened between 105–107° and melted between 150–160°. It was extracted with hot ether and the ether soluble product recrystallized three times from acetic acid. Twenty mg. of white needles was obtained, m. p. 169–171°. Kliegl[26] gives 169–169.5° for 9-phenylfluorenol acetate.

The compound apparently contained some of the polymerization product which is difficult to remove. The combined mother liquors were boiled with sodium acetate in acetic acid to hydrolyze the acetate still present and a white compound, m. p. 106–107°, precipitated on pouring on ice[26] (given for 9-phenylfluorenol 107–108°). This crude product was reduced with zinc, hydrochloric acid and acetic acid and the obtained hydrocarbon (about 50 mg.) recrystallized once from alcohol in which it is soluble with a distinct blue fluorescence, m. p. 142.8–144.6° (lit. 145–146°[27]); mixed m. p. 142.4–144.4.

2. Five hundred mg. of the ketone was dissolved in 10 cc. of acetic anhydride and heated on the steam-bath. One cc. of concentrated sulfuric acid was added. The yellow compound which separated melted over the wide range of 260–300° and had the properties of the polymer of 9-phenylfluorenol. It was dissolved in chloroform and reprecipitated with alcohol, as suggested by Kliegl.[26] It darkens at about 250° and melts between 300–330°. The cyclization of the ketone with hydrobromic acid is of no preparative value for making the carbinol because the polymer is always formed along with it. This makes the yield low and the carbinol hard to purify.

Summary

9-Methyl-1,2-benzacridine, 9-methyl-3,4-benzacridine, 9-methyl-1,2,3,4-dibenzacridine as well as 9-phenyl-1,2,5,6-dibenzfluorene and 9-phenyl 1,2,7,8-dibenzfluorene were synthesized by cyclizing the corresponding methyl ketones or dinaphthylphenylcarbinols, respectively. A mechanism for the cyclodehydration reaction is suggested which involves as the first step the formation of a positively charged fragment followed by an electrophilic aromatic substitution reaction.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS

RECEIVED SEPTEMBER 14, 1942

(24) Elbs, *J. prakt. Chem.*, **35**, 506 (1887).

(25) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., second edition, 1941, p. 192.

(26) Kliegl, *Ber.*, **38**, 290 (1905).

(27) Ullmann and Wurstemburger, *ibid.*, **37**, 74 (1904).

[CONTRIBUTION FROM THE PHYSICO-CHEMICAL LABORATORY OF THE NEW YORK STATE EXPERIMENT STATION]

The Reaction of Formaldehyde with 1(−)-Asparagine[1]

BY D. C. CARPENTER AND F. E. LOVELACE

The action of formaldehyde on various amino acids has been investigated by numerous workers. Much of the older work was concerned with the isolation and analysis of compounds.[1a] More recently the reactions have been followed by measurements of the unreacted amino groups and hydrogen-ion concentrations and various constants evaluated.[2] Lately measurements of the optical rotation have been used in a study of the reaction between formaldehyde and 1(−)-proline.[3]

In the present paper studies of the latter sort have been employed in indicating the progress of the reaction and the compounds formed. Under the experimental conditions we have used, methylene-1(−)-asparagine is formed which reacts further with a second mole of formaldehyde. The latter compound has not been isolated because of its ease of decomposition. The existence of these compounds is a valuable clue in interpreting the reaction of formaldehyde with proteins in the manufacture of plastics, etc.

Preparation of Materials

1(−)-Asparagine.—A commercial sample of 1(−)-asparagine was recrystallized twice from hot water as the monohydrate, m. p. 225° (cor.), and its moisture content determined by drying to constant weight *in vacuo* at 61° over phosphorus pentoxide (H_2O, 12.18; calcd., 11.99%). The amino nitrogen was determined by the Van Slyke method (amino N, 9.30; calcd., 9.33%).

Formaldehyde.—A very pure concentrated formaldehyde solution was brought to exactly *p*H 7.0 against the glass electrode by the addition of sodium hydroxide solution and the formaldehyde content of this stock solution determined by the sodium bisulfite method of Kleber.[4]

Experimental

Into each of a series of 50-ml. volumetric flasks exactly 0.02 mole of 1(−)-asparagine was weighed out (corrected for water content) and 0.02 mole of carefully standardized sodium hydroxide solution added and the mixture shaken until all the 1(−)-asparagine was in solution. Various amounts of the stock formaldehyde solution were added from a micro-buret to each flask and the volume of each solution made up to the 50-ml. mark with water and well shaken. Part of each solution was transferred to a 2-dm. polarizing tube and the reserve solutions and those in the polarizing tubes were kept at 20° in a constant temperature bath and the rotation of the latter read periodically in the polariscope with the sodium arc as a light source. In solutions containing small amounts of formaldehyde, equilibrium was attained very slowly (thirty-four days for solution 5 containing 0.02 mole of formaldehyde per 0.02 mole of 1-asparagine); however, equilibrium was reached in a much shorter period when higher aldehyde concentrations were employed. The angular rotations at equilibrium for a 2-dm. tube are recorded in Table I. When equilibrium was attained, the hydrogen-ion concentrations of the reserve solutions were measured with a standardized glass electrode against a saturated calomel half-cell.

TABLE I

OPTICAL ROTATION, DENSITY AND HYDROGEN ION CONCENTRATION OF SODIUM 1-ASPARAGINATE (0.02 MOLE) AND FORMALDEHYDE SYSTEMS AT 20°

Soln.	Total moles HCHO present	Rotation,[a] levo degrees	Density	C_H	Remarks
1	0.00000	0.90	1.0308	1.0×10^{-10}	
2	.00500	5.424	1.0320	1.55	
3	.01001	9.33	1.0327	2.10	
4	.01501	13.19	1.0334	3.5	
5	.02002	15.41	1.0339	3.1×10^{-9}	HCHO odor very faint
6	.02503	14.61	1.0346	2.0×10^{-8}	HCHO odor faint
7	.03004	13.06	1.0353	4.2	
8	.04005	10.14	1.0378	7.8	HCHO odor very noticeable
9	.06008	6.56	1.0408	1.3×10^{-7}	
10	.09012	5.00	1.0460	1.8	
11	.12016	4.55	1.0509	2.6	
12	.15020	4.38	1.0556	3.0	
13	.18024	4.28	1.0603	4.0	
14	.21028	4.23	1.0649	4.3	
15	.23834	4.20	1.0692	5.5	
16	.30040	4.19	1.0785	7.0	

[a] In this column the angular rotation of solutions containing 0.02 mole of 1-asparagine with equivalent of base (Na) and designated moles of formaldehyde are reported for 2-dm. tube length after reaching equilibrium.

For estimating the uncombined formaldehyde in the solutions, appropriate aliquots of the reserve solutions were taken and caused to react with dimethyldihydroresorcinol as described by Vorländer.[5] The crystalline methylene derivative was filtered off after three hours of interaction at room temperature onto fritted glass crucibles, washed several times with water, dried at 110° and weighed.

The solubility of methylene-(bis)dimethyldihydroresorcinol in a saturated aqueous solution of dimethyl

(1) Published by permission of the Director, New York State Experiment Station, as Journal Paper No. 521, August 12, 1942.

(1a) H. Schiff, *Ann.*, **310**, 25 (1899).

(2) M. Levy, *J. Biol. Chem.*, **99**, 767 (1932); M. Levy and D. E. Silberman, *ibid.*, **118**, 723 (1937); T. Tomiyama, *ibid.*, **111**, 51 (1935); A. Wadsworth and M. C. Pangborn, *ibid.*, **116**, 423 (1936); E. W. Balson and A. Lawson, *Biochem. J.*, **30**, 1257 (1936).

(3) E. H. Frieden, M. S. Dunn and C. D. Coryell, *J. Phys. Chem.*, **46**, 215 (1942).

(4) C. Kleber, *Pharm. Rev.*, **22**, 94 (1904).

(5) D. Vorländer, *Z. anal. Chem.*, **77**, 241 (1929).

TABLE II

ESTIMATION OF COMBINED FORMALDEHYDE IN SODIUM 1-ASPARAGINATE SERIES (0.02 MOLE)

Soln.	Moles HCHO originally present	Free aldehyde analysis: Aliquot factor	Dimedon compd., g.	Free HCHO present, g.	Moles free HCHO present	Moles HCHO combined
2	0.00500	5	0.0000			0.00500
3	.01001	5	.0000			.01001
4	.01501	5	.0000			.01501
5	.02002	5	.0000			.02002
6	.02503	5	.2922	0.1504	0.00501	.02002
7	.03004	16.66	.1749	.2992	.00997	.02007
8	.04005	16.66	.3503	.600	.02003	.02002
9	.06008	16.66	.6980	1.195	.0398	.02028
10	.09012	25	.8200	2.102	.07005	.02007
11	.12016	100	.2922	3.004	.10012	.02004
12	.15020	100	.3810	3.91	.1302	.02000
13	.18024	100	.4703	4.840	.1603	.01994
14	.21028	166.6	.3342	5.71	.1903	.01998
15	.23834	166.6	.3842	6.55	.2183	.02000
16	.30040	166.6	.4905	8.406	.2802	.02020

dihydroresorcinol was found to be 0.0025 g. per liter and 0.0050 g. per liter in water at 20°. The weights of methylene-(*bis*)dimethyldihydroresorcinol reported have been corrected for the above respective solubilities. One gram of methylene-(*bis*)dimethyldihydroresorcinol is equivalent to 0.1027 g. of formaldehyde.

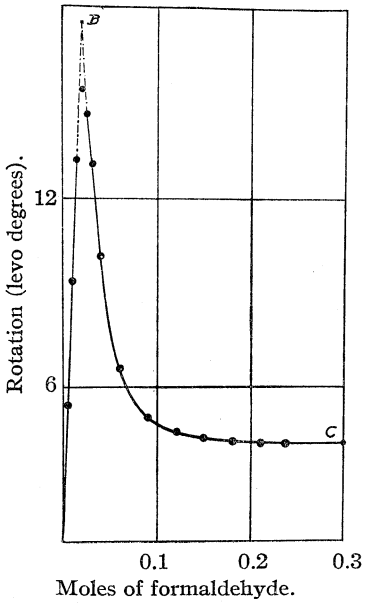


Fig. 1.—Effect of added formaldehyde on angular rotation (2 dm.) of 0.02 mole of sodium 1(−)-asparaginate in 50 ml. of solution: B, sodium salt of methylene-1(−)-asparagine; C, same with additional mole of formaldehyde forming unstable compound.

We have found it unnecessary to add acetic acid to effect the precipitation of the resorcinol derivative as was recommended by Wadsworth and Pangborn.[2] The addition of acid produces decomposition of methylene-1-asparagine and consequent liberation of formaldehyde and is to be avoided. In our experience the methylene-1-asparagine compound with one additional mole of formaldehyde is so unstable that, in the presence of an excess of dimethyldihydroresorcinol as is used in the precipitation, it decomposes giving formaldehyde and methylene-1-asparagine. The aldehyde so liberated reacts with dimethyldihydroresorcinol in addition to any free aldehyde remaining in the solution at equilibrium.

The results of the analyses for free formaldehyde are given in Table II. The optical rotation and hydrogen-ion concentrations are shown graphically in Figs. 1 and 2.

Discussion

It is clear from the results of the optical rotation work (Fig. 1) that a definite compound having a maximum levo rotation is formed when the mole ratios of asparagine and formaldehyde are 0.02 and 0.02, respectively. The compound formed is methylene - 1 - asparagine, inasmuch as we have obtained 6-oxy-5-bromopyrimidine 4-carbonic acid (m. p. 206–7° (cor.) with decomposition) therefrom by the action of sodium hypobromite, the same compound previously described by Cherbuliez and Starvitch.[6] From Fig. 2 it is clear that the maximum rate of change of hydrogen-ion concentration produced

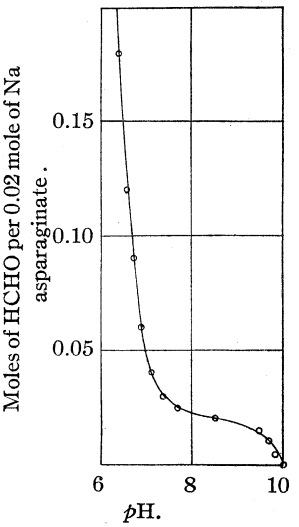


Fig. 2.—Effect of added formaldehyde on *p*H of 0.02 moles of sodium 1-asparaginate in 50 ml. of solution.

(6) E. Cherbuliez and K. N. Starvitch, *Helv. Chim. Acta*, **5**, 267 (1922).

TABLE III

CALCULATION OF EQUILIBRIUM CONSTANT

Completion of react.	Rotation, levo degrees	Formaldehyde concn. moles per liter: Total	Bound (AF)	Free (F)	k ($n = 1$)	A/AF	log A/AF	log F
0.20	14.83	0.094	0.080	0.014	0.056	4.00	+0.602	−1.854
.30	13.49	.171	.120	.051	.119	2.33	.368	−1.292
.40	12.16	.259	.160	.099	.149	1.50	.176	−1.004
.50	10.82	.342	.200	.142	.142	1.00	0	−0.848
.60	9.49	.455	.240	.215	.143	0.67	−0.176	.667
.70	8.16	.590	.280	.310	.133	.43	.368	.508
.80	6.82	.761	.320	.441	.110	.25	.602	.355

by adding formaldehyde is achieved in the region where 0.02 mole of formaldehyde reacts with 0.02 mole of asparagine. To this maximum we give the usual interpretation of compound formation in equimolecular proportions. That compound formation has been with the α-amino group rather than the amide group is confirmed from Fig. 2 by the rapid increase in acidic properties.

With regard to the further reaction of methylene-1-asparagine with additional formaldehyde (B-C section of Fig. 1), we have approached the problem from the basis of the equilibrium constant. If the concentrations of formaldehyde, methylene-1-asparagine and the reaction product be represented by C_F, C_A and C_{AF_n}, respectively, and n moles of formaldehyde take part in the reaction, then at equilibrium $(C_A \times C_F^n)/C_{AF_n} = k$, where k is the equilibrium constant. On the assumption that the optical rotation of substances A and AF_n are of different magnitude and each proportional to its concentration and further that the presence of neither species has an influence on the rotation of the other, we may calculate k from the rotation data. From examination of the first few experimental points it is clear that n cannot be greater than unity. In evaluating k we have employed the extrapolated values −17.50 and −4.15° for the maximum and minimum ends, respectively, of the curve. Points where the reaction is 0.20, 0.30, 0.40, etc., complete have been chosen and the respective formaldehyde concentrations read off from the curve. It is difficult to estimate the aldehyde concentrations near the beginning of the curve on account of its steepness and likewise near the end on account of its flatness, and partly for this reason only the central section has been employed in the calculations, which latter are carried out on a moles per liter basis. These data are given in Table III. In the column headed Total Formaldehyde, the 0.40 mole of formaldehyde required to form 0.40 mole of methyleneasparagine has been subtracted from the total formaldehyde in the system as read from the graph. The equilibrium constant k shows a fair constancy in the region 0.14.

The equilibrium constant may also be evaluated from the logarithmic form of the equilibrium equation $\log (C_A/C_{AF}) + \log C_F = \log k$ as employed by Frieden, Dunn and Coryell,[3] in which a graph of $\log (A/AF)$ plotted against $\log F$ should give a straight line. This relation is given in Fig. 3. A straight line can be drawn through several of the points, which gives a graphical solution for k of 0.142 in reasonable agreement with the foregoing treatment.

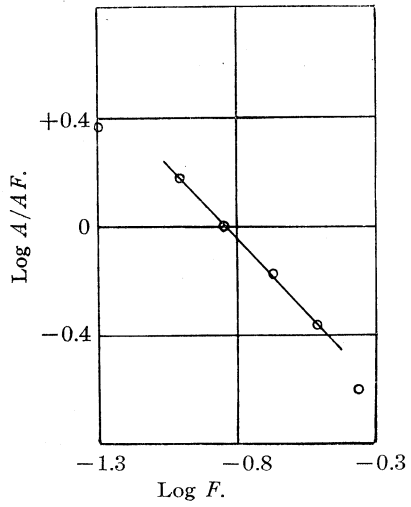


Fig. 3.—Graph of $\log A/AF$ against $\log F$ for unstable compound of methylene-1(−)-asparagine with formaldehyde.

While the data show that methylene-1-asparagine binds an additional mole of formaldehyde to form an unstable compound, evaluation of the data depends on the validity of the assumptions mentioned earlier, of which the lack of constancy of rotation of the two species with respect to concentration seems to be the main disturbing feature for the compounds under consideration.

There can be little doubt that the first mole of formaldehyde reacts with the α-amino group of

asparagine to give a methylene derivative. One might expect that the second mole of formaldehyde reacts with the amide group forming a methylol derivative. In support of this view it may be said that many methylol compounds of acid amides and formaldehyde have been reported in the literature, and in common with our second asparagine compound all are unstable and give off formaldehyde. Further work is in progress in this Laboratory to ascertain the formaldehyde binding of 1(+)-aspartic and 1(+)-glutamic acids, in an effort to elucidate the point of attachment of the second mole of formaldehyde.

In 6.64% aqueous solution $[\alpha]^{20}D$ is $-116.04°$ for the sodium salt of methylene-1(−)-asparagine and $-23.06°$ for the sodium salt of the methylene-1(−)-asparagine compound with one additional mole of formaldehyde, the latter concentration being 9.04% and dissolved in 14.4% formaldehyde solution. For sodium 1(−)-asparaginate $[\alpha]^{20}D$ is $-7.28°$ for a 6.16% solution in water. Clough[7] records for the latter a value of $-7.53°$ for a 14.51% solution at 25° and Becker[8] a value of -7.42 for a 11.68% solution at 20°. Clough notes that the rotation becomes more negative as the temperature is raised and hence our value compares well with the older data.

Summary

1. The reaction between solutions of (1−)-asparagine containing an equivalent of sodium hydroxide and various amounts of formaldehyde was followed by polariscopic and hydrogenion measurements, and estimation of unreacted aldehyde.

2. 1(−)-Asparagine reacts with formaldehyde, mole per mole, to form methylene-1(−)-asparagine. The latter reacts further with one additional mole of formaldehyde to form an unstable compound of unestablished constitution which readily loses aldehyde.

(7) G. W. Clough, *J. Chem. Soc.*, **107**, 1509 (1915).
(8) A. Becker, *Ber.*, **14**, 1028 (1881).

GENEVA, N. Y. RECEIVED AUGUST 17, 1942

[CONTRIBUTION FROM THE STAMFORD RESEARCH LABORATORIES OF THE AMERICAN CYANAMID COMPANY]

Studies in Chemotherapy. VI. Sulfanilamido Heterocycles[1]

BY GEORGE W. ANDERSON, H. ELDRIDGE FAITH, HARRY W. MARSON, PHILIP S. WINNEK AND RICHARD O. ROBLIN, JR.

On the basis of our present knowledge, N^1-heterocyclic substituted sulfanilamide derivatives still appear to offer the greatest possibilities for therapeutically effective sulfanilamide type compounds. Continuing our investigations in this field,[2] we have prepared a number of new derivatives of this type. These compounds, together with pertinent data concerning them, are listed in Table I. Several of the amino heterocycles required as intermediates have not been reported previously. The syntheses and properties of these substances are described in the Experimental part.

Most of the sulfanilamide derivatives were prepared by the standard procedure. In a few cases, such as the conversion of 2-aminoöxazole to the corresponding sulfanilamido compound, it was necessary to use *p*-nitrobenzenesulfonyl chloride. Even this method was hardly satisfactory, since in this particular case, the over-all yield, including the synthesis of the amino heterocycle, was only about 0.2%. Numerous attempts to prepare an unsubstituted sulfanilamido triazine from 2-amino-1,3,5-triazine were unsuccessful. Under all of the conditions employed, this intermediate appeared to be unstable in the presence of sulfonyl chlorides. Both sulfanilamide and sulfaguanidine were isolated as final products of the various reactions.

Some of the sulfanilamido derivatives are of interest because of their chemical relationship to well-known sulfonamides. For example, 2-sulfanilamidoöxazole is the oxygen analog of sulfathiazole, and 3-sulfanilamidopyridazine is an isomer of sulfadiazine and sulfapyrazine. The imidazole derivative corresponds to sulfadiazine in the five-membered ring series. 4-Sulfanilamido-1,2,4-triazole represents a somewhat different type of heterocyclic derivative, in that the sulfanilamido group is joined to the ring through one of the hetero-atoms rather than through a carbon atom.

(1) Presented in part before the Division of Medicinal Chemistry, Buffalo meeting of the American Chemical Society, Sept. 9, 1942.
(2) Roblin, Williams, Winnek and English, THIS JOURNAL, **62**, 2002 (1940).

TABLE I

PROPERTIES OF SULFANILAMIDO HETEROCYCLES

Compound[a]	M. p., °C. (cor.)[b]	Water soly.[c] 37°	Max.[c] blood[d] level	Chemotherapeutic activity in vivo[e]	Chemotherapeutic activity in vitro[f]	Ref. to intermed.	Formula	Analyses,[g] % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-S-imidazole[h]	262	178	2.2	Inactive	+	*j*	$C_9H_{10}O_2N_4S$	45.4	4.2	23.5	45.8	4.6	23.7
3-S-1,2,4-triazole	195–96	60	11.4	Inactive	±	*k*	$C_8H_9O_2N_5S$	40.2	3.8	29.3	40.6	3.8	29.1
4-S-1,2,4-triazole[i]	237	216	0.9	Inactive	±	*l*	$C_8H_9O_2N_5S$	40.2	3.8	29.3	40.1	3.8	29.4
2-S-oxazole	175–76	282	20.6	Inactive	+++	*m*	$C_9H_9O_3N_3S$	45.2	3.8	17.6	45.0	3.9	17.6
5-S-3-methylisoxazole	169–70	104	7.4	Sl. active	++	*n*	$C_{10}H_{11}O_3N_3S$	47.4	4.4	16.6	47.4	4.2	16.5
3-S-4-methylfurazan	148–50	180	8.1	Inactive	++	*o*	$C_9H_{10}O_3N_4S$	42.5	3.9	22.0	42.3	4.4	22.0
3-S-5-methyl-1,2,4-oxadiazole	211–13	113	5.5	Sl. active	++	*m*	$C_9H_{10}O_3N_4S$	42.5	3.9	22.0	42.7	3.8	22.2
2-S-5-amino-1,3,4-thiadiazole	259	36.3	2.1	Inactive	++	*p*	$C_8H_9O_2N_5S_2$	35.4	3.3	25.8	35.3	3.5	25.5
3-S-pyridazine	189–90	221	50.9	Inactive	+++	*m*	$C_{10}H_{10}O_2N_4S$	48.0	4.0	22.4	47.7	4.0	22.8
2-S-4-aminopyrimidine	271–72	186	0.7	Inactive	+	*q*	$C_{10}H_{11}O_2N_5S$	45.3	4.2	26.4	45.7	4.6	26.5
2-S-4-diethylaminopyrimidine	>300	4.2	0.4	Inactive	±	*m*	$C_{14}H_{19}O_2N_5S$	52.3	5.9	21.8	52.5	5.8	21.7
2-S-4,6-diamino-1,3,5-triazine	290–95	728	1.7	Inactive	+	*r*	$C_9H_{11}N_7O_2S$	38.4	3.9	34.9	38.9	4.3	34.7

[a] S = Sulfanilamido. [b] With decomposition in most cases. [c] Mg./100 cc. [d] White mice; dosage 0.5 g./kg. body weight. [e] Against experimental streptococcal or pneumococcal infections or both in white mice. [f] Approx. as follows: ± < sulfanilamide, + = sulfanilamide, ++ = sulfapyridine, +++ = sulfathiazole, against *E. coli* in a synthetic medium. [g] Microanalyses were carried out in these Laboratories by Mrs. Thelma Kirk and the Misses Helen Chubb, Margaret Oliver, Rebecca Teston and Lucy Vanderwort. [h] Ewins and Ashley, British Patent 521,821, reported m. p. 259°. [i] N^4-acetyl deriv. m. p. 237°; N, calcd. 29.3%; N, found 29.4%. [j] Fargher and Pyman, *J. Chem. Soc.*, **115**, 243 (1919). [k] Morgan and Reilly, *ibid.*, **109**, 159 (1916). [l] Ruhemann and Merriman, *ibid.*, **87**, 1772 (1905). [m] See experimental. [n] Burns, *J. prakt. Chem.* (2), **47**, 120 (1893). [o] Ponzio and Ruggeri, *Gazz. chim. ital.*, **52**, I, 289 (1922); **53**, 297 (1923); *Chem. Abst.*, **16**, 2676 (1922); **17**, 3873 (1923). [p] Fromm, *Ann.*, **433**, 8 (1923). [q] Johnson and Johns, *Am. Chem. J.*, **34**, 190 (1905). [r] American Cyanamid Company, New York, N. Y.

In vitro bacteriostatic tests against *E. coli* are included in Table I for comparison with the results in experimental animals.[3] None of the new sulfanilamido heterocycles showed much *in vivo* activity. All of them, however, showed some degree of bacteriostasis, including two compounds (2-sulfanilamidoöxazole and 3-sulfanilamidopyridazine) which were as active as sulfathiazole. In spite of high blood levels, these two derivatives were without activity in experimental mouse infections. This phenomenon has been encountered previously.[2,4] It was suggested that some of the discrepancies between *in vitro* and *in vivo* results, where lack of absorption could be ruled out, might be due to the formation of less active substances in the animal body.[4c] On the other hand, all cases of this type may not be explainable on the basis of a breakdown to less active products.

Davis[5] has suggested that the *in vivo* activity of sulfonamides may be influenced by the binding effect of serum proteins. Based on preliminary bacteriostatic experiments, he also suggested the possibility that the bound form might be inactive. Since the degree of binding appeared to be a function of the particular sulfonamide, it is possible that such a phenomenon may explain some of the differences between *in vitro* and *in vivo* activity. In any event, it is evident from the data in Table I that factors other than bacteriostasis, absorption and generally recognized variables are important to the chemotherapeutic activity of sulfonamides against experimental animal infections. These observations emphasize again the number of variables, both known and unknown, which may complicate any attempts to correlate *in vivo* activity with chemical structure.

(3) The pharmacological and bacteriological studies were carried out in these Laboratories under the direction of Dr. W. H. Feinstone.

(4) (a) Roblin and Winnek, THIS JOURNAL, **62**, 1999 (1940); (b) Roblin, Williams and Anderson, *ibid.*, **63**, 1930 (1941); (c) Roblin, Winnek, and English, *ibid.*, **64**, 567 (1942).

(5) Davis, *Science*, **95**, 77 (1942).

Experimental

Aminoheterocycles, in general, were prepared by methods which have been described in the literature (see references in Table I). Several of these intermediates have not been described previously, and the data for these compounds are recorded in Table II. The following is a description of the procedures employed for the synthesis of the new aminoheterocycles.

2-Aminoöxazole was prepared by one of the standard methods for the synthesis of the analogous thiazole derivative,[6] substituting urea for thiourea. In spite of the numerous modifications tried, the yields were much poorer when urea was used. 379 g. (2.65 moles) of α,β-dichlorodiethyl ether, 800 cc. of water and 318 g. (5.3 moles) of urea were refluxed gently, with stirring, for five and one-half hours. After standing overnight, the clear solution was

(6) v. Traumann, *Ann.*, **249**, 36 (1888).

TABLE II

AMINOHETEROCYCLES

Compound	M. p., °C. (cor.)	Yield,[a] %	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-Aminoöxazole	96– 98	4.4	42.9	4.8	33.3	43.0	4.9	33.1
3-Amino-5-methyl-1,2,4-oxadiazole	117–119	9.8	36.4	5.1	42.4	36.4	5.3	42.2
3-Aminopyridazine	168– 70	58	50.5	5.3	44.2	50.5	5.1	44.5
2-Amino-4-diethylaminopyrimidine	86– 88	59	57.8	8.5	33.7	58.2	8.7	33.3

[a] Yield of material suitable for conversion to the corresponding sulfanilamido derivative. In several cases samples were further purified before analysis; the melting point is that of the analyzed sample.

extracted with 200 cc. of ether, in two portions, to remove any chloroacetaldehyde. A solution of 240 g. (6 moles) of sodium hydroxide in 320 cc. of water was added with cooling. The strongly basic solution was then extracted with 1.3 liters of ethyl ether in five portions. After drying over flake sodium hydroxide and distilling to dryness, a residue of 2-aminoöxazole remained. Recrystallization from octanes gave 7.6 g. of the compound, m. p. 93–96°; 2.8 g. more was obtained by continuous extraction of the mother liquor (4.4% total yield, based on the α,β-dichlorodiethyl ether used). This product was suitable for the coupling reaction. A sample recrystallized from heptane had a m. p. of 96°–98°. Variations in the proportions of urea used and the time of reflux did not improve the yield. The reaction of bromoacetaldehyde and urea in water[7] gave similar yields.

3-Amino-5-methyl-1,2,4-oxadiazole was obtained by a procedure analogous to the preparation of 3-amino-5-phenyloxadiazole by Wieland and Bauer.[8] To a solution of 50 g. (0.29 mole) of dioxyguanidine hydrobromide in 135 cc. of glacial acetic acid was added 65 g. (0.65 mole) of acetic anhydride with cooling so that the temperature did not rise above 25°. Then 23.5 g. (0.29 mole) of sodium acetate was added and the mixture stirred overnight at room temperature. The insoluble salts were filtered off and washed with glacial acetic acid. Vacuum distillation of the filtrate left a viscous residue containing diacetoxyguanidine. Addition of 40% sodium hydroxide with cooling caused an evolution of gas. The alkaline solution was heated to 70–80° for twenty minutes to cyclize the diacetyl derivative. After cooling, 2.4 g. of 3-amino-5-methyloxadiazole was obtained by repeated ether extractions. It was purified by recrystallization from toluene, using activated alumina.

For the preparation of 3-aminopyridazine, 10.7 g. (0.093 mole) of 3-chloropyridazine[9] dissolved in 30 cc. of absolute alcohol and 30 cc. of anhydrous ammonia were heated at 175° in a steel autoclave for three hours, with shaking. The cooled reaction mixture was removed, heated to boiling while nitrogen was bubbled through, and filtered. The filtrate was evaporated to dryness under a reduced pressure of nitrogen. 3-Aminopyridazine was extracted from the residue with hot ethyl acetate, from which it crystallized as a light yellow solid; yield 5.1 g. It was then recrystallized from ethyl acetate.

2-Amino-4-diethylaminopyrimidine was prepared by heating 9 g. (0.07 mole) of 2-amino-4-chloropyrimidine[2] with 35 g. (0.49 mole) of diethylamine in a bomb-tube at 110°–120° for three hours. The product was dissolved in water, made alkaline with sodium hydroxide and extracted with ether. The ether was distilled off and the residue extracted with hot hexane. Cooling gave a crystalline precipitate of 9.8 g. of 2-amino-4-diethylaminopyrimidine. This was recrystallized from hexane.

Sulfanilamidoheterocycles (Table I) were prepared, in general, by the reaction of the aminoheterocycle with acetylsulfanilyl chloride in dry pyridine followed by hydrolysis.[4a] Dioxane was used as a reaction solvent for the preparation of 2-(N[4]-acetylsulfanilyl)-4-aminopyrimidine and *t*-butanol for 2-(N[4]-acetylsulfanilyl)-4-diethylaminopyrimidine. No rigid proof of structure for the former compound was attempted. The position of the sulfanilamido group on the pyrimidine ring was inferred from the instability of 4-(N[4]-acetylsulfanilamido)-pyrimidine to hydrolysis.[2,4c] If the acetylsulfanilyl chloride reacted with the 4-amino group, it was assumed that the 4-(N[4]-acetylsulfanilyl)-2-aminopyrimidine would have been decomposed in the subsequent hydrolysis.

2-(*p*-Nitrobenzenesulfonamido)-oxazole was prepared by refluxing 42.8 g. (0.19 mole) of *p*-nitrobenzenesulfonyl chloride with 16.2 g. (0.19 mole) of 2-aminoöxazole and 23.7 cc. (0.3 mole) of dry pyridine in 200 cc. of dry acetone for thirty minutes. The acetone was distilled off, and the gummy residue extracted with dilute ammonium hydroxide. Careful neutralization of the extracts with hydrochloric acid gave a first precipitate which was a sticky gum. This was removed and the desired compound was precipitated as a solid by further addition of acid. After recrystallization from water, 4.7 g. (9.0% of the theoretical) of *p*-nitrobenzenesulfonamidoöxazole was obtained. The m. p. of a further recrystallized sample was 175–177°.

Reduction by ferrous sulfate and ammonium hydroxide[10] gave 2-sulfanilamidoöxazole. Recrystallization from water did not improve the melting point. By dissolving in dilute hydrochloric acid, stirring with decolorizing carbon, filtering and precipitating by neutralization with ammonium hydroxide, colorless crystals of pure 2-sulfanilamidoöxazole were obtained. The yield of pure compound in the reduction step was 45% of the theoretical.

3-Sulfanilamido-1,2,4-triazole and 2-sulfanilamido-4,6-diamino-1,3,5-triazine were prepared by treating *p*-nitrobenzenesulfonyl chloride with the appropriate amine and then reducing with iron dust in dilute acetic acid.

Summary

The preparation and properties of a number of new sulfanilamido heterocycles are described.

(7) *Cf.* Leitch and Brickman, U. S. Patent 2,230,962.

(8) Wieland and Bauer, *Ber.*, **40**, 1689 (1907).

(9) Gabriel, *ibid.*, **42**, 655 (1909).

(10) Jacobs and Heidelberger, THIS JOURNAL, **39**, 1435 (1917).

Several of these compounds are closely related chemically to well-known sulfanilamido derivatives of the same type.

All of the sulfonamides showed some degree of bacteriostatic activity, but very little effect on experimental animal infections. Two compounds, in particular, were highly active *in vitro* and well absorbed. Possible explanations for these discrepancies and their bearing on the relation of molecular structure to chemotherapeutic activity, are discussed.

STAMFORD, CONN. RECEIVED JULY 31, 1942

[CONTRIBUTION FROM THE STAMFORD RESEARCH LABORATORIES OF THE AMERICAN CYANAMID COMPANY]

Studies in Chemotherapy. VII. A Theory of the Relation of Structure to Activity of Sulfanilamide Type Compounds[1]

BY PAUL H. BELL AND RICHARD O. ROBLIN, JR.

For the past three years we have been trying to find some relationship between the molecular structure and the chemotherapeutic activity of sulfanilamide type compounds. In spite of the many hundreds of derivatives which have been prepared and tested, no adequate explanation for the profound changes in therapeutic effect resulting from variations in structure has been proposed. Our approach to this problem has been through an attempt to utilize a fundamental physical property related to both structure and activity.[2] The present theory is based on the experimental observation that acid dissociation constants, which can be correlated with the structure of sulfanilamide derivatives, are also related to their bacteriostatic activity. The following is a description of this theory and a discussion of its implications.

I. Chemotherapeutic Activity and Mode of Action.—Before attempting to correlate the structure of sulfonamides with their chemotherapeutic activity, a reasonably accurate method for the determination of relative effectiveness is essential. Experimental animal tests for activity are frequently misleading because of the many factors, such as lack of absorption, rapid excretion, effect of diet and possible chemical changes in the compounds, as well as other less obvious variables,[3] which may affect the results. To a lesser degree, *in vitro* tests carried out in complex media are also somewhat confusing. In this investigation the term activity is used to indicate bacteriostatic activity against *E. coli* when the organisms are grown in a synthetic medium. This method of testing provides a more consistent and reproducible basis for the determination of relative activities by reducing the number of variables to a minimum. The relation of *in vitro* to *in vivo* results,[4] and the lack of any great degree of specificity among sulfanilamide derivatives,[5] appear to warrant this method of evaluation.

Another important prerequisite to this type of work is at least a partial understanding of the mechanism by which the compounds exert their bacteriostatic effects. None of the hypotheses advanced in recent years appeared to offer a very useful or convincing explanation, until Woods[6] demonstrated that *p*-aminobenzoic acid prevents the bacteriostatic action of sulfanilamide and sulfapyridine. This observation has since been extended by other investigators[7] to include sulfanilamide type compounds in general. Woods and Fildes[8] postulated that *p*-aminobenzoic acid is an essential metabolite associated with one or more of the enzymatic processes involved in bacterial growth. They pointed out the close structural relationship between the sulfonamides and this acid, and suggested that the former may act by blocking the enzyme system or systems with which *p*-aminobenzoic acid is involved and on which many bacteria depend for normal growth and development. Subsequent investigations have confirmed the essential nature of *p*-aminobenzoic acid,[9] and have shown experimentally

(1) Presented in part before the Divisions of Medicinal and Physical Chemistry, Buffalo Meeting of the American Chemical Society, September 9 and 10, 1942.

(2) Roblin and Bell, *Science*, **90**, 328 (1939).

(3) See, for example, Davis, *ibid.*, **95**, 78 (1942).

(4) White, Bratton, Litchfield and Marshall, *J. Pharmacol.*, **72**, 120 (1941).

(5) Wyss, Grubaugh and Schmelkes, *Proc. Soc. Exptl. Biol. Med.*, **49**, 618 (1942).

(6) Woods, *Brit. J. Exptl. Path.*, **21**, 74 (1940).

(7) Landy and Wyeno, *Proc. Soc. Exptl. Biol. Med.*, **46**, 59 (1941); Strauss, Lowell and Finland, *J. Clin. Investigation*, **20**, 189 (1941).

(8) Fildes, *Lancet*, **238**, I, 955 (1940).

(9) Rubbo and Gillespie, *Nature*, **146**, 838 (1940); Lampen and Peterson, THIS JOURNAL, **63**, 2283 (1941); Park and Wood, *Bull. Johns Hopkins Hosp.*, **70**, 19 (1942).

TABLE I

DISSOCIATION CONSTANTS AND BACTERIOSTATIC ACTIVITY OF SULFANILAMIDE TYPE COMPOUNDS

No.	Compound[a]	Acid constants pK_a	Acid constants K_a	$K_b \times 10^{12}$ 1st	$K_b \times 10^{12}$ 2nd	*In vitro* tests, C_R, Molar × 10^5	Ref.
1	*p*-Aminobenzoic acid	4.68	2.1×10^{-5}[b]	2.6[b]			
2	Sulfanilamide	10.43	3.7×10^{-11}[c]	2.3[c]		20.0	
3	N^1-Methylsulfanilamide	10.77	1.7×10^{-11}	1.6		30.0	*d*
4	N^1,N^1-Dimethylsulfanilamide	...	...	1.3		30.0	*d*
5	N^1-Hydroxyethylsulfanilamide	10.92	1.2×10^{-11}	2.0		50.0	*d*
6	Sulfanilylglycine	3.52	3.0×10^{-4}[e]	*f*		>90.0	*d*
7	N^1-Phenylsulfanilamide	9.60	2.5×10^{-10}[f]	1.4		3.0	*d*
8	N^1-*o*-Tolylsulfanilamide	9.96	1.1×10^{-10}[f]	1.1		10.0	*d*
9	N^1-*m*-Tolylsulfanilamide	9.74	1.8×10^{-10}[f]	1.3		5.0	*d*
10	N^1-*p*-Tolylsulfanilamide	9.82	1.5×10^{-10}[f]	1.4		5.0	*d*
11	N^3-Sulfanilylmetanilamide	8.23	5.9×10^{-9}[g]	1.6		2.0	*d*
12	N^4-Sulfanilylsulfanilamide	7.85	1.4×10^{-8}[g]	0.8		0.5	*d*
13	N^1-*p*-Aminophenylsulfanilamide	10.22	0.6×10^{-10}[f]	$>10^{-9}$	0.7	5.0	*d*
14	N^1-Furfurylsulfanilamide	10.88	1.3×10^{-11}[f]	1.8		20.0	*d*
15	Sulfapyridine	8.43	3.7×10^{-9}[g]	3.8	.1	0.6	*d*
16	3-Sulfanilamidopyridine	7.89	1.3×10^{-8}[g]	10	.4	.2	*d*
17	2-S-5-bromopyridine	7.15	7.1×10^{-8}[g]	0.8		.5	*h*
18	5-S-2-bromopyridine	7.12	7.6×10^{-8}[g]	1.0		.2	*h*
19	2-S-5-aminopyridine	8.47	0.34×10^{-8}	10	.3	.6	*h*
20	5-S-2-aminopyridine	8.82	$.15 \times 10^{-8}$	160[i]	.8	2.0	*h*
21	2-Sulfanilamidoimidazole	9.72	1.9×10^{-10}	*k*		40.0	*j*
22	3-Sulfanilamidopyridazine	7.06	0.87×10^{-7}	3.0	.2	0.08	*j*
23	Sulfadiazine	6.48	3.3×10^{-7}	1.0		.08	*l*
24	2-S-4-methylpyrimidine	7.06	0.87×10^{-7}	1.2		.2	*l*
25	2-S-4,6-dimethylpyrimidine	7.37	$.43 \times 10^{-7}$	2.3		.3	*m*
26	2-S-4-aminopyrimidine	9.44	3.6×10^{-10}	13.5[i]		20.0	*j*
27	4-S-pyrimidine	6.17	6.7×10^{-7}	22[i]	.2	0.1	*l*
28	5-S-pyrimidine	6.62	2.4×10^{-7}	0.8		.2	*m*
29	5-S-2-chloropyrimidine	5.80	1.6×10^{-6}	*k*		.1	*m*
30	2-Sulfanilamidopyrazine	6.04	0.91×10^{-6}[g]	0.6		.08	*n*
31	4-S-1,2,4-triazole	4.66	2.2×10^{-5}	.7		>80.0	*j*
32	2-Sulfanilamidoöxazole	6.5	3.2×10^{-7}	*k*		0.08	*j*
33	5-S-3-methylisoxazole	4.2	6.3×10^{-5}	*k*		.6	*j*
34	Sulfathiazole	7.12	7.6×10^{-8}[o]	2.3		.08	*d*
35	2-S-4-methylthiazole	7.79	1.6×10^{-8}	2.3		.2	*d*
36	3-S-4-methylfurazan	4.10	7.9×10^{-5}	0.8		1.0	*j*
37	3-S-5-methyloxadiazole	4.40	4.0×10^{-5}[f]	.5		2.0	*j*
38	2-S-1,3,4-thiadiazole	4.77	1.7×10^{-5}	1.4		0.6	*l*
39	2-S-5-methylthiadiazole	5.45	3.5×10^{-6}	1.6		.2	*p*
40	Sulfanilylcyanamide	2.92	1.2×10^{-3}	*f*		100	*q*
41	Sulfanilylurea	5.42	3.8×10^{-6}	0.6		10.0	*q*
42	Sulfanilylguanidine	...	...	5.6	.03	10.0	*h*
43	Sulfanilylaminoguanidine	...	...	3.0	.2	0.9	*q*
44	N^1-Acetylsulfanilamide	5.38	4.2×10^{-6}	0.6		.7	*d*
45	N^1-Chloroacetylsulfanilamide	3.79	1.6×10^{-4}	.4		10.0	*r*
46	N^1-Benzoylsulfanilamide	4.57	2.7×10^{-5}	.6		0.3	*d*
47	N^1-*p*-Aminobenzoylsulfanilamide	5.20	6.3×10^{-6}	2.7	.3	.5	*d*
48	N^1-Ethylsulfonylsulfanilamide	3.10	7.9×10^{-4}	0.3		1000	*d*
49	N^1-Sulfanilylsulfanilamide	2.89	1.3×10^{-3}	*f*		60.0	*d*
50	4,4′-Diaminodiphenylsulfone	...	...	3.1	.2	2.0	*s*

[a] S = Sulfanilamido; nomenclature according to Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2217 (1938). [b] Bjerrum, *Z. physik. Chem.*, **104**, 164 (1923), reported $pK_a = 4.8$; K_b, ref. 12. [c] Albert and Goldacre, *Nature*, **149**, 245 (1942), gave $K_a = 6.3 \times 10^{-11}$; $K_b = 1.6 \times 10^{-12}$. [d] See ref. 11. [e] First K_a represents carboxyl; second very weak. [f] Insol. glacial HAc. [g] Nielson and Wolffbrandt, *Dansk. Tids. Farm.*, **14**, 113 (1940); *J. Am. Pharm. Assoc.* (*Pharm. Abst.*), **31**, 29 (1942), reported $pK_a = 8.7$. [h] Roblin and Winnek, THIS JOURNAL, **62**, 1999 (1940). [i] In water. [j] Anderson, Faith, Marson, Winnek and Roblin, *ibid.*, **64**, 2902 (1942). [k] No measurements made. [l] Roblin, Williams, Winnek and English, *ibid.*, **62**, 2002 (1940). [m] Roblin, Winnek and English, *ibid.*, **64**, 567 (1942). [n] Ellingson,

ibid., **63**, 2524 (1941). [o] Ref. (g) gave $pK_a = 7.6$. [p] Ganapathi, *Proc. Indian Acad. Sci.*, **13A**, 386 (1941); *Chem. Abs.*, **36**, 1022 (1942). [q] Winnek, Anderson, Marson, Faith and Roblin, THIS JOURNAL, **64**, 1682 (1942). [r] Ref. 23. [s] Fromm and Wittmann, *Ber.*, **41**, 2264 (1908). [t] Values in water calculated from measurements carried out in alcoholic solution (see Experimental).

that the type of inhibition produced by sulfanilamide derivatives is competitive with respect to *p*-aminobenzoic acid.[10]

If the bacteriostatic action of the sulfanilamide type compounds is due to a competition with the required *p*-aminobenzoic acid for an essential enzyme system, then the more closely the competitor compound resembles this acid, the greater should be its blocking or bacteriostatic effect. The characterizing groups in *p*-aminobenzoic acid are the carboxyl group and the aromatic amino group para to it. Aside from geometric configuration, probably the most important property of a group is its positive or negative character. This is reflected in an amino group by its basic, and in a carboxyl group by its acidic, properties. Since many of the sulfanilamide derivatives contain both an acidic sulfonamide, and a basic para amino group, this work was undertaken to compare their physical properties with the corresponding groups in *p*-aminobenzoic acid. Dissociation constants were selected because they provide a readily measurable property which furnishes a direct indication of the positive or negative character of the groups.

II. Acid and Base Dissociation Constants (Qualitative Discussion).—During this investigation, the acid and base constants of over one hundred sulfonamides and related compounds were determined. A number of the values obtained are recorded in Table I. To conserve space, only a fraction of the total number of compounds studied is listed in this table. The results on the derivatives which are not recorded confirmed the conclusions drawn from the reported data. Methods employed for the determination of acid and base constants are described under Experimental. For convenience, the compounds are listed according to the classification of Northey.[11] The term C_R in Table I represents the minimum molar concentration necessary to cause bacteriostasis of *E. coli* in a buffered (*p*H 7) synthetic medium under standardized condition; thus, the smaller the number, the greater the activity. It is difficult to obtain a high precision in such tests, and small differences in bacteriostatic activity (factor of 2) are within experimental error.

Only brief consideration need be given to the base constants. The range of basic strength of the aromatic para amino group of practically all the sulfonamides studied was small [$(0.5–2.3) \times 10^{-12}$]. However, in order to establish this small range, it was necessary to make base constant determinations on nearly all the compounds studied. Several of the first base dissociation constants listed in Table I are greater than 2.3×10^{-12}. In these cases it is possible to show, by comparing the basic strength of the corresponding acetyl and benzene sulfonamide derivatives, that the first base constant probably does not represent the aromatic para amino group. Neither is the second base constant for these compounds a true measure of the basic strength of the aromatic amino group, because of the presence of the ion resulting from the determination of the first base constant (see Experimental).

The ionization constant for the basic amino group in *p*-aminobenzoic acid is approximately 2.6×10^{-12}.[12] To the extent that all the active sulfanilamide derivatives have identical unsubstituted para amino groups with constants which are close to this value, the base constants may be an important factor in bacteriostatic activity. But due to the very small variations in basic strength, no relation between these constants and bacteriostatic activity could be found.

Acid dissociation constants, which vary over a wide range ($< 10^{-11}$–10^{-3}), present an entirely different picture. The relationship between the *in vitro* activity of N^1-substituted sulfanilamide derivatives and their acid strength is shown in Fig. 1 (data from Table I). For convenience in plotting the curve, log $1/C_R$ is used rather than C_R. An examination of this figure indicates that as the pK_a of the sulfonamides increases, the bacteriostatic activity passes through a maximum and then decreases. In order to account for this phenomenon, several factors must be considered.

p-Aminobenzoic acid has been shown to be in the "non-zwitter ion" form in solution.[13] Never-

(10) Wyss, *Proc. Soc. Exptl. Biol. Med.*, **48**, 122 (1941); Wood, *J. Exptl. Med.*, **75**, 369 (1942).

(11) Northey, *Chem. Revs.*, **27**, 85 (1940).

(12) Winkelblech, *Z. physik. Chem.*, **36**, 546 (1901), reported 2.3×10^{-12}.

(13) Harris, *Proc. Roy. Soc.* (London), **97B**, 364 (1925); **104B**, 412 (1929); *Biochem. J.*, **24**, 1080 (1930).

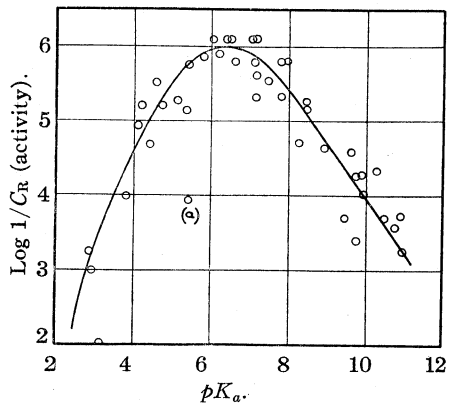


Fig. 1.—Relation of *in vitro* activity to acidity. Limits of error in log $1/C_R = \pm 0.3$.

theless, it is a sufficiently strong acid so that in dilute solution in a medium buffered at *p*H 7, the carboxyl group is better than 99% ionized. The neutral solution is particularly important, since the form in which the compounds exist in bacterial culture media or in body fluids is of primary interest. Under these conditions, *p*-aminobenzoic acid consists of a benzene ring containing an NH_2 group, para to which is an ionic group having two very negative oxygens. Geometrically, these two oxygens are about 2.3 Å. apart,[14] while sulfones and sulfonamides both have a group similar to the CO_2 ion, namely, an SO_2 group, containing two negative oxygens[15] with an oxygen–oxygen distance of approximately 2.4 Å.[16] In general, the *p*-aminobenzene sulfonyl groups of the sulfones and sulfonamides are geometrically very similar in dimensions to the *p*-aminobenzoic ion as illustrated in Fig. 2.

Nearly all the amino groups of (a), (b) and (c), Fig. 2, have been shown to have base constants of the same order of magnitude. Consequently, the differences in the SO_2 groups of the various sulfonamides, compared with the CO_2 ion, must now be considered as a possible determining factor in the relative bacteriostatic activity of these compounds. Dipole moment studies have shown the SO_2 to be a relatively negative group.[15] However, the CO_2^- should be more negative than the SO_2, because the ion actually carries an electronic charge. It seems logical then, that the more negative the SO_2 group, the more closely it will resemble the CO_2 ion. On the basis of this reasoning, the theory which we shall attempt to develop may be stated as follows: *the more negative the SO_2 group of a sulfanilamide type compound, the greater the bacteriostatic activity of the compound.*

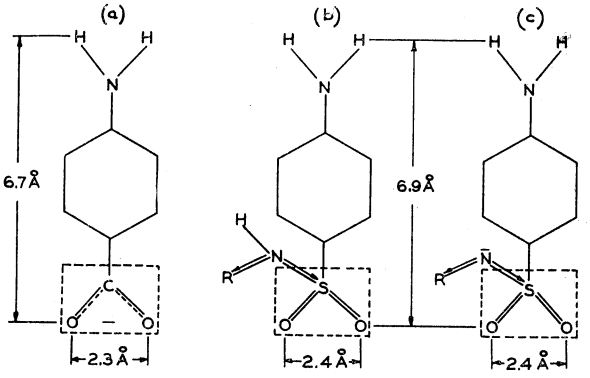


Fig. 2.—Geometric configurations.

The problem now becomes one of evaluating the relative negative character of the SO_2 group of the various sulfonamides in terms of their acid constants, to determine to what extent this property is related to bacteriostatic activity. Since the R group (Fig. 2) is the only variable involved in the N^1-substituted derivatives, it must be the factor controlling the acid constants of these compounds. For R to be acid strengthening, it must be an electronegative (electron attracting) group.[17] Under these conditions, R attracts electrons from the adjacent amide nitrogen so that the hydrogen can escape as a proton in solution, leaving the anion represented by form (c). The acid constants furnish an excellent indirect measure of the relative electronegative character of R, because any change in the acid strength of the sulfonamides should be proportional to the change in the electronegativity of the R group.

Since we are concerned with the form of the sulfanilamide type compounds in a medium buffered at *p*H 7, the effect of acid strength (as regulated by the properties of the R group) on the quantities of the molecular and ionic forms ((b) and (c), Fig. 2) existing at this *p*H must be considered. The fraction ionized, x, for any acid is given by the equation

$$x = \frac{K_a}{K_a + [H^+]} \text{ or at } p\text{H } 7 \quad x = \frac{K_a}{K_a + 10^{-7}} \qquad (1)$$

Using this equation, a plot of pK_a *versus* the fraction ionized may be made (Fig. 3). At *p*H 7, compounds which are strong acids (pK_a up to

(14) Zachariasen, *Phys. Rev.*, **53**, 917 (1938).

(15) Bergmann, *Ber.*, **65**, 457 (1932); Kumler and Halverstadt, THIS JOURNAL, **63**, 2182 (1941).

(16) Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 2nd ed., 1940.

(17) The term electronegative refers throughout to the electron attracting power of a group.[16] Negative is used to indicate the relative electron density or negative charge around a group.

5–6) are practically completely ionized, weaker acids (pK_a = 6–12) are partly ionized, and the very weak acids (pK_a > 12) are almost entirely in the un-ionized form.

With the amounts of the molecular and ionic forms of any given sulfonamide known, the relative activities of the two species must be considered on the basis of the assumption that the bacteriostatic activity is proportional to the negative character of the SO_2 group. The ionic form has an electronic charge on the amide nitrogen, as shown in (c) (Fig. 2). This electronic (negative) charge *increases greatly* the negative character of the adjacent SO_2, since the SO_2 group is also electron attracting and acquires part of the ionic charge from the amide nitrogen. Consequently, *the SO_2 group of any sulfanilamide derivative in the ionized form (c) is much more negative than the SO_2 of the same compound in the un-ionized form (b). Therefore, the ionic form of any sulfonamide should be much more active than the molecular form.*[18]

The effect of the R group (Fig. 2) on ionization, and the relative activity of the ionic and molecular forms, have been discussed. Remaining to be considered is the effect of different R groups on the negative character of the SO_2 group. Consider first the ionic form (c). As the electron attracting power of R increases, the SO_2 group should become less negative because, under these conditions, a greater part of the ionic charge of the amide nitrogen will be taken by the R group which will be competing more strongly with the SO_2 for the ionic charge. The arrows in Fig. 2 illustrate the competition between the attracting forces of these two groups for the ionic charge on the adjacent amide nitrogen. As the SO_2 becomes less negative, its ion should be less active than an ion whose R is a weaker electron attracting group. Applying the same reasoning to the molecular form (b), we arrive at similar conclusions concerning the relative negativity of the SO_2 groups. Since the electron attracting power of R is proportional to the acid strength, it follows that, *the more acidic the sulfonamide, the less negative the SO_2 group of the ionic and molecular forms and the less the bacteriostatic activity of either form.* It should be recalled here that up to a certain point this decrease in activity with increasing acid strength is more than compensated for by the increasing proportion of highly active ions. Because the ions are much more active than the corresponding molecules, the over-all effect of increasing acid strength produces an increase in activity up to the point where the sulfonamides are largely ionized. Further increases in acid strength are not accompanied by a proportionate increase in the number of ions. The predominant effect beyond this point should be the decreasing negative character of the SO_2 group, accompanied by decreasing activity. Consequently, a maximum would be expected in the curve relating pK_a to bacteriostatic activity (compare Fig. 1).

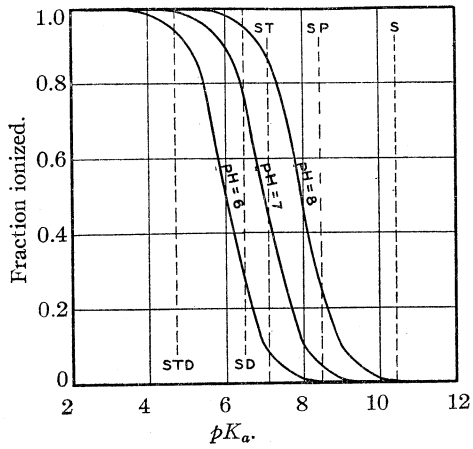


Fig. 3.—Acid ionization in buffers (nos. from Table I): S, sulfanilamide (2); sulfapyridine (15); ST, sulfathiazole (34); SD, sulfadiazine (23); STD, sulfathiadiazole (38).

It is also possible for the electron attracting power of R to change until it is actually an electron donor group. Under these conditions, R should repulse electrons toward the SO_2 group. As a result, the SO_2 group would become more negative. The acid strength also reflects the electron donor power of R. However, these compounds can become such weak acids that the effect of the highly active ions is negligible, and as a result the bacteriostatic effect should be of a lower order of magnitude. Even so, as pointed out above, the activity of the un-ionized forms should show a continuous increase as the acid strength

(18) During the preparation of this manuscript, two papers appeared in which experimental evidence supporting this conclusion is reported. See Fox and Rose, *Proc. Soc. Exptl. Biol. Med.*, **50**, 142 (1942); Schmelkes, Wyss, Marks, Ludwig and Sandskov, *ibid.*, **50**, 145 (1942). However, the present theory is not in accord with the conclusions of these authors that the ionic form of sulfanilamide derivatives is the only active form. For example, such a conclusion fails to account for the activity of sulfones, sulfaguanidine and N^1-disubstituted sulfanilamide derivatives, none of which exist as ions in solution, although they are also inhibited by *p*-aminobenzoic acid. Furthermore, we do not agree with Fox and Rose that the ions of different derivatives are equally active. Actually, the experimental data in both of these papers appear to support the view that the ions of the stronger acids are less active. Moreover, the idea of equal activity for all ions obviously is not in agreement with the experimental data for strong acids as shown in Fig. 1. This phase of the problem is considered in the subsequent discussion.

decreases. Thus, when the ionic form can be neglected, the curve relating pK_a to bacteriostatic activity should pass through a minimum and then increase as the acid strength decreases. Because compounds in which R is an electron donor group are extremely weak acids, it is not possible to determine their dissociation constants in aqueous solution. Evidence such as the relatively high bacteriostatic activity of sulfaguanidine, too weak an acid to be measured in aqueous solution, strongly suggests that a minimum may also be found in the experimental curve. Possibly studies in a basic solvent such as liquid ammonia would furnish quantitative data with which to fit these sulfonamides into this general picture.

III. Acid Constants (Quantitative Discussion).—In order to obtain optimum activity among acidic sulfanilamide derivatives, the problem is apparently one of obtaining a proper balance between the acid strengthening effect of the R group (Fig. 2) and the formal ionic charge on the sulfonamide nitrogen to give the maximum over-all negative character to the SO_2 group. Branch and Calvin[19] have shown that the dissociation constant of an organic acid can be predicted quantitatively by an equation of the type

$$\log K = \log K_a + \Sigma I_R \alpha^i \qquad (2)$$

where K_a is the acid constant of the parent acid, I_R the inductive constants for each atom or group other than hydrogen, α the fraction that reduces the inductive effect for the transmission across each bond, and i the number of bonds through which the effect must be transmitted. I_R multiplied by 2.3 RT then becomes a potential and has the units of free energy.

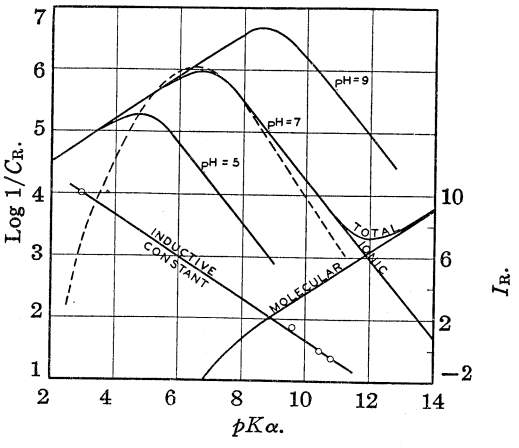


Fig. 4.—Theoretical activity *versus* pK_a: dotted line represents experimental activity from Fig. 1.

(19) Branch and Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941.

Assuming that bacteriostatic activity is proportional to the potential of the SO_2 group, then, when the total activity is due almost entirely to the highly active ions (pK_a 2–11)

$$2.303\ RT \log (k/xC_R) = 2.303\ RT\ [\alpha(12.3 - I_R\alpha) - I_R\alpha^2] \qquad (3)$$

where C_R = minimum molar concentration of a sulfonamide required to exhibit a given bacteriostatic activity, attributing all activity to the ions, x = fraction of the total concentration of the compound in ionic form, k = proportionality constant (determined experimentally), to adjust the potential energy of the SO_2 to experimental conditions, I_R, α, as defined for equation (2), $(12.3 - I_R\alpha)$ = inductive effect of the ionic charge reduced by the effect of I_R on it, $I_R\alpha^2$ = inductive effect of R on SO_2 directly.

As a first approximation, resonance and polarization effects were neglected, and α was taken as $1/2.8$ (the value of Branch and Calvin for a covalent bond); then

$$\log \frac{k}{xC_R} = 4.04 - 0.255\, I_R \qquad (4)$$

Using Branch and Calvin's inductive constants for various radicals, it was found that I_R was a linear function of the pK_a values of the corresponding sulfanilamides.

From Fig. 4

$$I_R = -1.33\, pK_a + 13.88 \qquad (5)$$

also, for any acid at pH 7 (where the *in vitro* tests were made)

$$pK_a = 7 - \log x/(1 - x) \qquad (6)$$

Substituting (5) and (6) in equation (4), we have

$$\log 1/C_R + \log k = 3.23 + 0.661 \log x + 0.339 \log (1 - x) \qquad (7)$$

at conditions of maximum activity ($\log 1/C_R$ = max.)

$$\frac{d \log 1/C_R}{dx} = 0 = \frac{0.661}{x} - \frac{0.339}{1 - x}$$

$x = 0.661$ at maximum activity

This corresponds to a sulfanilamide derivative with a pK_a of 6.7 as calculated by equation (6), and agrees very well with the experimentally observed maximum (Fig. 1). This pK_a value of maximum activity is independent of the *in vitro* tests and depends only on the inductive effects of the R groups.

Using the experimental maximum activity, $\log 1/C_R = 6.1 \pm 0.3$, k may be evaluated by substi-

tuting $\log 1/C_R = 6.1$ and $x = 0.661$ in equation (7), and solving for k.

The final ion activity equation is then

$$\log 0.001/C_R = 3.23 + 0.661 \log x + 0.339 \log (1 - x) \quad (8)$$

A similar equation may be derived for the activity of the un-ionized form

$$\log \frac{0.001}{(1 - x)C_R} = -1.3\alpha - 2 I_R\alpha^2 \quad (9)$$

from which it can be shown that its contribution toward activity will be small except for very large pK_a values.

Combining equations (9) and (4) we may show that

$$\log \frac{(1 - x)\ C_R\ (\text{un-ionized})}{x\ C_R\ (\text{ionized})} = 4.85 \quad (10)$$

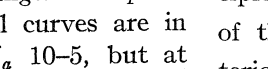
which means that any ion is approximately $10^{4.85}$ times more active than the corresponding molecule. Now, if C_R (un-ionized) = C_R (ionized)

$$\log (1 - x)/x = 4.85$$

and pK_a must be 11.85 to fulfil this condition. At this pK_a, log 2.0 should be added to $\log 1/C_R$ from equation (7). In this way the ion activity curve was corrected for the molecular activity at pK_a's greater than 10, and the total activity curve drawn as shown in Fig. 4.

The theoretical curves of Fig. 4 at pH 5 and 9 show how the pK_a of maximum activity may shift if the pH of the medium changes. At pH 7 the experimental and theoretical curves are in very good agreement from pK_a 10–5, but at lower pK_a values the compounds are less active than predicted. Probably the most important factor contributing to this deviation is the limitations in the development of the theory. As pointed out by Branch and Calvin, an exact equation of the type of equation (2) should contain summation terms for the polarization and resonance, as well as the inductive effect. While polarization is probably a function of pK_a, the relationship cannot be readily established experimentally. On the other hand, resonance is probably dependent on the specific character of the R group, and no general relationship between resonance and inductive effect can be established. In equation (3) polarization and resonance have been neglected, and therefore α is not equal to 1/2.8 (the simple covalent bond value) unless these effects are small. Where R is not too electronegative (weaker acids) the value for α probably is a good approximation; however, as R becomes strongly electronegative, the SO_2–N–R bonds should become more ionic, and α should be greater than 1/2.8. Such an increase in α would give better agreement between the theoretical and experimental curves in the low pK_a range.

This treatment also takes no account of the inductive effects on the p-amino group. The very acid compounds, in general, have less basic p-amino groups. In the extreme cases there appears to be considerable "zwitterion" formation, as indicated in the case of sulfanilylcyanamide by titrations in formaldehyde solution. Any large variation in the character of the p-amino group compared with the corresponding group in p-aminobenzoic acid may be expected to result in a decrease in activity.

IV. Relation of Structure to Activity.—The preceding discussion has been concerned primarily with an attempt to show how both structure and activity can be related to a common denominator, namely, the negative character of the SO_2 group, and how acid dissociation constants can be used to evaluate the relative negativity of the SO_2 group. Of necessity, this discussion has been limited largely to N^1-monosubstituted sulfanilamide derivatives, since they are the only active compounds on which measurements of the acid strength of the sulfonamide group can be made. Nevertheless, we believe that the principles outlined above apply to any substance of the type  , provided its bacteriostatic activity is inhibited by p-aminobenzoic acid. If the properties of the NH_2 are constant, the activity should depend on the relative negative character of the XO_2 group. In addition to sulfonamides and sulfones, the type formula should include compounds in which X is phosphorus, arsenic, selenium, or other elements.

The term "sulfanilamide type compounds," as used throughout this paper, is limited to derivatives of the type shown above. This limitation, of course, excludes N^4-substituted compounds; orthanilamide, metanilamide and their derivatives; nuclear substituted compounds; and substances in which the NH_2 or XO_2 groups are separated from the benzene ring by an alkyl, aryl or other radical. N^4-Substituted compounds have not been considered because it now appears to be generally accepted that these derivatives are active chemotherapeutic agents only after the N^4-substituent has been removed by some bio-

chemical process. First demonstrated by the Tréfouël's and their co-workers[20] for the original "Prontosil," this process has since been confirmed many times for a number of different N^4-substituents.

The mode of action of sulfanilamide type compounds proposed by Woods[5] and Fildes[8] should exclude all the types of compounds listed above on the basis of steric effects. The high degree of specificity of enzyme systems is well recognized. If the action of sulfonamides is based on the competitive inhibition of an enzyme system normally requiring *p*-aminobenzoic acid, then in order to be effective, a compound should have a spacial configuration as closely resembling that of the normally required substance as possible. Obviously, a substituted amino group no longer resembles a free NH_2 from this standpoint.[21] Similarly, orthanilamide and metanilamide derivatives, nuclear substituted compounds, and substances in which the groups are separated from the benzene ring, are much less closely related sterically to *p*-aminobenzoic acid than the compounds formulated above. Perhaps the most convincing argument in favor of this hypothesis is the experimental evidence that up to the present, so far as we are aware, no compounds of the types excluded have been reported to show bacteriostatic activity *per se*. In general, compounds not inhibited by *p*-aminobenzoic acid are considered to be outside the scope of the present theory.[22]

It should now be possible to generalize on the effects of various types of N^1-substituents on bacteriostatic activity, using sulfanilamide as the basis for comparison. Among these compounds all degrees of potency may be found, although none of them appears to be completely inactive. In the following discussion groups are referred to hydrogen which is considered as neutral. An electronegative substituent is one which tends to acquire electrons at the expense of the group to which it is attached. Such a group makes the resulting sulfanilamide derivative a stronger acid. By the same criterion, an electropositive substituent tends to donate electrons and form less acidic sulfonamides.

(20) Tréfouël, Tréfouël, Nitti and Bovet, *Compt. rend. soc. biol.*, **120**, 756 (1935).

(21) This effect is in contrast to an N^1-substituent which in most cases probably has very little influence on the spacial configuration of the SO_2 group.

(22) For example, *p,p'*-diaminodiphenyl sulfide has bacteriostatic activity, but its mode of action evidently is quite different since it is not inhibited by *p*-aminobenzoic acid (W. H. Feinstone, personal communication).

Alkyl groups are slightly electropositive and acid weakening. Hence, their effect in the region of weak acids should be to reduce the activity slightly (see Table I, nos. 3 and 5). Chain length should not alter the effect appreciably, as evidenced by the nearly constant acidities of the fatty acids. From a practical standpoint, of course, long chains may reduce solubility to a point where the bacteriostatic power can no longer be demonstrated. Introducing a strong electron attracting radical on the α-carbon atom of an aliphatic acid makes the group more electronegative, while further along the chain such a substituent has a much smaller effect.[19] Thus, an electronegative group (*e. g.*, halogen) in the α-position of an N^1-alkylsulfanilamide derivative should increase activity, but the effect in any other position should be relatively weak.

A second N^1-alkyl group should not exert much influence, since the monosubstituted compounds are too weakly acidic to ionize appreciably (*cf.* nos. 3 and 4). The effect of an alkyl group on another substituent such as a heterocyclic ring is also slightly acid weakening (*cf.* nos. 23, 24 and 25). For the purposes of this discussion, saturated rings (carbocyclic or heterocyclic) would be classified as alkyl substituents. Similarly, from the standpoint of their slightly electropositive character, aromatic or heterocyclic groups separated from the N^1-nitrogen by one or more methylene radicals should be considered as substituted alkyl groups (*e. g.*, no. 14).

Aromatic rings are slightly electronegative. Consequently, the activity of these derivatives, in general, should be somewhat greater than that of sulfanilamide, because they are relatively stronger acids. Moreover, since the electron attracting power of the ring may be increased or decreased considerably by substituents, the N^1-aromatic substituted compounds show rather large variations in bacteriostatic power. As might be anticipated, substituents in the ortho and para positions exert a more pronounced influence than in the meta position. For example, the electronegative sulfonamide group in N^4-sulfanilylsulfanilamide (no. 12) increases the activity over that of the unsubstituted phenyl, while in the meta position (no. 11) the effect is smaller. On the other hand, the electropositive amino group in the para position (no. 13) reduces activity.

Heterocyclic substituents show by far the greatest variation in electronegativity. As a result,

the potency of the N^1-heterocyclic sulfanilamide derivative varies widely. The bacteriostatic activity of this class of compounds increases to a maximum and then falls off as the acidity of the compounds increases (see Fig. 1). As demonstrated in Part II above, the effect of increasing ionization appears to be more than counterbalanced by a decrease in the negative character of the SO_2 group, when the sulfonamides become too strongly acidic. Consequently, compounds such as nos. 36 and 38 are stronger acids, but less potent than derivatives containing two hetero-atoms (nos. 32 and 34). Conversely, derivatives with only one hetero-atom are too weakly acidic, and again show less activity. In most cases, two hetero-atoms in the ring appear to promote optimum bacteriostatic power. Introducing substituents in the heterocyclic nucleus affects the activity differently, depending on the acidity of the unsubstituted derivative. If the compounds are too weakly acidic, an electronegative group (*e. g.*, halogen, as in the bromopyridines, nos. 17 and 18) increases their potency. But, an electropositive amino group in the pyridine ring reduces activity (nos. 19 and 20). On the other hand, when the unsubstituted N^1-heterocyclic derivatives are too strongly acidic, the presence of an electron donor group increases bacteriostasis (no. 39), while an electronegative group should cause the activity to decrease.

The carbonic acid derivatives such as sulfanilylurea (no. 41) and sulfaguanidine (no. 42) present interesting differences. The urea derivative is quite acidic, whereas sulfaguanidine is too weak an acid to be measured in aqueous solution. Sulfanilylurea is considered in the discussion of exceptions below. At first, the guanidines may also appear to be out of line with the theory. But, guanidine should be an electron donor group, since it is a very strong base. Consequently, this compound and others of the same type should fit somewhere beyond the minimum point on the high pK_a side of the total activity curve of Fig. 4.

Acyl and sulfonyl groups are strongly electronegative. Practically all of the sulfanilamide derivatives of this class are too acidic to show maximum bacteriostatic power. An electron attracting group in the α-position further reduces the activity (*cf.* nos. 44 and 45). The sulfonyl group, being more strongly electronegative than the acyl group, has an even greater tendency to reduce the bacteriostatic effect (*cf.* nos. 47 and 49).

A second N^1-substituent of any type, on a sulfanilamide derivative which is capable of appreciable ionization, should cause a pronounced decrease in the activity. Introducing such a group completely blocks the formation of the more potent ionic form, which in turn should result in a considerable reduction in the total activity. The *in vitro* data available in the literature appear to support this conclusion.[4,11]

A certain number of exceptions to any theory relating to biological phenomena which involve unknown variables are to be expected. So little is known about the mechanism of the inhibition of enzyme systems, that all the factors cannot be evaluated with our present knowledge. Considering the large group of compounds studied, the exceptions are not sufficiently numerous to detract from the general trend. Moreover, while positive exceptions (*i. e.*, compounds more active than predicted) would invalidate the preceding discussion, negative exceptions are less disconcerting. In Fig. 1 there is one point (a) which falls outside the possible limits of experimental error for the bacteriostatic tests. The compound sulfanilylurea (no. 41) is considerably more active during the first part of the test period than at the standard end-point. A plausible explanation for the low activity of the urea derivative is that it may be slowly broken down by the bacteria to sulfanilamide or some other less active substance. The fact that there is a biological mechanism for the breakdown of urea supports this supposition.

There are two other compounds listed in Table I (nos. 6 and 31) which, although definite values for bacteriostatic activity were not obtained, appear to be negative exceptions to the theory. In the case of sulfanilylglycine (no. 6), the first acid constant undoubtedly represents the carboxyl group. The second constant, which should correspond to the sulfonamide group, is too weak to be measured in aqueous solution. In general, it is possible that compounds with amino and carboxyl substituents may be less active than predicted. These substituents, in particular, may cause an improper orientation of the molecule in an enzyme system, due to their identity with the groups in *p*-aminobenzoic acid. No adequate explanation for the low activity of 4-sulfanilamido-1,2,4-triazole (no. 31) can be given at present. Undoubtedly there are other exceptions in addition to the ones encountered in this investigation, but it seems possible that practically all negative ex-

ceptions might find simple explanations if one could account for all the factors involved.

V. Implications of the Proposed Theory.—An example illustrates to what extent the proposed theory enables one to make predictions. When the curve in Fig. 1 was first plotted, there were no compounds available with a pK_a of approximately 4. Since there were fewer points on this side of the curve, it seemed desirable to strengthen the evidence by the preparation of a sulfonamide of this type. From the well-known electronegative character of the chloroacetyl group, it was possible to predict, before the compound had been synthesized, that N^1-chloroacetylsulfanilamide[23] would have a pK_a of about 4, and consequently a bacteriostatic activity of approximately 10×10^{-5} (*cf.* Table I).

In general, we believe that sufficient data are now available so that, without the aid of physical measurements, the relative electronegativity of any substituent group can be approximated from its molecular structure. Thus, for the first time, a relationship between structure and activity is established which enables one to predict the bacteriostatic effect of any new N^1-substituted sulfanilamide derivative. Furthermore, it is possible that the approach used in this study may find application to similar investigations among other types of chemotherapeutic agents, particularly those depending on enzyme inhibitions for their activity as proposed by Fildes.[8]

From the biological standpoint, a number of interesting implications are evident. It should be possible, for instance, to show a reversal in the order of activity of a selected series of compounds with changes in *p*H. This effect would be predicted on the basis of the relative change in the proportion of ions to molecules. In going from a lower to a higher *p*H this ratio does not change appreciably for a strong acid, while a weaker acid shows an appreciable increase in the ratio of ions to molecules. Conversely, passing to a lower *p*H has the opposite effect on this ratio. If organisms such as *E. coli* can be grown from *p*H 5–9 on a synthetic medium, it is possible to design an experiment to test this prediction. The relative activity of the three compounds, sulfathiadiazole (no. 38, $pK_a = 4.77$), sulfathiazole (no. 34, $pK_a = 7.12$) and sulfapyridine (no. 15, $pK_a = 8.44$), at *p*H 7 is in the order sulfathiazole > sulfathiadiazole = sulfapyridine (Table I). But at *p*H 5 the relative activities should change so that sulfathiadiazole > sulfathiazole > sulfapyridine, and at *p*H 9 the order should be sulfapyridine > sulfathiazole > sulfathiadiazole (Fig. 4). Smaller *p*H ranges probably would not be sufficient to overcome the rather large limits of error inherent in the bacteriostatic tests.[24]

Perhaps the most important implication based on both experimental and theoretical considerations is that the optimum in bacteriostatic activity of N^1-substituted sulfanilamide derivatives appears to have been reached. The maximum in the experimental curve, and the limitations on the negative character of the SO_2 group imposed by the conflicting effects of increasing acidity, both point to such a conclusion. This, of course, does not mean that better chemotherapeutic agents of this type, from the standpoint of lower toxicity or differences in absorption and excretion and other factors of practical importance, are not possible, but it does suggest that inherently more active sulfanilamide derivatives are not likely to be found.

Experimental

Materials.—All inorganic and common organic chemicals were of "Analytical Reagent" grade. Aniline was freshly distilled from zinc dust (water white, b. p. 94–95° (25–30 mm.)). Hydrogen gas (electrolytic, from pressure tanks) was further purified by passing it through an alkaline pyrogallol solution, dilute potassium permanganate and concentrated sulfuric acid. Chloranil, m. p. 298–300°; *m*-nitroaniline, m. p. 112–113°; *p*-nitroaniline, m. p. 146–147°; tetrachlorohydroquinone, m. p. 234–236°; *p*-toluidine, m. p. 44–45°; and triethylamine, b. p. 88–90°, were all obtained from Eastman Kodak Co., and further purified when necessary. The compounds listed in Table I were prepared in these Laboratories or obtained from the Calco Chemical Division, American Cyanamid Co.

Apparatus.—Electromotive force (e. m. f.) measurements were made with a Leeds and Northrup no. 7660 vacuum-tube meter. Acid constants in 50% ethyl alcohol were measured with a Beckman (Model G) *p*H meter, employing a glass electrode and a saturated potassium chloride-calomel electrode. Hydrogen and calomel electrodes were of standard type. Measurements in acetic acid were made using a chloranil electrode[25] and a calomel reference electrode. The two electrodes were connected by a salt bridge, fitted with ground glass joints, and containing acetic acid saturated with lithium chloride.[26] Two smooth platinum inert electrodes were used for the chloranil part of the cell. These electrodes were flamed before each immersion and all readings discarded in which the two electrodes failed to give the same e. m. f.

(23) English, Chappell, Bell and Roblin, THIS JOURNAL, **64**, 2516 (1942).

(24) Work is now in progress in these Laboratories to determine whether or not such an experiment can be carried out.

(25) Hall and Werner, THIS JOURNAL, **50**, 2367 (1928).

(26) Hall and Conant, *ibid.*, **49**, 3047 (1927).

The conductance bridge was made by using a Kohlrausch bridge, a Leeds and Northrup no. 4750 resistance box, and a Freas type conductance cell. This bridge was balanced by amplifying the signal with a General Radio no. 814-A amplifier and obtaining the null point from the minimum observed on a General Radio no. 726-A vacuum-tube voltmeter.

Acid Constant Determination.—The N^1-substituted sulfanilamide derivatives are amphoteric, since they contain a basic amino, as well as the acid sulfonamido, group. Formaldehyde titrations indicated that all the sulfanilamides used in this study, except the very acidic ones, were in the "non-zwitterion" form. Hence, the usual weak acid and weak base theories could be applied without considering the other group. The acid constants were determined from the pK_a values obtained from 0.05 N NaOH electrometric titration curves (hydrogen electrode). Experimentally, it was impossible to measure all the compounds by this method, since some were extremely insoluble in water, and, because of their high molecular weights, the pK_a values were not significant.

For the very insoluble sulfanilamides it was possible to use 50% ethanol as the solvent. It has been shown that in methanol–water and ethanol–water mixtures, acid constants, within each class of acids, exhibit roughly equal changes in any given solvent mixture.[27,28] It was found that compounds in the sulfanilamide series, which were measurable in water, when measured in 50% ethanol gave a smooth curve of $pK_{a(H_2O)}$ versus $pK_{a(50\%\ EtOH)}$ as shown in Fig. 5. From this curve, it was possible to determine the acid constants, for compounds in the same series, from $pK_{a(50\%\ EtOH)}$ measurements. The alcohol values in Table I have all been corrected, by means of Fig. 5, so that they may be compared directly with the values obtained in water.

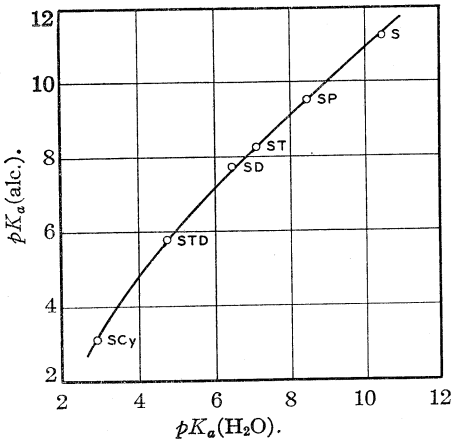


Fig. 5.—Standardization curve for 50% ethanol titrations (nos. from Table I): S, sulfanilamide (2); SP, sulfapyridine (15); ST, sulfathiazole (34); SD, sulfadiazine (23); STD, sulfathiadiazole (38); SCy, sulfanilylcyanamide (40).

Using these methods, it was possible to determine the acid constants for sulfanilamides more acid than approximately $K_a = 2 \times 10^{-11}$. Titration of acids weaker than this did not give curves sufficiently different from a blank titration to be reliable.

Base Constant Determination.—The basic groups of the sulfanilamides were all weak (pK_b = 11–13) and the results of 0.05 N HCl titrations were not significant unless the compounds were quite water soluble. Sulfanilamide, metanilamide and p-aminobenzoic acid were carefully studied by this method, using a hydrogen electrode. The base constants of sulfanilamide and p-aminobenzoic acid were also determined from conductance measurements on their hydrochlorides.[29] These results agreed very well with the water titration values. It was not possible to obtain the base constants of other sulfanilamides by this method, because of the low solubility of the free bases in water.

Using an acidic solvent such as 100% acetic acid, it was possible to increase the basic properties of these very weak bases and titrate them with a very strong acid. The chloranil electrode, which is reversible in 100% acetic acid,[26] was used to follow a titration of the base with 0.0835 N perchloric acid. Because of the low dielectric constant of the solvent, it was necessary to maintain a constant ionic strength. All the solvent had enough neutral triethylammonium perchlorate added to give an ionic strength of 0.2.[30] Employing the method of Hall[31] a standardization curve of $pK_{b(H_2O)}$ *versus* e. m. f. of chloranil electrode, at the $pK_{b(HAc)}$ point in the titration, was made as shown at Fig. 6.

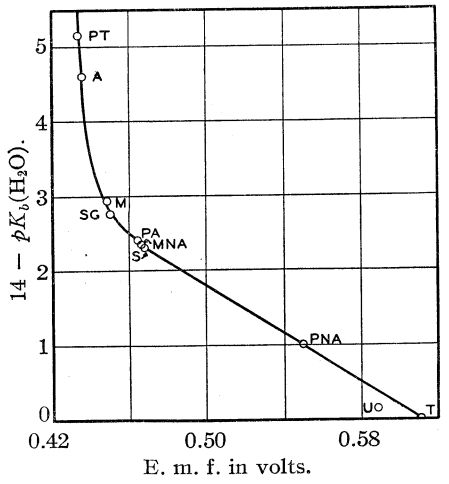


Fig. 6.—Standardization curve for acetic acid titrations (nos. from Table I): e. m. f. is that of a chloranil electrode *vs.* satd. calomel at pK_b (HAc) point of the titration: PT, p-toluidine; A, aniline; M, metanilamide; SG, sulfaguanidine (42); PA, p-aminobenzoic acid (1); MNA, m-nitroaniline; S, sulfanilamide (2); PNA-p-nitroaniline; U, urea; T, theory.

The $pK_{b(H_2O)}$ values for the compounds used to establish the points of the curve in Fig. 6 are all

(27) Michaelis and Mizutani, *Z. physik. Chem.*, **116**, 135–159 (1925).

(28) Mizutani, *ibid.*, **118**, 318–326 (1925).

(29) MacInnes, "The Principles of Electro-chemistry," Reinhold Publishing Corp., New York, N. Y., 1939.

(30) Conant and Werner, THIS JOURNAL, **52**, 4436–4450 (1930).

(31) Hall, *ibid.*, **52**, 5115–5128 (1930).

from the literature[32,33] except sulfanilamide, metanilamide and sulfaguanidine which were soluble enough to be measured in water, as outlined above. By means of the curve in Fig. 6, the K_b values in Tables I and II were obtained: the first K_b from the e. m. f. given when one-half equivalent of perchloric acid had been added and the second K_b when one and one-half equivalents had been added.

It should be pointed out that the second K_b obtained in this manner is not a measure of the group's basic character as it normally exists in a neutral solution, unless the stronger basic group is strong enough to be ionized at *p*H 7. The effect of ionic charge, depending on its sign, may either increase or decrease the apparent basic properties of the group being measured. A positive ion should decrease the negative character and the basic strength of the group, while a negative ion should have the reverse effect.

As pointed out above, the carboxyl group of *p*-aminobenzoic acid is better than 99% ionized at *p*H 7. The presence of the carboxyl ion may increase the basicity of the *p*-amino group somewhat over the value given in Table I, since this result was obtained in an acid medium where the carboxyl was not ionized. It is possible to show a relationship between the basic strength of substituted anilines and the acid constants of the N^1-sulfanilamides derived from them. From this relationship and the second K_a of N^1-*p*-carboxyphenylsulfanilamide (2nd pK_a = 8.24, for the sulfonamido group para to the completely ionized carboxyl) it may be possible to estimate the basic strength of the amino para to the carboxyl ion. Such indirect evidence suggests that the carboxyl ion of *p*-aminobenzoic acid increases the para amino basicity approximately threefold over the value obtained when the carboxyl group was un-ionized. If this is true, it is evident that the influence of a carboxyl ion on the base constant of *p*-aminobenzoic acid is relatively small.

The para amino groups of the sulfanilamide derivatives are the basic groups of primary interest. However, a number of the sulfanilamides contain two or more basic groups. The first K_b of Table I is only a true measure of the *p*-amino base constant when that group is the strongest in the molecule. When there was any question as to whether or not the paraamino was the strongest basic group in the polybasic compounds, it was checked by blocking the para amino group or removing it. In a large number of cases the benzenesulfonamido and N^4-acetyl derivatives (see Table II) were so much weaker bases than the corresponding *p*-amino compounds, that there was little doubt but that the para amino was the strongest basic group.

(32) Urea, *m*-nitroaniline, aniline, and *p*-toluidine: Landolt-Börnstein, "Tabellen," 5th ed., 1936.

(33) *p*-Nitroaniline: Farmer and Warth, *J. Chem. Soc.*, **85**, 1726 (1904).

TABLE II

BASE CONSTANTS OF SULFONAMIDE COMPOUNDS

Compounds[a]	$K_b \times 10^{13}$	Ref. (Table I)
2-B-pyridine	5.0	*r*
2-A-pyridine	11.0	*d*
2-B-pyrimidine	0.14	*r*
2-B-4-methylpyrimidine	0.4	*r*
2-A-4-methylpyrimidine	0.8	*l*
4-A-1,2,4-triazole	3.2	*j*
2-B-thiazole	0.04	*r*
2-B-thiadiazole	very weak	*r*
Acetylsulfanilylguanidine[b]	26.0	

[a] B = benzenesulfonamido; A = acetylsulfanilamido. [b] Marshall, Bratton, White and Litchfield, *Bull. Johns Hopkins Hosp.*, **67**, 163 (1940).

In each of these cases the *p*-amino was a weaker basic group than the *p*-amino of sulfanilamide. This is consistent with the corresponding acid constants, since any N^1-substituent which is more electronegative than hydrogen should be acid strengthening and base weakening. Because of these facts it did not seem likely that the first K_b of Table I was the base constant of the desired *p*-amino group for compounds nos. 13, 15, 16, 19, 20, 22, 26, 27, 42, 43 and 47 (nos. from Table I).

Acknowledgment.—We are greatly indebted to Dr. W. Harry Feinstone, Dr. Herbert Florestano and Mr. Roger D. Williams for the bacteriostatic results reported in this paper.

Summary

Based on the experimental observation that the acid dissociation constants of N^1-substituted sulfanilamide derivatives are related to their chemotherapeutic activity, a theory of the relation of structure to activity of these compounds is proposed.

The acid and base constants of a large number of sulfanilamide type compounds have been determined. A plot of acid constants *versus* bacteriostatic activity, gives a smooth curve which passes through a maximum as the acid strength

increases. This correlation between acidic dissociation and activity is shown to be directly associated with the negative character of the SO_2 group. In brief, the theory may be stated as follows: the more negative the SO_2 group of an N^1-substituted sulfanilamide derivative, the greater is its bacteriostatic power.

The inductive constants of the various N^1-substituents have been evaluated. Based on this method, a quantitative treatment of the theory has been developed. The calculated value of the acid constant for optimum activity agreed very well with the experimental results. The relative activity of the ionic and molecular forms of the sulfonamides has also been predicted by this treatment.

Since acid constants are related to both the structure of the N^1-substituent and the activity of the derivative, an indirect correlation between structure and chemotherapeutic activity is established. Knowing something about the relative electron attracting power of the N^1-substituent, it is possible for the first time to predict the bacteriostatic power of any new sulfanilamide derivative of this type. A discussion of the relation of structure to activity, and a description of the proposed theory and its implications are given.

STAMFORD, CONN. RECEIVED JULY 31, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE JOHNS HOPKINS UNIVERSITY]

Mixed Heteropoly Acid Catalysts for the Vapor Phase Air Oxidation of Naphthalene[1]

BY HENRY TRUEHEART BROWN[2] AND J. C. W. FRAZER

Catalysts prepared from heteropoly acids were first used for the partial oxidation of naphthalene in the vapor phase by Marisic.[3] The chief products from this reaction were phthalic and maleic anhydrides together with traces of naphthoquinone and benzoic acid. The reader is referred to Marisic's paper for a discussion of other catalysts used in this reaction and of the reasons for investigating heteropoly acid catalysts.

The present investigation arose from a consideration of the catalyst prepared from ammonium phospho-vanado-tungstate,[3] which gave considerably higher conversions of naphthalene to phthalic anhydride than either vanadium pentoxide or tungsten oxide alone.

In view of the fact that (1) heteropoly acid ions have a cage-like structure[4] into which only groups of the right size can fit, *i. e.*, octahedrally coördinated molybdenum, tungsten, and vanadium oxide complexes, and that (2) mixed compounds of the phospho-vanado-tungstate type exist, it seemed desirable to attempt the preparation of mixed heteropoly acids which should vary in composition from 12-molybdosilicic acid to 12-tungstosilicic acid wherein the mixed anions should contain both tungsten and molybdenum. It was expected that a series of catalysts prepared from such acids should exhibit coactivation similar to that in ammonium phospho-vanado-tungstate.

Experimental

Preparation of the Catalysts.—The general method employed in preparing the "mixed heteropoly acids" was a stepwise acidification of a solution containing tungstate, molybdate and silicate ions in the desired proportions and then an ether extraction of the product. This method was adapted from North's[5] preparations of 12-molybdosilicic acid with careful attention to all of the precautions which he mentions.

Catalysts were prepared from carefully purified acid crystals of 8–14 mesh size. These crystals were slowly heated in a stream of air to 400° and maintained at that temperature for one hour.

Preparations of the Heteropoly Acids.—Because of the importance of this step in the work, detailed directions will be given for preparing a typical "mixed acid" while directions for the others, together with their analyses, are summarized in Table I.

6-Molybdo-6-tungsto-silicic acid was prepared by dissolving 12.5 g. sodium molybdate and 17.1 g. sodium tungstate in 100 ml. of water heated to 65°. Then 5 ml. of concentrated hydrochloric acid was added dropwise with mechanical stirring, followed by 2.8 g. of sodium silicate solution (d. 1.375) diluted with a little water. Seventeen ml. of concentrated hydrochloric acid was added dropwise with vigorous stirring and the hot solution was filtered through asbestos to remove a slight precipitate of silica. After cooling, 22 ml. of concentrated hydrochloric acid was added and the clear solution was extracted with ether and the ether layer was purified as directed by North.[5] The

(1) Condensed from a dissertation submitted by H. T. Brown to the faculty of The Johns Hopkins University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Present address: Standard Oil Company (Indiana), Whiting, Indiana.

(3) Marisic, THIS JOURNAL, **62**, 2312 (1940).

(4) Keggin, *Proc. Roy. Soc.* (London), **A144**, 75 (1934).

(5) North, in Booth "Inorganic Syntheses," McGraw-Hill Book Co., Inc., New York, N. Y., 1939, Vol. I, pp. 127–129.

TABLE I

Acid	Preparation: Na_2MoO_4 $-2H_2O$ in g.	Na_2WO_4 $-2H_2O$ in g.	Water-glass d. 1.375 in g.	Vol. of water ml.	Temp., °C.	Concd. HCl, ml.	Analyses, %: MoO_3 Calcd.	MoO_3 Found	WO_3 Calcd.	WO_3 Found	SiO_2 Calcd.	SiO_2 Found
$H_4SiMo_{12}O_{40}$	30	..	3.0	120	60	48	..	..	..	..	..	..
$H_4SiMo_9W_3O_{40}$	21	9.6	2.9	100	60	44	63.1	68.5	34.0	28.8	2.9	2.7
$H_4SiMo_6W_6O_{40}$	12.5	17.1	2.8	100	65	39	37.3	36.2	60.1	61.6	2.6	2.2
$H_4SiMo_3W_9O_{40}$	5.6	23.0	2.7	75	70	35	17.0	20.4	80.6	77.0	2.4	2.7
$H_4SiW_{12}O_{40}$		30.0	2.5	60	100	32						

resulting crystals were dried in a vacuum desiccator before use.

Analysis of the Catalysts.—A dried sample of each catalyst was ignited below 400° in a porcelain boat and then heated to 270° in a stream of dry hydrogen chloride. This procedure removed molybdic oxide quantitatively[6] as an oxychloride and weighing gave molybdic oxide by difference. Similarly tungstic oxide was removed at about 500° leaving a white residue of silica. The results are given in Table I.

Apparatus and Experimental Procedure.—The apparatus employed was that described by Marisic[3] except that only one condenser loosely filled with glass wool was used to catch the condensable products, and the exit gases were analyzed. These gases were dried with phosphorus pentoxide, carbon dioxide was absorbed in soda lime, and "Hopcalite" catalyzed the oxidation of carbon monoxide which was then absorbed in soda lime. The two soda lime towers were weighed to 1 mg. before and after each run. Because of a better air regulator reproducible results were obtained with half-hour runs but otherwise the experimental procedure and analysis of the products were identical with Marisic's.

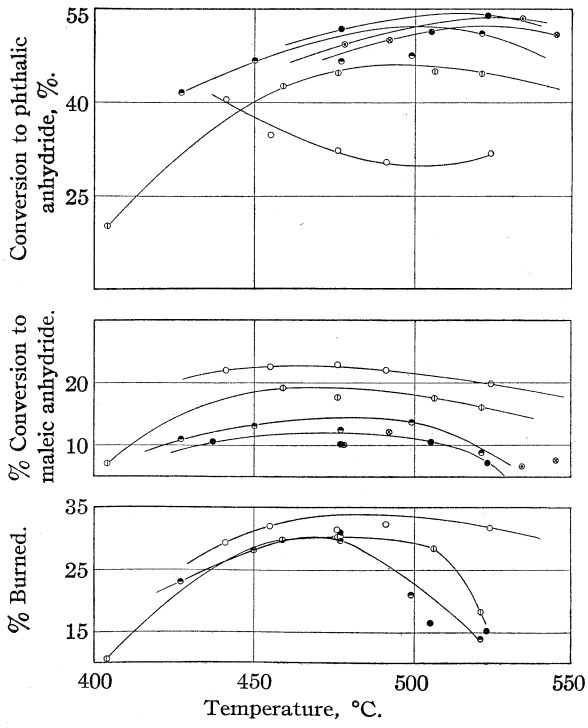


Fig. 1.—Catalyst from $H_4SiMo_{12}O_{40}$ at space velocity: O, 6,850; ⦶, 13,700; ◓, 24,000; ⊗, 26,200; ●, 29,200; ⊙, 32,000.

(6) Treadwell and Hall, "Analytical Chemistry," Vol. II, 7th ed., John Wiley and Sons, Inc., New York, N. Y., 1928, pp. 274 and 277.

Experimental Data

Results for the air oxidation of naphthalene are given in Figs. 1–4.

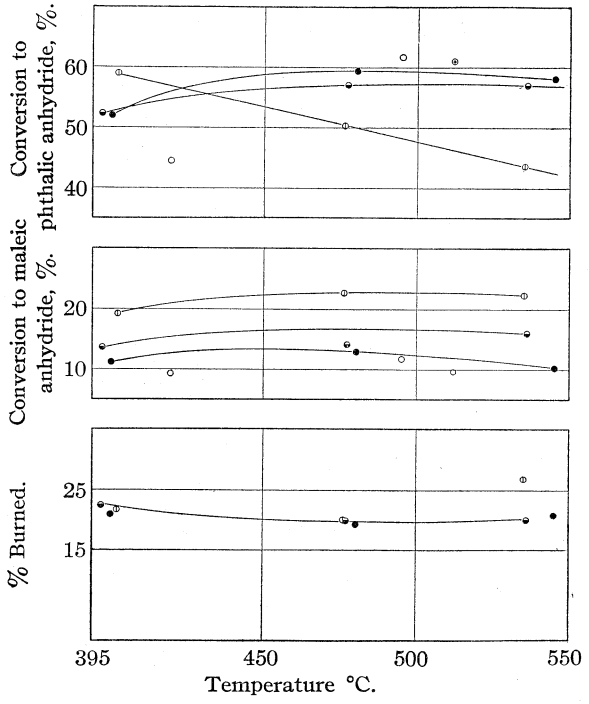


Fig. 2.—Catalyst from $H_4SiMo_9W_3O_{40}$ at space velocity: ⦶, 13,700; ◓, 24,000; ●, 29,200; O, 42,000; ⊙, 51,000.

Carbon Monoxide from the Catalytic Oxidation of Naphthalene.—It was observed in preliminary runs on the 12-molybdosilicic acid catalyst that carbon monoxide makes up a considerable proportion of the exit gases. In a series of runs at 476° the molar ratio of carbon dioxide to carbon monoxide was found to be a function of the space velocity and fell from 2.89 at s. v. 3420 to 1.87 at 8570, remaining constant at 1.87 up to a space velocity of 29,200.

This would seem to indicate that carbon monoxide is produced in large amounts at some stage

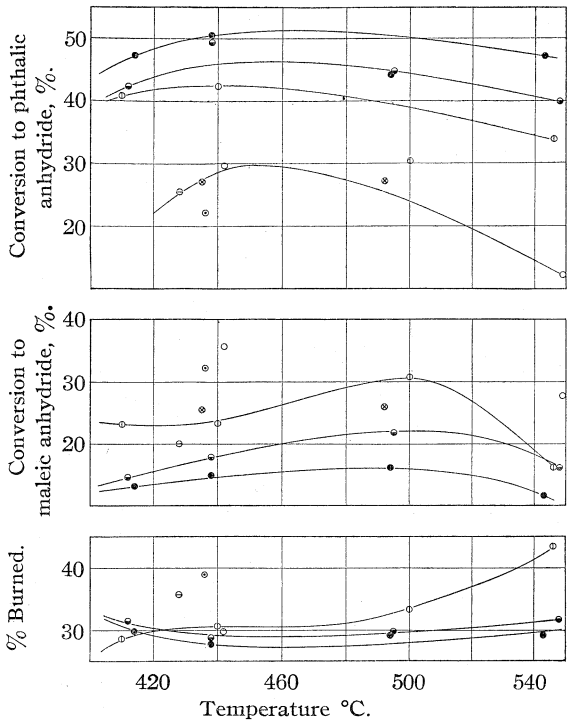


Fig. 3.—Catalyst from $H_4SiMo_6W_6O_{40}$ at space velocity: O, 8,900; ⊙, 13,700; ⊕, 17,800; ⊗, 24,000; ◒, 31,100; ●, 37,800.

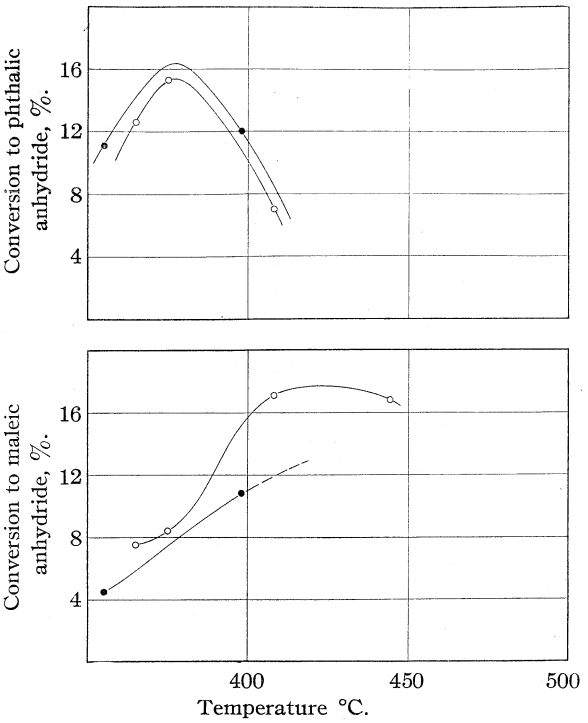


Fig. 4.—Catalyst from $H_4SiMo_3W_9O_{40}$ at space velocity: O, 24,000; ●, 29,200.

of the oxidation and that part of the carbon dioxide detected comes from the oxidation of carbon monoxide. Later expts. showed that these catalysts are slightly active for the oxidation of carbon monoxide.

Effect of Carbon Dioxide.—It was found that the addition of carbon dioxide to the air-naphthalene mixture suppressed the formation of maleic anhydride and increased the amount of phthalic anhydride. Using the catalyst from 12-molybdo-silicic acid at 496°, space velocity 24,000 and an air/carbon dioxide ratio of 6/1, 53.8% of the naphthalene was converted to phthalic and 14.1% to maleic anhydride. This represents an increased phthalic yield of 13% over a run under the same conditions with pure air.

Oxidation of Phthalic Anhydride.—Weighed samples of phthalic anhydride were vaporized into the air stream and passed over the catalyst from 9-molybdo-3-tungsto-silicic acid under conditions comparable to those in the oxidation of naphthalene. The results of these experiments are presented in Table II (vol. of catalyst was 2 cc.).

TABLE II

Temp., °C.	Space velocity	Phthalic anhydride, g.	Phthalic anhydride: Not oxidized, %	Phthalic anhydride: Converted to maleic, %	Burned, %
485	24,000	0.2608	56	17.6	26.4
490	36,000	.2525	68	10.0	22.0
492	51,000	.3110	73	8.1	18.9

Oxidation of Naphthoquinone-1,4.—Because it was suspected that naphthoquinone-1,4 might be an intermediate product in the formation of phthalic anhydride, small weighed samples were vaporized and oxidized over the 9-molybdo-3-tungsto-silicic acid catalyst as above. The amount of complete combustion at 500° and s. v. 24,000 was three times as much as naphthalene gave under the same conditions and the yield of phthalic anhydride was much smaller. These experiments seem to indicate that naphthoquinone-1,4 is not an important intermediate between naphthalene and phthalic anhydride.

Discussion of Results

The experimental results from this work seem to throw little new light on the mechanism of the catalytic oxidation of naphthalene. It seems likely that only a small part of the naphthalene is oxidized to phthalic anhydride via naphthoquinone-1,4. Possibly the other naphthoquinones, 1,2 and 2,6, may be intermediates, but the first decomposes at the melting point and the second was not readily obtainable, so neither could be

TABLE III

Catalyst	Temp., °C.	Space velocity	% Conversion to Phthalic	Maleic	Complete combustion
12 Mo	523	29,000	54.0	7.2	15.2
9 Mo–3 W	495	42,000	61.6	11.7	....
6 Mo–6 W	438	37,800	50.5	14.9	27.7
3 Mo–9 W	375	24,000	15.3	8.4	Very high
12 W	410	Any or all	Practically complete combustion		

tested. It may also be concluded that perhaps all of the maleic anhydride results from the oxidation of phthalic anhydride and that with a given catalyst the amount of maleic is a function of the space velocity. If the oxidation data for $H_4SiMo_9W_3O_{40}$ at 495° are plotted against space velocity it can be seen that decreasing the time of contact increases the yield of phthalic at the expense of the maleic anhydride. At the same time the amount of complete combustion is essentially unchanged. This last fact together with the results from oxidizing phthalic anhydride seems to indicate that phthalic and maleic anhydrides are burned at approximately the same rate and that the reaction is not just a series of steps leading finally to complete oxidation.

The effect of catalyst composition is summarized in Table III, giving conditions for optimum yields.

It may be seen that the effect of increasing the ratio of tungsten to molybdenum in these catalysts is to lower the temperature for optimum yields of phthalic anhydride. The catalyst 9 Mo–3 W gives a maximum yield of 61.6% phthalic anhydride, which is considerably better than the 54% for 12 Mo, at a temperature which is 28° lower. These two effects can hardly be explained by assuming a mixture of crystals of 12 Mo and 12 W and constitute the strongest indication that the catalysts were prepared from mixed acid ions.[7]

Summary

1. A series of catalysts has been prepared from heteropoly acid crystals containing tungsten and molybdenum.

2. The activities of these catalysts have been studied for the partial oxidation of naphthalene.

3. The catalyst from $H_4SiMo_9W_3O_{40}$ gave considerably higher conversion to phthalic anhydride than either of the parent acids, $H_4SiMo_{12}O_{40}$ or $H_4SiW_{12}O_{40}$.

4. The addition of carbon dioxide to this air oxidation reaction improved the yield of phthalic and decreased the yield of maleic anhydride.

6. The catalyst from $H_4SiMo_9W_3O_{40}$ was employed in the oxidation of phthalic anhydride, naphthoquinone-1,4 and carbon monoxide.

(7) An unsuccessful attempt was made to obtain more direct evidence for the existence of mixed acid ions by means of their ultraviolet absorption spectra.

BALTIMORE, MARYLAND RECEIVED MAY 11, 1942

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF CALIFORNIA]

The Catalytic Interchange of Groups in Aliphatic Amines. I

BY KENZIE NOZAKI

A number of reactions are known in which the groups attached to a given kind of atom are exchanged between molecules under the influence of certain metal halide catalysts. Two thoroughly studied examples are the migration of alkyl groups in benzene derivatives,[1] and the redistribution of organo-metallic substances, recently investigated by Calingaert and co-workers.[2] The reactions so far observed have been confined almost exclusively to the exchange of groups attached to either carbon or metals. In this paper we wish to report a case where groups attached to nitrogen are exchanged.

It was found from preliminary experiments that when aliphatic amines are heated in the presence of metal halide catalysts, the alkyl groups and the hydrogen atoms attached to the nitrogen atom may be redistributed. In this redistribution process, all the possible combinations of the alkyl groups and the hydrogen atoms with the nitrogen atom occur. Calingaert and co-workers found similar results with the metal alkyls. Since the

(1) (a) Jacobsen, *Ber.*, **18**, 338 (1885); (b) Buddeley and Kenner, *J. Chem. Soc.*, 303 (1935); (c) Moyle and Smith, THIS JOURNAL, **59**, 1417 (1937).

(2) Calingaert and co-workers, *ibid.*, **61**, 2748 (1939); **63**, 947 (1941).

interconversion of amines is of practical as well as of theoretical importance, it seemed worth while to study the reaction. In this paper some of the work which has so far been carried out is reported.

Experimental Results

Much of the work reported in this paper involves the use of di-*n*-butylamine, which was chosen for study because it is relatively inexpensive, has a moderately high boiling point, and can readily be separated from *n*-butylamine and tri-*n*-butylamine by fractional distillation.

Characteristics of the Reaction.—The reaction described in this paper is apparently free of side reactions below 200°. Above this temperature a slow reaction occurs which produces a high boiling product. However, in all runs reported in this paper, the amount of this reaction was negligible. This side reaction, which is being studied further, is believed to be an alkylation of the alkyl groups of the tertiary amine.

During redistribution, the alkyl groups do not undergo the structural rearrangements which are often observed in Friedel–Crafts reactions.[3] Thus, careful observation of boiling points and the preparation of picrate derivatives has indicated that whenever a *n*-butylamine was taken initially, the reaction products were *n*-butylamines and ammonia. The absence of rearrangement within the alkyl groups during the redistribution of organometallics has been reported.[4]

Experiments in Open Vessels.—Experiments were first carried out in which di-*n*-butylamine was heated with a catalyst at atmospheric pressure. Under these conditions the ammonia which was formed in the reaction escaped and was lost. Thus equilibrium was never reached. However, the amount of tri-*n*-butylamine found at the end of any period of heating gave an indication of the amount of redistribution which had occurred.

In Table I are listed the results obtained when di-*n*-butylamine was refluxed with four different substances. It is observed that sulfuric acid has no catalytic effect and that the order of the catalytic activity of the metal halides, $AlCl_3 > FeCl_3 > ZnCl_2$, is the same as has been found for the Friedel–Crafts and allied reactions. Since aluminum chloride was the best catalyst, it was used in all subsequent work. It should be mentioned that di-*n*-butylamine heated alone in a sealed tube at 300° for several hours showed no evidence of redistribution or decomposition.

(3) (a) Ipatieff, Pines and Schmerling, *J. Org. Chem.*, **5**, 253 (1940); (b) Gilman and Calloway, THIS JOURNAL, **55**, 4197 (1933).

(4) Calingaert, Beatty and Soroos, *ibid.*, **62**, 1099 (1940).

TABLE I

THE ACTION OF DIFFERENT CATALYSTS ON DI-*n*-BUTYLAMINE

Catalyst	Moles of catalyst per mole of amine	Reflux time, min.	Composition of reaction products, mole per cent. $NH_2(C_4H_9)$	$NH(C_4H_9)_2$	$N(C_4H_9)_3$
$AlCl_3$	0.126	240	9.7	74.2	16.1
$FeCl_3$	.129	240	4.6	89.6	5.8
$ZnCl_2$	.124	240	2.1	95.7	2.2
H_2SO_4	.422	1500	0.0	100.0	0.0

In order to obtain some information concerning the nature of the reaction, experiments were carried out in which the dependence of the rate of redistribution on the catalyst concentration was determined. It was found that when the quantity of aluminum chloride added to a given amount of di-*n*-butylamine was doubled, the time necessary for a certain fraction to be converted into tri-*n*-butylamine was decreased to one fourth. For example, the periods of heating required at 164° to produce 0.0072 mole of tri-*n*-butylamine in mixtures in which 0.0075, 0.015 and 0.030 mole of aluminum chloride had been added initially to 0.119 mole of di-*n*-butylamine were one hundred and twenty, thirty and eight minutes, respectively. These results seem to indicate that the reaction is of second order with respect to aluminum chloride concentration.

Experiments were next conducted to determine the effect of time of heating upon the amount of redistribution. In Table II are summarized the results of several runs in which 0.252 mole of aluminum chloride was added per mole of di-*n*-butylamine and the mixture refluxed for the period given. It is observed that, although the rates of formation of *n*-butylamine and tri-*n*-butylamine were probably the same at the start of the reaction, the rate of formation of *n*-butylamine fell off much more rapidly with time than that of tri-*n*-butylamine, and eventually the concentration of *n*-butylamine started to decrease. Substitution of the data into integrated rate expressions indicated that the rate of tri-*n*-butylamine formation fell off much more rapidly with time than it should have if the reaction were of first order with respect to di-*n*-butylamine concentration. The results of run 7 indicate that a nearly complete conversion of di-*n*-butylamine to tri-*n*-butylamine may be obtained when the heating is continued for a considerable period.

TABLE II

THE ACTION OF ALUMINUM CHLORIDE ON DI-*n*-BUTYLAMINE AT THE BOILING POINT

0.252 mole of aluminum chloride added initially per mole of amine.

Run	Reflux period, min.	Composition of reaction products, mole per cent. $NH_2(C_4H_9)$	$NH(C_4H_9)_2$	$N(C_4H_9)_3$
1	8	4.7	89.4	5.9
2	30	8.5	79.7	11.8
3	60	10.8	73.3	15.9
4	120	16.4	61.1	22.5
5	255	15.8	49.3	34.9
6	360	12.2	45.7	42.1
7	1440	0.5	15.9	83.6

Although the temperature coefficient of the reaction was not determined, it was found that no redistribution occurred at room temperature. Only the starting materials could be isolated from mixtures of aluminum chloride and di-*n*-butylamine which had stood for ten days.

Experiments in Sealed Tubes.—In order to study the reaction further, experiments were conducted in sealed tubes. In this manner the presence of ammonia among the reaction products was shown. For example, upon heating a mixture containing 0.045 mole of aluminum chloride and 0.18 mole of di-*n*-butylamine at 250° for 1800 minutes, the products were found to consist of 20.4, 6.2, 26.8, and 46.6 mole per cent. of ammonia, *n*-butylamine, di-*n*-butylamine and tri-*n*-butylamine, respectively. It was also shown that the same four products could be obtained by heating a mixture of ammonia and tri-*n*-butylamine with aluminum chloride. Thus a mixture made up of 0.040 mole of aluminum chloride, 0.014 mole of ammonia and 0.16 mole of tri-*n*-butylamine was found to consist of 5.6, 1.4, 5.0 and 88.0 mole per cent. of ammonia, *n*-butylamine, di-*n*-butylamine and tri-*n*-butylamine, respectively, after being heated at 250° for 1800 minutes.

In order to obtain a comparison of the reactivity of the *n*-butylamines and the ethylamines, di-*n*-butylamine and diethylamine were mixed separately with aluminum chloride in a mole ratio of 4 to 1 and the mixtures were sealed in tubes. After being heated at 190° for 1440 minutes, the tube to which di-*n*-butylamine had been added was found to contain 29 mole per cent. of tri-*n*-butylamine, while the tube to which diethylamine had been added was found to contain only about 1 mole per cent. of triethylamine. Thus, there is a very large difference in reactivity between the two amines.

Discussion

The mechanism of the reaction reported in this paper probably involves the initial formation of complexes between the amine and the catalyst, in which the metallic atom of the catalyst shares the free pair of electrons of the nitrogen atom. The attachment of the catalyst undoubtedly weakens the other bonds of the nitrogen, giving polarized addition products of the type, $R^+—\overset{R}{\underset{R}{\ddot{N}}}:AlCl_3$. This view is strongly supported by the work of Meerwein and co-workers[5] on complexes between boron trifluoride and alcohols. These complexes of the structure, $R:\overset{H}{\ddot{O}}:BF_3$, were not only strong acids, but also good alkylating agents. It should be added that Dougherty[6] had suggested some time ago that polarized or ionized intermediates of the type, $\overset{+}{R}—\overset{-}{\ddot{Cl}}:AlCl_3$, were involved in the Friedel–Crafts reaction. It is not considered likely that actual ionization of an alkyl group as a cation occurs in our proposed complexes since there was no indication of rearrangement within a primary alkyl group such as *n*-butyl. According to the views of Whitmore,[7] a rearrangement to the secondary or tertiary form would be expected if an alkyl cation were formed.

Our work has indicated that the reaction is of second order with respect to aluminum chloride concentration. This suggests that two complexes, such as we have discussed above, are involved in the step during which exchange occurs. In this step a larger complex may be formed which is held together by the ability of each aluminum atom to attain a coördination number of five[8] by sharing a pair of electrons of a chlorine atom attached to the other aluminum atom. Evidence for the existence of large complexes made up of two molecules of aluminum halide and two organic molecules has been supplied by Kohler[9] and more recently by Norris and co-workers.[10] Assuming that such complexes are involved, the role of the catalyst is not only to polarize the amine molecules, but also to hold them close enough together so that exchange may occur.

(5) (a) Meerwein, *Ber.*, **66B**, 411 (1933); (b) Meerwein and Pannwitz, *J. prakt. Chem.*, **141**, 123 (1934).

(6) Dougherty, THIS JOURNAL, **51**, 576 (1929).

(7) Whitmore, *ibid.*, **54**, 3274 (1932).

(8) Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, p. 362.

(9) Kohler, *Am. Chem. J.*, **24**, 385 (1900).

(10) (a) Norris and Ingraham, THIS JOURNAL, **62**, 1298 (1940); (b) Norris and Wood, *ibid.*, **62**, 1428 (1940).

Experimental

Materials.—The amines were all Eastman Kodak Co. products, and they were carefully fractionated before use. The aluminum chloride, ferric chloride, zinc chloride and sulfuric acid were anhydrous C. P. products and were used without further purification.

Experiments in Open Vessels.—The catalyst and amine were mixed, with considerable evolution of heat, and the resulting mixture was heated under reflux. In almost every case a two-phase system was obtained. In experiments for which a constant temperature was desired, a large electrically heated oil-bath was used and the solution was frequently shaken. At the end of a definite period the mixture was cooled in an ice-bath and a considerable excess of aqueous sodium hydroxide was added. The amine layer was separated, washed with water, dried over potassium carbonate and finally fractionated.

For large quantities a fractionating column, 40 cm. long, 13 mm. i. d., electrically heated, and packed with glass helices was used. However, many runs were made using only about 30 cc. of solution, and in such cases a Vigreux column, 25 cm. long, and of 8 mm. i. d., was used. The column was very efficient, and, in general, a reflux ratio of 30 to 1 was maintained.

Experiments in Sealed Vessels.—Pyrex bomb tubes were used in this work. Ammonia, if required, was added to mixtures by condensing the gas in the tubes, using a dry ice–alcohol bath. Sealed tubes containing the reactants were heated in an electric furnace. After heating, the tubes were cooled in a dry ice–alcohol bath and then opened. The contents of the tubes were poured into an excess of cold aqueous sodium hydroxide, and the amine layer was separated. The aqueous layer was extracted twice with ether, the ether extracts being added to the amine layer. The aqueous layer was then distilled into a standard hydrochloric acid solution and the ammonia concentration was determined from the amount neutralized. The amine–ether fraction was dried over potassium carbonate and fractionated, using one of the columns described above.

Preparation of Picrates.—Although the boiling points of the amine fractions indicated that no rearrangements within the alkyl groups had occurred during redistribution, a check was desirable. This was done by preparing the picrates of amine fractions obtained by redistribution. Mixed melting point determinations with picrates prepared from amines obtained from the Eastman Kodak Co. indicated that no changes had taken place within the alkyl groups. The picrates were prepared by mixing 1 g. each of picric acid and the amine and heating until a brown solution was obtained. Six cc. of ethanol was then added and the mixture cooled. The fine yellow crystals which formed were filtered, washed and finally recrystallized from ethanol. The picrates of *n*-butylamine, di-*n*-butylamine and tri-*n*-butylamine melted at 151, 59 and 105°, respectively.

Summary

It has been found that when aliphatic amines are heated with metal halide catalysts, the groups attached to the nitrogen are redistributed. This redistribution reaction has been studied with respect to the catalytic activity of several substances and the order of the reaction with respect to catalyst concentration. The mechanism of the reaction has been discussed.

DAVIS, CALIFORNIA RECEIVED FEBRUARY 24, 1942

[COMMUNICATION NO. 827 FROM THE KODAK RESEARCH LABORATORIES]

Some Effects of Solvents upon the Absorption Spectra of Dyes. I. Chiefly Polymethine Dyes

BY S. E. SHEPPARD, P. T. NEWSOME AND H. R. BRIGHAM

Introduction

To examine the effect of solvents upon the absorption spectrum of a substance, it is desirable that the spectrum should be measured originally for the substances present as a gas at low pressures and at temperatures comparable with those of the solutions. This is far from easy with dyes, which possess rather large and complicated polyatomic molecules. Low pressures and rather high temperatures are required to volatilize them. Also, they are very liable to decomposition (pyrolysis) with formation of colored (yellow to brown) reaction products.

Experimental

The dyes in which we are primarily interested are photographically active sensitizing and desensitizing dyes such as cyanines (polymethine dyes), and xanthene and phenazine derivatives. Most of these are salts, and, while it was found possible to volatilize (sublime) a number of them, there was generally too much decomposition for satisfactory spectral measurement. Certain non-saline *merocyanines* first prepared by Brooker[1] could be volatilized at low pressures without contamination. Because of the low pressures necessary, a quite long optical path was used, *viz.*, a 15-ft. tube, operated as an electrical resistance heater furnace by wrapping it with nichrome wire and asbestos (*cf.* Fig. 1).

(1) L. G. S. Brooker, U. S. Patents 2,177,401-2-3.

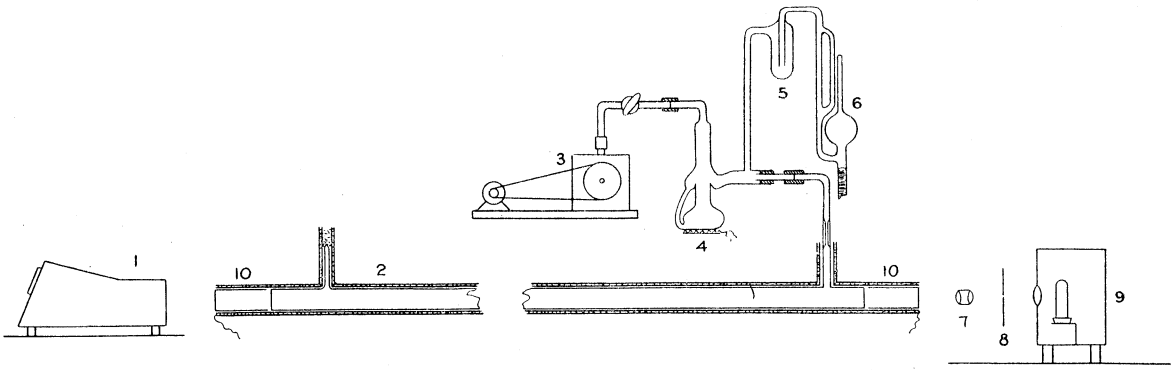


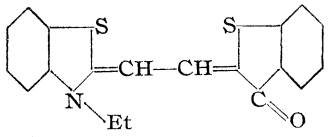
Fig. 1.—Diagram of vapor absorption apparatus: 1, spectrograph; 2, absorption tube with heating coils and insulation; 3, Hyvac pump; 4, condensation pump; 5, trap; 6, McLeod gage; 7, lens; 8, diaphragm; 9, light source; 10, end guards.

The total pressure was about 0.1 μ; the partial pressure of the dye was not measured. Consequently, we were unable to measure actual extinction coefficients, defined as

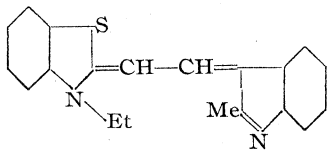
$$\epsilon_\lambda = \frac{1}{cd} \log \frac{I_0}{I}$$

where c = molar concentration, and d = thickness in cm.

However, the envelope of the band spectrum could be measured spectrophotometrically in terms of optical density; after analysis, the relative extinctions of the band maxima were obtained.

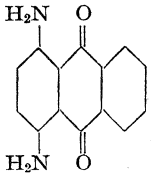


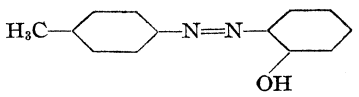
XXIII



XXXI

Beside the *merocyanines*, XXIII and XXXI (see above), measurements in the gas phase were made of *1,4-diaminoanthraquinone*, of *p-toluidine azo-β-naphthol*,





and of *indigo*. It is to be noticed further that, while absorption measurements were made at low pressures, the *temperatures* were much higher than those in the solutions. This is more or less inevitable, since rough calculation shows that to obtain an optical density of 1.0 at 25°, lengths of tube of the order of 10^7 to 10^{16} would be necessary.

Previous measurements on some vaporized dyes (indigo, alizarin, dianilidoanthraquinone) have been made by Koenigsberger and Küpferer.[2]

Representation and Analysis of Extinction Curves

A common graphic representation is a plot of $\epsilon_\lambda \sim D_\lambda$ against λ (wave length in mμ or Å.). Curves of this type are shown for gaseous *merocyanine* (dye XXIII) and *1,4-diaminoanthraquinone* at different temperatures (*cf.* Fig. 2). Similar curves for *merocyanine* (dye XXIII) dissolved in various solvents are shown in Fig. 3. However, for comparison and analysis of the effects of structural and environmental changes, there are many advantages in taking reciprocal values of the wave length as abscissas, as wave numbers $1/\lambda$ in cm.$^{-1}$. The use of log ϵ as ordinate is frequently useful, either to obtain compactness, or to enhance the apparent strength of minor bands[3]; ϵ_λ is a quantity having no dimensions, and representing the *probability* of the event occurring at the value λ.

The curves shown in Figs. 2 and 3 are only the envelopes of a definite group of related bands; in some cases, one or more of the subsidiary peaks are clearly defined; in others, they may be present only as a hump or shoulder, or merely as a strongly marked asymmetry of the extinction curve. Changes of environment may affect the relative sharpness and strength of the individual bands.

Such band complexes may be analyzed by semi-empirical methods, assuming that the ϵ ($\sim$ prob-

(2) J. Koenigsberger and K. Küpferer, *Ann. Physik*, [4] **37**, 601 (1912).

(3) G. N. Lewis and M. Calvin, *Chem. Revs.*, **25**, 310 (1939).

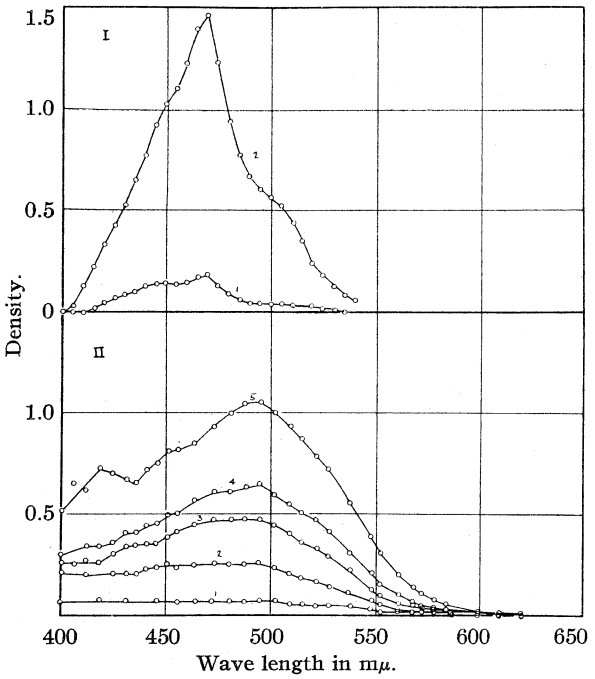


Fig. 2.—I, Merocyanine gas at 1, 228°; 2, 250°. II, 1,4-diaminoanthraquinone gas at 1, 135°; 2, 154°; 3, 168°; 4, 183°; 5, 195°.

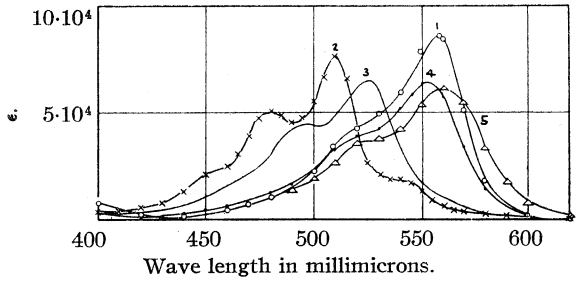


Fig. 3.—Merocyanine in 1, methyl alcohol; 2, *n*-hexane; 3, carbon tetrachloride; 4, quinoline; 5, methylene iodide.

ability of absorption) values are distributed about a maximum, usually according to a Gaussian function. We have used the method originally introduced by Henri,[4] and by Henri and Bielecki.[5] Their function

$$\epsilon_\nu = ke^{-[(\nu_0-\nu)^2]/2a^2} \text{ or } y = ke^{-x^2/2a^2}$$

where k is the ordinate, ϵ_{ν_0}, at the center of the distribution curve, *i. e.*, when $x = \nu_1 - \nu = 0$ and $2a$ is the breadth at a value 0.606 k, and ϵ_ν = the molar extinction coefficient.

It was observed that in the organic solvents employed, Beer's law is generally followed by these dyes.

In Figs. 4 and 5 are presented comparative extinction curves for the *merocyanine* dye—and *diaminoanthraquinone*—in which the analyzed components of the envelope are indicated.

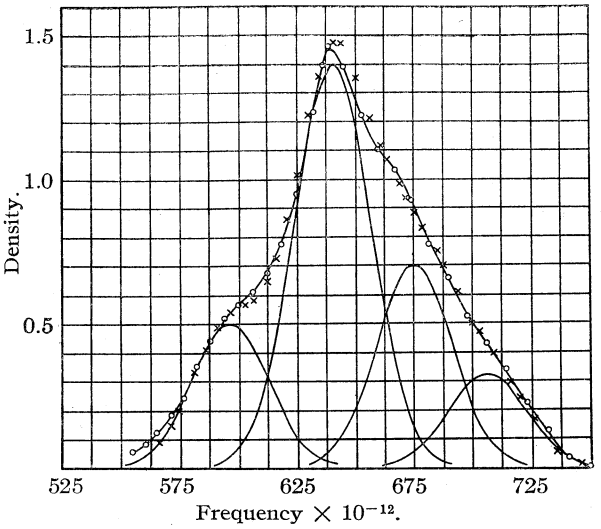


Fig. 4.—Analysis of merocyanine absorption.

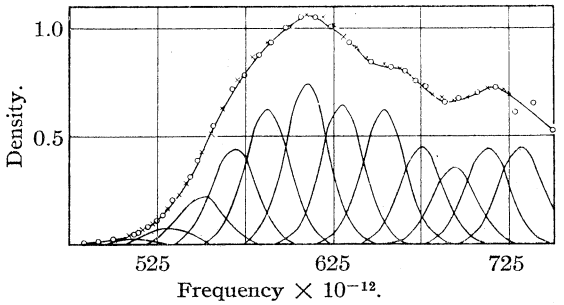


Fig. 5.—Analysis of 1,4-diaminoanthraquinone absorption (gaseous).

The data indicate that the band group persists as a whole in different media, and is displaced as a whole, not only with the merocyanine XXIII, a polymethine dye, but with diaminoanthraquinone, representing a quite different class. This conclusion is supported by graphic representation of the intensity ratios in the spectrum shown elsewhere.[6]

The persistence of this group of bands, adjacent to the band of maximum intensity, in the gaseous state, and in organic solutions, wherein Beer's law is followed, is of considerable importance. In aqueous solutions the ratio of intensities of the bands may change with the concentration. The auxiliary bands have been attributed to polymers of the single dye molecules.[7] But it is evident that this is incorrect, since these bands are

(4) V. Henri, *Physik. Z.*, **14**, 516 (1913).
(5) J. Bielecki and V. Henri, *Comp. rend.*, **158**, 1114 (1914).
(6) S. E. Sheppard, R. H. Lambert and R. D. Walker, *J. Chem. Phys.*, **9**, 96 (1941).
(7) G. Scheibe, *Kolloid-Z.*, **82**, 1–14 (1938).

definitely present both in the gaseous state and in organic solutions following Beer's law. They correspond, therefore, to electronic transitions proper to the individual molecule, and all that can be said is that aggregation or polymerization may change the relative probabilities of these transitions.

The wave-number differences between successive bands in the polymethine dyes range from 900 cm.$^{-1}$ to 1700 cm.$^{-1}$; these are of the same order as such differences in the polyenes and linear benzenes.

Effect of Temperature on Solutions

A considerable range of temperature is open to study with solutions of dyes in organic solvents. A mixture of ethyl alcohol and ether is a good solvent for many cyanine (polymethine) dyes. The most evident effect is to sharpen the band components as the temperature is lowered, or conversely, increased diffusion as it is raised. This can be expressed to some extent quantitatively as the change of ϵ_{max} with temperature. Here it is most useful to plot log ϵ_{max} against $1/T$, where T is the absolute temperature, and characteristic curves are shown for several cyanine (polymethine) dyes (Fig. 6). The increased sharpening at lower temperature is due to reduction of rotational and vibrational energies, which cause the diffusion of the individual band. As very low temperatures are approached, this elimination becomes less, and the sharpening—shown by increase of ϵ_{max} and reduction of the half-width of the band—asymptotically approaches a limit, or a maximum. This latter phenomenon is very possibly due to separation of the dye from solution, but further study is required.

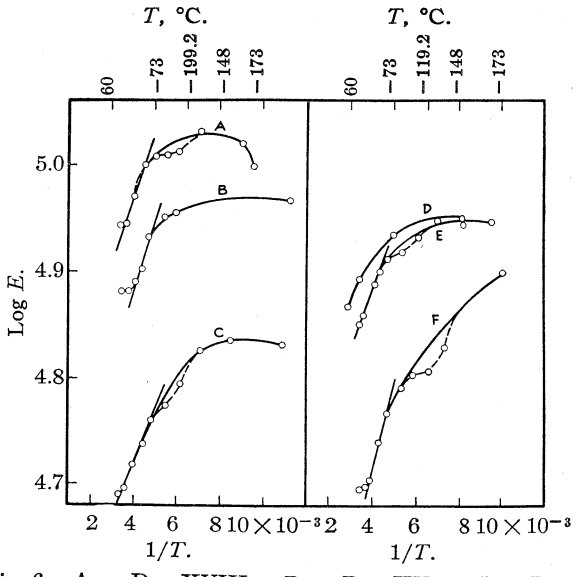


Fig. 6.—A = Dye XVIIIa; B = Dye XVIa; C = Dye XIXa; D = Dye Va; E = Dye XXa; F = Dye XVIIa.

There is liable to be a specific effect in aqueous solution, namely, a redistribution of intensities in the band complex. In consequence of this, the extinction coefficient ϵ_{max} of the long wave band tends to *increase* with rising temperature.

Comparison of Solvent Effects

There are at least two parameters for which solvent effects on absorption could be evaluated, *viz.*, in respect of band strength $\int \epsilon dv$ and band position—ν_{max} or λ_{max}. In regard to the former, Chako[8] made a comparison of expressions for band strength for a large variety of organic substances, but not including dyes, in various solvents. The principal expression, derived from classical theory, evaluates the influence of neighboring molecules due to the Lorentz–Lorenz force, *i. e.*, the force coming from the polarization of the surrounding molecules. According to this, if F_s is the transition probability in solution, and F_g, that in the gas state, then

$$F_s = F_g\left(\frac{9}{(n_0^2+2)^2}\right)$$

where n_0 is the refractive index of the solvent. Chako concluded from his review that "it is impossible to account for the influence of the solvent through the Lorentz–Lorenz force."

If the width of the absorption band in the different solvents is constant, we can substitute ϵ_{max} for $\int \epsilon dv$, and should have

$$\epsilon_{max}\frac{9}{(n_0^2+2)^2} = \epsilon_{gas} = \text{constant}$$

This has been computed for the merocyanine in various solvents having values of n_0 ranging from 1.327 to 1.576. The calculated values of ϵ_{gas} varied from 3×10^4 to 6×10^4. Some improvement occurs by evaluating the band strength F_s, but far from sufficient to account for 100% variation of ϵ_{gas}.

Displacement of Bands

In 1878 Kundt[9] concluded that with increasing (partial) dispersion of the solvent the absorption maximum of a dye is shifted toward longer wave lengths. Usually, the refractive index n_D is

(8) N. Q. Chako, *J. Chem. Phys.*, **2**, 644 (1934); *cf.* also, R. S. Mulliken and C. A. Rieke, "Reports on Progress in Physics," Vol. VIII, 1941, pp. 234–236.

(9) A. Kundt, *Ann. der Physik und Chemie*, **4**, 34–54 (1878).

TABLE I

DISPLACEMENT $\Delta\nu$ IN CM.$^{-1}$ CALCULATED FROM $\Delta\nu = a\,(1 - 1/K)$

Solute	Vapor ν_{max} in cm.$^{-1}$	Solvent C_6H_{14} obs.	C_6H_{14} calcd.	C_6H_{12} obs.	C_6H_{12} calcd.	CCl_4 obs.	CCl_4 calcd.	C_6H_6 obs.	C_6H_6 calcd.	CS_2 obs.	CS_2 calcd.
Benzene	39540	278	320	278	350	440	380	365	400		
Diphenyl-octatetraene	27933	2566	2760					3166	3450	4033	3710
p-Toluidine–azo-*p*-naphthol	25000	3261	3100			3724	3660	3495	3880	4167	4170
Merocyanine XXIII	21276	1668	1920	1859	2110	2228	2260	2408	2400	2928	2570
Cyanine IVb	(18692)					1240	1260	1240	1350	1539	1450

considered instead of the dispersion. Numerous exceptions were observed, but chiefly for the ultraviolet absorption bands of substances other than dyes.

However, we found that if we definitely separate non-polar from polar solvents, Kundt's rule holds quite well, not only for dyes but for certain hydrocarbon prototypes, such as the polyenes, polyphenyls, and *lin*-benzenes. In many cases, the relation of γ_{max} to n_D is approximately linear —including the gaseous state with $n_D = 1.00$ (*cf.* Fig. 7). A relation between λ_{max} and the *dielectric constant* K was examined also for the merocyanines in non-polar media.

Simple electrostatic considerations[10] suggest that the change of energy required to displace an electron in a medium of dielectric constant K compared with that in a vacuum would be given by the relation

$$\Delta E = \frac{e}{2r^2}\left(1 - \frac{1}{K}\right)$$

Hence, for the displacement of an absorption band in a solvent of dielectric constant K, we should have $\Delta\nu = a(1 - (1/K))$, for constant r. Keeping to non-polar solvents, values are given in Table I for near ultraviolet bands for aromatic hydrocarbons, and a diphenyl polyene, and for visible bands of certain dyes.

It is thought that somewhat better agreement might be obtained if variation of a, the molecular radius parameter, could be allowed for. One or two calculations for benzene, using the volume change on mixing, indicate this.

Effect of Polar Moment

An over-all survey of our data for the merocyanine seemed to indicate that no direct and simple relation between the band displacement and the polar moment could be observed. However, on analyzing the results in terms of families of homologous compounds, in general, of increasing chemical complexity, certain regularities became apparent, as exhibited in Tables II, III, IV, and V. The displacement changes but slightly in this series and accords with the change of dielectric constant.

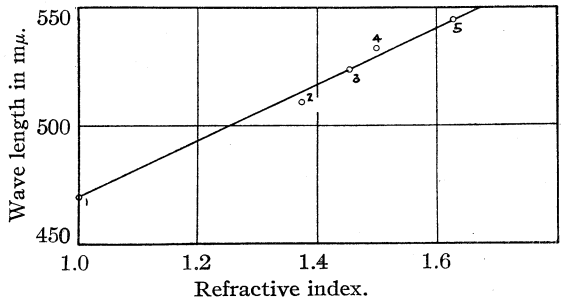


Fig. 7.—1, Merocyanine (gas) *in vacuo;* 2, in *n*-hexane; 3, in CCl_4; 4, in C_6H_6; 5, in CS_2 (non-polar solvents).

TABLE II

ALIPHATIC HYDROCARBONS

Substance	λ_{max} in mμ	$\Delta\nu$ in cm.$^{-1}$	n_D	K	μ
n-Pentane	510	1668	1.358	1.80	0
n-Hexane	510	1668	1.375	1.87	0
n-Octane	514	1821	1.394	1.96	0
n-Decane	515	1859	1.409	1.95	0
n-Dodecane	515	1859	1.423		0
n-Tetradecane	517	1934	1.430		0
Cyclohexane	515	1859		2.05	0
Carbon tetrachloride	524	2192	1.458	2.20	0
Carbon disulfide	545	2928	1.629	2.65	0

TABLE III

ALKYL ETHERS

Ether	λ_{max}	$\Delta\nu$ in cm.$^{-1}$	n_D	K	$\mu \times 10^{18}$
Diethyl	520	2045	1.351	4.33	1.12
Dibutyl	520	2045	1.398		

TABLE IV

ACETATES

Acetate	λ_{max}	$\Delta\nu$ in cm.$^{-1}$	n_D	K	$\mu \times 10^{18}$
Methyl	530	2408	1.361	7.30	1.74
Ethyl	530	2408	1.374	6.40	1.81
n-Propyl	530	2408	1.384	6.30	1.78
n-Butyl	530	2408	1.394	5.0	1.84
n-Amyl	530	2408	1.405	5.1	1.91

(10) A. F. Joffe, "The Physics of Crystals," McGraw-Hill Book Co., Inc., New York, N. Y., 1928, p. 140.

TABLE V

ALKYL KETONES

Ketone	λ_{max}	$\Delta\nu$ in cm.$^{-1}$	n_D	K	$\mu \times 10^{18}$
Acetone	535	2584	1.356	21.4	2.74
Diethyl	535	2584	1.393	17.3	2.74
Di-*n*-propyl	535	2584	1.407	12.6	2.73
Methyl-*n*-hexyl	535	2584	1.416	10.7	2.70

To these series the alcohols (Table VI) form an exception in the sense that they give a larger displacement while having a lower polar moment than the acetates, ethers and ketones.

TABLE VI

ALIPHATIC ALCOHOLS

Substance	λ_{max}	$\Delta\nu$ in cm.$^{-1}$	n_D	K	$\mu \times 10^{18}$
Methanol	558	3355	1.327	33.1	1.68
Ethanol	555	3258	1.360	26.5	1.70
n-Propanol	555	3258	1.383	26.0	1.66
n-Butanol	555	3258	1.397	17.8	1.65
Iso-amyl alcohol	555	3258	1.408	15.3	1.70
n-Heptanol	555	3258	1.425	6.7	1.71

It is interesting to compare the values for aliphatic with aromatic groups of the same character.

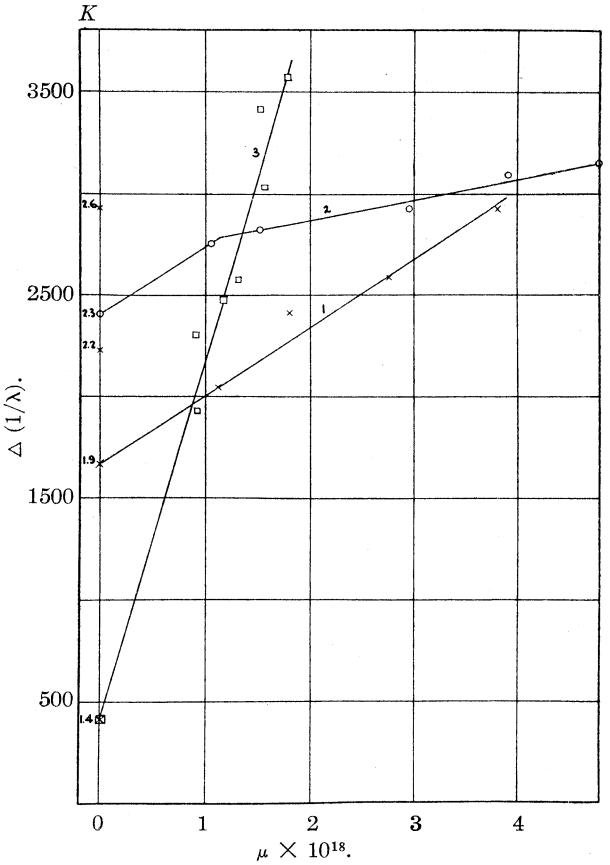


Fig. 8.—Merocyanine in polar solvents: 1, aliphatic series; 2, aromatic series; 3, amino bodies.

TABLE VII

	Aliphatic ν in cm.$^{-1}$	Aliphatic μ	Aromatic ν in cm.$^{-1}$	Aromatic μ	$\delta(\Delta\nu)$ cm.$^{-1}$
Hydrocarbon	19600	0	18868	0 to 0.4	732
Ether	19231	1.12	18519	1.05	712
Ketone	18692	2.73	18348	2.74	344
Alcohol	18018	1.70	17689	1.69	329

A fairly regular progression of the displacement with the polar moment was observed with the amines (including certain heterocyclic bases—piperidine, pyridine).

TABLE VIII

DYE XXIII IN AMINES AND NITROGENOUS BASES

Solvent	μ	λ	$1/\lambda$	$\Delta 1/\lambda$
(Nitrogen)[a]	0		20876	400
Triethylamine	0.8	517	19342	1934
Diethylamine	1.0 to 0.90	527	18976	2300
Piperidine	1.17	532	18797	2479
n-Amylamine	1.30	532	18797	2479
n-Butylamine	1.30	532	18797	2479
n-Propylamine	1.30	532	18797	2479
Ethylamine	1.30	535	18692	2548
Ammonia	1.50	548	18248	3028
Aniline	1.54	560	17857	3419
o-Chloroaniline	1.77	565	17699	3577
α-Picoline	1.72	542	18450	2826
Quinoline	2.16	553	18083	3193
Pyridine	2.11	550	18182	3094

[a] Values for N_2 (nitrogen) by extrapolation.

A plot of the results so far is shown in the following graph (Fig. 8). This exhibits the following features: (i) progressive increase of the displacement Δ with K, (dielectric constant) for non-polar liquids ($\mu \cong 0$); (ii) progressive increase of Δ with μ for the aliphatic series Hydrocarbon → Ethers → Alkyl acetates → Ketones → Nitro·C_nH_{2n+1}. The alcohols form an outstanding exception. There is a distinct tendency for the sequence to give either two lines of different slope or perhaps to approach a "saturation" value. (iii) Starting with benzene ($\mu = 0$), the same types of compounds give, in part, a linear array of the same slope, but with a constant difference. Again, there is a well-marked trend or branch, of lower slope; the convergence of this with the "aliphatic" series, at the nitro-anisole "value" may be coincidental. It seems possible, however, that with the higher bond moments, *e. g.*, $>C(-NO_2)$, this becomes of preponderant effect, and that a "saturation" limit is approached. (iv) The series of amines, $N<^{R_1}_{R_2}_{R_3}$ (including NH_3 and $HN = C_5H_{10}$ (piperidine), gives a linear series; the line extrapolated back to $\mu = 0$ gives a

displacement corresponding approximately with that to be expected for liquid nitrogen (K = 1.47). While these results indicate definite regularities, it must be noticed that very definite exceptions occur. Thus, the *alcohols* give values quite out of proportion to their mean (molecular) moments: Aliphatic $\mu = \sim 1.70$ $\Delta = 3260$ cm.$^{-1}$, aromatic $\mu = \sim 1.70$ $\Delta = 3240$ cm.$^{-1}$. (Roughly as though the aliphatic alcohols had *three* times the monomeric moments, the aromatic, *twice* the measured moment.) Another group of related compounds which appears at first to defy reduction to order is that of the alkyl halides. The measurements so far obtained are given in Table IX.

TABLE IX

HALIDES OF METHANE AND ETHANE

	ΔCl	ΔBr	ΔI
CH_3X	..	992	2757
CH_2X_2	2757	3094	3419
CHX_3	2928	2479	..
CX_4	2228	..	..
CH_3CH_3	..	..	..
CH_3CH_2X	2408	2300	2689
CH_3CHX_2	2584	2757	..
CH_3CHX_3	2408	..	..
CH_2XCH_2X	2757	2757	..
CH_2XCHX_2	2826	2995	..
CH_2XCH_3	..	..	..
CHX_2CX_3	2654	..	..
CX_3CX_3	..	..	..

When these are plotted as functions of the average moments (best available values at 25°), it will be seen that something like a peculiar "shotgun pattern" is obtained. (The oblique line is the principal aliphatic line repeated from Fig. 9.) It would appear evident that very specific—even individual—combinations of the molecular forces are required to account for these results.

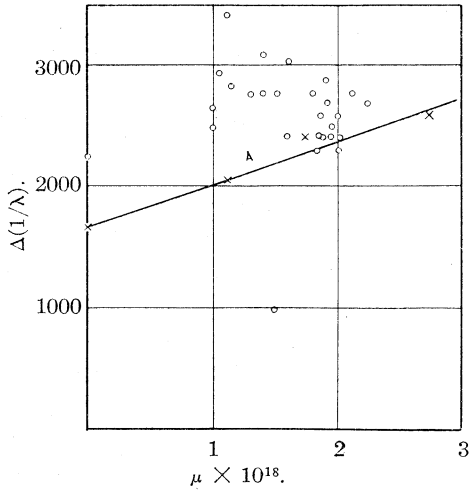


Fig. 9.—Merocyanine in alkyl halides: A, principal aliphatic curve.

Basicity and Acidity of Solvents

The avidity of a molecule for a proton (H^+ ion) is termed its basicity,[11] and, conversely, its facility in donating one to another molecule, its acidity. As is well known, quantitative measures of these values depend upon the solvent. For example, in water there is possible a pH range from 0 to 14; superacid solutions can be made in acetic acid plus acetic anhydride, but the relating of these to the water scale values is a matter of considerable uncertainty.

The relations of proton addition to the constitution and color of dyes is *per se* outside our subject.[12] However, two aspects of it affect the question of solvent influence, in particular with certain dyes which we have used.

Evidently a comparison of the basicities or acidities of our "solvents" obtained with these as "solutes" in a common, solvent medium, *e. g.*, water, or acetic acid will only give their relative order in the common medium. It will not give much, if any, information as to the absolute basicities or acidities of these solvent molecules in the presence only of their own congeners. It is none the less interesting to note that with two merocyanines (XXIII and XXXI) the displacement parameter varies in a very similar fashion with the (aquo) basicity figure.[13] The behavior of merocyanine XXIII with definitely acidic solutions and solvents may throw some light on the problem. First, in the series of media

$$\text{Water} \longrightarrow \text{Water: } \underset{\text{dilute}}{H_2SO_4} \longrightarrow \underset{\text{conc.}}{H_2SO_4} \longrightarrow \begin{cases} H_2SO_4 \\ SO_3 \end{cases}$$

the curves in Fig. 10 show a certain swing between two systems. Thus, in *water* the absorp-

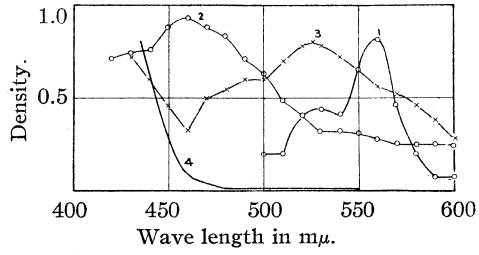
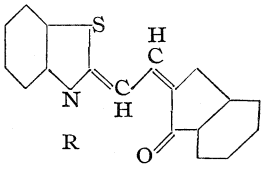


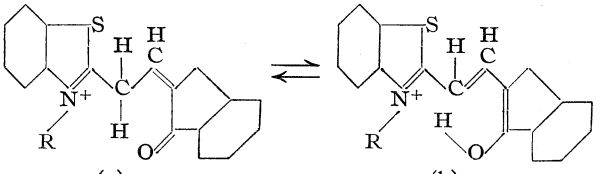
Fig. 10.—Absorption curves of merocyanine XXIII: 1, in water; 2, H_2O and H_2SO_4; 3, H_2SO_4; 4, H_2SO_4 and SO_3.

(11) J. N. Brönsted, *Z. angew. Chem.*, **43**, 229 (1930).
(12) G. Schwarzenbach, *Z. Elektrochem.*, **47**, 40–52 (1941).
(13) N. F. Hall, THIS JOURNAL, **52**, 5115 (1930).

tion curve is much the same as in alcohol or other hydroxylated solvent. And this is also the case *initially* in concentrated sulfuric acid, which is perhaps behaving as $O_2S(OH)(OH)$. However, on standing, the absorption system in the visible region disappears, to be replaced by a powerful system on the violet edge of the visible region and in the ultraviolet with its longest wave band at 4150 Å. By neutralization, the absorption in the visible region is restored, but to that in dilute sulfuric acid rather than to that in water alone. The absorption in *dilute* sulfuric acid is remarkable as giving a maximum at *ca.* 4600 Å. (see Fig. 10) which appears identical with that given by the dye in *formic acid*—but not in the other fatty acids.

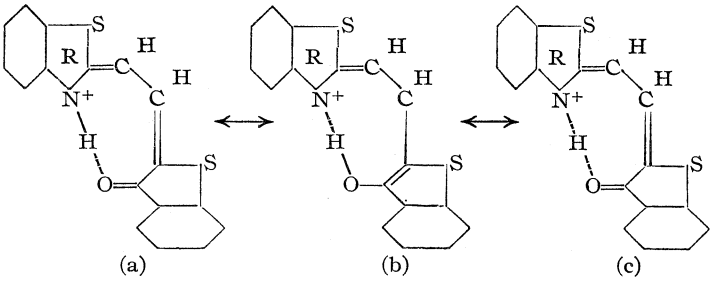
On considering the formula for merocyanine XXIII, it seems possible that the initial addition of a proton can give the alternative structures (a) and (b).





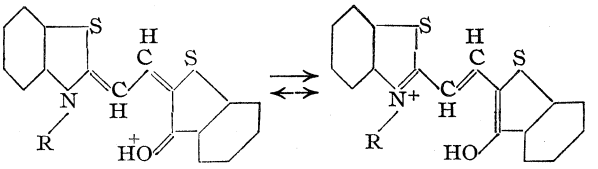
(a) (b)

And there might be actually resonance (mesomerism) between these structures, by which is developed the band at 4600 Å. in dilute sulfuric and in formic acid. M. L. Huggins has suggested the alternative possibility of the 8-ring shown below



(a) (b) (c)

with the same type of mesomerism over a wider circuit. This requires a slightly greater strain on the bond angles involved, to about 129°. Another configurational treatment is suggested in the following resonance scheme.



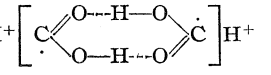
Owing to the instability of the $=OH^+$ grouping, the left-hand configuration would have considerably higher energy, and the passage from the merocyanine would involve "reversed halochromy"—hence the band at shorter wave length, 4600 Å. The behavior of the lower homologous fatty acids is interesting; the absorption curves are shown in Fig. 11. In order to remove traces of water, a small amount of acetic anhydride was added. It will be seen that the spectrum in formic acid is quite distinct from that in the higher homologs, while that in acetic acid shows a tendency to an intermediate type, with enhancement of a band at about 4800 Å. The position of the longest wave band, as shown in the table (Table X) is practically the same as that in the alcohols (588–555 mμ) so that these "associating" acids show the same tendency to behave as if having a much higher moment than that of the monomeric molecule. Usually it appears that the moments of the polymers in associated liquids are reduced or entirely internally compensated. It is interesting that abnormal "displacements" of the same order are produced by *ethyl acetoacetate, acetylacetone,* and *acetonyl acetone*—all liquids in which the existence of similar configurations, potentially mesomeric, is highly probable. This general similarity is brought out in Table XI.

TABLE X

MEROCYANINE XXIII IN FATTY ACIDS

Acid	λ_m in mμ		$\Delta\nu$	μ
Formic	460	..	..	(1.2)
Acetic	480	557	3350	1.4
Propionic		555	3258	1.74
n-Butyric		555	3258	1.4
n-Valeric		560	3419	(0.9)

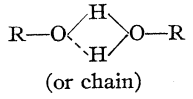
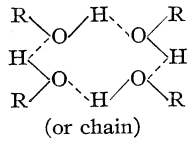
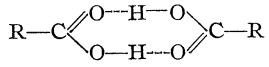
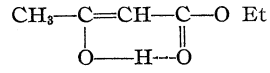
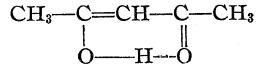
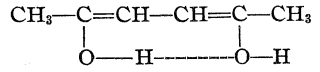
The "odd" behavior of formic acid is perhaps to be attributed to much higher "acidity" in the dimeric state, with ionization of the —CH and formation of dicarbeniate ions



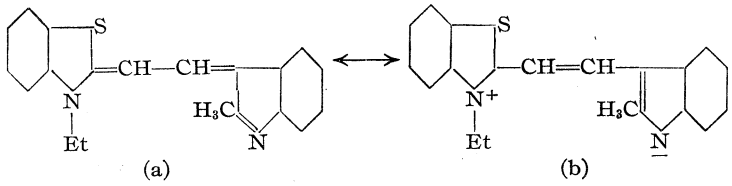
also, *ethyl acetoacetate,* if accounted as acetate ester, has a high moment—2.93 compared to 1.8.

TABLE XI

"HIGH" DISPLACEMENTS

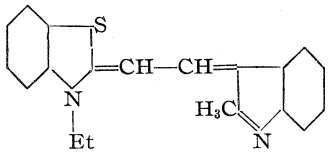
Substance	Tautomer or Polymer	Dipole moment μ	Δ Observed	Δ calcd. from μ
Water	 (or chain)	1.84	3419	2200
Alcohols	 (or chain)	1.70	3258	2300
Fatty acids		1.4 to 1.70	3258	2300
Ethyl acetoacetate		(2.93)	2757	2400
Acetylacetone		3.00	3193	2750
Acetonylacetone		2.8	2757	2680

Its "displacement" is about normal for its moment, but abnormal as an ester. Acetylacetone, so near in structure, has a slightly high moment as a ketone, but a "displacement" which is high both for the keto structure and for its moment.



Some Observations with Merocyanine Dye XXXI

We come now to some observations on a dye, representative of a class first prepared by Brooker, Sprague, Smyth and Lewis[14] which, while specifically a merocyanine, is especially interesting as being at the same time an ansolvo-base of an actual cyanine; Dye XXXI is



Brooker and his collaborators have shown that this base gives rise to "reversed halochromy," in that, on salt formation, by combination either with alkyl halide, or with acid (thus forming a cyanine), the main absorption shifts not to longer but to shorter wave lengths than for the base itself. To the base can be attributed two principal limit structures

(14) L. G. S. Brooker, R. H. Sprague, C. P. Smyth and G. L. Lewis, THIS JOURNAL, **62**, 1116 (1940).

Although having a very similar configuration to merocyanine XXIII, with the same length of conjugate chain between the key atoms in each case, the maximum absorption is very definitely dis-

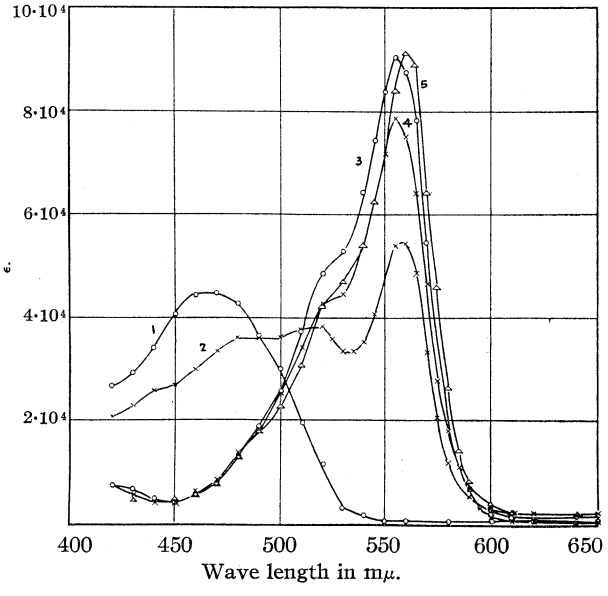


Fig. 11.—Merocyanine XXIII in fatty acids: 1, formic; 2, acetic; 3, propionic; 4, *n*-butyric; 5, *n*-valeric.

placed to higher frequencies than that for XXIII, a fact which may be attributed to the lower stability of the negatively charged N atom in (b) compared with the negatively charged O atom of XXIII. While XXXI can be volatilized at low pressures, so far we have not succeeded in obtaining a satisfactory value for the absorption curve *in vacuo* because of too considerable decomposition. At present actual "displacement" values cannot be given for the solvent influence, but instead the absolute values of $1/\lambda_m$ may be compared; and, owing to the complexity of the absorption spectrum, it is not always easy to be sure that the comparison *is* being made for the same member of the band complex.[15] The largest complicating factor is the "acidity" of the solvent, whether derived from extrinsic hydrogen ions (acid) or the intrinsic "acidity" of the liquid solvent molecules. It is a complicating factor because, by salt formation and development of one full charge, a true cyanine is developed, which, however, (reversed halochromy) has its absorption at higher frequencies than the base. The addition of another proton, giving two full charges, results in discharge of visible color, by blocking the resonance. Where possible, to assure the presence of the dye as free base, we may add a small amount, comparable with that of the dye, of a base such as diethylamine, following the procedure of Brooker, *et al.*, for methyl alcohol. The following table (XII) shows that in non-polar solvents the absorption band is displaced steadily toward the red with increase of dielectric constant (and refractive index) of the solvent.

The values with "+ d. e." indicate controls with the addition of diethylamine to ensure removal of the "acid" form. In order to control the origin of such values, some of the free base

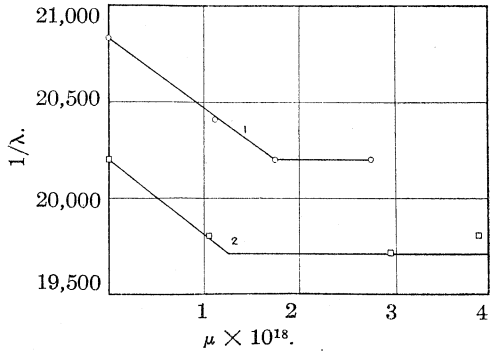


Fig. 12.—Merocyanine XXXI in polar solvents: 1, aliphatic series; 2, aromatic series.

(15) Compare the band system of merocyanine XXIII.

TABLE XII

DYE XXXI IN NON-POLAR SOLVENTS

Solvent	K	$\mu \times 10^{18}$	λ_m, α	λ_m, β
n-Hexane + d. e.	1.87	0	480	450
n-Decane + d. e.	1.95	0	482	455
Cyclohexane + d. e.	2.05	0	480	455
			480	455
Decalin	2.15	0		460
Carbon tetrachloride	2.20	0	490	465
Benzene + d. e.	2.38	0	495	470
			495	470
Carbon disulfide	2.65	0	510	478

was converted to the methiodide, as described by Brooker, Sprague, Smyth and Lewis. As they observed, the absorption of the "salt" is generally identical with that of the alkyl halide, but in certain solvents the methiodide gave a maximum at a somewhat longer wave length than the simple salt. It may be noted in advance that both the H-salt and the methiodide behaved like other full cyanine dyes in showing very little effect of polarity of solvent on the position of the absorption maximum.

In the following table (XIII) are summarized positions of the α-band maximum in a series of aliphatic solvents used with Dye XXXIII.

TABLE XIII

DYE XXXI IN ALIPHATIC SOLVENTS

Solvent	$\mu \times 10^{18}$	$\frac{1}{\lambda_m}$	Trace λ_m Base	Trace λ_m Acid
Hexane	0	20833		
Ethyl ether	1.12	20408	490	475
Alkyl Acetate	1.74 to 1.90	20202	495	
Alkyl ketone	2.7	20202	497	478
Propionitrile	3.4 to 3.66	20000	500	
Nitromethane	3.8	[20000]	?	

In the next table (XIV) a comparable series of aromatic solvents is presented.

TABLE XIV

DYE XXXI IN AROMATIC SOLVENTS

Solvent	$\mu \times 10^{18}$	$\frac{1}{\lambda_m}$	Trace λ_m Base	Trace λ_m Acid
Benzene	0	20202	495	
Diphenyl ether	1.05	19800 ←	505	
Phenyl acetate	1.50	19608		
Benzophenone	2.95	19724	507	495
Nitrobenzene	2.90	[20202]		

The "aliphatic" and "aromatic" series plotted in Fig. 12 show a general similarity with the corresponding series for merocyanine XXII; some deviations may be due to incomplete suppression of the salt form of XXXI. For example, in *nitromethane* the dye is definitely present for the most part in that condition. The addition of a drop of

diethylamine produces a quite transient deepening (reddening) of color. In *nitrobenzene* this deepening is more persistent and allows a value for XXXI (base) in this solvent. We have assembled also the results with Dye XXXI in associated and tautomeric solvents (Table XV).

TABLE XV

Solvent	$\mu \times 10^{18}$	$\frac{1}{\lambda_m}$	Trace λ_m Base	Trace λ_m Acid
Water	1.90	19800	505	
Alcohol	1.68	19800	505	482
Benzyl alcohol	1.69	19417	515	
Ethyl acetoacetate	2.93			
Acetyl acetone	3.00		490	

As in the case of merocyanine XXIII, the frequency is much lower than would correspond with the moment, except for *benzyl alcohol.*

It seems reasonable to regard the initial red displacement (bathochromy) as the same effect of the solvent as that upon merocyanine XXIII. This is supported by the fact that the slopes $\delta\nu/\delta\mu$ are the same in both cases, *viz.*, 350 cm.$^{-1}/1\mu$. But in the case of merocyanine XXXI, the solvents with the higher moments tend to stabilize the acid, or rather salt, form of the dye.

Ionized Cyanine Dyes

Dye XXII—the methiodide of XXXI—and the H-salt behave as cyanine dyes with a one full positive charge in respect of solvent action. Features of this behavior are low solubility in non-polar solvents (but increasing somewhat with increase of dielectric constant) and relative *independence* of the spectrum of the moment of polar solvents (see Tables XVI and XVII).

TABLE XVI

DYE XXXII IN SOLVENTS

Solvent	K	$\mu \times 10^{18}$	$1/\lambda_m$ (cm.$^{-1}$)
Carbon disulfide	2.65	0	20000
Benzene	2.38	0	20202
Ether	..	1.12	Insoluble
Alkyl acetate	..	1.74	20620
Ketone	..	2.74	20747
Propionitrile	..	3.50	20830
Nitromethane	..	3.80	20620

Comparing a symmetrical with an unsymmetrical dye, the independence of the band position in polar solvents was confirmed.

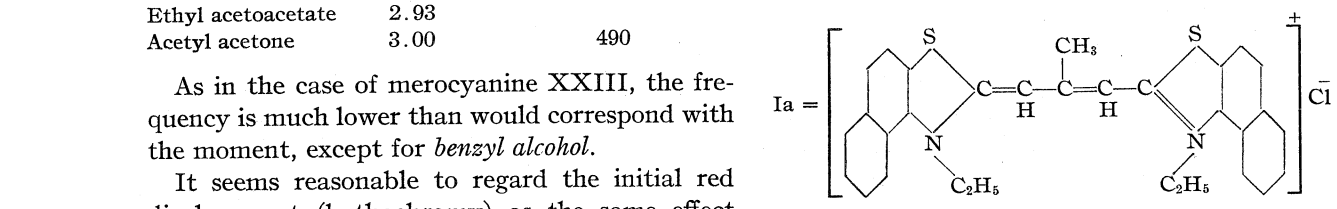
TABLE XVII

	Dye	$1/\lambda$ (Aliphatic)	$1/\lambda$ (Aromatic)
(Sym.)	Ia	17270 (±100) cm.$^{-1}$	16960 (±260) cm.$^{-1}$
(Unsym.)	XVb	20000 (± 90) cm.$^{-1}$	19600 (± 94) cm.$^{-1}$

The possibility that the solvent effect (of polar moment) might vary with the length of the conjugated chain between the nuclei was tested with three thiacyanine homologs. No difference was observed.

Alkyl Halides

In this group of solvents the behavior of the cyanine (ionized) dyes is more analogous to that of the merocyanines. The displacement is very variable, and seems to bear no direct relation to the dipole moment of the solvent nor to the dielectric constant. Using the (symmetrical) dye



Ia, there appears to be a rather significant advance in the magnitude of the "displacement" on passing from chloride → bromide → iodide, as shown in Table XVIII.

TABLE XVIII

	HALIDES OF METHANE ΔCl	ΔBr	ΔI in cm.$^{-1}$
CH_3X	..	610	1182
CH_2X_2	550	844	1400
CHX_3	990	1400	..
CX_4	1130	..	..
	HALIDES OF ETHANE		
CH_3CH_2X	550	786	844
CH_2XCH_2X	550	1030	..
CH_2XCHX_2	610	844	..
CHX_2CHH_2	640	1130	..

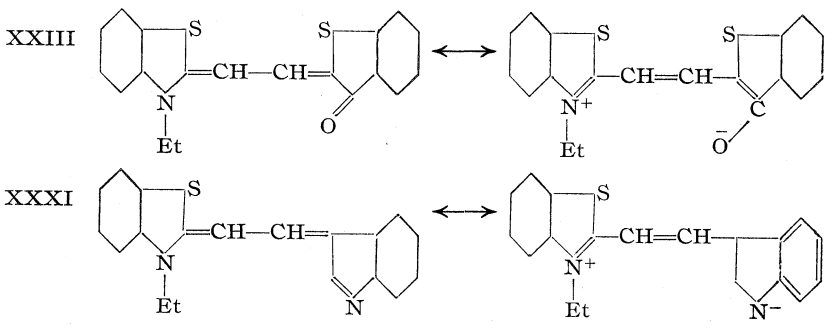
Discussion

The effect of solvents in displacing an absorption band may be attributed to van der Waals forces of three principal types: (i) dipole induction; (ii) orientation of permanent dipoles; (iii) mutual induction of electron clouds (dispersion forces). Of these, the first should be effective with dye molecules capable of a dipolar structure. The distance law is $F \propto 1/r^6$, and the electric forces operative between solute and solvent are not very powerful. The temperature coefficient is slight. The behavior of merocyanines in "non-polar" solvents may derive largely from this, but in part from "dispersion" forces, and to some extent from partial moments of the solvent molecule made effective by specific orientation.

The orientation of permanent dipoles permits more powerful intermolecular electric forces, the

distance law being $F \propto 1/r^3$. The temperature coefficient would be large; rise of temperature would disrupt orientation, and lower the "displacement" produced. This effect might be expected to diminish, the higher the polar moment of the solvent, and the nearer to saturation. How far "dispersion" forces can be expected to produce a displacement is uncertain. They have been invoked as favoring dimerization of dye cations, and thereby (in dimerization) coupling of vibrations with electronic transitions. The characteristic difference between aromatic and aliphatic solvents of the same chemical type certainly seems to indicate a specific "displacement" effect, which indeed persists with ionized cyanine dyes.

The merocyanines XXIII and XXXI are dyes of the type termed by Dilthey and Wizinger[16] "intramolecular ionoid," that is, they can be ascribed in ordinary valence symbols two structures; one a hybrid ion and the other neutral.



In general, in such molecules the two structures represent considerably different energy levels; depending upon the characters of the terminal nuclei A and B, one or the other may principally constitute the ground level, the other a relatively high excitation level, or the two configurations may be sufficiently near in energy for quantum mechanical resonance to occur.

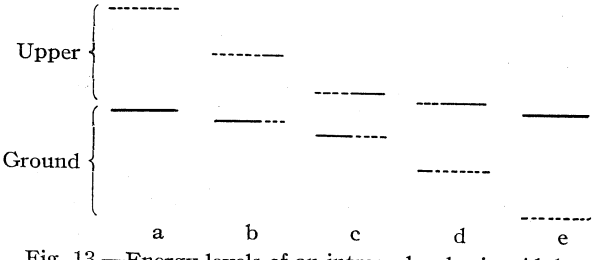


Fig. 13.—Energy levels of an intramolecular ionoid dye, with polar character increasing from *a* to *d*: – – – – proportion of polar; ——, proportion of non-polar contribution to the ground and excited states.

(16) R. Wizinger, "Organische Farbstoffe," F. Dummlers Verlag, Berlin, 1933, p. 44.

The various possibilities have been discussed by Th. Förster[17] (*cf.* Fig. 13). In the case represented by (a) the polar form has a much higher energy than the non-polar form, and represents an excited state which would only be produced by absorption of relatively short wave radiation or by an equivalent activation energy. As the energies of the two configurations are brought closer, the energy difference between the ground state and the lowest excited state is reduced, and absorption occurs at longer wave lengths. This is expressed in the diagram by a more equal "weighting" of the two limit structures in the ground and excited states, corresponding to increasing resonance. Such a progressive change could be brought about by change in the character of the auxochrome A and anti-auxochrome B (in the language of Dilthey and Wizinger), or more analytically, as pointed out by L. G. S. Brooker, *et al.*, [14] by change in the basicities of the terminal groups. Förster suggests that this progression might be carried over to an inverse state, in which the non-polar configuration became increasingly the *less* stable, or of higher energy than the dipolar form. This is indicated in the diagram for *d* and *e*, with reversion to shorter wave absorption. The tendency to reduction of the electrostatic energy of the dipole, with consequent relaxation to the non-polar form seems to make this little likely. Instead of the progression toward greater resonance $a \rightarrow b \rightarrow c$ being effected by internal change in the molecule, it could be brought about by change in the immediate environment, *e. g.*, of solvent.

Assuming that the action of induced and permanent solvent dipoles upon such "intramolecular ionoids" is to approach the energy states of the dipolar and non-polar configurations, the actual effect should be less, the nearer these two energies are in the isolated dye molecule. But a solvent effect still remains with dyes whose constitution guarantees equality of the energies of the limiting structures, and which, moreover, are not susceptible of dipole exaltation. Such for example are the ionized cyanine dyes.

With dyes carrying a full ionic charge, little or no effect of induced or permanent dipoles of the

(17) *Cf.* Th. Förster, *Z. Elektrochem.*, **45**, 548 (1939).

solvent molecules is to be expected, but, in terms of van der B. Houckgeest's theory,[18] there is a large effect upon solubility. However, there can be notable changes in the absorption with change of solvent for such dyes.[19] It seems unlikely to be due to dipole induction, and is at present most conveniently plotted as a function of refractivity (*cf.* Fig. 14). This effect—with ionized dyes—may be caused by the dispersion forces, as a resonance effect between the mobile electron cloud of the solvent and that of the dissolved dye. The increased "displacement" for a cyanine dye in alkyl halides in passing from the *chloride* to the *bromide* to the *iodide* is consistent with this view.

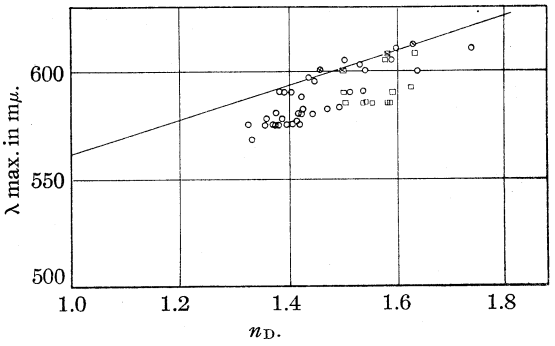


Fig. 14.—Dye Ia in polar O, aliphatic liquids; □, aromatic liquids. Line refers to non-polar liquids.

The "dispersion" contribution is also manifest in the difference between aliphatic and aromatic solvents of the same polar moment. Polar solvents of the same refractive index show, in general, a lower displacement than the non-polar ones. This is brought out in Fig. 14, which shows a reference line for non-polar solvents, and the generally lower group of polar ones. The effect of polar character is to reduce the displacement effect corresponding to a given refractive index, but is not expressible by a simple subtractive quantity. It appears indeed to be pronouncedly individual. Empirically, the nearest approximation is found in the expression

$$\lambda_s = \frac{kN^p}{\sqrt{1+\mu}}$$

where p is an integer. Since N^2 has some theoretical basis we illustrate the correlation in that case (Fig. 15).

Structure of Bands

The origin of the auxiliary bands of dye absorption in the optical region is not too clear at present. The principal band, *i. e.*, generally the long wave band of maximum extinction, is assigned to an electronic transition or charge transfer determined by the resonance structure of the dye.[20] A dye can be regarded as derived from an aromatic hydrocarbon or chain of conjugated ethylene bonds as a prototype (or a hybrid of these two types) by the introduction of auxochromes and anti-auxochromes.[16] The principal ultraviolet spectrum of anthracene—as a homolog of benzene—was first derived on quantum mechanical grounds by Sklar[19] and Förster,[16] with the important corollary of the displacement of the absorption to longer wave lengths with the number of linearly conjugated benzene nuclei. Similar considerations obtain for the polyenes. Development of the theory for the introduction of auxochromes has been carried out by Förster[17] with particular application to the triphenylmethane cation on substitution of —NH_2 groups. The conditions are not unlike the substitution of —NH_2 groups into anthraquinone

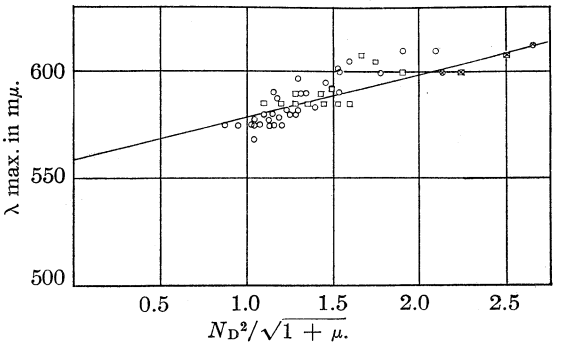


Fig. 15.—Dye Ia in polar O, aliphatic liquids; □, aromatic liquids.

(Anthracene) ⟶ Anthraquinone ⟶ { 1-amino anthraquinone ⟶ { 1,4-diamino- anthraquinone

In Fig. 16 are given very approximate term-diagrams for the evolution of the spectrum of anthraquinone with increase of auxochromic groups.

With the introduction of the auxochromes there appear not only new electronic transition bands, but increasing diffusion of the structure of the pre-existing shorter wave bands, owing to the increase in the number of vibrational levels and to the increased change of coupling of π-electrons (concerned in transitions) with others of antiparallel spin. The influence of solvents upon the *structure* of the absorption bands of dyes requires further investigation.

(18) J. P. W. A. van B. Houckgeest, *Rec. trav. chim.*, **59**, nos. 7/8, 560 (1940).

(19) S. E. Sheppard, *J. Chem. Soc.*, **95**, 15 (1909).

(20) A. L. Sklar, *J. Chem. Phys.*, **5**, 669 (1937).

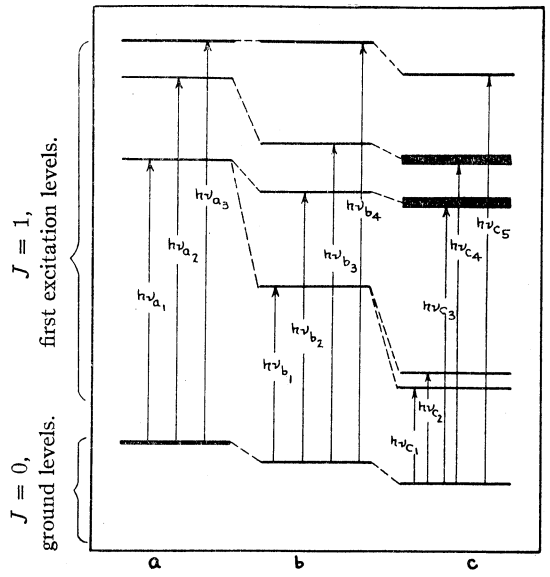


Fig. 16.—a, Anthraquinone; b, 1-aminoanthraquinone; c, 1,4-diaminoanthraquinone.

Associating Solvents

A systematic divergence in the effect of polar moment upon the merocyanine absorption spectrum was shown by "associating" solvents. This behavior is not shown by ionized cyanine dyes. It seems to be connected with the potential dipolar character of the merocyanines, and may indicate either an effectively higher dipole moment of these solvents in the liquid state, an effectively higher dielectric constant (than for individual molecules of the gas), or a marked effect of dispersion forces. Investigation of the temperature coefficient should help to decide.

Behavior of Alkyl Halides

A rather considerable degree of variation of the polar moment with temperature has been noted with these compounds, also a number of deviations from the theoretical values.[21] These derivations, however, are inadequate to explain the large variations of "red displacement" observed in these solvents. We believe that a rather definite approach to explanation of the facts is indicated in two articles by J. P. W. A. van B. Houckgeest[17] on the "Solvent and Dissociating Power of Chlorinated Hydrocarbons"—as exhibited in respect of quaternary ammonium salts. The "red displacement" with a merocyanine may be regarded as due to an "intramolecular ionization" or predissociation of a compound which is a potential or inner salt of a quaternary ammonium base. The arguments by which Houckgeest is able to place the alkyl halides in relative order as to their solvent powers are applicable to their displacement of the merocyanine spectrum, and we find that our results are concordant therewith. We have not space to detail the argument.[22] It deals in each case with orientation in the molecule of $\overset{+}{C}—\overset{-}{Cl}$ dipoles, of which the positive end is regarded as more active than the negative. The purely qualitative order was derived from stereochemical and energetic considerations alone. In the second paper the author derives a quantitative theory in terms of the thermodynamic potentials. This is perhaps less relevant to the displacement effect at one temperature, since then considerations as to change of number of molecular species are not involved. It may have definite application to the effects of temperature change upon the "displacement" in these solvents. In any case, the "solvation energies" calculated from the more complete theory fall in much the same order as our "displacements" of the merocyanine spectrum (*cf.* Table XIX). From the very specific behavior of the alkyl halides we suggest that with polar solvents and the merocyanine type of dye, there is formed an addition or molecular compound. This may be subject to a general "field" of the solvent molecules, but if there is only displacement, without radical transformation of the spectrum, it is probable that no quantum mechanical resonance occurs between the components.

TABLE XIX

SOLVENT POWER OF CHLORINATED ETHANES

Solvent	According to van B. Houckgeest[a] Cl	Br	I	$\Delta\nu$ obs. cm.$^{-1}$	$\mu \times 10^{18}$	K
CH_3CH_2Cl	100	92	82	2408	2.02	~11.0
CH_3CHCl_2	104	96	85	2584		10.8
CH_2ClCH_2Cl	122	114	102	2757	2.0 1.2	10.4
CH_3CCl_3	78	72	65	2408	1.60	7.2
$CH_2ClCHCl_2$	126	112	99	2826	1.15	7.1
CH_2ClCCl_3	75	70	63			5.8
$CHCl_2CHCl_2$	127	117	104	3028	1.60	8.2
$CHCl_2CCl_3$	66	61	55	2654	1.00	3.6

[a] The halide ions above refer to respective salts of quaternary ammonium bases.

Acknowledgments.—The cyanine and merocyanine dyes employed were prepared by Dr. L. G. S. Brooker and his staff, who synthesized them and determined their constitution. Our thanks are also due Dr. L. A. Jones and Mr. E. E.

(21) C. P. Smyth, "Dielectric Constant and Molecular Structure," A. C. S. Monographs, Chem. Catalog Company, 1931.

(22) If not available, copy may possibly be obtainable through the American Documentation Institute.

Richardson for certain absorption measurements in the ultraviolet region.

Summary

1. The absorption spectrum of a merocyanine dye has been determined for the gaseous state (*in vacuo*).

2. The displacement of the absorption band (or bands) in various solvents is referred to that *in vacuo*.

3. It is shown that, with certain families of compounds, there is a definite correlation of the displacement (to longer waves) with: (a) the refractive index and dielectric constant for non-polar solvents; (b) the polar moment for polar solvents.

4. With ionized (cyanine) dyes, it is shown that no displacement is effected by change of polar moment, but definite changes occur in non-polar solvents of increasing refraction and dielectric strength.

5. Theoretical considerations of the solvent effects are given in relation to the structures of the dyes. The exceptional behavior of the alkyl halides is discussed.

ROCHESTER, NEW YORK RECEIVED MARCH 25, 1942

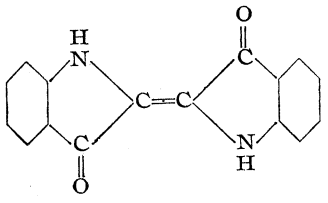
[COMMUNICATION NO. 869 FROM THE KODAK RESEARCH LABORATORIES]

The Effect of Solvents on the Absorption Spectra of Dyes. II. Some Dyes Other than Cyanines

BY S. E. SHEPPARD AND P. T. NEWSOME

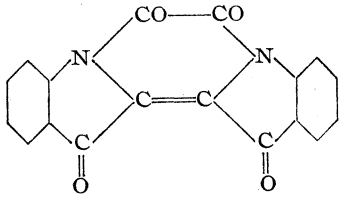
We have made some investigation of dyes other than the cyanines, and of which two can be vaporized and the absorption determined *in vacuo* (*i. e.*, as gas at low pressure) for comparison with solutions. These are *indigo* and *diaminoanthraquinone*, and they are of particular interest in comparison with the *merocyanines* since they are both non-ionic.

Indigo.—The formula usually assigned is

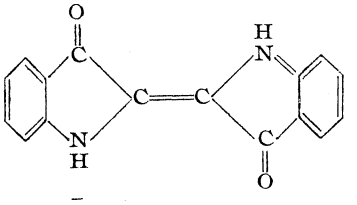


trans-form

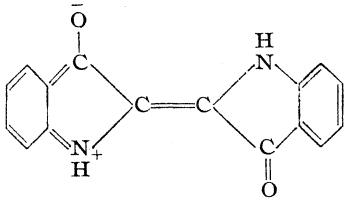
Evidence for a *cis*-form is mostly based on the production of cyclized derivatives of the *cis*-form, such as *oxalyl indigo*[1] and *N,N-styrolin-indigo*.[2]



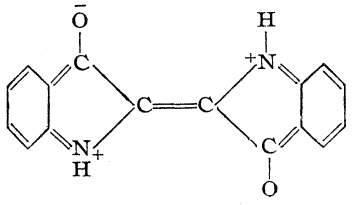
For the solid, crystalline form, the evidence favors the presence of the *trans*-form.[2] Apart from the steric variation, which in the case of the stilbenes[3] appears to affect the intensity of the absorption more than the location of the absorption bands, the nature of the "limit configurations" corresponding to the resonance and the color is not completely decided. For a review of the subject, papers by J. van Alphen[4] may be consulted. This author has suggested that indigo is a resonance hybrid having the following principal "limit structures"



(A)



(B)



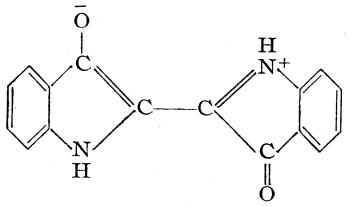
(C)

(1) *Cf.* R. Pummerer, H. Fiesselmann and O. Müller, *Ann.*, **544**, 206 (1940).

(2) A. Reis and W. Schneider, *Z. Krist.*, **68**, 543 (1928).

(3) A. Smakula and A. Wassermann, *Z. physik. Chem.*, **155A**, 353 (1931). There is some hypsochromic displacement in the *cis*-derivative relative to the *trans*-form.

(4) J. van Alphen, *Rec. trav. chim.*, **60**, 138–152 (1931).


(D)

A similar view was expressed by F. Arndt[5] and expanded by B. Eistert.[6] The latter considered the resonance A ⟷ D of principal importance, and form D, allowing "free" rotation about >C——C< according with the actual existence of only one form (*trans*) but with the possibility of *cis*-derivatives.

We have measured a number of absorption spectra of indigo in various solvents with the spectrophotometer; to conserve space the extinction curves are not given here but, as in Part I, only the absorption maxima and the corresponding "displacements." Compared with the merocyanines, the behavior of indigo in non-polar solvents is anomalous, in giving a smaller displacement in benzene and xylene than in carbon tetrachloride, although their dielectric constants are higher as are also the refractive indices. The solubility of indigo in this group of solvents is too low to permit extensive measurements.

TABLE I

INDIGO IN NON-POLAR SOLVENTS

Solvent	K	n_D	$\mu \times 10^{18}$	$1/\lambda_m$ in cm.$^{-1}$	$\Delta 1/\lambda$
Vacuum	1.0	1.0	0	18315	0
Hexane	1.87	1.375	insufficiently soluble		
Carbon tetrachloride	2.20	1.458	0	16667	1648
Benzene	2.38	1.498	0	16800	1515
p-Xylene		1.496	0	16800	1515
o-Xylene		1.503	0.5	16800	1515
m-Xylene		1.496	0.4	16800	1515
Carbon disulfide	2.65	1.629	0	16610	1704

TABLE II

INDIGO IN ALIPHATIC POLAR SOLVENTS

Solvent	$\mu \times 10^{18}$	$1/\lambda_m$ in cm.$^{-1}$	$\Delta 1/\lambda$
Hexane	0	insufficiently soluble	
Diethyl ether	1.12	16892	1423
Methyl acetate	1.74	16800	1515
Isoamyl acetate[a]	1.70	16450	1865
Acetone	2.74	16751	1564
Nitromethane	3.80	16751	1564
Methyl alcohol	1.68	16529	1786
Isoamyl alcohol[a]	1.70	16450	1865
Formic acid	1.77	15949	2366
Acetic acid	1.63	16260	2055
n-Valeric acid		16260	2055
Diethylamine	0.9	16340	1975
n-Butylamine	1.3	16393	1922
n-Propylamine	1.4	16393	1922

[a] The marked effect of the isoamyl group is noteworthy.

TABLE III

INDIGO IN AROMATIC SOLVENTS

Solvent	$\mu \times 10^{18}$	$1/\lambda_m$ in cm.$^{-1}$	$\Delta 1/\lambda$
Benzene	0	16800	1515
p-Xylene	0	16800	1515
Diphenyl ether	1.05	16610	1704
Phenyl methyl ether	1.20	16667	1648
Phenyl acetate	1.52	16667	1648
Acetophenone	2.94	16529	1786
Benzophenone	2.95	16584	1731
Nitrobenzene	3.90	16529	1786
Aniline	1.52	16129	2186
o-Chloroaniline	1.77	16129	2186

TABLE IV

INDIGO IN HETEROCYCLIC SOLVENTS

Solvent	$\mu \times 10^{18}$	$1/\lambda_m$ in cm.$^{-1}$	$\Delta 1/\lambda$
Pyridine	2.11	16340	1975
Quinoline	2.16	16260	2055
Piperidine	1.17	16340	1975

On comparing these results with the data for the *merocyanines* XXIII and XXXI (Part I), the following conclusions were reached: (i) the behavior in non-polar solvents seems less simple, but owing to restricted solubilities the data are very scant; (ii) in the typical aliphatic and aromatic series of polar solvents, there appears to be no definite displacement of λ_m with change of polar moment as was found with the merocyanines (Part I); (iii) no regularity was apparent with amines of different polar moments, but both aliphatic and aromatic amines, as well as heterocyclic nitrogenous bases, show considerably greater displacements than other solvents of the same polar moment. Scheibe, Dörfling and Assmann[7] concluded that *aniline* is outstanding as a solvent for indigo and derivatives, in respect of "red displacement" of the spectrum. Our observations (*cf.* Tables I to IV) show others of equal potency, *formic acid* giving the greatest displacement. The behavior of indigo in the *associated* solvents, the alcohols and fatty acids, and in the tautomeric acetoacetate, is similar to that of merocyanine.

Scheibe and his co-workers concluded, particularly from the behavior of indigo in mixtures of non-polar and polar solvents, that no grounds exist for assuming specifically different structures in

(5) F. Arndt, *Ber.*, **72**, 860 (1939).

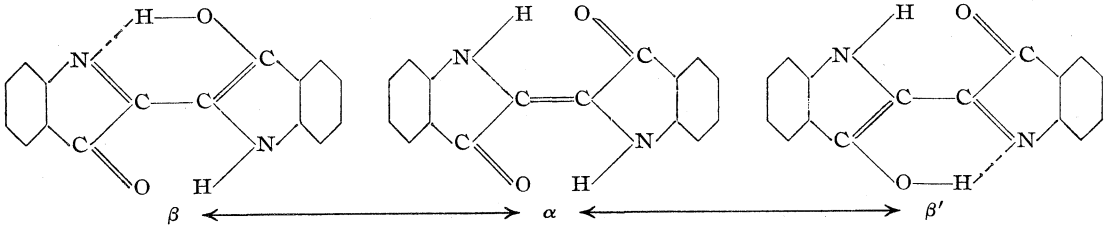
(6) B. Eistert, "Tautomerie und Mesomerie," F. Enke, Stuttgart, 1938, p. 189; also *Ber.*, **72**, 860 (1939).

(7) G. Scheibe, H. Dörfling and J. Assmann, *Ann.*, **544**, 240 (1940).

equilibrium as responsible for the color differences (tautomerism) nor for assuming molecular aggregation as a principal factor. As *positive* conclusions, they consider that the color changes are explainable "by displacement of the electron clouds within the molecules under the action of different solvents," and also that solvent molecules "whose dipoles are most strongly active outwardly (alcohols) displace the absorption most to the long waves."

The slight to inappreciable effect which a change of polar moment *per se* of a solvent has on the absorption spectrum indicates that the hybrid ion or bipolar (and quadrupolar) structures suggested by Eistert[6] and by van Alphen[4] are probably contributing little to the resonance system responsible for the first electronic transition band of indigo.

It seems possible that the resonance system in question is that indicated in the structural formulas



β and β′ are similarly hydrogen-bonded structures which are suggested as the two identical most stable structures, *i. e.*, energetically lowest.

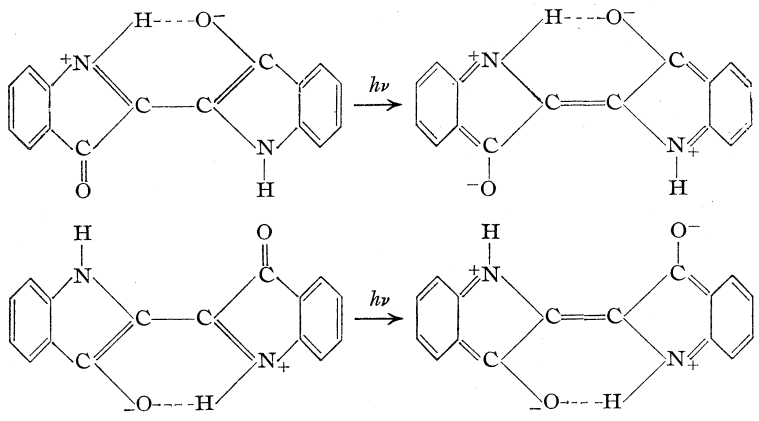
The normal structure α conventionally assigned to indigo would then represent an intermediate (mesomeric) state of higher energy.

It may be supposed that in associating solvents the structures β and β′ would be less stable, producing a reduction in the energy difference from the splitting of levels, and hence displacement of the absorption band to longer waves.

The figures in Table V show the considerably lower sensitivity to solvent influence exhibited by indigo as compared with the merocyanine.

It may be pointed out here that any effect of solvent upon the absorption of light must involve a "solvation" preceding the act of light absorption, in accordance with the Franck–Condon principle that no movements of atomic nuclei can be concerned in it. On the resonance theory this is quite consistent with the solvent shifting, so to say, the center of gravity of the resonance system of the molecule.

In discussion with Dr. M. L. Huggins, he has suggested as alternatives or modifications of the formulations β and β′ the structures γ and γ1



thus indicating a certain ionic strength of the hydrogen bridge. The structures γ and γ1 approach the structure D favored by Eistert (see above) but with diminished ionic strength (polarity) suggested; the structures indicated for excited states produced by absorption of light from γ and γ1 similarly approach the structure C of van Alphen (as above).

TABLE V

	XXIII Δ1/λ, cm.⁻¹	Indigo Δ1/λ, cm.⁻¹
Benzene	2408	1520
Alcohol	3300	1786
Formic acid	3258	2366

The hydrogen bonding possibilities of a solvent are undoubtedly very important for the spectrum of such molecules as indigo. The capability of such dye molecules to effect H-bridging *inter se* in condensed states might be expected therefore to be indicated in the spectrum of the *solid* state (*cf.* later, Fig. 7).

1,4-Diaminoanthraquinone.—Spectrophotometric absorption measurements were made in a

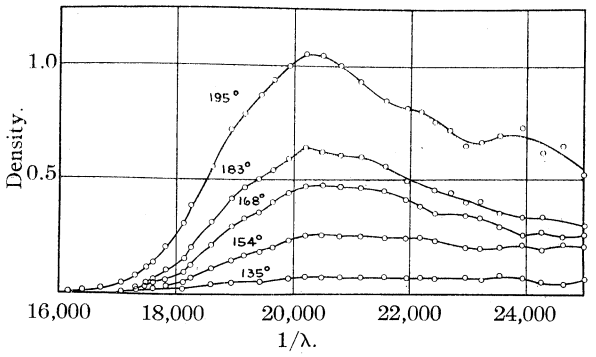


Fig. 1.—1,4-Diaminoanthraquinone vapor at various temperatures.

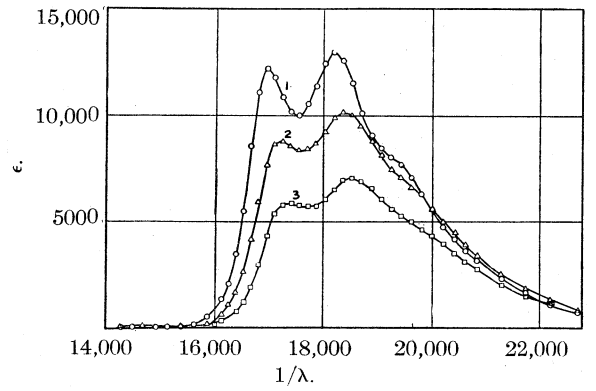


Fig. 2.—1,4-Diaminoanthraquinone in: 1, methyl alcohol; 2, benzene; 3, carbon tetrachloride.

number of non-polar and polar solvents. The absorption shows three fairly pronounced maxima, which have been termed α, β and γ, the α-band being of longest wave length (*cf.* Figs. 1 and 2).

TABLE VI

1,4-DIAMINOANTHRAQUINONE IN NON-POLAR MEDIA

Medium	n_D	K	α-Band λ	α-Band Δ1/λ	β-Band λ	β-Band Δ1/λ	γ-Band λ	γ-Band Δ1/λ
Vapor	1.000	1.00	525	0	492	0	470	0
n-Hexane	1.375	1.87	575	1657	535	1628	500	1276
n-Decane	1.409	1.95	575	1657	535	1628	500	1276
Carbon tetrachloride	1.458	2.24	576	1846	540	1801	508	1591
Benzene	1.498	2.28	580	1807	545	1972	510	1668
Carbon disulfide	1.629	2.65	587	2012	550	2138	515	1859

TABLE VII

1,4-DIAMINOANTHRAQUINONE IN ALIPHATIC SOLVENTS

Solvent	$\mu \times 10^{18}$	α-Band λ	α-Band Δ1/λ	β-Band λ	β-Band Δ1/λ	γ-Band λ	γ-Band Δ1/λ
Vapor		525	0	492	0	470	0
n-Hexane	0	575	1657	535	1628	500	1276
Diethyl ether	1.12	582	1868	542	1870	510	1668
Methyl acetate	1.74	580	1807	545	1972	510	1668
Acetone	2.74	585	1954	547	2039	510	1668
Nitromethane	3.80			550	2138		
Diethylamine	0.90	595	2248	552	2204	510	1668
Triethylamine	.90	590	2099	555	2302	510	1668
n-Butylamine	1.3	595	2248	555	2302	517	1934
Acetic acid	1.63	590	2099	550	2138	510	1668
Propionic acid	1.68	590	2099	550	2138	510	1668
Methyl alcohol	1.68	590	2099	550	2138	515	1859
Water	1.90	582	1866	545	1972	505	1474

The values for the maxima in non-polar media have been plotted as a function of the refractive index (Fig. 3). While they fall on fairly smooth curves, they do not give a linear relation, as in the case of the merocyanine, though there is approach to this with increasing index.

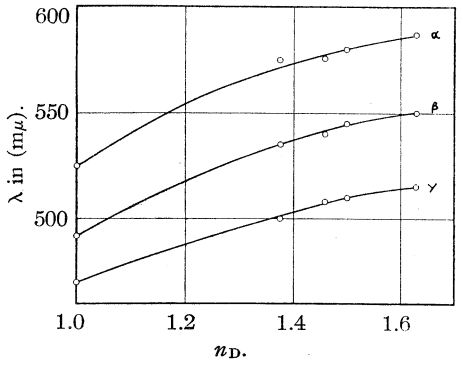


Fig. 3.—1,4-Diaminoanthraquinone in non-polar media.

In polar solvents, both aliphatic and aromatic, there is a very definite tendency for the displacement to increase with increase of polar moment of the solvent (*cf.* Figs. 4 and 5). The displacement,

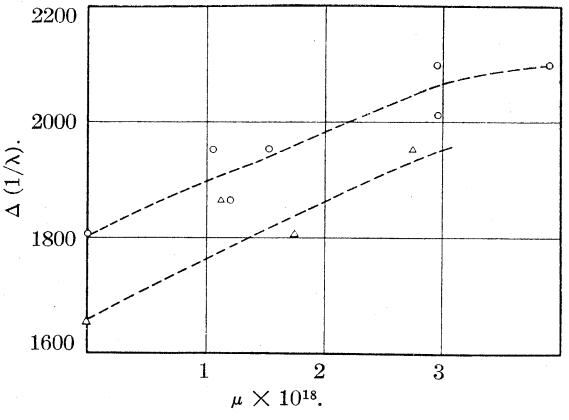


Fig. 4.—α-Band of 1,4-diaminoanthraquinone in polar media: Δ, aliphatic solvents; O, aromatic solvents.

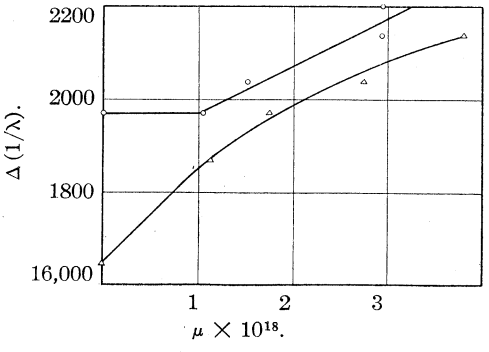


Fig. 5.—β-Band of 1,4-diaminoanthraquinone in polar media: Δ, aliphatic solvents; O, aromatic solvents.

in general, is greater in aromatic solvents than in aliphatic solvents of the same moment (*cf.* Table VIII and Figs. 4 and 5). The behavior is more like that of the merocyanines than is that of indigo.

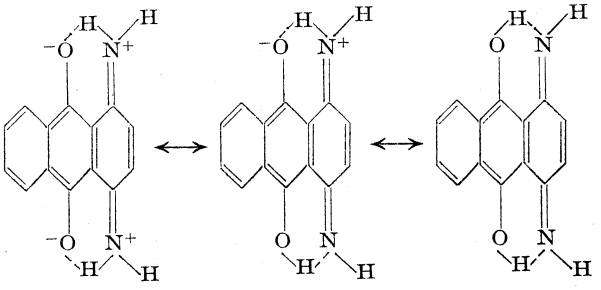
TABLE VIII

1,4-DIAMINOANTHRAQUINONE IN AROMATIC SOLVENTS

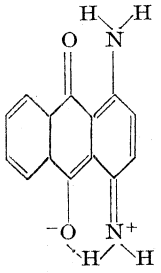
Solvent	$\mu \times 10^{18}$	α-Band λ	α-Band Δ1/λ	β-Band λ	β-Band Δ1/λ	γ-Band λ	γ-Band Δ1/λ
Benzene	0	580	1807	545	1972	510	1668
Diphenyl ether	1.05	585	1954	545	1972	510	1668
Anisole	1.20	582	1866	545	1972	510	1668
Phenyl acetate	1.52	585	1954	547	2039	510	1668
Acetophenone	2.94	590	2099	550	2138	515	1859
Benzophenone	2.95	587	2012	552	2204	515	1859
Nitrobenzene	3.90	590	2099	550	2138	510	1668
Aniline	1.52	590	2099	552	2204	515	1859
o-Chloroaniline	1.77	590	2099	552	2204	515	1859
Quinoline	2.16	598	2326	560	2463	520	2045

The normal constitution assigned to *1,4-diaminoanthraquinone* readily admits hydrogen-bonded structures, such as were previously cited for the dioxyanthraquinone.[8] In recent papers on the constitution of certain (acid) anthraquinone dyes,[9] C. F. H. Allen, C. V. Wilson and G. F. Frame have given an interpretation of certain characteristics of their spectra based on hydrogen bonding in 1,4- and 1,5-diaminoanthraquinone derivatives. One feature in particular is thus explained "when there are in the 1- and 4-positions two groups which are able to furnish electrons by a mesomeric shift, the main band of absorption will have a double head. If but one group of this type is present, only a single head will be observed." This appears to be in agreement with the secondary characteristic of the evolution of the spectrum of 1,4-diaminoanthraquinone, *via* 1-aminoanthraquinone illustrated in Part I; the second amino group in the 4-position produces not only a considerable displacement of the longest wave band toward the red, but a splitting of the band. Actually, however, there are present in most absorption spectra of 1,4-diaminoanthraquinone three fairly well-marked sub-bands. The question as to whether these are independent electronic transitions or are due to superpositions of vibrational quanta on a main electronic transition is perhaps not yet clear.

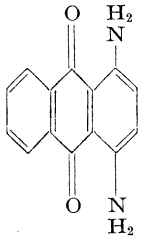
It is evident from the normal valence formula that a large number of structures could be written, not all of equal probability, but there are at present insufficient data to estimate more than roughly the energy differences implied. As in the case of indigo, we suppose hydrogen-bonded structures to be chiefly contributing to a lower state and normal and quadrupolar structures to higher levels. The structures of lower energy may be represented as follows



These represent three possible structures contributing to the resonance of the two parallel hydrogen bonds. As chiefly contributing to the first excited state, we may suggest such structures as



and the alternate: also, but chiefly contributing to a higher excited state, the structure shown.



We have again to thank Dr. Huggins for very helpful suggestions in regard to the formulation of the hydrogen-bonded structures. The interpretation proposed is quite tentative and purely qualitative. In Part I, in the discussion of the behavior of the merocyanines, there was reproduced a diagram from a paper of Th. Förster[10] indicating the participation of polar and non-polar structures of a dye in the principal lower and upper states corresponding to the main electronic transition, or absorption band. Förster indicated that *a priori* there would be a possibility of molecules in which (di)polar structures made the larger contribution to the ground state, these being more stable. We regarded this as improbable, in fact, because of the large coulombic energy in the separation of charges. However, it is possible that we were too hasty in this conclusion.

(8) L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940, p. 329.

(9) C. F. H. Allen, C. V. Wilson and G. F. Frame, *J. Org. Chem.*, **7**, 169 (1942).

(10) Th. Förster, *Z. Elektrochem.*, **45**, 548 (1939).

Hydrogen bonding can effect a relative stabilizing of (di)polar structures, which may lead to increased contribution of such structures to the ground state, though it may not allow the complete inversion suggested in Förster's discussion.

From the solvent data recorded in Part I for merocyanine (dye XXIII) and in this paper for *indigo* and 1,4-diaminoanthraquinone, as well as from the resonance systems indicated, we suggest the following approximate scheme for the polar, non-polar balance in the molecules of these dyes in the gas state (*in vacuo*). The diagram is based on that of Förster (Fig. 6) and expresses approximately the findings that the effects of increasing dielectric constant of non-polar liquids and of polar moment of polar liquids (normal or non-associated) are greatest with *merocyanine*, considerable with *diaminoanthraquinone*, and least (approaching zero) with *indigo*. From these considerations,

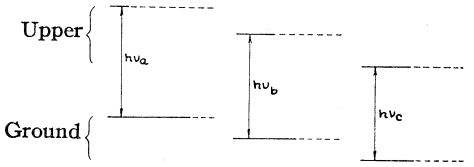


Fig. 6.—Polar non-polar characters of dyes in gaseous state:

	Merocyanine (XXIII) $h\nu_a = 2.63$ ev.	1,4-Diaminoanthraquinone $h\nu_b = 2.51$ ev.	Indigo $h\nu_c = 2.26$ ev.
λ_m in mμ =	470	492	544
$1/\lambda$ in cm.$^{-1}$ =	21,276	20,320	18,315

it appears probable that the "associated" liquids (alcohols, aliphatic acids, acetoacetate, etc.) which give "high" displacements with merocyanine (dye XXIII) do so because, having "high" dielectric constants in the liquid state or because developing effective polar moments two to three times that of the gaseous molecule. The relatively lower effect of these solvent liquids with 1,4-diaminoanthraquinone and with indigo may be explained perhaps by the following considerations. (a) Their dipole moment will have some positive weight for the anthraquinone dye, practically none for the indigo. (b) Their tendency to form hydrogen bonds may reduce the stability of internal structures of this type in a dissolved dye molecule. This could lessen the energy difference between the upper and lower levels and, hence, displace the absorption to longer wave lengths. The relative tendencies to intermolecular combination in these three dyes are indicated to some extent by comparison of the vapor spectra of the dyes with the spectra of solid films sublimed on glass (*cf.* Fig. 7). The positions of the maxima in the solid films, also the wave number differences between λ_m (solid) and λ_m (gas) are given below:

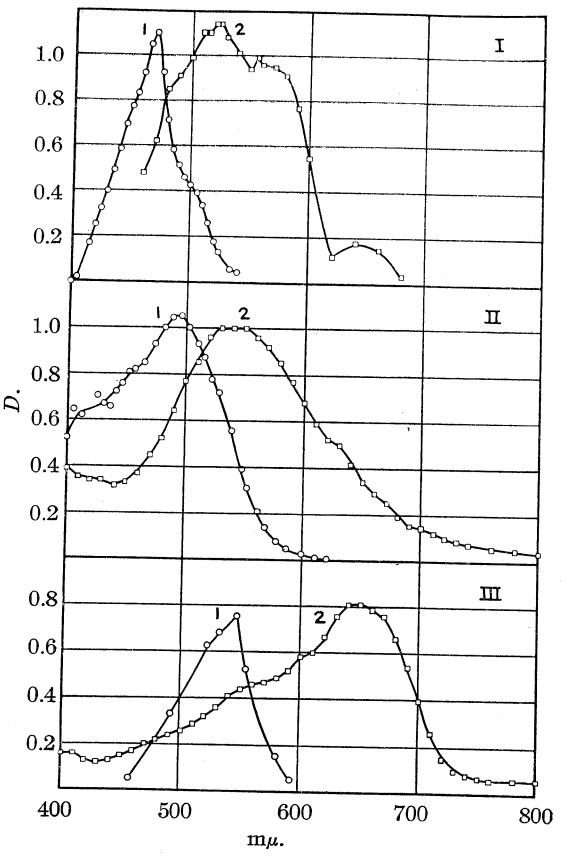


Fig. 7.—I, Merocyanine XXIII; II, 1,4-diaminoanthraquinone; III, indigo (1, vapor; 2, solid).

TABLE IX

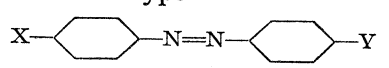
Merocyanine (XXIII)	1,4-Diaminoanthraquinone	Indigo
λ (solid) 520 mμ	540 mμ	650 mμ (670 mμ)[a]
$\Delta 1/\lambda$ 2036 cm.$^{-1}$	1820 cm.$^{-1}$	3015 cm.$^{-1}$

[a] From J. Königsberger and K. Küpferer (*Ann. Physik*, **37**, 601 (1912)).

There is a considerable change in each case, but largest for indigo. In view of the complications in the spectra of crystalline dyes[11] it appears premature to draw any very definite conclusions from these observations.

Azobenzene Derivatives

Molecules of the type



where X and Y are relatively basic and acidic (electropositive and electronegative) groups (Dilthey and Wizinger's auxochrome and antauxo-

(11) *Cf.* E. E. Jelley, *Ind. Eng. Chem.* (*Anal. Ed.*), **13**, 196 (1941).

chrome) give well-marked absorption bands in the near ultraviolet or the visible spectrum; the position varies with the potential drop between X and Y, being displaced farther to the long waves the greater the drop.

We have examined the influence of solvent (and of *p*H) on the following: (a) benzeneazodiphenylamine; (b) *p*-dimethylaminoazobenzene; (c) *p*-hydroxy-*p'*-nitroazobenzene; (d) *p*-amino-*p'*-nitroazobenzene; (e) *p*-dimethylamino-*p'*-nitroazobenzene.

The general character of the absorption spectra remains much the same with change of auxochrome groups. The long wave band is broad and considerably diffused, and this makes the assignment of values of $\lambda_{max.}$ (or $\nu_{max.}$) rather uncertain. Moreover, the addition of a proton (H^+) makes a large change in the resonance system, and consequently a large displacement of the absorption band. Since both bases and cations are "colored," overlap when conversion is incomplete can complicate the picture further. We shall give data only for *p-dimethylamino-p'-nitroazobenzene*, which are fairly representative of the group behavior.

The character of the absorption band and the shift with proton addition can be seen in Fig. 8. There can be discerned two major overlapping bands, α at longer, β at shorter wave lengths.

In Table X are given for λ_α and λ_β, the corresponding wave numbers for non-polar solvents, normal aliphatic and aromatic solvents of increasing polar moment.

TABLE X

p-DIMETHYLAMINO-*p'*-NITROAZOBENZENE

Solvent	n_D	$\mu \times 10^{18}$	α-Band 1/λ	β-Band 1/λ
Non-polar Solvents				
n-Hexane	1.375	0	(21400)	22720
Carbon tetrachloride	1.458	0	(21400)	22200
Benzene	1.498	0	20800	21740
Carbon disulfide	1.629	0	20400	21700
Aliphatic Solvents				
Diethyl ether	1.351	1.13	21400	22500
Methyl acetate	1.361	1.74	20600	21500
Acetone	1.356	2.74	20200	21300
Nitromethane	1.381	3.80	18900	19800
Aromatic Solvents				
Diphenyl ether	1.576	1.05	19600	20840
Phenyl acetate	1.500	1.52	20000	20840
Acetophenone	1.534	2.94	19600	20400
Nitrobenzene	1.553	3.90	19600	20300

Further, in Table XI are given the values for:

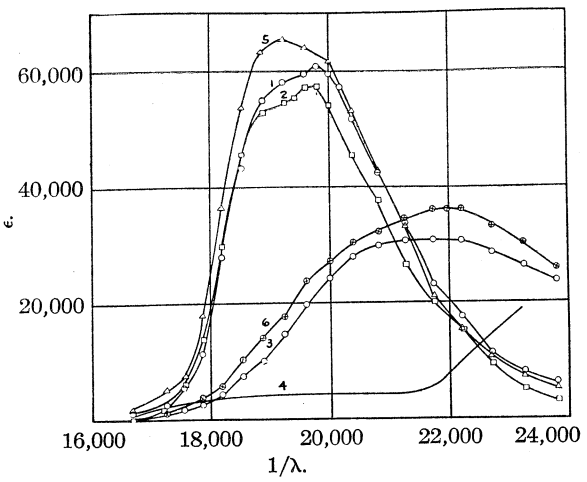


Fig. 8.—*p*-Dimethylamino-*p'*-nitroazobenzene in: 1, formic acid; 2, acetic acid + dilute H_2SO_4; 3, propionic acid; 4, concd. H_2SO_4; 5, dilute H_2SO_4; 6, diethylamine.

(i) normal aliphatic monocarboxylic acids; (ii) sulfuric acid and fatty acid with sulfuric; (iii) alcohol and acetone with sulfuric acid and with diethylamine, respectively; (iv) phenol, acetophenone, diethylamine.

TABLE XI

p-DIMETHYLAMINO-*p'*-NITROAZOBENZENE IN ACIDS, ALCOHOLS AND AMINES

	Solvent	$\mu \times 10^{18}$	α-Band 1/λ	β-Band 1/λ
i	Formic acid	1.77	19160	19800
	Acetic acid	1.63	20400	21740
	Propionic acid	1.68	20400	21740
	n-Butyric acid	1.9	20400	21700
ii	Concd. H_2SO_4		>23260	
	Dilute H_2SO_4 (1:1)		19200	20000
	Acetic acid + drop of dil. H_2SO_4		19000	19700
	Butyric acid + drop of dil. H_2SO_4		18800	19600
iii	Methyl alcohol	1.68	20200	21300
	Methyl alcohol + drop of dil. H_2SO_4		18600	19600
	Methyl alcohol + drop of diethylamine		20400	21300
	Acetone + drop of formic acid		20200	21300
	Acetone + drop of dil. H_2SO_4		18860	19800
	Acetone + drop of diethylamine		20400	21740
iv	Phenol	1.70	18200	19100
	Phenol + drop of dil. H_2SO_4		18200	19200
	Acetophenone + drop of dil. H_2SO_4		18300	19100
	Acetophenone + drop of diethylamine		19300	20400
	Diethylamine	0.9	20900	22000

The base, *p*-dimethylamino-*p'*-nitroazobenzene obeys Beer's law, *e. g.*, in benzene and in acetone, but in accord with the breadth and diffuseness of the absorption, the extinction coefficients are relatively low: benzene $E_{max} = 2.40 \times 10^4$; acetone $E_{max} = 2.56 \times 10^4$. The base in normal aliphatic and aromatic solvents shows "red displacement" with increasing polar moment of the solvent (Figs. 9 and 10), but the magnitude of the displacement is not large, and, as in the case of

merocyanine XXII (Part I), the behavior is complicated by the incidence of halochromy.

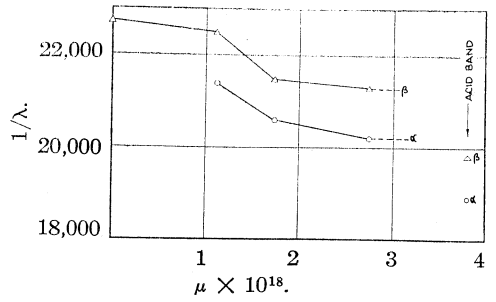


Fig. 9.—*p*-Dimethylamino-*p'*-nitroazobenzene (base) in aliphatic solvents.

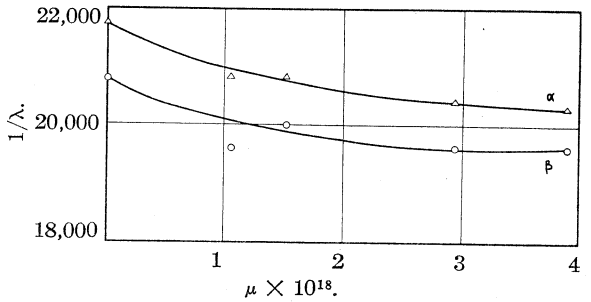


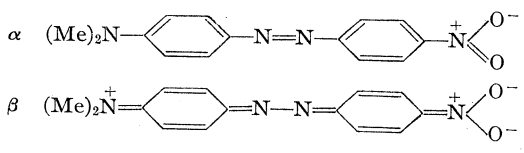
Fig. 10.—*p*-Dimethylamino-*p'*-nitroazobenzene (base) in aromatic solvents.

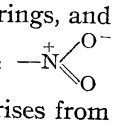
Addition of Proton

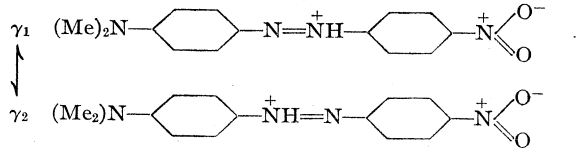
The weak acids, acetic, propionic and *n*-butyric, do not show the effect observed with merocyanine, with indigo, and 1,4-diaminoanthraquinone, of associating hydroxylated solvents. In fact, they behave as normal aliphatic solvents for the base. Formic acid, however, as found previously, behaves as a "strong" acid able to add a proton to the base.

The effect of this addition is quite strongly bathochromic, as may be seen from Fig. 8 and from the tables.

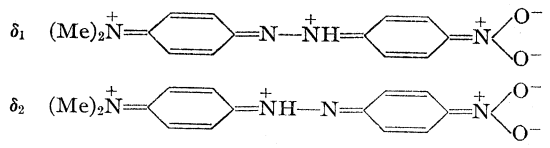
The two structures principally concerned in the resonance system of the base are very feasibly[12]



The upper structure α would be stabilized by the Kekulé resonance forms in the benzene rings, and perhaps, slightly by resonance in the  group. Perhaps the transition which arises from the splitting of the energy of these structures might give rise to an absorption of somewhat longer wave length than that of benzene, or rather of nitrobenzene itself, but it seems doubtful if we can assign even the shorter wave region of the main band of the base to this alone. The lower structure β is one of considerably lower stability, or of higher energy, than α, and as in the case of the merocyanines, may be considered as principally contributing to the first excited state. The effect of polarity of solvent on the "red displacement" is in accord with this interpretation. On adding a proton to the base we have two very similar but not identical alternates

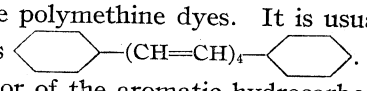


γ_1 and γ_2 are tautomeric, and each structure is stabilized, as in α, by the Kekulé resonance, etc. To these there similarly correspond structures of higher energy



All these will have a single net positive charge, and consequently, as observed with the ionic cyanines, little effect of polar moment of the solvent is to be expected. The addition of still another proton would block the resonance, and this possibly accounts for the decolorization produced in concentrated sulfuric acid (*cf.* Fig. 8).

Hydrocarbons

The dye molecules may be considered as derived from certain hydrocarbon protomorphs, which are, however, already resonance systems, by substitutions of reactive atoms and/or groups (*cf.* Part I). It has appeared well, therefore, to include for comparison some data: (a) on the behavior of a visible colored polyene—*diphenyl-octatetraene*—which has a constitution with some affinity to that of the polymethine dyes. It is usually formulated as  . (b) On the behavior of the aromatic hydrocarbons, benzene, naphthalene and anthracene.

Diphenyl-octatetraene

The absorption data are compiled from the

(12) *Cf.* G. N. Lewis and M. Calvin, *Chem. Revs.*, **25**, 305 (1939), for the similar system of *p*-nitro-aniline.

paper of Hausser, Kuhn and Kuhn,[13] (*cf.* Tables XII and XIII).

TABLE XII

DIPHENYL-OCTATETRAENE (BAND I) IN NON-POLAR MEDIA

Medium	n_D	K	$1/\lambda$	$\Delta 1/\lambda$
Vacuum	1.000	1.00	27933	
Hexane	1.375	1.87	25380	2553
Decalin	1.483		24938	2995
Benzene	1.498	2.28	24752	3181
Carbon disulfide	1.629	2.65	23923	4010

TABLE XIII

DIPHENYL-OCTATETRAENE (BAND I)

Solvent	$\mu \times 10^{18}$	$1/\lambda$	$\Delta 1/\lambda$
	Aliphatic		
Hexane	0	25380	2553
Ethyl ether	1.12	25252	2681
Acetic acid	1.63	25252	2681
Methyl alcohol	1.68	25445	2488
Ethyl alcohol	1.70	25252	2681
Formic acid	1.77	25189	2744
Acetone	2.74	25189	2744
	Aromatic		
Benzene	0	24752	3181
Xylene	0.4	24752	3181
Pyridine	2.11	24510	3423
Nitrobenzene	3.9	24332	3601

In non-polar solvents, the displacement increases continuously with increasing dielectric constant and refractive index (Fig. 11).

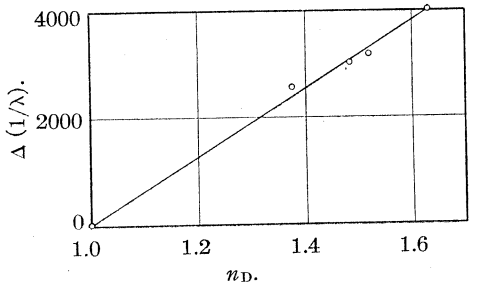
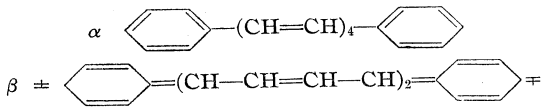


Fig. 11.—Diphenyl-octatetraene in non-polar media.

Data for the behavior in aliphatic and aromatic solvents of increasing polar moment are rather scant, and hardly permit definite conclusions. Certainly, it may be said that the displacement is greater in aromatic than in aliphatic solvents of comparable polar moment, but, while there are some indications of an influence of polar moment (*cf.* Fig. 12), they are not conclusive. Chloroform gives an apparently unduly large, methyl alcohol an unduly small displacement. The sensitivity to polar moment appears in any case to be small. The resonance system for the diphenyl polyene is probably somewhat similar to that of the azobenzenes



The upper structure α is stabilized by the Kekulé resonance of the terminal phenyl groups, and would contribute mostly to the ground level. The lower structures β are dipoles of considerably higher energy and would be expected to contribute mostly to the (first) excited level. Such effect as there is of polar moment would be in accord with this.

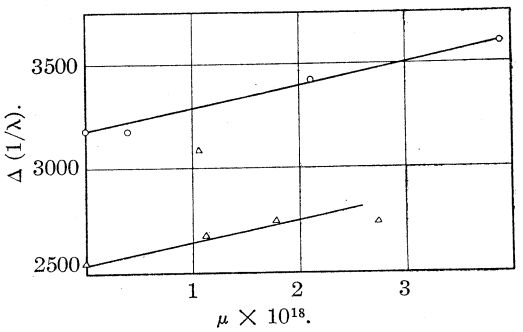


Fig. 12.—Diphenyl-octatetraene in polar media (Band I): Δ, aliphatic solvents; O, aromatic solvents.

Data on the solutions of *benzene* in different solvents are given by Lauer and Oda[14] for the absorption bands in the near ultraviolet. The first and second bands (the first band being of longest wave length and so on) show small *negative* displacements (*i. e.*, to shorter wave lengths) in solutions as compared with the vapor. These displacements—of the order of 300 cm.$^{-1}$—are much the same for the solvents tested, with the exception of water, in which it is smaller. The higher frequency bands show small *positive* displacements of the same order of magnitude, and again practically independent of the solvent, except that the shift in water is again smaller. The behavior of liquid benzene indicates an effect of the congener molecules little, if at all, different from that of the other solvents.

The insensitivity to solvents is in accord with the resonance system attributed to benzene,[15] and to the quantum mechanical theory developed by Sklar[16] and Förster.[10]

Similar in some respect to the aromatic fused-ring hydrocarbons are the phthalocyanine dyes

(13) K. W. Hausser, R. Kuhn and E. Kuhn, *Z. physik. Chem.*, **29B**, 417 (1935).

(14) K. Lauer and R. Oda, *Ber.*, **69**, 851 (1936).

(15) *Cf.* L. Pauling, *op. cit.*, p. 128.

(16) A. L. Sklar, *J. Chem. Phys.*, **5**, 669 (1937).

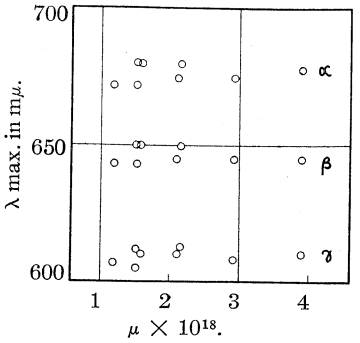
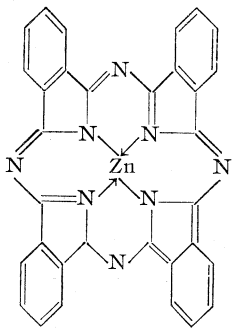


Fig. 13.—Zinc phthalocyanine in polar media.

(and thereby the porphine macrocyclic compounds in general).

Our spectrophotometric measurements on the phthalocyanines, exemplified by *zinc phthalocyanine* show no definite effect of polar moment of solvent on the absorption (Fig. 13). This indifference may be taken to mean that no ionized (dipolar) structures are represented in the first excited state; the resonance system is presumably by way of the two alternately covalently and coördinately linked pairs of the four interior N-atoms,[17] through the central atom, making the system resemble benzene with its basic Kekulé resonance. A notable difference from benzene, however, is the great intensity (extinction) of the longest wave absorption band.



(17) The conjugation extends, of course, through the external —N= links.

Acknowledgment.—We desire to express our thanks for helpful suggestions and criticisms to Dr. M. L. Huggins, and to Mr. H. R. Brigham for the preparation and spectrophotometry of sublimed solid films of certain dyes.

Conclusion

The results presented in this paper extend the tentative conclusions expressed in Part I. So far as these orienting investigations go, they indicate that the sensitivity of the absorption spectra of dyes to solvent influence is rather closely related to the resonance system of the dye, and may throw some light upon this. Correlatively, it appears possible that, with increased investigation, the effect of given solvents on the absorption spectrum of selected dyes may improve our understanding of the molecular structure of liquids. The rather notable behavior of halogenated alkyls suggests a promising field for further investigation as also the observations on hydroxylated solvents.

ROCHESTER, N. Y. RECEIVED JULY 29, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS UNIVERSITY]

The Solubility of Calcium Oxalate Monohydrate in Pure Water and Various Neutral Salt Solutions at 25°

BY WILBUR H. MCCOMAS, JR.,[1] AND WM. RIEMAN III

Because of the importance of calcium oxalate in analytical work, accurate data on its solubility are very desirable. A survey of the literature reveals, however, very discordant figures for the solubility in pure water and very few reliable data on the effect of neutral salts.[2] Table I summarizes the previous work on the solubility in pure water. Since the equilibrium between calcium oxalate and its saturated solution is established rather quickly, the major source of error in the solubility determinations probably lies in the failure to obtain pure calcium oxalate.

(1) This paper is taken from part of a thesis submitted by Wilbur H. McComas, Jr., in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Hammersten, *Compt. rend. trav. lab. Carlsberg*, **17**, 11 (1929), has studied the effect of several salts at 37°, mostly at ionic strengths below 0.2.

Solubility in Pure Water

Experimental.—Calcium oxalate monohydrate, product A, was prepared as follows:[2a] fifty mmol. of ammonium oxalate contained in 400 ml. was added slowly (twenty-five minutes) with vigorous stirring to 60 mmol. of calcium chloride contained in 1600 ml. at room temperature. Then 200 ml. of 0.1 *N* hydrochloric acid was added with vigorous stirring. The precipitate was digested for one day at 95–100°. After cooling, the precipitate was washed by centrifugation until a negative test for chloride ion was obtained in the wash water. It was stored under water until used.

(2a) Kolthoff and Sandell, *J. Phys. Chem.*, **37**, 459 (1933).

TABLE I

SOLUBILITY OF CALCIUM OXALATE IN PURE WATER AT 25°

Investigator	Solubility, molarity × 10^5
Richards, McCaffrey and Bisbee[3]	5.31
Herz and Muhs[4]	23.3
Kohlrausch[5]	4.84
Henderson and Taylor[6]	7.13
Scholder, Gadenne and Niemann[7]	5.23[a]
Hammarsten[2]	4.66[a]
Medes[8]	4.46[a]
Kolthoff and Sandell[9]	6.70
Pedersen[10]	4.84
Shehyn and Pall[11]	6.00[a]

[a] Solubility at 25° calculated from Kohlrausch's value of d log solubility/d(1/T).

Product B was prepared by an identical method except that the precipitation was performed in the presence of excess oxalate ions. Fifty mmol. of calcium chloride in 400 ml. were added to 60 mmol. of ammonium oxalate in 1600 ml., etc.

The solubility of each product was determined by agitating about a gram of precipitate with two liters of pure water for an hour at 25.0 ± 0.2°. Longer periods of saturation did not alter the result. The solution was separated from the precipitate by means of a porcelain micro filter stick. The first portions of the filtrate were rejected. Then 200-ml. portions were titrated with 0.02 N ceric sulfate by the method of Willard and Young.[12] Appropriate blank titrations were performed. The mean of six determinations for the solubility of product A was (4.46 ± 0.04) × 10^{-5} molar. The mean of seven determinations for product B was (4.63 ± 0.03) × 10^{-5} molar.

Discussion.—The close agreement between these two results is evidence for the purity of the products. The mean, 4.55 × 10^{-5} M, is in good agreement with the results of Kohlrausch, Hammarsten, Medes and Pedersen.

Solubility in Salt Solutions

Experimental.—About 1 g. of the pure calcium oxalate monohydrate in aqueous suspension was centrifuged and washed three times with portions of the standard salt solution. This precipitate was then added to about 2 liters of the standard salt solution, and the solubility was determined as in pure water.

Results.—The results are given in Table II. Each value in Column 4 is the mean of six determinations.

TABLE II

SOLUBILITY OF CALCIUM OXALATE IN SALT SOLUTIONS

Salt	Molarity of salt	Ionic strength	Solubility, molarity × 10^5	pS' Found	pS' Calculated
None	0.000	0.00018	4.55	8.684	8.670
NaCl	.100	.100	11.79	7.856	7.815
	.200	.20	15.47	7.621	7.623
	.300	.30	17.64	7.507	7.505
	.400	.40	19.50	7.420	7.415
	.500	.50	21.10	7.350	7.353
	.600	.60	22.58	7.292	7.300
	.700	.70	23.79	7.247	7.255
	.800	.80	24.82	7.210	7.216
	.900	.90	26.10	7.166	7.182
	1.000	1.00	27.08	7.135	7.151
KCl	0.64	0.64	22.99	7.277	7.281
$HCOONH_4$	.36	.36	22.34	7.302	7.450
Na_2SO_4	.213	.64	34.94	6.913	7.282

Since none of the solutions listed in Table II were sufficiently acid to change significant quantities of secondary oxalate ion to the primary anion, the classical solubility product, S', is simply the square of the molar solubility. Extrapolation of the experimental values of pS' to $\mu = 0$, gives 8.730 for the thermodynamic solubility exponent, pS. This figure was then used in conjunction with the equation of Gronwall, LaMer and Sandved[13] to calculate theoretical values of pS'. When a is 4.85 Å., the figures of Column 6 are obtained. These values are in good agreement with the experimental data for sodium and potassium chlorides to surprisingly high ionic strengths.

Summary

The solubility of pure calcium oxalate in water and in solutions of sodium chloride, potassium chloride, ammonium formate and sodium sulfate at 25° has been determined.

NEW BRUNSWICK, NEW JERSEY
RECEIVED AUGUST 13, 1942

(3) Richards, McCaffrey and Bisbee, *Z. anorg. Chem.*, **28**, 71 (1901).
(4) Herz and Muhs, *Ber.*, **36**, 3717 (1903).
(5) Kohlrausch, *Z. physik. Chem.*, **64**, 129 (1908).
(6) Henderson and Taylor, *J. Phys. Chem.*, **20**, 663 (1916).
(7) Scholder, Gadenne and Niemann, *Ber.*, **60**, 1510 (1927).
(8) Medes, *Proc. Soc. Exp. Biol. Med.*, **30**, 281 (1932).
(9) Kolthoff and Sandell, THIS JOURNAL, **55**, 2170 (1933).
(10) Pedersen, *ibid.*, **61**, 334 (1939).
(11) Shehyn and Pall, *J. Phys. Chem.*, **44**, 166 (1940).
(12) Willard and Young, THIS JOURNAL, **55**, 3260 (1933).
(13) Gronwall, LaMer and Sandved, *Physik. Z.*, **29**, 358 (1928).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF RUTGERS UNIVERSITY]

The Effect of *p*H on the Solubility of Calcium Oxalate

BY WILBUR H. MCCOMAS, JR.,[1] AND WM. RIEMAN III

The literature contains no accurate data on the effect of *p*H on the solubility of calcium oxalate. The purpose of our work was to supply such data and also to compare the observed effect of *p*H with theoretical predictions.

Theory

The solubility of calcium oxalate in any solution should follow the equation

$$[Ca^{++}]T = S' \frac{(H^+) + K_2'}{K_2'} \qquad (1)$$

where brackets denote the concentration of the enclosed species; parentheses denote activity; T is the total concentration of oxalate, *i. e.*, the sum of $[C_2O_4^=]$ and $[HC_2O_4^-]$; S' is the classical solubility product of calcium oxalate; and K_2' is the semiclassical second ionization constant of oxalic acid, defined by the equation

$$K_2' = \frac{(H^+)[C_2O_4^=]}{[HC_2O_4^-]} \qquad (2)$$

In the absence of excess calcium or oxalate

$$L = [Ca^{++}] = T \qquad (3)$$

where L is the solubility of calcium oxalate in moles per liter. Combination of these three equations yields

$$L = \sqrt{S' \frac{(H^+) + K_2'}{K_2'}} \qquad (4)$$

This equation can be used to predict the solubility of calcium oxalate in any given solution provided that values of S', (H^+), and K_2' are known. Data for S' are given in the previous paper. (H^+) may be calculated from *p*H measurements by the equation

$$pH = -\log (H^+) \qquad (5)$$

The non-thermodynamic assumptions implied in this equation do not introduce serious errors for our purpose.

Second Ionization Constant of Oxalic Acid

Solutions of the composition listed in Table I were prepared. Sodium hydrogen oxalate was not added as such, but sodium oxalate and oxalic acid were mixed to yield the indicated concentrations. The *p*H values of these solutions were measured at 25° with a Beckman *p*H meter (previously standardized against 0.0500 molal potassium acid phthalate), and the pK_2' values were calculated with equation (2). No corrections were applied to the concentrations of primary or secondary oxalate ions for the progress of the reaction

$$HC_2O_4^- \longrightarrow H^+ + C_2O_4^=$$

because these corrections would be smaller than the limit of error in measuring the *p*H, ±0.03 unit.

TABLE I

DATA FOR pK_2' OF OXALIC ACID

All concentrations are expressed as molarities.

$Na_2C_2O_4$	$NaHC_2O_4$	NaCl	μ	*p*H	pK_2'
0.01875	0.0125	0.0000	0.0688	4.14	3.96
.0375	.0250	.0000	.1375	4.06	3.88
.01875	.0125	.150	.2188	3.96	3.78
.01875	.0125	.250	.3188	3.90	3.72
.01875	.0125	.350	.4188	3.83	3.65
.01875	.0125	.450	.5188	3.82	3.64
.01875	.0125	.550	.6188	3.76	3.58
.01875	.0125	.650	.7188	3.73	3.55
.01875	.0125	.750	.8188	3.70	3.52
.01875	.0125	.850	.9188	3.68	3.50
.01875	.0125	.950	1.0188	3.64	3.46
		NH_4Cl			
.025	.025	.000	0.10	3.93	3.93
.025	.025	.100	.20	3.81	3.81
.025	.025	.200	.30	3.73	3.73
.025	.025	.300	.40	3.68	3.68
.025	.025	.400	.50	3.64	3.64
.025	.025	.500	.60	3.59	3.59
.025	.025	.540	.64	3.58	3.58
.025	.025	.600	.70	3.56	3.56
.025	.025	.700	.80	3.53	3.53
.025	.025	.800	.90	3.51	3.51
.025	.025	.900	1.00	3.49	3.49
.025	.025	1.80	1.90	3.36	3.36
		KCl			
.01875	.0125	0.050	0.1188	4.07	3.89
.01875	.0125	.350	.4188	3.91	3.73
.01875	.0125	.540	.6088	3.87	3.69
.01875	.0125	.850	.9188	3.82	3.64

By combining the data of Harned and Fallon[2] for the e. m. f. of the cell

$$H_2 \mid NaHC_2O_4(xm_1), Na_2C_2O_4(xm_2), NaCl(xm_3) \mid AgCl + Ag$$

with the data of MacInnes[3] for the single activity coefficient of the chloride ion, values of the semi-

(1) This paper is taken from part of a thesis submitted by Wilbur H. McComas, Jr., in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Harned and Fallon, THIS JOURNAL, **61**, 3111 (1939).

(3) MacInnes, *ibid.*, **41**, 1086 (1919).

classical second ionization constant of oxalic acid can also be computed. These values agree with ours within ± 0.03 pK unit throughout the range of Harned and Fallon's measurements ($\mu = 0.03$ to 0.17).

From a large-scale graph of the foregoing pK_2' values against the square root of ionic strength, it can be seen that the effect of sodium and ammonium chlorides is the same, but that the graph for potassium chloride lies above the other, the divergence beginning at about $\sqrt{\mu} = 0.4$.

Solubility of Calcium Oxalate in Formate Buffers

Buffers of formic acid and ammonium formate were prepared. Each buffer was 0.36 M with ammonium formate, and therefore had an ionic strength of 0.36. The concentration of formic acid in the buffers was varied. The solubility of calcium oxalate monohydrate at 25° was determined in each of these buffers as described in the previous paper. The pH of each filtrate was also determined with the Beckman pH meter. The results are presented in Table II.

The values in the last column were calculated by equation (4) with $S' = 4.97 \times 10^{-8}$ and $K_2' = 1.97 \times 10^{-4}$. Good agreement is obtained between the observed and theoretical solubilities up to 0.5 M formic acid. Greater concentrations of formic acid not only increase the hydrogen-ion activity but also alter the solvent properties of the medium. Since equation (4) does not take the latter effect into account, it is not accurate in high concentrations of formic acid.

TABLE II

SOLUBILITY OF CALCIUM OXALATE IN FORMATE BUFFERS

Molarity of HCOOH	pH	Solubility of CaC_2O_4, molarity $\times 10^4$ Observed	Calculated
0.0000	5.96	2.23	(2.23)
.0246	4.75	2.26	2.32
.0437	4.53	2.47	2.39
.0778	4.25	2.66	2.53
.138	4.02	2.86	2.73
.246	3.75	3.18	3.09
.437	3.50	3.48	3.60
.778	3.23	4.03	4.47
1.38	2.93	4.84	5.88
2.46	2.60	5.89	8.30

Summary

The semiclassical second ionization constant of oxalic acid has been determined at ionic strengths from 0 to 1 in the presence of sodium, potassium, and ammonium chlorides. The solubility of calcium oxalate monohydrate in formate buffers of constant ionic strength has been studied. Good agreement between observed and theoretical solubilities has been found.

NEW BRUNSWICK, NEW JERSEY
RECEIVED AUGUST 13, 1942

[CONTRIBUTION FROM THE WESTERN REGION BUREAU OF MINES, UNITED STATES DEPARTMENT OF THE INTERIOR]

The Specific Heats at Low Temperatures of Anhydrous Sulfates of Iron, Magnesium, Manganese, and Potassium.[1]

BY G. E. MOORE[2] AND K. K. KELLEY[3]

The Pacific Experiment Station of the Bureau of Mines for the past year has been engaged primarily in determining thermodynamic values of substances important in the metallurgy of strategic materials, particularly manganese and chromium. It is desirable to have these data not only for compounds of these metals themselves but also for the compounds of the metals associated with them in the ores and from which they must be separated. This paper deals with low-temperature specific heat measurements of anhydrous sulfates of iron, magnesium, manganese and potassium.

(1) Published by permission of the Director, Bureau of Mines, U. S. Department of the Interior. Not copyrighted.

(2) Associate Chemist, Western Region, Bureau of Mines.

(3) Senior Chemist, Western Region, Bureau of Mines.

Materials.—Reagent quality ferrous sulfate heptahydrate was heated slowly for several days to 125°, while evacuating with an oil-pump. It was then transferred to a high-vacuum line (mercury diffusion pump) and the heating continued. It was found necessary to heat to 235° to remove the last of the water, and some decomposition was unavoidable at this temperature. Analysis gave 37.30% Fe and 63.1% SO_4 compared with the theoretical figures 36.77 and 63.23%. Ferric iron corresponding to 1.6% Fe_2O_3 also was determined. Upon the basis of the iron analyses, which are the more significant, the purity of the sample is 98.4%. Higher purity would be desirable, but tests conducted at various stages in the dehydration process indicated that it is not possible to dry completely without decomposition. A 124.02-g. sample of this material was used in the measurements.

Reagent quality magnesium sulfate heptahydrate was dehydrated by heating in air in large nickel crucibles, the final temperature (400°) being maintained for two hours.

This procedure is essentially that recommended by Archibald.[4] Analysis gave 33.60% MgO; theoretical 33.49%. No calcium was found by the procedure given by Hillebrand and Lundell[5] for detecting small amounts of calcium in the presence of large amounts of magnesium. A small amount of magnesium oxide as such was found in the sample and directly determined by titration as 0.10 to 0.15%. The specific-heat measurements were made on a 142.95-g. sample.

Manganous sulfate tetrahydrate, reagent quality, was dehydrated by heating in air up to 400°, and this temperature was maintained overnight. After crushing and screening the heating was repeated, 400° being held for several hours.[6] The manganese content of the product was determined by precipitation as sulfide, washing and converting to anhydrous sulfate. This resulted in 36.33% (theoretical 36.38%). Sulfate analyses gave 63.77% (theoretical 63.62%). A 152.03-g. sample was used in the measurements.

Reagent quality anhydrous potassium sulfate was heated to 140° and used without further purification. Analysis for sulfate showed the material to be at least 99.7% pure. The sample used in the measurements contained 169.05 g.

Specific Heats.—The methods and apparatus used in the present work are the same as previously employed.[7] The results of the specific heat measurements, expressed in defined calories (1 calorie = 4.1833 int. joules), are given in Table I and shown graphically in Fig. 1. The formula masses employed and given in Table I are in accord with the 1941 International Atomic Weights.

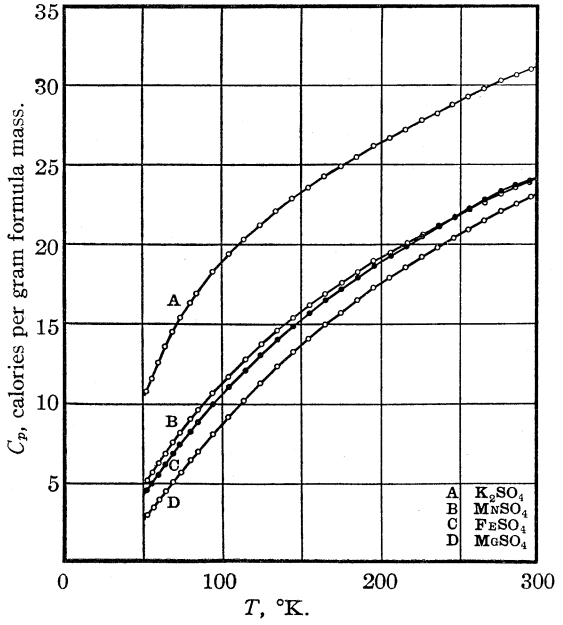


Fig. 1.—Specific heats of anhydrous sulfates.

(4) Archibald, "Preparation of Pure Inorganic Substances," John Wiley and Sons, New York, N. Y., 1932, p. 92.

(5) Hillebrand and Lundell, "Applied Inorganic Analysis," John Wiley and Sons, New York, N. Y., 1929, p. 488.

(6) The authors are indebted to Dr. G. W. Marks, Bureau of Mines, for dehydrating this material.

(7) Kelley, THIS JOURNAL, **63**, 1137 (1941).

TABLE I

SPECIFIC HEAT OF $FeSO_4$ (151.91 g.)

T, °K.	C_p cal./deg. mole	T, °K.	C_p cal./deg. mole	T, °K.	C_p cal./deg. mole
53.0	4.528	115.1	12.09	216.0	19.80
56.4	4.963	124.7	13.02	225.8	20.42
60.2	5.503	135.5	14.01	236.6	21.06
64.8	6.194	145.5	14.84	246.3	21.63
69.5	6.863	155.4	15.64	256.1	22.19
73.7	7.419	165.7	16.47	266.2	22.73
80.5	8.277	175.5	17.16	276.2	23.30
85.1	8.827	185.9	17.89	285.9	23.68
94.8	9.971	196.0	18.60	294.9	23.94
104.5	11.01	206.2	19.22		

Specific Heat of $MgSO_4$ (120.38 g.)

53.3	2.988	114.1	10.19	215.3	18.50
57.2	3.449	124.6	11.28	225.4	19.16
61.0	3.923	135.3	12.32	235.5	19.73
65.1	4.483	145.3	13.23	245.8	20.36
69.8	5.079	154.9	14.06	255.6	20.89
74.4	5.674	165.3	14.93	265.8	21.45
80.7	6.438	175.0	15.67	276.2	22.03
85.3	6.991	185.4	16.47	286.1	22.50
94.7	8.086	195.2	17.22	295.4	22.91
104.4	9.161	205.5	17.87		

Specific Heat of $MnSO_4$ (150.99 g.)

53.1	5.173	115.2	12.75	216.3	20.02
56.6	5.664	125.2	13.71	226.1	20.59
60.6	6.250	135.1	14.58	236.1	21.11
65.0	6.919	145.1	15.35	246.5	21.67
69.5	7.571	155.6	16.16	256.3	22.14
74.0	8.182	165.4	16.87	266.2	22.55
80.5	9.007	175.8	17.55	276.1	23.13
85.4	9.604	185.6	18.21	285.8	23.52
94.4	10.63	196.3	18.90	294.7	23.83
104.2	11.68	206.0	19.43		

Specific Heat of K_2SO_4 (174.25 g.)

52.7	10.73	114.0	20.26	215.1	27.13
56.1	11.52	124.2	21.15	225.5	27.74
60.3	12.51	134.2	22.03	235.2	28.17
64.8	13.54	144.6	22.82	244.8	28.71
69.2	14.45	154.7	23.51	255.1	29.23
74.2	15.36	164.6	24.21	265.2	29.72
80.2	16.29	175.0	24.83	276.0	30.26
84.2	16.87	184.8	25.42	286.1	30.60
94.5	18.22	195.4	26.11	295.4	30.99
104.7	19.34	205.3	26.61		

Figure 1 shows that all four substances exhibited normal behavior throughout the temperature range studied. Consequently, no discussion of the character of the specific heat curves appears necessary, and there are no previous data with which to compare. It should be mentioned that a small correction, ranging from 0.05 to 0.10%, depending on the temperature, has been applied to the magnesium sulfate results to compensate for the small quantity of oxide detected in the analysis.

No corrections for impurities were applied in the other instances.

It is desirable to record here that the heat capacity curve of the empty calorimeter was redetermined completely at the conclusion of the measurements reported in this paper. In the interim between these calibration measurements and the preceding set some 20 substances had been studied, a few minor repairs had been made, and a new White potentiometer had been installed. The new calibrations agree so well with the old that no error, in the specific heats of the substances studied in the interim, greater than 0.05% may be attributed to the combined sources of lack of constancy in the heat capacity of the empty calorimeter and difference in measuring instruments.

Entropies.—The entropies at 298.16°K. were obtained in the usual manner; the measured portions between 50.12° and 298.16°K. were computed graphically from C_p *vs.* log T curves, and the portions below 50.12°K. were extrapolated. For the latter purpose, the specific heat curves were fitted with the function sums listed below, and the temperature range represented is given in parentheses.

$FeSO_4$: $D\left(\frac{176}{T}\right) + 2E\left(\frac{329}{T}\right) + 2E\left(\frac{801}{T}\right)$, (51 to 200°K.)

$MgSO_4$: $D\left(\frac{242}{T}\right) + 2E\left(\frac{378}{T}\right) + 2E\left(\frac{866}{T}\right) + E\left(\frac{1683}{T}\right)$, (51 to 298°K.)

$MnSO_4$: $D\left(\frac{163}{T}\right) + 2E\left(\frac{304}{T}\right) + 2E\left(\frac{813}{T}\right)$, (51 to 220°K.)

K_2SO_4: $D\left(\frac{132}{T}\right) + 3E\left(\frac{198}{T}\right) + 2E\left(\frac{738}{T}\right)$, (51 to 225°K.)

The results are shown in Table II. Some correction of the ferrous and manganous sulfate values may be necessary to compensate for unextracted magnetic entropy when the pertinent data become available. The assigned errors apply only to the measurements and normal extrapolations made and do not allow for this contingency.

TABLE II

ENTROPIES AT 298.16°K. CAL./DEG. MOLE

	$FeSO_4$	$MgSO_4$	$MnSO_4$	K_2SO_4
50.12°K. (extrap.)	2.10	1.10	2.72	4.82
50.12–298.16°K. (graph.)	23.60	20.78	24.07	37.21
$S_{298.16}$	25.7 ± 0.3	21.9 ± 0.2	26.8 ± 0.3	42.0 ± 0.6

Previous entropy values have been reported for magnesium and potassium sulfates only[8]; 20 ± 2 and 44.8, respectively, have been estimated from decomposition data. The present values, of course, are preferable.

Related Thermal Data.—Free-energy-of-formation values from the elements, calculated from the third law of thermodynamics, are shown in column 4 of Table III. These values are based upon the present entropy results, the entropies of the elements,[8] and heat-of-formation data adopted by Bichowsky and Rossini,[9] except in the instance of manganous sulfate, for which the recent value of Southard and Shomate[10] is employed. Values computed from other considerations by Kelley,[11] in his survey of thermal properties of sulfur-containing compounds, are shown in column 5.

TABLE III

FREE ENERGIES OF FORMATION AT 298.16°K. CAL./MOLE

Substance	$\Delta H_{298.16}$	$\Delta S_{298.16}$	$\Delta F°_{298.16}$ (T.L.)	$\Delta F°_{298.16}$ (misc.)
$FeSO_4$	−221,300	−86.5	−195,500	...
$MgSO_4$	−304,950	−91.6	−277,640	−285,180
$MnSO_4$	−254,180	−86.5	−228,380	−228,020
K_2SO_4	−342,660	−94.1	−314,600	−314,580

Except for magnesium sulfate, the values are in good agreement. In this instance there exists a rather gross discrepancy between the third law and decomposition pressure results. At present the authors prefer the third-law value for this substance.

Summary

Specific heat measurements of anhydrous sulfates of iron, magnesium, manganese and potassium are reported in the temperature range 51 to 298°K.

The entropies at 298.16°K. were computed to be 25.7 ± 0.3 for $FeSO_4$, 21.9 ± 0.2 for $MgSO_4$, 26.8 ± 0.3 for $MnSO_4$, and 42.0 ± 0.6 for K_2SO_4.

Free-energy-of-formation values based upon the third law of thermodynamics are computed and compared with results from other data.

BERKELEY, CALIFORNIA RECEIVED AUGUST 7, 1942

(8) Kelley, Bureau of Mines Bulletin, 434, 1941, 115 pp.

(9) Bichowsky and Rossini, "Thermochemistry of Chemical Substances," Reinhold Publishing Co., New York, N. Y., 1936.

(10) Southard and Shomate, THIS JOURNAL, **64**, 1770 (1942).

(11) Kelley, Bureau of Mines Bulletin 406, 1937, 154 pp.

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 904]

The Molecular Structure of Methyl Isocyanide

BY WALTER GORDY[1] AND LINUS PAULING

It is known from its Raman spectrum[1a] and an earlier electron diffraction investigation[2] that the structure $CH_3—N{\equiv}C$: makes a larger contribution to the normal state of the methyl isocyanide molecule than the structure $CH_3—\dot{N}{=}C$:. If the latter structure were of much importance the C—N—C bond angle might differ somewhat from 180°. The infrared spectrum of the substance has been studied by Badger and Bauer,[3] who pointed out that the absence of splitting of certain lines indicates that the molecule is linear. We have made an electron diffraction investigation of the substance with the improved technique now available, and have verified that the molecule is linear or very nearly linear.

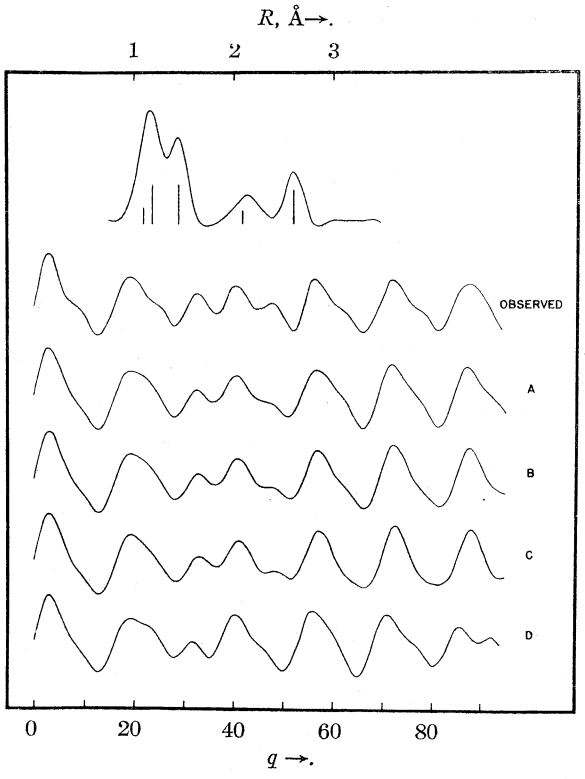


Fig. 1.—(Above) Radial distribution integral for methyl isocyanide, with lines indicating interatomic distances for the accepted structure. (Below) A curve representing the visual appearance of the photographs, and calculated simplified intensity curves for four models.

The samples used were prepared by Mr. David H. Brown from silver cyanide by the methods of Hartley and Gautier, and electron diffraction photographs were made and measured in the usual way. The photographs were much better than those obtained by Brockway, with seven measurable rings instead of three. The visual appearance of the photographs is represented by the sketched curve marked "Observed" in Fig. 1. The radial distribution integral calculated from this curve, also shown in Fig. 1, is seen to have principal peaks at 1.17, 1.43 and 2.59 Å. The first of these represents the shorter C—N bond distance with the C—H bond distance (1.09 Å.) unresolved. The effect of the latter on the position of the maximum should be small; we estimate it to be 0.01 Å., leading to 1.18 Å. for the shorter C—N bond distance. The peak at 1.43 Å. corresponds to the longer C—N bond distance and that at 2.59 Å. to the C—C distance.

The fact that the third distance is equal (to within 0.02 Å.) to the sum of the other two indicates that the C—N—C bond angle is close to 180°; for 160° the value 2.57 Å. would be expected, and for 150° the value 2.52 Å. Assuming that the probable errors of the radial distribution values are about 1%, we see that it is not likely that the angle is less than 160°.

Simplified intensity curves calculated for various models are shown in the figure[4]; the C—H distance was taken as 1.09 Å. and the methyl carbon bond angles as tetrahedral throughout. Temperature factors for the C—H terms were introduced as described by Stevenson, Burnham and Schomaker.[5] The other parameters of the models are the following

Model	$H_3C—N$, Å.	N—C, Å.	Angle C—N—C
A	1.44	1.18	180°
B	1.44	1.18	163°
C	1.44	1.18	156°
D	1.48	1.17	180°

(1) National Research Fellow in Physics; present address, Radiation Laboratory, Massachusetts Institute of Technology, Cambridge, Massachusetts

(1a) A. Dadieu, *Ber.*, **64B**, 358 (1931).

(2) L. O. Brockway, THIS JOURNAL, **58**, 2516 (1936).

(3) R. M. Badger and S. H. Bauer, *ibid.*, **59**, 303 (1937).

(4) The curves were calculated by an equation differing somewhat from that which we have used heretofore; this equation and a brief discussion of the radial distribution integral are given by R. A. Spurr and V. Schomaker, THIS JOURNAL, **64**, 2693 (1942).

(5) D. P. Stevenson, H. D. Burnham and V. Schomaker, THIS JOURNAL, **61**, 2922 (1939).

Curves C and D (Brockway's model) are unsatisfactory; C does not show the shelves for the 5th and 6th rings, and D makes the 4th ring much less pronounced than observed. A and B are about equally satisfactory. We conclude from this, as from the radial distribution integral, that the deviation from linearity is not greater than about 20°.

The observed frequency of the normal mode of oscillation corresponding mainly to bending of the CNC chain is 290 cm.$^{-1}$, and the corresponding force constant[6] has the value 0.205×10^{-11} erg radian^{-2}. The zero-point energy $h\nu$ for this degenerate oscillation corresponds to a root-mean-square deviation of 9.6° of the C—N—C angle from 180°, and the equipartition energy 2 kT at room temperature corresponds to the somewhat larger value 11.4°. The model indicated by the spectroscopic data would hence give a calculated intensity curve lying between A and B, and somewhat closer to B than to A. The electron diffraction photographs are accordingly compatible with this model.

The quantitative comparison of model A with the measured ring diameters leads to the C—N interatomic distances H_3C—N = 1.44 and N—C = 1.18 Å., in essential agreement with the radial distribution values. From these the average C—C distance is calculated, with consideration of the bending oscillation, to be 2.59 Å.

TABLE I

Max.	Min.	$q_{obs.}$	q_A	$q_A/q_{obs.}$
	1	12.7	13.0	(1.02)
1		19.2	19.3	1.005
	2	28.1	28.1	1.000
2		32.5	32.6	1.003
	3	36.4	35.8	0.983
3		40.2	40.6	1.010
	4	44.4	..	..
4		47.5	..	..
	5	51.4	50.9	0.991
5		56.5	56.7	1.003
	6	65.6	65.9	1.004
6		71.8	71.9	1.002
	7	80.9	81.2	1.003
7		87.5	87.0	0.994
			Average	1.000

(6) J. W. Linnett, *J. Chem. Phys.*, **8**, 91 (1940).

The H_3C—N value 1.44 Å. (which is 0.04 Å. smaller than that reported by Brockway) differs from the single-bond radius sum by only 0.03 Å., whereas the observed H_3C—C distance in methyl cyanide is 0.05 Å. smaller than the radius sum.[7] This indicates that hyperconjugation of the methyl group and the triple bond is smaller for the isocyanide than for the cyanide, which is reasonable in view of the fact that the corresponding structure $H^+CH_2{=}\overset{+}{N}{=}\ddot{C}:^-$ for the isocyanide has an unstable distribution of charge.

An explanation in terms of resonance can be given of the fact that the observed bending frequency of methyl isocyanide, 290 cm.$^{-1}$, is much smaller than that, 376 cm.$^{-1}$, for methyl cyanide, and that the bending force constants computed from the oscillational frequencies, 0.205×10^{-11} and 0.320×10^{-11} erg radian^{-2}, respectively, are similarly related. The force constant for the cyanide represents essentially the resistance to bending of a single bond and triple bond. In the case of the isocyanide the structure $H_3C{-}\ddot{N}{=}C:$, for which the bent configuration is the stable one, makes an increasing contribution to the normal electronic state as the molecule deviates by increasing amount from linearity, and the resultant increase in resonance energy lowers the wings of the electronic-energy curve, leading to a smaller force constant and oscillational frequency.

We thank Dr. V. Schomaker for his assistance and advice during this work.

Summary

The electron diffraction study of methyl isocyanide shows the molecule to be linear, with interatomic distances H_3C—N = 1.44 ± 0.02 Å. and N—C = 1.18 ± 0.02 Å.

PASADENA, CALIFORNIA RECEIVED JULY 20, 1942

(7) L. Pauling, H. D. Springall and K. J. Palmer, THIS JOURNAL, **61**, 927 (1939).

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

Non-carbohydrate Substances in the Cereal Starches

BY THOMAS JOHN SCHOCH

In a preliminary communication,[1] the author has reported the removal of fatty acids from the cereal starches by extraction with certain hydrophilic fat solvents. Recently, Evans and Briggs[2] have investigated the solvent extraction of corn starch, particularly as regards the identity of the fatty acids so liberated, and their development during ripening of the corn kernel. The present paper offers further data to indicate that the lipids of the common cereal starches are merely adsorbed on the starch. This is in contrast with the earlier views of Taylor and his co-workers,[3] who maintained that the fatty acids of the cereal starches were esterified with the alpha-amylose, contributing to the insolubility of that fraction.

The extent of removal of fatty material from corn starch depends on the nature of the solvent. Hydrocarbons or chlorinated hydrocarbons have little effect, while hydroxylated fat solvents remove much of the lipid material. This is illustrated by a series of Soxhlet extractions of corn starch with various solvents (Table I). While anhydrous dioxane gives inferior extraction, it will be noted that the constant boiling mixture of 80% dioxane with 20% water is among the most effective solvents.

Soxhlet extraction technique is limited to small quantities of material and to the use of pure solvents or constant boiling mixtures. Hence, extractions were likewise run by suspending one part of corn starch in three parts of the specified solvent, refluxing for one hour on the steam-bath with mechanical stirring, then filtering and digesting twice further in similar fashion with fresh solvent (Table II). Both dioxane and methanol were found to function more effectively when diluted with a small amount of water.

TABLE I

SOXHLET EXTRACTION OF CORN STARCH

Solvent	Hours extracted	Total material removed[a]	Fat content of extracted starch[b]
Mixed petroleum and ethyl ethers	18	0.04%	
Carbon tetrachloride	18	.04	
Ethyl acetate	18	.07	0.84%
Dioxane (anhydrous)	18	.15	.78
Isopropyl alcohol	18	.40	.72
Isoamyl alcohol	18	.42	
Methanol	18	.90	.10
Dioxane (80%)	18	.95	.06
Dioxane (80%)	3	.91	.26
Methyl cellosolve	3	.99	.18

[a] Determined by drying the extract to constant weight. Coloring matter and a portion of the protein are extracted from the starch by some of these solvents, and are included with fatty material under this heading. [b] The original raw starch analyzed 0.80% fat. All analyses for fat in starch reported in this paper were run in duplicate by the acid hydrolysis procedure,[4] and are corrected to dry starch basis. The precision of results by this method of analysis is of the order of ±0.02%. However, values tend to run slightly high, due to carry-over of dextrins by the mixed ethers used for extraction.

TABLE II

EXTRACTION OF FATTY MATERIAL FROM CORN STARCH

Solvent	Fat content of extracted starch[a]
Dioxane (anhydrous)	0.70%
Dioxane (80%)	.12
Dioxane (60%)	.34
Methanol (anhydrous)	.30
Methanol (85%)	.18
Methanol (75%)	.38
Methanol (65%)	.38

[a] By acid hydrolysis method. Original raw corn starch analyzed 0.84% fat.

The fat content of corn starch can be reduced by cold percolation with solvents, though this procedure is much less effective than hot extraction methods. Leaching with a large volume of cold 85% methanol decreased the fat content from 0.84 to 0.41%, or to 0.44% using 80% dioxane. Coloring matter is removed readily by this method.

The lipids extracted from corn starch prove to be free fatty acids, various samples ranging in acid number from 134 to 153. Exhaustive extraction with hot 85% methanol decreased the phosphorus content only slightly, from 0.017 to 0.015%. Most of this phosphorus must be esterified with the carbohydrate, since prolonged electrodialysis of an autoclaved paste of defatted corn starch at 1300 volts direct current potential merely reduced

(1) Schoch, THIS JOURNAL, **60**, 2824 (1938).

(2) Evans and Briggs, *Cereal Chemistry*, **18**, 443, 465 (1941); Evans, *ibid.*, **18**, 468 (1941).

(3) Taylor and Nelson, THIS JOURNAL, **42**, 1726 (1920); Taylor and Iddles, *Ind. Eng. Chem.*, **18**, 713 (1926); Taylor and Werntz, THIS JOURNAL, **49**, 1584 (1927); Taylor and Walton, *ibid.*, **51**, 3431 (1929); Taylor and Sherman, *ibid.*, **55**, 258 (1933).

(4) *Assoc. Official Agr. Chem.*, Official and Tentative Methods of Analysis, 4th ed., p. 208, 1935.

the phosphorus content to 0.013%, indicating the absence of any considerable amount of inorganic phosphate.

As estimated by Kjeldahl determinations, only a portion of the total protein is extracted from corn starch by 80% dioxane or by 85% methanol (Table III). It is assumed that the remainder of the protein either is of a different type, or is heat-denatured during extraction.

TABLE III

EXTRACTION OF PROTEIN FROM CORN STARCH

Treatment	% Protein
A, Raw corn starch	0.34
B, After four digestions with 85% methanol	.24
C, Product B, after twenty-four hours of Soxhlet extraction with 80% dioxane	.21
D, Raw corn starch, after forty-eight hours Soxhlet extraction with 80% dioxane	.26

The fatty material of rice starch can be similarly removed, but as the soap rather than the free fatty acid. It is presumed that the sample here employed was manufactured under alkaline steeping conditions.

Fat content of raw rice starch	0.59%
After seven successive digestions with 85% methanol	.03%
After forty-eight hours of Soxhlet extraction with 80% dioxane	.07%

In the case of wheat starch, the phosphorus appears to be present as a phospholipid, since both phosphorus and fat are removed concurrently (Table IV). After purification by solution in carbon tetrachloride, the extracted lipid analyzes high in phosphorus.

TABLE IV

EXTRACTION OF FATTY MATERIAL AND PHOSPHORUS FROM WHEAT STARCH

Treatment	% Fat[a]	% P[b]
Raw wheat starch, Sample A	0.50	0.054
Sample A, Soxhlet extracted forty-eight hours with 80% dioxane	.08	.008
Sample A, after seven digestions with 85% methanol	.04	...
Raw wheat starch, Sample B	.64	.059
Sample B, Soxhlet extracted forty-eight hours with 80% dioxane	.16	.022
Sample B, after seven digestions with 85% methanol	.03	...
Extracted fatty material from Sample B	...	2.25

[a] By acid hydrolysis. [b] Phosphorus was determined alkalimetrically, on the various starch samples after the dry-ashing procedure of Howk and De Turk,[5] and on the fatty extract by the A. O. A. C. method.[6] All analyses in duplicate.

These results are of particular interest since Stamberg and Bailey[7] have characterized the amylopectin fraction of wheat starch on the basis of its phosphorus content. From the above results, it appears that the phosphorus is present merely as an adsorbed phospholipid, and hence cannot be considered as truly characterizing either fraction. In contrast, prolonged Soxhlet extraction of potato starch with 80% dioxane does not materially reduce its phosphorus content.

Raw potato starch	0.095% P
After forty-eight hours of extraction with 80% dioxane	.087% P
After one hundred and twenty hours extraction with 80% dioxane	.084% P

Just as lipids can be removed by certain hydrophilic solvents, so it is also possible to impregnate starch with fatty acid by use of those same solvents. While this added fat cannot be removed by hydrocarbon solvents, it is readily extracted by hydrophilic solvents. Under similar conditions, carbon tetrachloride is inferior as a medium for impregnating starch with fatty acid:

A, 50 g. raw corn starch was suspended in 100 ml. of methanol containing 25 g. of oleic acid and evaporated to dryness on the steam-bath. The pasty mass was washed with hot xylene, then Soxhlet-extracted for twenty-four hours with carbon tetrachloride, dried and analyzed. Initial fat content of raw corn starch = 0.84%; final fat content = 2.26%.

B, Similar procedure, using defatted corn starch. Initial fat content = 0.17%; final fat content = 1.27%.

C, Similar procedure, but impregnating defatted corn starch with a 25% solution of oleic acid in carbon tetrachloride, instead of methanol. Initial fat content = 0.17%; final fat content = 0.26%.

D, Same procedure as in A, but using potato starch. Initial fat content of potato starch = negligible; final fat content = 0.77%. A portion of this fatted potato starch was Soxhlet-extracted for an additional twenty-four hours with carbon tetrachloride, thereafter analyzing 0.81% fat. A second portion was similarly extracted, but with 80% dioxane, which reduced the fat content to 0.04%.

The concept of a carbohydrate fatty ester is considered untenable. The selective removal of lipids by certain solvents cannot be attributed to ester exchange, since the free fatty acid or the soap is isolated. Also, no such mechanism could be formulated for dioxane. To ascertain whether a simple sugar fatty ester might decompose under the conditions of starch extraction, glucose penta-

(5) Howk and De Turk, *Ind. Eng. Chem., Anal. Ed.*, **4**, 111 (1932).

(6) *Assoc. Official Agr. Chem.*, Official and Tentative Methods of Analysis, 4th ed., p. 455, 1935.

(7) Stamberg and Bailey, *Cereal Chemistry*, **16**, 309, 319 (1939).

palmitate was refluxed for forty-eight hours with methanol and with 80% dioxane. In each case, the sugar ester was recovered quantitatively and unchanged. To clarify further the specific action of hydrophilic solvents in removing fatty material, oven-dried samples of corn starch were confined in closed containers over various solvents until constant weight was attained. The increase in weight of the starch due to solvent–vapor adsorption is directly related to the hydrophilic nature of the solvent, and hence is interpreted as a measure of solvent adsorption into the granule (Table V).

TABLE V

ADSORPTION OF VARIOUS SOLVENT VAPORS BY DRIED CORN STARCH

Solvent	Gain in weight, %
Benzene	0.6
Xylene	0.9
Carbon tetrachloride	1.1
Ethyl acetate	1.6
Dioxane (anhydrous)	3.3
Acetone	6.4
Methanol	19.6
Methyl cellosolve	20.6
Water	25.8

The lipids of the cereal starches appear to be distributed through the granule, loosely bound to the carbohydrate by polar adsorption, as suggested by Lehrman.[8] These lipids can only be displaced by fat solvents which can penetrate into the granule and adsorb preferentially on the starch by virtue of their hydrophilic loading. With dioxane and methanol, the hydrophilic qualities are markedly enhanced by the addition of a small amount of water.

The defatted cereal starches give clearer pastes possessing more pronounced gelling qualities than the original raw starches. The alkali lability is not increased by removal of lipid material. With corn starch, the apparent alkali number[9] drops slightly (*e. g.*, from 12.1 to 10.7), due to removal of fatty acid and protein, which consume a small amount of alkali in this test. Extraction of fatty acid raises the *p*H of corn starch to 6.0, within the range of minimum hydrolysis at elevated temperatures.[9] While raw corn starch pastes undergo slight hydrolysis during autoclaving, due to the acidity imparted by the presence of free fatty acid, no such effect is noted with pastes of defatted corn starch. At concentrations of 1–3%, defatted corn starch pastes may be dispersed by autoclaving for two hours at 19 pounds pressure, without any rise in the alkali number. The presence of lipid material appears to promote retrogradation of the cereal starches, and for this reason may interfere with enzymatic conversions. To avoid these effects, and for purposes of purification, it is the general practice in this Laboratory to defat all cereal starches intended for fundamental investigations. Recommended procedure is as follows: one part of starch is suspended in three parts of 85% (by volume) methanol, refluxed for several hours on the steam-bath with adequate stirring, filtered hot, then resuspended in fresh 85% methanol and extracted four times further in similar fashion. Five such extractions are sufficient to reduce the fat content of corn, wheat and rice starches to the vanishing point.

(8) Lehrman, THIS JOURNAL, **61**, 212 (1939); Lehrman has recently shown [*ibid.*, **64**, 2144 (1942)] that the adsorption of palmitic acid from methanol solution by potato starch or defatted corn starch follows a Freundlich isotherm, and that this adsorbed fatty acid is not removed by extraction with carbon tetrachloride.

(9) Schoch and Jensen, *Ind. Eng. Chem., Anal. Ed.*, **12**, 531 (1940).

Summary

The fatty acids of corn starch are removed without hydrolytic degradation by extraction with suitable hydrophilic fat solvents. Similarly, the fatty material can be removed from rice starch as the soap and from wheat starch as a phospholipid, together with substantially all the phosphorus of the original raw wheat starch. Consequently, these lipids cannot characterize any amylose fraction, but must be considered as natural impurities adsorbed on the starch. By the use of such hydrophilic fat solvents, corn starch or potato starch can be impregnated with fatty acid, and this added fat can only be removed by the same type of solvent used to introduce it.

Prior to use for any fundamental studies, it is recommended that the common cereal starches be purified of such lipid material by successive extractions with hot 85% methanol.

ARGO, ILLINOIS RECEIVED AUGUST 12, 1942

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

Fractionation of Starch by Selective Precipitation with Butanol

BY THOMAS JOHN SCHOCH

Introduction

The existence of several component amyloses in the common cereal and tuber starches has long been presumed. However, the literature records little agreement on the methods for isolating these components, or on their individual chemical and physical characteristics and relative proportion in the native starch. Most of this confusion can be traced to four principal sources of error: 1, incomplete dispersion of the starch prior to separation studies, thus including swollen and partially fragmented granules in the insoluble fraction; 2, slow separation methods, as by prolonged leaching or electrophoresis, permitting the starch to "retrograde" to less soluble form; 3, hydrolytic changes suffered either preliminary to or during the fractionation, as the use of starch solubilized by ball-milling or by alcoholic acid treatment, or the application of doubtful enzymatic methods to effect a separation; 4, interference by non-carbohydrate impurities, especially by fatty acid in the case of corn starch.

Based on the selective precipitant action of normal butyl alcohol toward starch sols,[1] a new technique of fractionation has been developed which avoids the above difficulties and which yields products[2] of markedly different physical and chemical characteristics. It has not as yet been established whether this mode of separation isolates two specific amyloses existing in the starch, or whether it fractionates a graded series of starch components. However, it is hoped that the methods here presented will help to clarify the problem of starch structure, by affording two chemically different fractions which may be studied individually and by comparison with one another. The fractionation involves four separate steps: (1) dispersion of the starch without attendant hydrolysis by autoclaving within carefully controlled *p*H limits, (2) selective precipitation of one fraction under conditions which prevent retrogradation, presumably through complex formation with the precipitating agent, (3) separation of this product by supercentrifuging, and (4) a system of purification of this fraction by washing or by reprecipitation. The specific application of these methods to corn starch, potato starch and waxy maize will be considered in turn.

(1) Schoch, *Cereal Chem.*, **18**, 121 (1941).

(2) The author prefers not to identify these fractions as alpha and beta amyloses, nor as amylose and amylopectin, since these terms have been so confused by indiscriminate usage. Until a more exact nomenclature can be devised, based on the identification of specific configurational differences between these fractions, they will be designated merely as the "butanol precipitated fraction" and the "butanol non-precipitated fraction."

Corn Starch

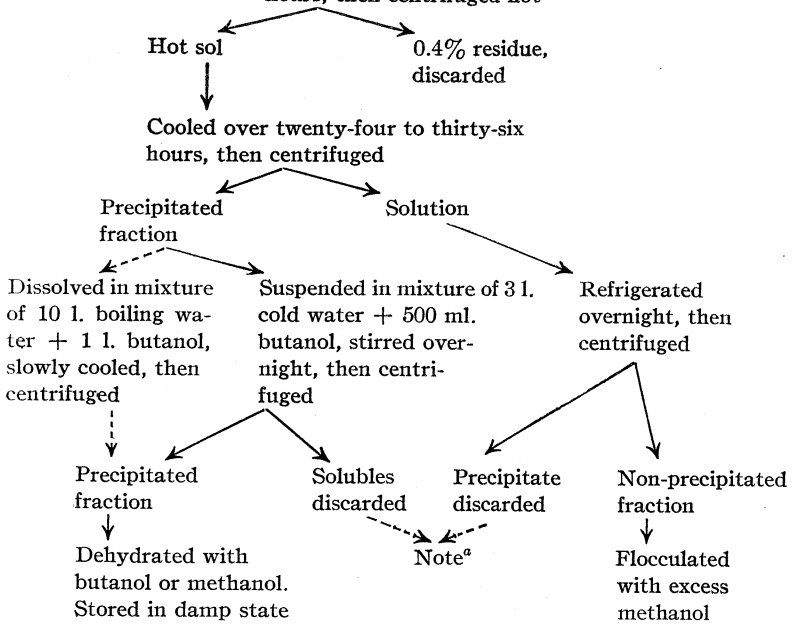
Removal of Fatty Material.—In a previous publication,[3] the use of defatted corn starch has been advised for all investigations of a fundamental character, and a method of purification has been outlined, consisting of five successive extractions with hot 85% methanol. This defatted starch is preferred as starting material for fractionation studies, since its *p*H is stabilized at 5.9–6.0 permitting autoclaving without glucosidic hydrolysis. While raw starch can be used, the lower *p*H (5.0–5.3) prohibits autoclaving and the presence of fatty acid interferes with the fractionation.

Dispersion of the Starch.—Regardless of whether the several fractions of starch are uniformly distributed throughout the granule, or whether one fraction constitutes an outer envelope, it is imperative to effect optimum dispersion of the granule structure preliminary to any fractionation study. In the opinion of the author, autoclaving affords the nearest approach to ideal dispersion, provided that hydrolytic breakdown is prevented by rigid maintenance of the *p*H between 5.9–6.3.[4] If a raw corn starch paste is adjusted within these limits by means of sodium hydroxide, the *p*H will drift badly during autoclaving. If sufficient buffer salts are added to maintain a stable *p*H, the presence of this electrolyte interferes with subsequent flocculation of the butanol precipitated fraction. Fortunately, the *p*H of defatted corn starch stabilizes at 5.9–6.0 during the entire separation. Presence of butanol during the autoclaving aids the breakdown of granule structure, by markedly lowering the gelatinization temperature of the starch, possibly a surface tension effect. A mixture of 14 liters of water and 2 liters of butanol in a 5-gallon Pyrex stock bottle is heated to boiling on the steam-bath, and a suspension of 150–450 g. (preferably 300 g.) of defatted corn starch in 1 l. of water is slowly added with vigorous mechanical stirring (Flow Sheet). This amount of butanol is considerably in excess of the 8% required to saturate the aqueous phase, to provide for loss during autoclaving. Also, it is desirable to have a supernatant layer of excess butanol present during the entire separation, to prevent the formation of insoluble "skins" by surface evaporation. The 1–3% paste is then autoclaved for two to three hours at 18–20 lb. pressure. Tests have shown that the viscosity drops to a minimum (indicative of granule disinte-

(3) Schoch, THIS JOURNAL, **64**, 2954 (1942).

(4) Schoch and Jensen, *Ind. Eng. Chem., Anal. Ed.*, **12**, 531 (1940).

FLOW SHEET.—FRACTIONATION OF CORN STARCH: 150–450 g. of defatted corn starch pasted in a mixture of 15 l. of water + 2 l. of butanol, autoclaved two hours, then centrifuged hot



Dotted lines indicate alternative procedures.

[a] Soluble and precipitated residues are usually slight in amount and may be discarded. Where total recovery is desired, they may be combined at this point, dissolved by autoclaving, then reprecipitated and separated.

gration) in one to one and one-half hours under these conditions. If maximum purity of product is desired, the hot starch sol may be passed through the continuous supercentrifuge at this point, removing impurities and incompletely dispersed starch, totalling approximately 0.4% of the original starch. This insoluble residue is dark in color and may analyze as high as 10% ash. It appears to represent an irreducible minimum of undispersed material.

As an alternative but somewhat less effective method of dispersion, the butanol–water–starch paste may be boiled under reflux for five to six hours with vigorous mechanical agitation. This digestion time exceeds that required to reduce the viscosity to a minimum. The hot sol is then passed through the supercentrifuge, removing 1–3% of undispersed material. While this method is not recommended, it yields products similar in properties and amount to those obtained from autoclaved pastes, thus justifying use of the more efficient autoclave methods for dispersing the starch.

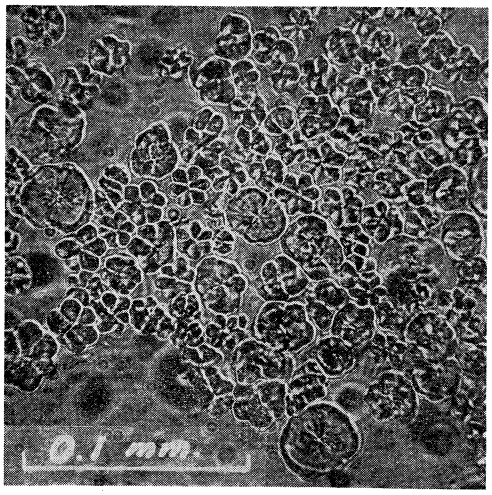


Fig. 1.—Butanol precipitate from corn starch.

Flocculation and Separation.—The hot starch sol, by whichever method prepared, is cooled slowly and without agitation to room temperature over a period of twenty-four to thirty-six hours. This can be accomplished by insulating the container with a thick wrapping of cloth. A "crystalline" floc forms in the neighborhood of 50°, usually as more or less perfect six-segmented spherulites, 15–50 microns in diameter (Fig. 1). Separation is preferably effected by means of a Sharples continuous supercentrifuge, fitted with a clarifier bowl, operating at 50,000 r. p. m., and capable of passing 20 l. of liquid per hour. The precipitated fraction is deposited in the rotor of the centrifuge as a stiff white cream. When operating satisfactorily, the centrifugate should be optically void under the polarizing microscope.

The Precipitated Fraction.—These spherocrystalline formations are birefringent under polarized light, giving an interference pattern somewhat similar to the familiar "Maltese Cross" of native starches. If lightly stained with a solution of iodine in butanol, they become dichroic under crossed nicols. The crystalline form is not disturbed by treatment with cold water saturated with butanol. However, if treated with cold water alone, the spherulites instantly fracture and swell. The product as removed from the bowl of the centrifuge may be dehydrated with methanol or butanol without altering its character, provided that the alcohol is not permitted to dry off. If the butanol precipitated fraction from corn starch is thoroughly dried, the spherulites lose all birefringence, though retaining their outward form. While this product swells in hot or cold water, it does not dissolve. The damp product as removed from the centrifuge, or after dehydration with methanol or butanol, is readily soluble in boiling water, either in the presence or absence of butanol. Relatively clear solutions can be prepared at concentrations as high as 10–15% solids. These are highly unstable, showing exaggerated retrogradation tendencies and forming insoluble skins with great facility. Even at dry solids concentrations as low as 1.5%, solutions of the precipitated fraction will set to hard irreversible gels on cooling to room temperature. At concentrations below 0.5%, solutions are reasonably stable at room temperature, though they eventually retrograde on standing. From its mode of prepara-

TABLE I

BUTANOL FRACTIONATION OF CORN STARCH

Batch	Method	% Yield of precipitated fraction	Alkali no. of fractions Precipitated	Alkali no. of fractions Non-precipitated
CA	Single precipitation from autoclaved 1.5% defatted corn starch paste	25		
CB	Similar	29		
CC	Similar	27		
CD	Similar, but at 3% concentration	28		
CE	Precipitated from 1.5% autoclaved defatted starch paste, then dissolved and reprecipitated	21	31.3	8.3
CF	Similar to Batch CE	23	29.5	6.1
CG	Similar to Batch CE, but butanol precipitate was dissolved and re-autoclaved before second precipitation	21		
CJ	Precipitated from 1.5% boiled paste of defatted corn starch, then dissolved and reprecipitated	23	21.9	
CM	Single precipitation from 1.5% boiled paste of defatted corn starch	22.8		
CP	Precipitated from 1.5% boiled paste of raw corn starch, then dissolved and reprecipitated	16	23.6	5.5
CQ	Similar to Batch CP	13	22.7	5.3
CS	Similar to Batch CE	22.4	24.4	4.7
CU	Precipitated from 1.5% boiled paste of defatted corn starch, then washed with butanol–water mixture	20.3	23.2	5.1
CV	Precipitated from 1.5% autoclaved defatted starch paste, then washed with butanol–water mixture	23.6		
CW	Similar to Batch CV, but at 2% concentration	22.2		5.7
CX	Similar to Batch CV, but at 3% concentration	22.8		5.9
CY	Similar to Batch CV, but at 1% concentration	23.3		5.8

tion and solubility behavior, it is suggested that the spherulites may represent a crystalline addition compound between butanol and a specific starch fraction. This product is stable in the presence of excess butanol, but reverts to insoluble form on removal of the latter, whether by treatment with cold water or by drying.

The reason for the selective precipitating action of normal butyl and isoamyl alcohols is obscure, possibly depending on some undefined optimum of molecular volume or "hydrophil balance." No satisfactory separation could be effected with lower alcohols, while octyl alcohol or cyclohexanol precipitated all the starch substance indiscriminately.

After removal of the butanol precipitated fraction, the centrifugate gives no further precipitate, either on long standing, or on refrigeration, or after a second autoclaving. The non-precipitated fraction can be obtained readily by the usual practice of flocculating with excess methanol and triturating with fresh portions of methanol until dehydrated.

Purification.—Either of two methods may be used for purifying the butanol precipitated fraction. The product may be merely suspended in water previously saturated with butanol, thoroughly stirred, then centrifuged. In most cases, this simple washing procedure is adequate. For more thorough purification, the precipitated fraction may be "recrystallized." The moist product as removed from the centrifuge (representing 30–100 g. of dry substance) is slowly added with vigorous agitation to a boiling mixture of 10 l. of water and 1 l. of butanol. On slow cooling, the butanol precipitated fraction flocculates out in minute particles, possibly 1–2 microns in diameter. Efforts to increase the size of these crystals by various cooling procedures have not been successful. However, the product is readily centrifuged, and recovery is 90–95%. This reprecipitated product is dehydrated by suspending in butanol, then filtered on a Büchner and bottled as a damp product, containing 40–50% dry solids. The yields of butanol precipitated fraction from corn starch have averaged 22% (on dry starch basis), under various conditions of preparation, isolation and purification (Table I).

Properties of the Corn Starch Fractions.—After thorough drying, the non-precipitated fraction from corn starch is soluble in cold water to the extent of 4–5%, and in hot water to 10–12%. When hot 10% solutions are cooled down, they give pasty gels which are readily liquefied by heating. Solutions show no tendency to retrograde on long standing, even at refrigerator temperatures. This behavior suggests that the non-precipitated fraction constitutes the more stable and colloidally soluble portion of the starch. In contrast, the butanol precipitated fraction might be considered as responsible for the gelation and retrogradation tendencies of corn starch.

An outstanding chemical difference between the butanol separated fractions lies in their respective alkali labilities. Various samples of the precipitated fraction average an alkali number[4] of 25, much higher than the original defatted corn starch. The non-precipitated fraction is correspondingly lower, averaging 5.6. Calculating the composite alkali number of the original defatted starch from these average values and from the proportion of each fraction in the starch, an estimated value of 10.0 is obtained, in good agreement with the observed alkali number of 11.0. This is taken as evidence that fractions of high and low alkali lability exist as such in the original starch, and are not produced by some obscure hydrolytic change during the process of fractionation.

It is believed that the alkali number is an index of ter-

minal aldehyde content. However, in view of the possible presence of branched chain configurations in starch, no direct relationship can be deduced between alkali number and molecular weight. In this connection, Bear[5] has recently reported that the butanol precipitated fraction gives a V-type X-ray pattern, while that of the non-precipitated fraction is relatively diffuse and amorphous. On the basis of the degree of orientation during flow, Rundle and Baldwin[6] suggest that the precipitated fraction consists of the unbranched component of the starch, while the non-precipitated fraction is composed of branched material.

The Ostwald viscosity of the two fractions can be compared by dissolving the dried products in cold 0.4 *N* sodium hydroxide solution. In this medium, the non-precipitated fraction has been slightly but consistently more viscous than the butanol precipitated material.

Behavior toward butanol must be considered as a specific difference between the fractions. For example, after alkali number determinations on the individual fractions (involving extensive degradation in hot aqueous alkali), if butanol is added to the cooled and neutralized solutions, the butanol precipitated fraction gives an immediate crystalline floc. The non-precipitated fraction remains clear, even on refrigeration.

Pacsu and Mullen[7] have recently reported an exceedingly interesting method of starch fractionation by selective adsorption on cotton. The butanol precipitated fraction possesses a strong affinity for cellulose, while the non-precipitated fraction is not adsorbed. While not necessarily identical, the two methods of starch separation appear to be very similar, not only in the nature of the fractions produced, but likewise in the adsorption mechanisms involved. A comparative study of the two methods is now in progress.

Periodic acid does not distinguish between the butanol separated fractions, since both oxidize at the same rate and with the same total consumption of oxidizing agent.

Phosphorus does not appear to have any very significant function in characterizing the corn starch fractions. The non-precipitated portion can be separated into sub-fractions of high and low phosphorus content by electromigration of a 1.5% solution at 1300 volts direct current potential. These sub-fractions do not differ materially in solubility behavior or in alkali number (Table II).

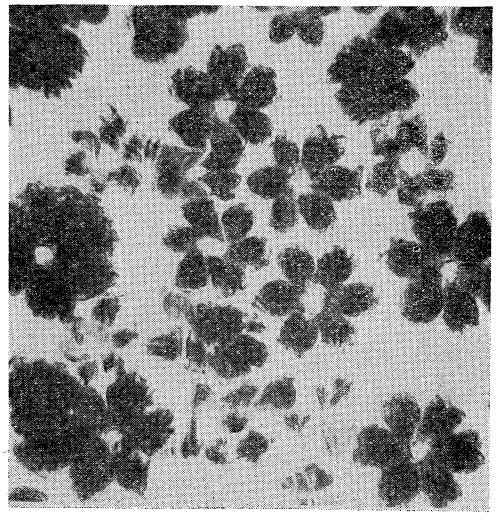


Fig. 2.—Butanol precipitate from potato starch, stained with iodine.

TABLE II

DISTRIBUTION OF PHOSPHORUS IN THE CORN STARCH FRACTIONS

Sample	Alkali no.	% Phosphorus[a]
Defatted corn starch	11.0	0.0153
Dried butanol precipitated fraction, extracted with hot water	23.2	.0088
Non-precipitated fraction	5.1	.0107
Migrated sub-fraction (77% recovery from non-precipitated fraction)	5.2	.0116
Non-migrating sub-fraction (20% recovery from non-precipitated fraction)	5.0	.0029

[a] Phosphorus determined by the method of Howk and De Turk, *Ind. Eng. Chem., Anal. Ed.*, **4**, 111 (1932).

Potato Starch

Fractionation of potato starch is accomplished in much the same manner as described for corn starch. Obviously, defatting is unnecessary. Samples of potato starch employed in this investigation tested 6.0 *p*H and no adjustment was required. The concentration of the autoclaved paste should not exceed 2%. Centrifugal clarification of the hot autoclaved sol may be omitted, since undispersed material runs less than 0.1%.

The yields of butanol precipitated fraction from potato starch averaged 22%, identical in amount with that from corn starch. However, several pronounced differences have been noted between the butanol precipitated fractions from corn starch and from potato starch. The latter separates either as large, well-formed, six-petalled rosets, 50–80 microns in diameter (Fig. 2), or as clumps of hair-like needles. After thorough drying, the precipitated fraction from potato starch remains relatively water-soluble, with little tendency to gel or retrograde. Its alkali number averages 11.

TABLE III

BUTANOL FRACTIONATION OF POTATO STARCH

Batch	Method	% Yield of precipitated fraction	Alkali no. of fractions Precipitated	Non-precipitated
PA	Slow precipitation from 1.5% boiled starch paste, washed with butanol–water	21.3	10.6	5.9
PB	Slow precipitation from 3% autoclaved paste, then washed with butanol–water	24.6	10.1	5.0
PC	Slow precipitation from 1.5% autoclaved paste, then dissolved and reprecipitated	21.0	11.5	6.6

(5) Bear, THIS JOURNAL, **64**, 1388 (1942).
(6) Rundle and Baldwin, *ibid.*, to be published.
(7) Pacsu and Mullen, *ibid.*, **63**, 1168 (1941).

The phosphorus content of potato starch is located principally in the non-precipitated fraction. Unlike corn starch, this fraction migrates completely in an electrophoretic cell, retaining substantially all its phosphorus.

TABLE IV

DISTRIBUTION OF PHOSPHORUS IN THE POTATO STARCH FRACTIONS

	Alkali no.	% Phosphorus
Original potato starch	7.5	0.072
Butanol precipitated fraction	11.5	.0103
Non-precipitated fraction	6.6	.079
Non-precipitated fraction, electromigrated (98.6% recovery)	6.4	.072

These results correct earlier observations by Taylor and Schoch.[8] In the latter investigation, no fractionation of potato starch could be obtained by electrophoresis, and it was assumed that the phosphorus was randomly distributed, without characterizing any specific fraction. With the more sensitive butanol precipitation technique, the presence of fractions is definitely established, and phosphorus is shown to be preferentially attached to the non-precipitated portion.

The butanol precipitated fraction from potato starch gives a pure blue coloration with iodine, while the non-precipitated portion tends toward the purple.

Waxy Maize Starch

Waxy maize starch has recently occasioned considerable interest, by reason of its red coloration with iodine and its reputed lack of retrogradation tendencies.[9] Since these qualities are suggestive of the non-precipitated fraction, an investigation of its behavior toward butanol was undertaken.

Waxy maize starch was defatted in the prescribed manner, reducing the total fat content from 0.11 to 0.04%. This defatted starch analyzed an alkali number of 4.1, much lower than any of the common cereal or tuber starches. Butanol treatment of autoclaved pastes gave no trace of crystalline flocculate. A small amount of slime and impurities (less than 3%) was separated by the supercentrifuge, but most of this material could be dispersed by further autoclaving and did not subsequently precipitate with butanol.

(8) Taylor and Schoch, THIS JOURNAL, **55**, 4248 (1933).

(9) Hixon and Sprague, *Ind. Eng. Chem.*, **34**, 959 (1942).

Summary

By means of selective precipitation with butanol, a method of starch fractionation has been developed which avoids retrogradation and hydrolytic degradation. The precipitated fraction (constituting 22% of either corn or potato starch) is isolated in unique spherocrystalline form, probably as an addition compound with the butanol. The butanol precipitated fractions from corn and potato starches are more alkali labile than the respective raw starches, while the non-precipitated fractions are correspondingly more alkali stable, indicative of definite chemical differences.

The butanol precipitated fraction from corn starch tends to revert to insoluble form and appears to be the component of the starch responsible for gelation and retrogradation. The non-precipitated fraction from corn starch constitutes the more soluble and stable component.

With potato starch, the physical differences between the fractions are less pronounced, since the butanol precipitated portion is more soluble and less subject to retrogradation than the corresponding fraction from corn starch. The phosphorus in potato starch is principally associated with the non-precipitated fraction.

Waxy maize starch is peculiar in possessing an unusually low alkali lability and in giving no precipitate with butanol.

ARGO, ILLINOIS RECEIVED SEPTEMBER 8, 1942

[CONTRIBUTION FROM THE PEDIATRIC RESEARCH LABORATORY OF THE JEWISH HOSPITAL OF BROOKLYN]

Synthesis of Derivatives of Diphenylethane Related to Materials Occurring Naturally. IV. Stilbene-2-acetic Acid

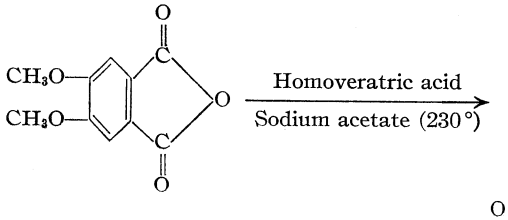
BY SAMUEL NATELSON AND SIDNEY P. GOTTFRIED[1]

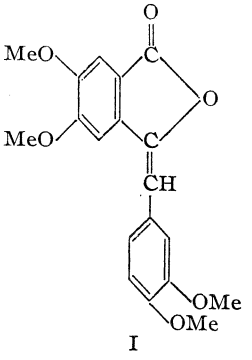
In an earlier communication[1a] the authors indicated the relationship between benzalphthalide and benzylisoquinoline. In order to continue the study of this series, it was necessary to convert the previously synthesized stilbene-2-aldehyde to stilbene-2-acetic acid ($C_6H_5CH{=}CHC_6H_5CH_2COOH$).

At first this was accomplished by the condensation of the aldehyde with hippuric acid, and the hydrolysis and oxidation of the resulting azlactone.

While studying the method for the hydrolysis of the azlactone, it was observed that the intermediate, *o*-styryl-α-benzamido cinnamic acid could be obtained in excellent yield with dilute barium hydroxide. This compound could be hydrolyzed and oxidized to stilbene-2-acetic acid by boiling with sodium hydroxide solution and then treating the resultant solution with hydrogen peroxide.

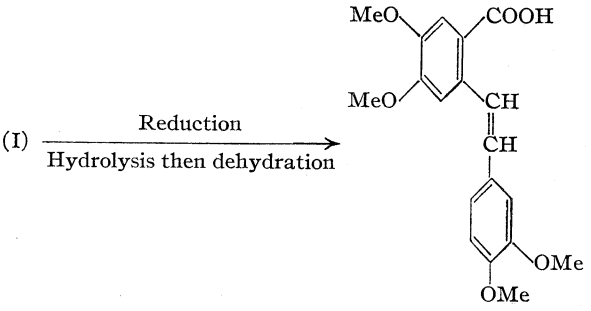
The yields of stilbene-2-acetic acid from the aldehyde through the azlactone were unsatisfactory. It was decided, therefore, to devise an alternate method of synthesis. The aldehyde was converted to the alcohol, then to the corresponding chloride and the latter to the cyanide. The cyanide yielded, on hydrolysis, stilbene-2-acetic acid and some stilbene-2-acetamide. Although this process is lengthier, the over-all yield is better. Stilbene-2-acetamide hydrolyzes to stilbene-2-acetic acid and the amount of this material obtained depends upon the length of time of the hydrolysis.





I

In anticipation of the application of this method to the preparation of papaverine, itself, *m*-hemipinic anhydride was condensed with homoveratric acid to yield tetramethoxybenzalphthalide (I). Reduction of (I), hydrolysis and dehydration yielded tetramethoxystilbene-2-carboxylic acid.



Preliminary attempts to convert stilbene-2-acetic acid to the lactone and then to the imide were unsuccessful. This imide, if obtained, could be converted to benzylisoquinoline by reduction and dehydration. Attempts in this direction are being maintained.

Experimental

Stilbene-2-aldehyde.—This compound is prepared, essentially by the procedure described previously[1a] with this improvement. 2-Stilbene-carboxylic hydrazide is prepared in about 60% yield by refluxing stilbene-2-carboxylic ester with 85% hydrazine hydrate (10% excess) with mechanical stirring for twenty hours. Any unreacted ester is recovered by extracting the reaction mixture with benzene. The residue is the hydrazide. On evaporating the benzene, the ester is recovered.

Before the 2-stilbene-carboxylic hydrazide is condensed with toluenesulfonyl chloride, it is made anhydrous by drying with benzene using a distillation trap of the type employed in determining moisture content of materials.

Stilbene-2-methyl Alcohol.—0.2 mole (41.6 g.) of stilbene-2-aldehyde is added to 1 liter of molar aluminum isopropylate in anhydrous isopropyl alcohol. The mixture is refluxed for one-half hour and slowly distilled until the distillate shows no test for acetone with 2,4-dinitrophenylhydrazine. The residue is poured into 1000 cc. of 10%

(1) Now in the armed forces of the U. S. A.

(1a) Natelson and Gottfried, THIS JOURNAL, **63**, 487 (1941).

sulfuric acid. The alcohol, which crystallizes in pearly plates, is filtered off, and recrystallized from dilute alcohol; yield 40 g.; m. p. 92–93°.

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.71; H, 6.67. Found: C, 85.32; H, 6.72.

Stilbene-2-methyl Chloride.—Forty grams of stilbene-2-methyl alcohol is dissolved in 80 cc. of ether and 160 cc. of thionyl chloride (large excess) is added slowly with stirring and cooling. The mixture is refluxed for one-half hour; the ether and thionyl chloride are removed under vacuum. The residue is picked up in ether and washed well with water and dilute sodium bicarbonate. The mixture is dried over anhydrous sodium sulfate and vacuum distilled; yield 32 g., b. p. 170–185° (15 mm.).

Anal. Calcd. for $C_{15}H_{13}Cl$: Cl, 15.51. Found: Cl, 15.10, 15.30.

Stilbene-2-acetonitrile.—Seventeen grams of stilbene-2-methyl chloride, 4.5 g. of sodium cyanide dissolved in a minimum quantity of water, and 25 cc. of ethyl alcohol are refluxed for eight hours. The mixture is thrown into 200 cc. of water and extracted with ether. The ether is washed with water, dried over anhydrous sodium sulfate, and vacuum distilled, collecting from 200–210° (fifteen minutes). The distillate crystallizes; yield 10 g., m. p. 81–82°.

Anal. Calcd. for $C_{16}H_{13}N$: N, 6.39. Found: N, 6.38, 6.27.

Stilbene-2-acetic Acid. Method 1.—Ten grams of stilbene-2-acetonitrile is refluxed with 100 cc. of glacial acetic acid, containing 40 cc. of concentrated hydrochloric acid, for four hours. The mixture is poured into water and extracted with ether. The ether is extracted with sodium bicarbonate solution. The bicarbonate solution is then acidified. The precipitated acid is recrystallized from ligroin. White needles are obtained; yield 7 g., m. p. 105–106°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.67; H, 5.93; neut. equiv., 238. Found: C, 80.24; H, 6.04; neut. equiv., 245.

Stilbene-2-acetamide.—The ether extract of the sodium bicarbonate solution was evaporated to dryness, and the residue treated with hot 10% sodium hydroxide to remove traces of the acid. The alkali insoluble portion was recrystallized from alcohol to yield white leaflets (2 g.), m. p. 152–153°. Hydrolysis of this product with glacial acetic acid and concentrated hydrochloric acid, as described for the nitrile, yielded stilbene-2-acetic acid.

Anal. Calcd. for $C_{16}H_{15}ON$: N, 5.90. Found: N, 5.83, 5.79.

Stilbene-2-acetic Acid. Method 2.—Twenty grams of sodium hydroxide in 200 cc. of water is added to 10 g. of stilbene-2-(benzamido)-acrylic acid. The solution is refluxed for eight hours, and treated at 0° with 10 cc. of 30% hydrogen peroxide (excess). The mixture is allowed to stand overnight in the refrigerator. It is then acidified and the mixture of stilbene-2-acetic acid and benzoic acid is recrystallized from dilute alcohol to remove the benzoic acid. The residue of stilbene-2-acetic acid is further recrystallized from benzene or ligroin; yield 2 g.; m. p. 105–106° (mixed m. p. with the product from method 1 showed no depression).

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.67; H, 5.93; neut. equiv., 238. Found: C, 80.48; H, 6.01; neut. equiv., 242.

***o*-Styryl-α-benzamidocinnamic Acid.**—2-Phenyl-4-*o*-styrylbenzylidene-5(4)-oxazolone (20 g.) from hippuric acid and stilbene-2-aldehyde (1), is mixed with 1000 cc. of water and 250 g. of hydrated barium hydroxide and heated at 85° with stirring for eight hours. The white barium salt is filtered off and washed several times with warm water. The free acid is obtained by boiling the barium salt with 100 cc. of alcohol and 20 cc. of concentrated hydrochloric acid mixture. The mixture is cooled, filtered, and the precipitate washed well with water. The acid is recrystallized from alcohol to yield a pale yellow crystalline powder; yield 13.6 g.; m. p. 199–202°.

Anal. Calcd. for $C_{24}H_{19}O_3N$: C, 78.03; H, 5.14; N, 3.79; neut. equiv., 369. Found: C, 78.41; H, 5.47; N, 3.90, 4.01; neut. equiv., 370, 376.

Tetramethoxybenzalphthalide.—Ten grams of *m*-hemipinic anhydride and 10 g. of homoveratric acid were mixed with 0.5 g. of anhydrous sodium acetate. The mixture was heated at 230° for two hours in an open flask. The mixture was cooled, broken up, dissolved in hot alcohol and filtered. The alcohol was allowed to cool, yield 10 g. of yellow crystals, m. p. 179–180°; soluble in glacial acetic, slightly soluble in hot alcohol, almost insoluble in cold alcohol.

Anal. Calcd. for $C_{19}H_{18}O_6$: C, 66.67; H, 5.26. Found: C, 67.01; H, 5.39.

Tetramethoxybenzylphthalide.—Ten grams of the tetramethoxybenzalphthalide was dissolved in 100 cc. of hot 20% sodium hydroxide and then diluted to a liter with water. The solution was cooled to room temperature, 2 g. of sodium, dissolved in 60 g. of mercury was added and the mixture was vigorously stirred for four hours. The solution was acidified and the separated tetramethoxybenzylphthalide was recrystallized from alcohol; yield 9.5 g., m. p. 146–148°.

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.28; H, 5.81. Found: C, 66.01; H, 6.00.

Tetramethoxystilbene-2-carbonic Acid.—Ten grams of tetramethoxybenzylphthalide was dissolved in 200 cc. of ethyl alcohol containing 3 g. of potassium hydroxide. The mixture was slowly evaporated to dryness on a hot-plate. The temperature was raised to 180° and kept there for one hour. The residue was dissolved in water, filtered and acidified. The tetramethoxystilbenecarbonic acid obtained was recrystallized from alcohol, m. p. 209–211°; yield, 7 g.

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.28; H, 5.81. Found: C, 66.47; H, 5.97.

Summary

Stilbene-2-acetic acid and tetramethoxystilbenecarbonic acid, proposed intermediates for the preparation of benzylisoquinoline and papaverine, respectively, have been prepared.

BROOKLYN, NEW YORK RECEIVED AUGUST 10, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Grignard Reactions. XVI[1]

BY FRANK C. WHITMORE AND C. E. LEWIS[2]

The effect of an accumulation of substituents adjacent to the functional group of a carbonyl compound on its reaction with a Grignard reagent was first shown by Conant and Blatt.[3]

The present study is a continuation of the work started in this Laboratory on the enolization of aliphatic hindered carbonyl compounds by Grignard reagents.[1,4] Many of the compounds studied exhibit sufficient steric hindrance to prevent the addition reaction entirely. The results of the enolization studies are given in Table I.

The Grignard machine used in this work is essentially the same as the one originally designed by Kohler[5] and has been in use in this Laboratory.[1] The usual procedure was followed except for a few modifications. The reaction flask was always heated to ensure optimum reaction conditions. Aniline was used instead of water for decomposition of the excess Grignard reagent in order to eliminate the variation due to the vapor pressure of water. This allowed the elimination of a drying tower from the system. All calculations were based on the assumption that the amount of condensation of these carbonyl compounds is negligible.

TABLE I

Compound	Enolization, %	Addition, %
Et_3CCOCH_3	94	0
$Et_2MeCCOCH_3$	84	0
$EtMe_2CCOCH_3$	14	74
Me_3CCOCH_3[a]	5	86
$Me_3CCH_2COCH_3$	0	100
$Et_3CCOCH_2CHMe_2$	85	0
$Et_3CCOCH{=}CH_2$	0	58
Et_3CCO_2Et	0	0
Et_3CCO_2Me	0	0
Et_2MeCCO_2Et	25[b]	45
Et_2MeCCO_2Bu	22[b]	60
$EtMe_2CCO_2Et$	0	100
$Et_3CCOCH_2CH_2OH$	58[c]	27
$(Et_3CCO)_2CH_2$	91/2	55/2
$(Et_3CCO)_2CHCH_3$	79/2	19/2

[a] Ref. 1. [b] The apparent enolization of these compounds is due to that of the ketones formed from the methylmagnesium bromide and the esters. [c] Corrected for the CH_4 liberated by the alcohol group.

The reactions in the series, methyl triethylcarbinyl ketone, methyl methyldiethylcarbinyl ketone, methyl dimethylethylcarbinyl ketone and pinacolone, illustrate the effect of an accumulation of substituents on the carbon adjacent to the carbonyl, the percentage enolization being 94, 84, 14 and 5, respectively. The difference in the amount of steric hindrance exerted by the methyl and ethyl groups is again clearly demonstrated. That substituents on the beta carbon have less effect on the carbonyl reaction than those on the adjacent carbon is shown by the fact that methyl neopentyl ketone gave 100% addition and no enolization while pinacolone gave 5% enolization. The effect of ethyl groups on the addition reaction is also shown in the action of the Grignard reagent with the esters of triethylacetic, methyldiethylacetic and dimethylethylacetic acids. These esters gave per cent. additions of 0, 45 and 100, respectively.

Vinyl triethylcarbinyl ketone gave only the addition reaction. This is to be expected since enolization would necessitate the formation of an allene system. The effect of introducing a substituent into the active methylene of beta-diketones is shown by the action of the Grignard reagent with bis-triethylacetylmethane and with 1,1-bis-triethylacetylethane. This introduction of a methyl group decreased both the enolization and addition reactions. The greater effect is shown on the addition reaction.

None of the monoketones investigated gave a positive test for the enol form by the usual ferric chloride and peroxide tests. Thus the "enolization reaction" between the carbonyl compound and the Grignard reagent starts with the carbonyl group. It is a competitive reaction, the extent of which is determined by the nature of the groups adjacent to the carbonyl.

We thank R. S. George of this Laboratory for his help.

Preparations

The Grignard reagents used in this work were prepared in the usual way. All fractionations were done with the

(1) XV, Whitmore and Block, THIS JOURNAL, **64**, 1619 (1942).
(2) Present address: Calco Chem. Div., American Cyanamid Co., Bound Brook, New Jersey.
(3) Conant and Blatt, THIS JOURNAL, **51**, 1227 (1929).
(4) Whitmore and George, *ibid.*, **64**, 1239 (1942).
(5) Kohler, Stone and Fuson, *ibid.*, **49**, 3181 (1927).

usual type of column[6] having 12–18 theoretical plates. The procedure used in making the enolization measurements was the same as that described by Whitmore and Block.[1] Methylmagnesium bromide in dibutyl ether was used. For the monoketones the reaction mixture was heated for two to five minutes at reflux temperature. Comparable results were obtained for several different periods of heating. Methyl methyldiethylcarbinyl ketone gave the same results when heated at reflux temperature for two minutes as when it was heated at 90° for one hour. In no case did prolonged heating have a noticeable effect. The diketones required longer heating at the reflux temperature, maximum reaction being obtained in ten minutes. The esters were heated by immersing the reaction flask in a water-bath at 75–80° upon addition of the methylmagnesium bromide, heating to 95–100° in ten minutes and holding at that temperature for thirty minutes. In all cases refluxing provided the necessary agitation.

The preparations of triethylacetyl chloride, methyl triethylcarbinyl ketone, bis-triethylacetylmethane and 3-keto-4,4-diethylhexan-1-ol have been described.[7] The methyldiethylacetyl chloride was prepared by standard reactions as follows

$$MeCOEt \xrightarrow{EtMgBr} MeEt_2COH \xrightarrow{HCl} MeEt_2CCl \xrightarrow{Mg} MeEt_2CMgCl \xrightarrow{CO_2} MeEt_2CO_2H \xrightarrow{SOCl_2} MeEt_2COCl.$$

The acid chloride had b. p. 157° at 734 mm.

Vinyl Triethylcarbinyl Ketone.—Dehydration of 3-keto-4,4-diethylhexan-1-ol[7] by refluxing over anhydrous cupric sulfate gave vinyl triethylcarbinyl ketone, b. p. 97° at 36 mm., $n^{20}D$ 1.4495–8. The ketone polymerized to a transparent resin on standing.

Isobutyl Triethylcarbinyl Ketone.—To one mole of isobutylmagnesium bromide was added 49 g., 0.3 mole, of triethylacetyl chloride. Decomposition and fractionation gave 16 g., 0.12 mole, or 40% of 2,2-diethylbutan-1-ol, b. p. 96–100° at 40 mm., $n^{20}D$ 1.4392–1.4412, α-naphthylurethan m. p. 131–132° and 24.4 g., 0.13 mole, or 43% of isobutyl triethylcarbinyl ketone, b. p. 86–87° at 12 mm., $n^{20}D$ 1.4381–2. No derivative of the ketone could be made.

Methyl Methyldiethylcarbinyl Ketone.—To an excess of methylmagnesium bromide was added 37.1 g., 0.25 mole, of methyldiethylacetyl chloride. Decomposition and fractionation as usual gave 15.3 g., 0.12 mole, or 48% of methyl methyldiethylcarbinyl ketone, b. p. 77–79° at 20 mm., $n^{20}D$ 1.4489–98, 2,4-dinitrophenylhydrazone, m. p. 73–74°.

Methyl Dimethylethylcarbinyl Ketone.—Methyl-*t*-amylcarbinol was prepared by the action of *t*-amylmagnesium chloride with acetaldehyde. A solution of 33 g. of chromic oxide in 60 cc. of 65% aqueous acetic acid was added slowly to 56 g. of the carbinol in 25 cc. of glacial acetic acid. The reaction mixture was kept below 30°. About 150 cc. of water was then added, the oil layer was steam distilled and dried. Fractionation gave about 20 g. of methyl dimethylethylcarbinyl ketone, b. p. 130° at 733 mm., $n^{20}D$ 1.4100, 2,4-dinitrophenylhydrazone m. p. and mixed m. p. 112°.

(6) Whitmore and Lux, THIS JOURNAL, **54**, 3451 (1932).

(7) Whitmore and Lewis, *ibid.*, **64**, 1618 (1942).

Preparation of the Ethyl Esters.—The ethyl esters were all prepared according to the same procedure. The addition of triethylacetyl chloride to sodium ethylate illustrates the procedure used.

To 50 cc. of absolute ethanol was added 6 g. of metallic sodium. After the reaction was completed, 24 g., 0.15 mole, of triethylacetyl chloride was added slowly. The excess sodium ethylate was decomposed by pouring on ice. The oil layer was separated, dried and fractionated.

Ester	B. p. °C.	Mm.	$n^{20}D$	Yield, %
Ethyl triethylacetate	85–7	30	1.4218–9	57
Ethyl methyldiethylacetate	73	35	1.4129–32	64
Ethyl dimethylethylacetate	140–141	744	1.4025	63

Methyl Triethylacetate.—The procedure described above was used except that absolute methanol was substituted for ethanol, and the oil layer was distilled from a Claisen flask. The ester had b. p. 164–5° at 734 mm., $n^{20}D$ 1.4240–1.

***n*-Butyl Methyldiethylacetate.**—To 250 cc. of *n*-butyl alcohol was added 12 g. of metallic sodium. When the reaction was completed, 26 g., 0.17 mole of ethyl methyldiethylacetate was added. The reaction mixture was heated for twelve hours at 125° under a reflux condenser held at 100°. The ethyl alcohol was thus removed as it was formed. The solution was acidified with 20% hydrochloric acid with cooling in an ice-bath. The alcoholic solution of ester was separated and dried. Fractionation gave 14.6 g., 0.08 mole, or 46% of *n*-butyl methyldiethylacetate, b. p. 104–5° at 38 mm., $n^{20}D$ 1.4212–8.

Alkylation of Bis-triethylacetylmethane.—Metallic sodium, 1.5 g., and 25 cc. of anhydrous ether were added to 17.2 g., 0.064 mole, of bis-triethylacetylmethane.[7] The reaction mixture was refluxed on a steam-bath for forty-eight hours. The ether was removed by evaporation, and 25 cc. of dioxane and 21 g., 0.15 mole, of methyl iodide were added. This reaction mixture was heated on a steam-bath for twenty-four hours. The dioxane and the excess methyl iodide were distilled off. The residue was cooled, and just enough water to dissolve the sodium iodide was added. The oil layer was separated and dried. Fractionation gave 7.4 g., 0.026 mole, or 41% of 1,1-bis-triethylacetylethane, b. p. 164° at 6 mm., $n^{20}D$ 1.4718–22. The beta-diketone did not give a positive test with ferric chloride or a derivative with ammoniacal cupric acetate.

Methyl Neopentyl Ketone.—This ketone was prepared by the dichromate oxidation of diisobutylene. It had b. p. 125.5° at 727 mm., $n^{20}D$ 1.4038.

Summary

1. The study of sterically hindered aliphatic carbonyl compounds, especially in relation to their enolization, has been continued.

2. Fifteen such compounds have been analyzed in the Grignard machine with methylmagnesium bromide.

3. The degree of enolization of the carbonyl compounds was shown to be dependent upon the character of the substituents on the carbon ad-

jacent to the carbonyl. Substitution on the beta carbon had no noticeable effect on the reactions of the carbonyl.

4. Vinyl triethylcarbinyl ketone gave only the addition reaction.

5. Substitution in the active methylene of a beta-diketone decreased the extent of both enolization and addition.

STATE COLLEGE, PENNSYLVANIA
RECEIVED JANUARY 13, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Grignard Reactions. XVII.[1] The Reactions of Esters and Acid Chlorides with Grignard Reagents

BY FRANK C. WHITMORE AND W. S. FORSTER[2]

In the course of the preparation of large amounts of diethyl-*t*-butylcarbinol, it was found that while ethylmagnesium bromide reacted with trimethylacetyl chloride to give 26% of this tertiary alcohol and 60% of the secondary alcohol, ethyl-*t*-butylcarbinol, the same reagent reacted with methyl trimethylacetate to give 78.5% of the tertiary alcohol and only 8.6% of the secondary alcohol.

TABLE I

TRIMETHYLACETYL CHLORIDE–METHYL TRIMETHYLACETATE

Grignard reagent	Products[a]	Acid chloride	Ester
Ethyl	Ethyl-*t*-butylcarbinol	60	8.6
	Diethyl-*t*-butylcarbinol	26.1	76.5
n-Propyl	Neopentyl alcohol	20[3]	0[4]
	n-Propyl-*t*-butylcarbinol	76[3]	48[4]
	Di-*n*-propyl-*t*-butylcarbinol	0[3]	40[4]
Isopropyl	Neopentyl alcohol	23[3]	0
	Isopropyl-*t*-butylcarbinol	53[3]	44.8
n-Butyl	Neopentyl alcohol	28[3]	0
	n-Butyl-*t*-butylcarbinol	71[3]	40[4]
	Di-*n*-butyl-*t*-butylcarbinol	0[3]	50[5]
Isobutyl	Neopentyl alcohol	61[3]	0
	Isobutyl-*t*-butylcarbinol	26[3]	25.7
	Isobutyl-*t*-butyl ketone	0	29.4
	t-BUTYLACETYL CHLORIDE–METHYL *t*-BUTYLACETATE		
Ethyl	Diethylneopentylcarbinol	57.6[5]	68.5
	Ethyl neopentyl ketone	0[5]	5
n-Propyl	*n*-Propylneopentylcarbinol	24.4[5]	20.4
	Di-*n*-propylneopentylcarbinol	57[5]	61.8
	n-Propyl neopentyl ketone		7
Isopropyl	Isopropylneopentylcarbinol	26.7	16.1
	Isopropyl neopentyl ketone	32.7	55.3
n-Butyl	*n*-Butylneopentylcarbinol	20.5	0
	Di-*n*-butylneopentylcarbinol	9.9	71.4
	n-Butyl neopentyl ketone		trace
Isobutyl	Isobutylneopentylcarbinol	48.9	9.2
	Diisobutylneopentylcarbinol	13.8	34.2
	Isobutyl neopentyl ketone	20.1	32

[a] The percentage yields of products given by the acid chloride and the ester are listed under the respective headings.

These results made desirable a comparison of the reactions of Grignard reagents with esters and with the chlorides of the corresponding acids. The results in Table I include those of this investigation as well as some from other work which completes the comparison.

Although use of the ester in place of the acid chloride decreased the amount of reduction product, it will be seen that structure is also a factor. When a normal Grignard reagent was used, the yield of tertiary alcohol from the ester was greater than from the acid chloride. However, methyl Grignard reagent with the methyl ester of methyl-*t*-butylneopentylacetic acid, beta-Butlerow's acid,[6] gave no reaction at 34° in diethyl ether or at 142° in di-*n*-butyl ether. This is in contrast to the reaction of the corresponding acid chloride which has been shown by Whitmore and Randall[7] to give a 90% yield of methyl methyl-*t*-butylneopentylcarbinyl ketone when treated with the methyl Grignard reagent. With trimethylacetyl chloride only methyl and ethyl Grignard reagents gave tertiary alcohols. With *t*-butylacetyl chloride only the primary reagents gave tertiary alcohols. Reduction to the primary alcohol fails with the primary *t*-butylacetyl chloride as compared with the tertiary trimethylacetyl chloride. It is significant that in no case was any primary alcohol found from the reaction of an ester with a Grignard reagent. This would indicate that aldehydes are not intermediates in the formation of secondary alcohols from esters.[8] This is in sharp contrast to the fact that trimethylacetyl chloride is reduced to neopentyl alcohol even by primary Grignard reagents in yields as high as 60%.[3] *t*-Butylacetyl chloride, however, gave no primary alcohol with the Grignard reagent.[5]

(1) XVI, Whitmore and Lewis, THIS JOURNAL, **64**, 2964 (1942).
(2) Present address: Calco Chemical Div., American Cyanamid Co., Bound Brook, New Jersey.
(3) Whitmore and co-workers, THIS JOURNAL, **60**, 2788 (1938).
(4) Leroide, *Ann. chim.*, **16**, 354–410 (1921).
(5) Whitmore and co-workers, THIS JOURNAL, **60**, 2462 (1938).
(6) Whitmore and Laughlin, *ibid.*, **56**, 1128 (1934).
(7) Whitmore and Randall, *ibid.*, **64**, 1242 (1942).
(8) Compare Whitmore and co-workers, *ibid.*, **63**, 643 (1941).

Dimethylethylacetyl chloride reacts with isopropylmagnesium bromide to give products corresponding in structure and yields to those given by trimethylacetyl chloride.[3] This lack of effect of a single ethyl group corresponds to the observations on the related methyl ketones.[1]

We thank Dr. W. A. Mosher of the Hercules Powder Company and R. S. George of this Laboratory for their help.

Experimental

All Grignard reagents were prepared from the corresponding alkyl bromides in the usual manner.[9] The addition of the ester or acid chloride, unless specified, was carried out at room temperature; the rate of addition was about 1 mole per hour. The products were worked up by shaking with cracked ice, separating the ether and steam distilling the residues. The steam distillates were combined with the respective ether extracts. This method minimized any dehydration of the tertiary alcohols. After stripping off the ether, the products were fractionated through columns of 12–15 theoretical plates.

Preparation of Materials.—Trimethylacetic acid was obtained from the oxidation of triisobutylene with sodium dichromate and sulfuric acid.[10] The crude acids from the oxidation were dried and fractionated through a 12-plate column to give material of b. p. 93° (45 mm.). The pure acid was converted to the chloride by treatment with thionyl chloride at steam-bath temperature. The excess thionyl chloride was distilled off, and the crude chloride was fractionated through a 14-plate column to give an 80% yield of material with b. p. 57.6° (150 mm.) and $n^{20}D$ 1.4121–2. The methyl ester was prepared from the acid chloride, either crude or fractionated, by the addition of methanol and subsequent distillation to give the ester, b. p. 99.5° (731 mm.), $n^{20}D$ 1.3891–1.3900; the yield of ester was about 50% from the acid.

t-Butylacetyl chloride, b. p. 79.5° (165 mm.), $n^{20}D$ 1.4210–6, was prepared from the acid in 84% yield by treatment with thionyl chloride. The crude acid chloride was refluxed with methanol; the product was washed with water and sodium bicarbonate solution and fractionated to give a 94% yield of ester, b. p. 128° (735 mm.), $n^{20}D$ 1.3995–9.

Dimethylethylacetic acid was prepared by carbonating *t*-amyl Grignard reagent. The *acid chloride*, b. p. 129.8° (727 mm.), $n^{20}D$ 1.4242–8, was obtained in 50% yield by refluxing with thionyl chloride.

Reaction of Methyl Trimethylacetate with Ethylmagnesium Bromide.—The reaction of 1.87 moles of methyl trimethylacetate with 4.5 moles of ethylmagnesium bromide gave 18.4 g. or 8.6% of ethyl-*t*-butylcarbinol,[3] b. p. 67° (55 mm.), $n^{20}D$ 1.4223–32, and 196.2 g. or 76.5% of diethyl-*t*-butylcarbinol, b. p. 84° (40 mm.), $n^{20}D$ 1.4410–26. No neopentyl alcohol was found.

Reaction of Methyl Trimethylacetate with Isopropylmagnesium Bromide.—The reaction of 1.5 moles of ester with 4.5 moles of the Grignard reagent gave 34.2% of unreacted ester and 87.4 g. or 44.8% of isopropyl-*t*-butylcarbinol; b. p. 75.5° (53 mm.); $n^{20}D$ 1.4268–92; phenylurethan m. p. and mixed m. p. 88–90°. No neopentyl alcohol could be detected.

Reaction of Methyl Trimethylacetate with Isobutylmagnesium Bromide.—The reaction of 0.5 mole of ester with 1.7 moles of the Grignard reagent gave 27.2% of unchanged ketone, 29.4% of isobutyl-*t*-butyl ketone, b. p. 70° (38 mm.), $n^{20}D$ 1.4128–72, 2,4-dinitrophenylhydrazone m. p. and mixed m. p. 94–95°, and 25.7% of isobutyl-*t*-butylcarbinol, b. p. 74° (23 mm.), phenylurethan m. p. and mixed m. p. 114–115.5°. Isobutyl-*t*-butylcarbinol was oxidized to the corresponding ketone, 2,4-dinitrophenylhydrazone m. p. and mixed m. p. 94–95°, by treatment with sodium dichromate and sulfuric acid. No neopentyl alcohol was found.

Reaction of Methyl *t*-Butylacetate with Ethylmagnesium Bromide.—Addition of 1 mole of ester to 4 moles of the Grignard reagent gave 108.4 g. or 68.5% of diethylneopentylcarbinol, b. p. 54° (5 mm.), $n^{20}D$ 1.4394–1.4403, d_{20} 0.845, mol. ref. calcd. 49.6, found, 49.4; and 7.6 g. or 5% of ethyl neopentyl ketone, b. p. 75–80° (63 mm.), $n^{20}D$ 1.4158–63, 2,4-dinitrophenylhydrazone m. p. and mixed m. p. 135–7°.

Reaction of Methyl *t*-Butylacetate with *n*-Propylmagnesium Bromide.—The reaction of 1 mole of ester with 4 moles of the Grignard reagent gave 10.6 g. or 7% of *n*-propyl neopentyl ketone, b. p. 42° (5 mm.), $n^{20}D$ 1.4161–70, semicarbazone m. p. and mixed m. p. 93–5°, 29.3 g. or 20.4% of *n*-propylneopentylcarbinol, b. p. 47.5° (5 mm.), $n^{20}D$ 1.4261–78, phenylurethan m. p. and mixed m. p. 81.5–82°, and 115 g. or 61.8% of di-*n*-propylneopentylcarbinol, b. p. 67° (3 mm.), $n^{20}D$ 1.4423–8, d_{20} 0.8386, mol. ref. calcd., 58.8; found, 58.9. There was no evidence of neopentylcarbinol.

Reaction of Methyl *t*-Butylacetate with Isopropylmagnesium Bromide.—The ester, 1 mole, was added to 4 moles of the Grignard reagent to give 78.6 g. or 55.3% of isopropyl neopentyl ketone, b. p. 107.2° (180 mm.), $n^{20}D$ 1.4114–29, 2,4-dinitrophenylhydrazone m. p. 128–129°, semicarbazone m. p. and mixed m. p. 168–169° and 23.3 g. or 16.1% of isopropylneopentylcarbinol, b. p. 74.8° (25 mm.), $n^{20}D$ 1.4286–95, d_{20} 0.825, mol. ref. calcd., 45.0; found, 45.2, *α-naphthylurethan* m. p. 88–90°.

Anal. Calcd. for $C_{20}H_{27}O_2N$: N, 4.47. Found: N, 4.49.

Reaction of Methyl *t*-Butylacetate with *n*-Butylmagnesium Bromide.—The addition of 0.9 mole of ester to 3.6 moles of Grignard reagent gave 137.4 g. or 71.4% of di-*n*-butylneopentylcarbinol, b. p. 83° (3 mm.), $n^{20}D$ 1.4462–9, d_{20} 0.8403, mol. ref., calcd., 67.96; found, 67.8; a small amount of material believed to be *n*-butyl neopentyl ketone was obtained, semicarbazone m. p. 79–80°, but identification was not conclusive. No *n*-butylneopentylcarbinol was found.

Reaction of Dimethylethylacetyl Chloride and Isopropylmagnesium Bromide.—To 4.16 moles of Grignard reagent was added 1 mole of the acid chloride. The products were *t*-amylcarbinol, 30 g., 29.4%, b. p. 34.5° (7 mm.), $n^{20}D$ 1.4208–12, phenylurethan m. p. and mixed m. p. 65–68°; isopropyl-*t*-amylcarbinol, 76 g., 49.3%, b. p. 52–3° (6.5 mm.), $n^{20}D$ 1.4395–1.4400, d_{20} 0.8489, mol. ref. calcd.,

(9) Greenwood, Whitmore and Crooks, THIS JOURNAL, **60**, 2028 (1938).

(10) Unpublished work by C. S. Miner, Jr., in this Laboratory.

44.9; found, 45.0, phenylurethan m. p. 58–59°, *α-naphthylurethan* m. p. 76.5–77.5°.

Anal. Calcd. for $C_{20}H_{27}O_2N$: N, 4.47. Found: N, 4.52.

Reaction of Trimethylacetyl Chloride with Ethylmagnesium Bromide.—The reaction of 2.54 moles of acid chloride with 6.1 moles of the Grignard reagent gave 26.1% of diethyl-*t*-butylcarbinol,[3] b. p. 59.2° (35 mm.), $n^{20}D$ 1.4230 and 60% of ethyl-*t*-butylcarbinol,[3] b. p. 73° (24 mm.), $n^{20}D$ 1.4424–6. No neopentyl alcohol was found.

Reaction of *t*-Butylacetyl Chloride with Isopropylmagnesium Bromide.—The reaction of 1 mole of acid chloride with 4 moles of Grignard reagent gave 32.7% of isopropyl neopentyl ketone, b. p. 61° (26 mm.), $n^{20}D$ 1.4120–9, 2,4-dinitrophenylhydrazone m. p. 128–129°, semicarbazone m. p. and mixed m. p. 168–9° and 26.7% of isopropylneopentylcarbinol, b. p. 76.7° (32 mm.), $n^{20}D$ 1.4283–1.4302, d_{20} 0.825, mol. ref. calcd., 45.0; found, 45.2; *α-naphthylurethan* m. p. 88–90°.

Anal. Calcd. for $C_{20}H_{27}O_2N$: N, 4.47. Found: N, 4.49.

Attempted Reaction of the Methyl Ester of Methyl-*t*-butylneopentylacetic Acid with Methylmagnesium Bromide.—The ester was made from methanol and the acid chloride[6] in 88% yield; b. p. 97–8° (13 mm.), $n^{20}D$ 1.4450–2. The treatment of the ester with the Grignard reagent was carried out in diethyl ether at 34° and in di-*n*-butyl ether at 142°. The lower temperature gave almost quantitative recovery of unreacted ester. At 142° there were obtained a 70.3% recovery of unchanged ester and a 13% yield of methyl-*t*-butylneopentylacetic acid formed by the splitting of the ester.

Reaction of *t*-Butylacetyl Chloride with Isobutylmagnesium Bromide.—The reaction of 0.5 mole of the acid chloride with 1.45 moles of the Grignard reagent gave isobutyl neopentyl ketone, 15.7 g., 0.102 mole, 20.1%, b. p. 65.5° (15 mm.), $n^{20}D$ 1.4127–91; isobutylneopentylcarbinol, 38.6 g., 0.244 mole, 48.9%, b. p. 75° (15 mm.), $n^{20}D$ 1.4237–79, α-naphthylurethan m. p. and mixed m. p. 100–100.5°; diisobutylneopentylcarbinol, 14.7 g., 0.069 mole, 13.8%, b. p. 68.5° (3 mm.), $n^{20}D$ 1.4395–1.4410, d_{20} 0.8317, mol. ref. calcd., 67.96; found, 68.0.

Reaction of Methyl *t*-Butylacetate with Isobutylmagnesium Bromide.—To isobutylmagnesium bromide prepared from 1.7 gram atoms of magnesium and 1.83 moles of isobutyl bromide was added 65 g., 0.5 mole, of the ester. Fractionation gave isobutyl neopentyl ketone, 32.1 g., 0.16 mole, 32%, b. p. 66.4° (15 mm.), $n^{20}D$ 1.4120–98; isobutylneopentylcarbinol, 15.2 g., 0.046 mole, 9.2%, b. p. 43–44° (3 mm.), $n^{20}D$ 1.4232–82, *α-naphthylurethan* m. p. and mixed m. p. 99–101°; diisobutylneopentylcarbinol, 27.0 g., 0.17 mole, 34.2%, b. p. 69.5° (2 mm.), $n^{20}D$ 1.4375–1.4411, d_{20} 0.8313, mol. ref. calcd., 67.96; found, 68.0.

Anal. Calcd. for $C_{21}H_{29}O_2N$: N, 4.26. Found: N, 4.25.

Summary

1. A comparison of the reactions of trimethylacetyl chloride and methyl trimethylacetate and of *t*-butylacetyl chloride and methyl *t*-butylacetate with ethyl, *n*-propyl, isopropyl, *n*-butyl and isobutyl Grignard reagents has been made. The esters were found to give distinctly less reduction products than the corresponding acid chlorides.

2. The fact that no primary alcohol was found in the reaction of the esters with Grignard reagents indicates that aldehydes are not intermediates in this reaction.

3. The methyl ester of methyl-*t*-butylneopentylacetic acid did not react with methyl Grignard reagent at 34° or at 142°.

4. Isopropylneopentylcarbinol and isopropyl-*t*-amylcarbinol have been prepared.

STATE COLLEGE, PENNSYLVANIA
RECEIVED JANUARY 21, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Grignard Reactions. XVIII.[1] Reactions of Benzylmagnesium Chloride

BY FRANK C. WHITMORE AND T. K. SLOAT[2]

The type of rearrangement given by the benzyl Grignard reagent is well known. The first case reported was the reaction of formaldehyde with benzylmagnesium chloride to give *o*-tolylcarbinol instead of the expected benzylcarbinol.[3] The action of a variety of substances with benzylmagnesium chloride has been reported. Not all reactants give rearranged products with this Grignard reagent. The products of rearrangement are usually *o*-tolyl derivatives. In some cases the *p*-tolyl derivative has been reported.[4] Excellent investigations and reviews of the reactions of benzylmagnesium chloride have been made by Gilman and Kirby[5] and by Austin and Johnson.[6] More recently Coleman and Forrester[7] have investigated the action of benzylmagnesium chloride with monochloramine. No rearranged products were found in this case.

(1) XVII, Whitmore and Forster, THIS JOURNAL, **64**, 2966 (1942).

(2) Present address: Research Division, Westinghouse Electric and Manufacturing Co., East Pittsburgh, Pa.

(3) Tiffeneau and Delange, *Compt. rend.*, **137**, 573 (1903).

(4) Gilman and Kirby, THIS JOURNAL, **51**, 3475 (1929).

(5) Gilman and Kirby, *ibid.*, **54**, 345 (1932).

(6) Austin and Johnson, *ibid.*, **54**, 647 (1932).

(7) Coleman and Forrester, *ibid.*, **58**, 27 (1936).

The present study was undertaken with the hope that repetition of some of the reactions of benzylmagnesium chloride, on a larger scale and with the fractionating equipment now available, might give some rearranged products with reactants which previously had shown no rearrangement. *The results of previous investigators were confirmed without exception.* Our experiments with benzylmagnesium chloride gave only the normal products with acetonitrile, acetamide, acetaldehyde, carbon dioxide, oxygen, ethyl acetate, benzyl chloride and water. The reaction of the benzyl Grignard reagent with acetyl chloride gave the rearranged product, methyl *o*-tolyl ketone. Temperature was shown to have little effect on the yield of ketone, this being 18% at 0° and 16.5% at 25°.

In our experiments the benzylmagnesium chloride was added to an excess of the reactant unless otherwise specified. The order of addition of the Grignard reagent had a decided effect on the yield of rearranged product. In the reaction of acetyl chloride with benzylmagnesium chloride, the yield of methyl *o*-tolyl ketone was 18% when the Grignard reagent was added to the acid chloride while addition of the acetyl chloride to the Grignard reagent gave only 3% of this ketone. This is in agreement with the work of Schmidlin and Garcia-Banùs[8] who reported similar results with aromatic aldehydes.

Several mechanisms have been proposed for the *o*-tolyl rearrangement.[5,6,9] In an attempt to investigate further the mechanism of this rearrangement, acetyl chloride, toluene and anhydrous magnesium chloride were mixed in diethyl ether and refluxed for several hours. No reaction took place. This type of process is similar to that investigated by Tzukervanik and Sidorova.[10] Furthermore, dry toluene was added to ethylmagnesium chloride and then a large excess of acetyl chloride was added. As in the first of these test reactions, no methyl benzyl ketone or methyl *o*-tolyl ketone could be found.

We thank R. S. George of this Laboratory for his help.

Experimental

The benzylmagnesium chloride used in this work was prepared in the usual manner.[11] Titration showed the yields to be over 90%. All fractionations were done with the usual type of column[12] having 12–18 theoretical plates. The reactions of benzylmagnesium chloride with the compounds investigated were all run according to conventional procedures. In many cases only the fractions in the boiling point ranges of the possible rearranged products were thoroughly investigated. The reaction of acetamide with the benzyl Grignard reagent illustrates the procedure used.

To 59 g., 1 mole, of acetamide was added 3 moles of benzylmagnesium chloride. The reaction products were worked up in the usual way. Fractionation gave 55.3 g. or 41.3% of ketone fraction; b. p. 122–125° (50 mm.). The ketone was characterized by its 2,4-dinitrophenylhydrazone; m. p. 152–153°; a mixed m. p. with derivative of authentic methyl benzyl ketone gave no depression.

The experimental part of the study can best be summarized in table form.

TABLE I

Compound	% Normal primary[a] addition	% Primary[a] rearranged product	Order of addition.[b] Direct—reagent added to soln. of benzylmagnesium chloride
Acetamide	41.3	None	Reverse, excess Grignard reagent
Acetaldehyde	65.6	None	Reverse, excess acetaldehyde
Acetonitrile	15.8[c]	None	Reverse
Carbon dioxide	62.7	None	Direct
Oxygen	69.4	None	Direct
Water	95.3	None	Direct
Benzyl chloride	67.6	None	Reverse
Ethyl acetate	2.7[d]	None	Reverse
Acetyl chloride	Trace	18	Reverse, excess acid chloride
	Trace	16.5	Reverse, ditto[e]
	...	3	Direct, excess acid chloride

[a] These figures represent only the products given by the first step of the Grignard reaction. The high boiling tertiary alcohol fractions were not investigated. [b] Unless specified the Grignard reagent and the reactant were present in equal molecular proportions, and the reaction was run at 0°. [c] About 70% of toluene was also obtained. [d] Yield of high boiling alcohol was about 90%. [e] The reaction temperature was 25°.

Acetyl Chloride, Toluene and Magnesium Chloride.—A mixture of 0.75 mole of toluene and 0.75 mole of magnesium chloride in anhydrous ether was stirred for sixteen hours. To this was added 1.5 moles of acetyl chloride, and the mixture was then refluxed for four days. Fractionation gave no methyl *o*-tolyl ketone or methyl benzyl ketone.

Ethylmagnesium Chloride, Toluene and Acetyl Chloride.—To 1 mole of ethylmagnesium chloride in ether and 1 mole of toluene was added 3 moles of acetyl chloride, and the mixture was refluxed for two days. Fractionation gave no methyl *o*-tolyl ketone or methyl benzyl ketone.

Summary

1. Acetaldehyde, acetonitrile, acetamide and water have been shown to give only normal products with benzylmagnesium chloride.

2. Repetition of the reactions of carbon di-

(8) Schmidlin and Garcia-Banùs, *Ber.*, **45**, 3193 (1912).

(9) Johnson, THIS JOURNAL, **55**, 3029 (1933).

(10) Tzukervanik and Sidorova, *J. Gen. Chem. Russ.*, **8**, 1512 (1938); *ibid.*, **8**, 1899 (1938).

(11) Greenwood, Whitmore and Crooks, THIS JOURNAL, **60**, 2028 (1938).

(12) Whitmore and Lux, *ibid.*, **54**, 3451 (1932).

oxide, oxygen, benzyl chloride, ethyl acetate and acetyl chloride with benzylmagnesium chloride on a larger scale has confirmed the results of previous investigators. Only acetyl chloride gave rearrangement.

3. The yield of rearranged product from the addition of benzylmagnesium chloride to acetyl chloride was found to be much higher than that obtained from the addition of acetyl chloride to the Grignard reagent.

STATE COLLEGE, PENNSYLVANIA
RECEIVED JANUARY 22, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

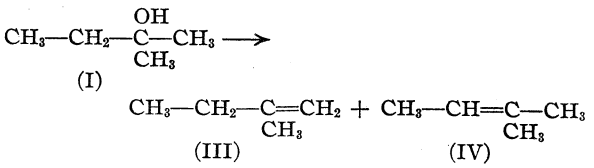
The Dehydration of Alcohols. XIX.[1-4] *t*-Amyl Alcohol and the Related Dimethylneopentylcarbinol

BY FRANK C. WHITMORE, C. S. ROWLAND,[5] S. N. WRENN AND G. W. KILMER

Despite the amount of work done on the dehydration of alcohols since the discovery of ethylene by the four Dutch chemists in 1795, practically no generalizations of any value have been presented. This is largely because few, if any, cases have been studied with proper control of the variables involved. Moreover, the dehydration mixtures obtained from any but the simplest alcohols are likely to be so complex as to be unmanageable with ordinary equipment and techniques.[1] Even with a simple alcohol like *t*-amyl alcohol (I) the results in the literature are highly conflicting.[6] In all this work the only consistent fact is that trimethylethylene (IV) is the chief product. The different proportions of olefins obtained by different investigators indicated that equilibrium conditions had not been obtained for the olefin mixture. The unasked question as to whether the olefin mixture obtained by dehydration of an alcohol is identical with the equilibrium mixture of the olefins has long existed. For strongly acid catalysts this question was answered in the affirmative in this Laboratory when essentially identical mixtures of olefins were obtained by passing the following over phosphoric acid on silica gel: (a) methyl-*t*-butylcarbinol, (b) *t*-butylethylene, (c) 1,1-methylisopropylethylene and (d) tetramethylethylene.[7] Recently Cramer and Glasebrook[8] published their results with a less acidic catalyst, namely, activated alumina, in which they obtained high yields of *t*-butylethylene from methyl-*t*-butylcarbinol instead of the 3–5% of that olefin characteristic of the equilibrium mixture.[7b] These results have been repeatedly checked in this Laboratory.[9] The method of Cramer and Glasebrook[8] is now recommended for the preparation of large quantities of *t*-butylethylene as more convenient than the pyrolysis of pinacolyl acetate.[10]

It may be mentioned in passing that making the catalyst even slightly alkaline prevents dehydration at anything below cracking temperatures.[11]

Since 1930 there have been repeated indications in this Laboratory that the two alcohols *t*-amyl alcohol (I) and dimethylneopentylcarbinol (II) behave differently on dehydration. This is in spite of remarkable similarities in structure. Both are tertiary alcohols containing two methyl groups and a methylene group and both are dehydrated readily without rearrangement. In each, the proton for dehydration must come from one of the two methyl groups or from the methylene group. The only difference is that in one the methylene group is attached to methyl while in the other it is attached to *t*-butyl. Evidently this difference has a profound effect on the otherwise identical methylene groups.



(I) (III) (IV)

(1) Whitmore and Karnatz, Diethylcarbincarbinol (2-ethyl-1-butanol), THIS JOURNAL, **54**, 3461 (1932).

(2) Whitmore and co-workers, *ibid.*, **54**, 3717, 4011, 4392 (1932); **55**, 406, 812, 1106, 1119, 1528, 3428, 3721, 3732, 3809, 4153 (1933).

(3) Whitmore and co-workers, *ibid.*, (a) Homeyer, **55**, 4195 (1933); (b) Church, **56**, 176 (1934); (c) Rohrmann, **63**, 2033 (1941).

(4) Whitmore and Mosher, 3,5,5-Trimethyl-3-heptanol, *ibid.*, **63**, 1121 (1941).

(5) Submitted in partial fulfillment for the M.S. degree.

(6) Kondakow, *J. prakt. Chem.*, [2] **54**, 454 (1896); Ipatiew, *Ber.*, **36**, 2002 (1903); Michael and Zeidler, THIS JOURNAL, **36**, 1002 (1914); Hibbert, *ibid.*, **37**, 1748 (1915); Church, *et al.*, *ibid.*, **56**, 176 (1934); Bourquel and Piaux, *Bull. soc. chim.*, **51**, 1051 (1932).

(7) (a) Whitmore and P. L. Meunier, THIS JOURNAL, **55**, 372 (1933). (b) Laughlin, Nash and Whitmore, *ibid.*, **56**, 1395 (1934).

(8) Cramer and Glasebrook, *ibid.*, **61**, 230 (1939).

(9) Unpublished results of R. K. Smith and N. C. Cook and others.

(10) Whitmore and Rothrock, THIS JOURNAL, **55**, 1107 (1933); unpublished results of V. C. Meunier and N. C. Cook.

(11) Unpublished results of M. R. Fenske and co-workers.

$$(CH_3)_3C-CH_2-\underset{CH_3}{\overset{OH}{C}}-CH_3 \longrightarrow$$

(II)

$$(CH_3)_3C-CH_2-\underset{CH_3}{C}=CH_2 + (CH_3)_3C-CH=\underset{CH_3}{C}-CH_3$$

(V) (VI)

This pair of alcohols was chosen for study because of the facts given above. Moreover, they are both dehydrated by refluxing with an excess of 15% sulfuric acid. This allows dehydration under almost identical conditions and avoids the vigorous treatment required to dehydrate primary or secondary alcohols. The olefins III and IV are readily separable in a 60-plate column.[12] This Laboratory had long been familiar with olefins V and VI, the well-known diisobutylenes.[13]

Repeated dehydrations of the alcohols, I and II, with 15% sulfuric acid and careful study of the resulting olefin mixtures indicate that *t*-amyl alcohol (I) gives 1,1-methylethylethylene (III) and trimethylethylene (IV) in the ratio 1:7 while dimethylneopentylcarbinol (II) gives 1,1-methylneopentylethylene (V) and 1,1-dimethyl-2-*t*-butylethylene (VI) in the ratio 4.5:1. Thus, a methylene group attached to methyl loses a proton about 30 times as readily as a methylene attached to *t*-butyl. In other words, an ethyl group loses a proton much more readily than does a neopentyl group. This greater activity of the ethyl group has been observed repeatedly in this Laboratory.[3b] The sluggishness of the neopentyl group in this respect is well illustrated by the dehydration of diethylneopentylcarbinol, which takes place 90% from the ethyl group to yield 2,2-dimethyl-4-ethyl-4-hexene.[3c] The dehydration of 3,5,5-trimethyl-3-heptanol indicates an even more sluggish behavior for the neohexyl group (*t*-amylcarbinyl).[4]

A good example of the difficulty of drawing generalizations regarding the dehydration of alcohols is given by a comparison of dimethylneopentylcarbinol and methylneopentylcarbinol.[3a] As stated above, the former gives dehydration from the two methyl groups and the one neopentyl group in the ratio of 4.5:1. It might thus be argued that *one* methyl group would give up a proton about twice as readily as one neopentyl group. This is contrary to the fact[3a] that methylneopentylcarbinol undergoes dehydration from the one methyl group and the one neopentyl group in the ratio of about 1:4:5. The fallacy here lies in comparing a tertiary alcohol with a secondary alcohol, the one being dehydrated with excess 15% sulfuric acid at about 100° and the other with a small amount of 100% sulfuric acid at perhaps 135°.

In connection with the present work it should be noted that the ratio 4.5:1 for the olefins V and VI checks with the equilibrium present in the diisobutylenes.[13] The equilibrium between III and IV is being studied. It has been found that 15% sulfuric acid does not isomerize either III or IV.

The dehydration of alcohols and the study of equilibrium relations of the resulting olefin mixtures is being continued.

We thank Dr. W. A. Mosher of the Hercules Powder Co. for help in the preparation of this paper.

Experimental

Materials.—Commercial *t*-amyl alcohol, Sharples, was fractionated through a 15-plate column to give material of b. p. 101° (742 mm.), $n^{20}D$ 1.4049. Dimethylneopentylcarbinol was prepared by the action of methylmagnesium bromide on methyl neopentyl ketone, $n^{20}D$ 1.4038. The product, after decomposition in the usual manner, was fractionated through a 10-plate column to give material of b. p. 70.5° (43 mm.), $n^{20}D$ 1.4286.

Dehydration of *t*-Amyl Alcohol.—*t*-Amyl alcohol, 319 g., was dissolved in 395 ml. of 15% sulfuric acid and refluxed under a column of 60 theoretical plates while the olefins formed distilled out. The yield of olefin was 97.8% allowing for 16.7 g. of recovered alcohol. The olefin mixture, 227 g., was dried over potassium carbonate and fractionated through a 60-plate column with 0.5 g. of potassium carbonate in the still pot to prevent isomerization. Ice-water was circulated through the condenser and receiver system while dry-ice traps protected all outlets. The loss on distillation was 2%.

Two olefins were found on fractionation: 2-methyl-1-butene, 27 g., 33–35° (740 mm.), 1.3788, 11.9%; and 2-methyl-2-butene, 195 g., 39.5° (740 mm.), 1.3870, 85.9%. The structures were confirmed by ozonolysis.

Dehydration of Dimethylneopentylcarbinol.—The alcohol, 150 g., was dehydrated by refluxing with an equal weight of 15% sulfuric acid under a 10-plate column and distilling off the olefins as formed. Taking 33 g. of recovered carbinol into account, the yield of olefin was 96%. Distillation of the olefin through a 60-plate column gave 2,4,4-trimethyl-1-pentene, 77.2 g., 78%, 103° (742 mm.), 1.4086–8; and 2,4,4-trimethyl-2-pentene, 17.7 g., 17%, 106.5 (740 mm.), 1.4152–5. The identity of these olefins has been repeatedly checked by ozonolysis in this Laboratory.

Summary

1. The difficulty in drawing generalizations on the dehydration of alcohols is emphasized.

(12) Rose, *Ind. Eng. Chem.*, **33**, 594 (1941); Fenske, Tongberg, Quiggle and Cryder, *ibid.*, **28**, 644–5 (1936).

(13) Whitmore and co-workers, THIS JOURNAL, **53**, 3126 (1931), **54**, 3706, 3710 (1932).

2. The relation of acidity of the dehydrating catalyst to the equilibrium in the resulting olefin mixture is considered.

3. Two closely related tertiary alcohols have been dehydrated under mild but definitely acidic conditions. In *t*-amyl alcohol and dimethylneopentylcarbinol, under similar conditions, the ethyl group yields a proton in dehydration about thirty times as readily as does the neopentyl group.

STATE COLLEGE, PENNSYLVANIA RECEIVED JULY 23, 1942

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

Factors Determining the Course and Mechanism of Grignard Reactions. V. The Effect of Metallic Halides on the Reaction of Grignard Reagents with Benzalacetophenone and with Benzophenone

BY M. S. KHARASCH AND D. C. SAYLES

It has been shown that small amounts of some metallic halides exert a profound effect on the reactions of Grignard reagents with many compounds.[1] The present paper describes the results obtained when methyl- and ethylmagnesium bromides react with benzalacetophenone (chalcone) and benzophenone in the presence of ferric chloride, cuprous chloride, manganous chloride or cobaltous chloride.

The structures of the products formed by the addition of Grignard reagents to some α,β-unsaturated aldehydes and ketones have been determined by Kohler and his co-workers.[2] They report that, with chalcone, phenyl- and ethylmagnesium bromides give, respectively, 94 and 99% of the 1,4-addition product.[2c] The reaction between methylmagnesium bromide and chalcone has not been investigated, but Kohler reports that methylmagnesium bromide reacts with benzalethyl methyl ketone to give 70% of the 1,4-addition product. Smith and Hanson,[3] on the other hand, record only the 1,2-addition product of benzalpropiophenone and methylmagnesium iodide.

It is desirable to elucidate the conditions under which an optimum yield of β-phenylbutyrophenone (the 1,4-addition product) is obtained by condensation of methylmagnesium bromide with chalcone. Kohler and Peterson[2d] state explicitly that an excess of Grignard reagent is necessary to prevent the formation of "secondary" products, but they do not mention the exact proportion of the reagents employed. In the experiments here reported in detail, a 40% excess of Grignard reagents was used, and (Table I) large quantities of 1,3,5-triphenyl-4-benzoylhexadiene-1,3 (m. p. 176°) (III) were produced, probably according to the equation

$$\underset{\text{I}}{C_6H_5CH(CH_3)CH_2COC_6H_5} + \underset{\text{II}}{C_6H_5CH{=}CHCOC_6H_5} \xrightarrow{CH_3MgBr} \underset{\text{III}}{C_6H_5CH(CH_3)C(COC_6H_5){=}C(C_6H_5'){=}CHC_6H_5}$$

The structure of III was confirmed by independent syntheses from I and II where pyridine, trimethylamine or sodium ethylate was used as condensing agent. Other experiments showed that in order to avoid completely the formation of III, a very large excess of the Grignard reagent (200%) was required.

Although (Table I) no one of the metallic halides (2 to 5 mole per cent.) has any effect on the ratio of the 1,2 and 1,4 addition of methylmagnesium bromide to chalcone, yet they profoundly influence the nature of the products formed in the reaction. This effect is most marked with cobaltous chloride. In the presence of this metallic halide the Grignard reagent does not add to the chalcone, but acts as a reducing agent leading to the formation of two products which melt at 197 and 276°, respectively.

$$C_6N_5CH{=}CHC_6H_5 + 2CH_3MgBr \xrightarrow{CoCl_2} [(C_6H_5COCH_2CHC_6H_5)]_2$$

(IV, m. p. 197° and V, m. p. 276°)

These two substances (IV and V) were shown by analyses, molecular weight determinations and the melting points of mixtures to be identical

(1) (a) Kharasch, Kleiger, Martin and Mayo, THIS JOURNAL, **63**, 2305 (1941); (b) Kharasch and Lambert, *ibid.*, **63**, 2315 (1941); (c) Kharasch and Tawney, *ibid.*, **63**, 2308 (1941); (d) Kharasch and Fields, *ibid.*, **63**, 2316 (1941).

(2) (a) Kohler, *Am. Chem. J.*, **31**, 642 (1904); (b) *ibid.*, **37**, 369 (1907); (c) *ibid.*, **38**, 511 (1907); (d) Kohler and Peterson, THIS JOURNAL, **55**, 1073 (1933).

(3) Smith and Hanson, *ibid.*, **57**, 1376 (1935).

TABLE I

EFFECT OF METALLIC HALIDES ON THE ADDITION OF METHYLMAGNESIUM BROMIDE[a] TO CHALCONE

Product	Control	Yield, %[b] 1 mole % of metallic halide $FeCl_3$	Cu_2Cl	$MnCl_2$	$CoCl_2$[c]
β-Phenylbutyrophenone	59	66	69	73	..
1,3,5-Triphenyl-4-benzoyl-hexadiene-1,3, m. p. 176° (III)	41	9	24	27	..
Dibenzyldiacetophenone, m. p. 197° (IV)	..	21	7	..	82
Stereoisomer of (II), m. p. 276° (V)	..	4	..	..	18

[a] A 40% excess of Grignard reagent was used in all experiments. [b] Total yield of products was between 93 and 95% of the amount calculated on the basis of chalcone used. [c] One mole per cent. was added at the beginning of the reaction, and another mole per cent. midway in the addition of the chalcone.

with products previously obtained by reducing chalcone with zinc dust and glacial acetic acid,[4] or with vanadous sulfate.[5] Substance IV is considered to be 1,4-dibenzoyl-2,3-diphenylbutane because it readily undergoes intramolecular condensation to form a cyclopentene derivative.[4] Substance V is regarded as a stereoisomer of IV, since distillation partly converts it into that substance.

Compounds IV and V have not hitherto been observed as products in the reaction of any Grignard reagent on chalcone. They are, however, formed whenever chalcone is treated with a powerful reducing agent or with methylmagnesium chloride in the presence of small amounts of cobaltous chloride. The latter reaction is readily explained by the chain mechanism proposed by Kharasch and Fields[1d] to account for the catalytic effects of cobaltous, nickelous and ferrous chlorides on certain Grignard reactions.

$$CH_3MgBr + CoCl_2 \longrightarrow CH_3CoCl + MgBrCl$$
$$CH_3CoCl \longrightarrow CH_3 + (CoCl)$$
$$(ClCl) + C_6H_5CH{=}CHCOC_6H_5 \xrightarrow{MgBrCl} C_6H_5\underset{\displaystyle OMgBr}{\underset{|}{C}}HCH{=}\underset{\displaystyle |}{C}C_6H_5 + CoCl_2$$
$$2C_6H_5\underset{\displaystyle OMgBr}{\underset{|}{C}}HCH{=}\underset{\displaystyle |}{C}C_6H_5 \xrightarrow[\text{and hydrolysis}]{\text{dimerization}} C_6H_5COCH_2CHC_6H_5CHC_5H_5CH_2COC_6H_5$$
IV and V

In all such catalytic reactions the rate of the reaction and the stability of the compound RCoCl at the temperature used are highly important. Their influence is illustrated in the reaction of ethylmagnesium bromide and benzophenone. At ordinary temperatures (20–25°) ethylmagnesium bromide adds to benzophenone either in the presence or in the absence of cobaltous chloride to give diphenylethylcarbinol; no reduction to benzopinacol or benzohydrol occurs.[6] However, at −12°, a 50% yield of benzopinacol is readily obtained even though only 2 mole per cent. of cobaltous chloride is used. This large temperature effect is explained by the fact that at higher temperatures C_2H_5CoCl decomposes almost instantaneously with the liberation of metallic cobalt. Thus no chain reaction of the kind indicated is initiated.

Phenylmagnesium bromide, when added to chalcone, yields by 1,4 addition a saturated ketone, the product isolated by Kohler. The presence of small amounts of metallic halides has little effect on the course of this reaction; it is, however, significant that in the presence of ferric or cobaltous chloride (2–5 mole per cent.) even this Grignard reagent yields 2–5% of V.

The results here reported for the addition of ethylmagnesium bromide to chalcone differ considerably from the 94% of 1,4 addition reported by Kohler. In a number of experiments a 60% yield of the saturated ketone (β-phenylvalerophenone VI) was obtained. The remaining 40% was an oil which could not be crystallized. This oil readily absorbed bromine and decolorized potassium permanganate solution; it gave no ketonic reactions, and could not be acetylated by acetic anhydride in pyridine. It decomposed when distilled *in vacuo*. The only feasible method for purifying this oil was first to free it of ketonic materials by shaking it with a water solution of acethydrazide pyridinium chloride,[7] and then to decolorize an ethyl alcohol solution of the water insoluble residue with norite. Evaporation of the alcohol again yielded an oil. Analysis of this oil indicated that it is probably styrylphenylethylcarbinol (VII). The additions of ethyl- and methylmagnesium bromide to chalcone thus differ significantly in the proportion of 1,2- and 1,4-addition products formed.

The discrepancy between the results here reported and those obtained by Kohler is not to be explained by the order in which the reagents are

(4) Harries and Hübner, *Ann.*, **296**, 326 (1897).
(5) Conant and Cutler, THIS JOURNAL, **48**, 1016 (1926).
(6) Blicke and Powers, *ibid.*, **54**, 2503 (1932); Kharasch and Weinhouse, *J. Org. Chem.*, **1**, 210 (1936).
(7) Girard and Sandulesco, *Org. Syntheses*, **18**, 10 (1938).

$$C_6H_5CH{=}CHCOC_6H_5 + C_2H_5MgBr \begin{cases} \xrightarrow{\text{1,4 Addition}} C_6H_5CH(C_2H_5)CH_2COC_6H_5 \text{ (VI), 60\%} \\ \xrightarrow{\text{1,2 Addition}} C_6H_5CH{=}CHC(OH)(C_2H_5)C_6H_5 \text{ (VII), 40\%} \end{cases}$$

added to the reaction mixture. For the present no explanation can be offered.

The effect of temperature on the direction of addition of ethylmagnesium bromide to chalcone is slight. The amount of 1,2 addition is about 20–30% less at low temperatures (−25°) than at 25°.

Experimental Part

The organic compounds used were first purified by distillation or crystallization. Methyl bromide was obtained from the Dow Chemical Company. Benzalacetophenone was prepared according to "Organic Syntheses."[8] The cuprous chloride was the commercial anhydrous reagent; anhydrous manganous chloride was prepared by heating the hydrated chloride in an oven for eight hours at 120°; anhydrous ferric chloride was prepared from analytical grade iron wire and chlorine; anhydrous cobalt chloride was prepared by heating the hydrated dihalide at 150° in a stream of hydrogen chloride.

Preparation of Grignard Reagent.—Each Grignard reagent (prepared from sublimed magnesium) was siphoned from the reaction vessel through a glass tube filled with a glass wool plug into a dark storage bottle. Two milliliter aliquots were removed for standardization by the acid titration method.

General Procedure.—Aliquot parts of the Grignard reagent were transferred to three-necked flasks, each fitted with reflux condenser, mercury seal stirrer, dropping funnel and calcium chloride tubes. One flask was used as a control. Weighed quantities of anhydrous metal halides were added to the other flasks. The Grignard solution upon the addition of the metal salts changed color. Cobalt chloride produced a black solution; cuprous chloride, a blue-green solution; manganous chloride, a yellow solution.

Reaction of Methylmagnesium Bromide and Chalcone.—Benzalacetophenone (0.19 mole) dissolved in anhydrous ether was added drop by drop to an excess of Grignard reagent (0.26 mole). During the addition, the temperature of the reaction mixture was maintained at 0–5°. After addition was complete, the reaction mixture was stirred for an additional thirty minutes; then the temperature was allowed to rise; finally, the mixture was refluxed for one hour and allowed to stand.

The reaction mixture was decomposed by pouring it onto 200 g. of cracked ice mixed with excess glacial acetic acid (25 cc.). The solution was filtered. The ethereal layer was separated, and the aqueous layer was extracted with ether. The combined ethereal layers after being washed with aqueous bicarbonate and water, were dried over anhydrous sodium sulfate. The ether was finally evaporated. The ethyl alcoholic extract of the residue (when methylmagnesium bromide was used) yielded a substance melting at 72°. The material insoluble in alcohol after crystallization from an ethanol–dioxane mixture yielded a compound melting at 176°.

Anal. Calcd. for $C_{31}H_{26}O$: C, 89.83; H, 6.28; mol. wt., 414. Found: C, 89.20; H, 6.90; mol. wt., 400.

The structure of this latter compound was proved by its synthesis. To an anhydrous ether solution of 0.5 g. of chalcone and 0.5 g. of β-phenylbutyrophenone was added a condensing agent (either pyridine or methylmagnesium bromide), the whole mixture was refluxed for one hour. The solvent was evaporated, and the residue crystallized from a mixture of ethanol and dioxane. A quantitative yield of a solid melting at 176° was obtained. This melting point was not lowered by addition of the compound (m. p. 176°) obtained from the reaction of methylmagnesium bromide with chalcone.

Dibenzyldiacetophenone.—In the experiments in which ferric, cuprous or cobalt chloride was used as a catalyst, a solid separated at the ether–water interface, when the reaction mixture was decomposed. This solid, when crystallized from an ethanol–dioxane mixture, melted at 197–198°. The material insoluble in the ethanol–dioxane, after crystallization from pyridine, melted at 276°.

Determination of β-Phenylvalerophenone (VI).—In the reactions between ethylmagnesium bromide and chalcone, the dried ethereal solution obtained as described above was transferred to a 100-cc. volumetric flask and made up to volume. A 5-cc. aliquot was removed to a weighed 50-cc. Erlenmeyer flask, the solvent evaporated and the flask reweighed. The total weight of product was thus obtained.

The ketonic material in this oil was determined by precipitation with 2,4-dinitrophenylhydrazine.[9] The validity of this method of analysis was checked by control precipitations on chalcone and β-phenylvalerophenone.

Separation of the β-Phenylvalerophenone from Styrylphenylethylcarbinol (VII).—An aliquot of the ethereal solution was taken, and the solvent evaporated. The residue was dissolved in absolute alcohol containing 10% acetic acid and acethydrazide pyridinium chloride.[8] The reaction mixture was then refluxed for an hour, and finally decomposed by being poured into ice-water containing sodium carbonate. The aqueous solution was extracted several times with ether, and the combined ethereal extracts were washed with water. When the solvent was evaporated, the unsaturated alcohol, styrylphenylethylcarbinol, was obtained.

Anal. Calcd. for $C_{17}H_{18}O$: C, 85.71; H, 7.56, mol. wt., 238. Found: C, 84.68; H, 7.84; mol. wt., 269.

Estimation of Styrylphenylethylcarbinol (VII) by Oxidation.—The solvent was evaporated from an aliquot of the ethereal solution, and the residue was dissolved in purified acetone. Finely powdered potassium permanganate was added to the solution, and the whole was vigorously stirred. The temperature was kept below 20°. The unused potas-

(8) "Org. Syn." Coll. Vol. I, p. 71.

(9) Cooper, Ph.D. Thesis, University of Chicago.

sium permanganate was finally titrated. The accuracy of this oxidation method was checked by oxidation of chalcone.[2]

An unusual compound was isolated in one determination where manganous chloride was used as a catalyst. The ethereal solution was evaporated, and the residue crystallized from alcohol. A solid which melted at 136° was obtained.

Anal. Calcd. for $C_{32}H_{32}O_2$: C, 85.71; H, 7.14; mol. wt., 448. Found: C, 85.82; H, 7.14; mol. wt., 470.

This compound could possibly be formed by the condensation of β-phenylvalerophenone and chalcone in a manner similar to the substance obtained from β-phenylbutyrophenone and chalcone. This compound yielded a 2,4-dinitrophenylhydrazone.

Anal. Calcd. for $C_{38}H_{36}O_5N_4$: N, 8.92. Found: N, 9.11.

The compound could not be synthesized by condensing β-phenylvalerophenone with chalcone when either pyridine or ethylmagnesium bromide was used as a condensing agent.

Addition of Benzophenone to Ethylmagnesium Bromide.—Benzophenone (0.5 mole) in 40 cc. of anhydrous benzene was added slowly to a 100% excess of ethylmagnesium bromide containing 6 mole per cent. of cobaltous chloride. The temperature of the reaction was kept below 20°. A mixture of diphenylethylcarbinol and diphenylpropylene was obtained. The reaction product was dehydrated to diphenylpropylene by distillation with a trace of iodine. The yield was quantitative.

Benzophenone, 0.05 mole, in 40 cc. of anhydrous benzene containing 6 mole per cent. of cobaltous chloride was slowly added to 100% excess of ethylmagnesium bromide; the reaction temperature was kept at −12°. The reaction mixture was then stirred for two hours at −12°, and allowed to stand overnight at room temperature. By the usual methods of isolation, benzopinacol (45%) and diphenylethylcarbinol (55%) were obtained from this mixture.

Summary

1. The effect of some metallic chlorides on the reaction of Grignard reagents with benzalacetophenone has been studied.

2. It has been shown that manganous chloride has little catalytic effect on the reaction between methylmagnesium bromide or iodide and chalcone. Cobalt chloride is a powerful catalyst for the formation of reduction dimers. Cuprous and ferric chlorides are intermediate in their catalytic effect.

3. Metallic halides do not markedly affect the reaction between ethylmagnesium bromide and chalcone; they slightly favor 1,2 addition. Variations in temperature and in the order of addition of the reagents also produce only a slight effect.

4. Benzophenone at 25° reacts with ethylmagnesium bromide containing cobalt chloride to give only the addition product. Benzophenone at −12° reacts with ethylmagnesium bromide containing cobalt chloride to give both benzopinacol and diphenylethylcarbinol.

CHICAGO, ILLINOIS RECEIVED APRIL 27, 1942

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

Carboxylation. IV. Direct Introduction of the Chloroformyl (—COCl) Group into Alicyclic and Aliphatic Acid Chlorides

BY M. S. KHARASCH, KENNETH EBERLY AND MORTON KLEIMAN

In the course of work on the introduction of the chloroformyl (—COCl) group[1] into cyclohexane by the use of trichloromethyl chloroformate, there was obtained under optimum conditions (six hours of heating at 225°) a 3% yield of a disubstitution product, identified as 1,1-dichloroformylcyclohexane by hydrolysis to cyclohexane-1,1-dicarboxylic acid. Despite careful search, no hexahydrobenzoyl chloride could be detected.

This rather striking result suggested that diphosgene reacts more readily with hexahydrobenzoyl chloride than with cyclohexane. Upon further investigation, it was found that ten hours of heating of hexahydrobenzoyl chloride with diphosgene in a sealed tube at 225°, subsequent hydrolysis of the reaction product, and crystallization of the hydrolyzate from an ether–ligroin mixture, gave an 81% yield of cyclohexane-1,1-dicarboxylic acid.

In a like manner, diphosgene reacts with isobutyryl chloride to give a 70% yield of dimethylmalonyl chloride; with α-ethylbutyryl chloride to give a 90% yield of diethylmalonyl chloride; and with α-ethylhexoyl chloride to give a 30% (or possibly higher) yield of ethylbutylmalonyl chloride. In many experiments with propionyl chloride and diphosgene, however, the maximum yield of methylmalonic acid was only 15%. No

(1) For previous references, see Kharasch, Kane and Brown, THIS JOURNAL, 64, 1621 (1942).

malonic acid was obtained from acetyl chloride. With phenylacetyl chloride, the best yield of phenylmalonic acid so far obtained is only 2%.

From these findings, it appears that a chloroformyl group derived from diphosgene readily replaces a tertiary hydrogen atom on the α carbon atom of an acid chloride. The same reagent replaces secondary hydrogen atoms with considerable difficulty (if low yield be regarded as a criterion). Replacement of a primary hydrogen atom by this method seems to be impossible.

Experimental

Reaction of Cyclohexane with Diphosgene.—A mixture of 7 g. of cyclohexane and 8.3 g. of diphosgene was sealed in a bomb-tube and heated for ten hours at 225°. The tube was then allowed to come to room temperature, cooled by immersion in liquid nitrogen, and opened. After allowing the volatile products to boil away, the content of the tube was poured into water, allowed to stand for a few hours at room temperature, and finally evaporated to dryness on a steam-bath. A solid material (0.2 g.) which melted at 172° (dec.) was thus obtained. This substance, after crystallization from a mixture of ether and ligroin, melted at 178° (dec.) and did not depress the melting point of a known sample of cyclohexane-1,1-dicarboxylic acid.[2]

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.78; H, 7.03. Found: C, 55.59; H, 6.96.

The cyclohexane-1,1-dicarboxylic acid was further identified by decarboxylation (at 200°) to the hexahydrobenzoic acid and conversion of the latter substance (with the aid of thionyl chloride and ammonia) to the known hexahydrobenzamide (m. p. 186°).

Anal. Calcd. for $C_7H_{13}ON$: N, 11.02. Found: N, 11.01.

The volatile components were distilled from the mixture obtained by the interaction of cyclohexane and diphosgene. In order to prepare the diamide of cyclohexane-1,1-dicarboxylic acid, the residue was poured into a large excess of aqueous ammonia. The dark sludge which separated was taken up in hot dilute alcohol, treated with bone black, and filtered. The filtrate was reduced to a small volume and allowed to stand. Small, colorless crystals melting at 261° were obtained. The melting point of this material was not altered by further crystallization from dilute alcohol. *Anal.* Calcd. for $C_8H_{14}O_2N_2$: N, 16.47. Found: N, 16.21. The melting point of this diamide recorded by Dox and Yoder[2] is 237°. The reason for this discrepancy is unknown.

Preparation of Cyclohexane-1,1-dicarboxylic Acid from Hexahydrobenzoyl Chloride.—A mixture of 4 g. of hexahydrobenzoyl chloride and 5.4 g. of diphosgene was heated for ten hours in a sealed tube at 225°. The bomb-tube, after being cooled in the usual manner, was opened, and the volatile products were allowed to boil away. The residue was then hydrolyzed with water. When the water solution was evaporated to dryness, 3.8 g. of crude cyclohexane-1,1-dicarboxylic acid (m. p. 170°) was obtained. This yield is 81% of that calculated on the basis of the amount of hexahydrobenzoyl chloride used. Recrystallization (with bone black) of the crude product from an ether–ligroin mixture gave colorless crystals of the acid melting at 176° (dec.).

Synthesis of Dimethylmalonyl Chloride by Interaction of Isobutyryl Chloride with Diphosgene.—A mixture of 3 g. of isobutyryl chloride and 2 g. of diphosgene was sealed *in vacuo* in a heavy glass bomb-tube and heated for ten hours at 225°. The bomb-tube was cooled to −80° before opening. The combined products of eleven such bomb reactions, when fractionated, yielded unreacted isobutyryl chloride (5.2 g.) and dimethylmalonyl chloride (31 g.), b. p. 153–159° (749 mm.). The dimethylmalonyl chloride was further identified by hydrolyzing it to the corresponding dimethylmalonic acid, m. p. 187°. The yield of dimethylmalonyl chloride, based upon the amount of isobutyryl chloride consumed in the reaction, was 70%.

Synthesis of Diethylmalonyl Chloride by the Interaction of α-Ethylbutyryl Chloride with Diphosgene.—A mixture of 4 g. each of α-ethylbutyryl chloride and diphosgene was sealed *in vacuo* in a heavy glass bomb-tube and heated at 225° for ten hours. The combined products of ten such bomb-tube reactions, when fractionated, yielded 9 g. of unreacted ethylbutyryl chloride and 39.4 g. of diethylmalonyl chloride (b. p. 190–194°). This yield is 90% of that calculated from the amount of ethylbutyryl chloride consumed in the reaction. The diethylmalonyl chloride was further identified by preparing the known diamide, m. p. 224–226° (cor.).

Synthesis of Ethylbutylmalonyl Chloride by the Interaction of α-Ethylhexoyl Chloride with Diphosgene.—Many attempts were made to carry out this reaction in glass bomb-tubes; however, except when extremely small amounts of reactants were used, the bomb-tubes exploded. A steel bomb proved more satisfactory. But, unfortunately, despite all efforts to make this bomb gas-tight, it leaked slightly at the high pressure produced during the reaction. In this steel bomb, a mixture of 25 g. of ethylhexoyl chloride and 35 g. of diphosgene was heated ten hours at 225°. The reaction mixture when fractionated yielded 3.5 g. of unreacted ethylhexoyl chloride, and 9 g. of crude ethylbutylmalonyl chloride, b. p. 190–220°; the latter was identified by hydrolyzing it to the known ethylbutylmalonic acid, m. p. 116–117°. Since the yield of ethylbutylmalonyl chloride (based upon the amount of the ethylhexoyl chloride consumed in the reaction) was 30%, it seems likely that, with satisfactory apparatus, a higher yield of this acid chloride may be obtained.

Reaction of Propionyl Chloride with Diphosgene.—A mixture of 3.5 g. of propionyl chloride and 7.5 g. of diphosgene was heated in a bomb-tube for ten hours at 225°. After cooling and opening the tube in the usual manner, the content was hydrolyzed with water and the solution evaporated to dryness on a water-bath. A 15% yield (0.65 g.) of crude methylmalonic acid was thus obtained. Crystallization (with bone black) of this product from an ether–ligroin mixture gave colorless crystals of methylmalonic acid [m. p. 132–133° (dec.)].

Reaction of Phenylacetyl Chloride with Diphosgene.—A mixture of 4 g. of phenylacetyl chloride with 5.1 g. of

(2) Dox and Yoder, THIS JOURNAL, **43**, 1366 (1921); Vogel, *J. Chem. Soc.*, **123**, 1487 (1929), report a melting point of 179.5° (dec.).

diphosgene was heated in a bomb-tube for ten hours at 150–175°. After cooling and opening the tube in the usual manner, the reaction mixture was hydrolyzed with water (over a period of twelve hours at room temperature), and evaporated to dryness on a water-bath. Since phenylmalonic acid is readily decarboxylated, the last traces of water were removed by drying the product over phosphorus pentoxide *in vacuo*. The mixture of phenylacetic acid and phenylmalonic acid thus obtained (3.8 g.) was decarboxylated at 220°. The carbon dioxide evolved was collected quantitatively. From the amount of carbon dioxide formed, it is estimated that the phenylmalonic acid present in the reaction mixture amounted to a 1.4% yield.

Summary

1. It has been demonstrated that the chloroformyl (—COCl) group can be directly introduced (at the α carbon atom) into aliphatic and aryl-substituted-aliphatic acid chlorides by the use of trichloromethylchloroformate (diphosgene) as the "carboxylating" agent.

2. The experimental conditions requisite for carrying out this type of carboxylation have been determined.

3. The syntheses with good yields of several di-substituted malonyl chlorides have been described.

4. The chloroformyl group (derived from diphosgene) replaces hydrogen atoms attached to the α carbon atoms of acid chlorides most easily when these α carbon atoms are tertiary and least easily when they are primary.

CHICAGO, ILLINOIS RECEIVED AUGUST 13, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF INDIANA UNIVERSITY]

Alkylation of Amines. I[1]

BY JOHN H. BILLMAN, A. RADIKE AND B. W. MUNDY

The esters of sulfuric,[2] sulfurous,[3] and *p*-toluenesulfonic acids[4] have been used frequently for the alkylation of amines. Now that the methyl, ethyl and *n*-butyl esters of orthophosphoric acid have become readily available within recent years,[5] it was of interest to investigate the possibility of using these esters as alkylating agents for amines since Noller[6] has shown that they may be used to alkylate phenols.

All of the esters investigated appeared to be non-toxic under normal conditions and were quite stable toward hydrolysis. Three-quarters of an hour was required to saponify triethyl phosphate completely when boiled with the calculated amount of sodium hydroxide.

It was found that all three groups in the ester could be utilized in the alkylation. The reaction may be represented by the equation

$$3ArNH_2 + 2(RO)_3PO \longrightarrow 3Ar\text{—}\overset{R}{N}\text{—}R + 2H_3PO_4$$

Several attempts to alkylate *p*-nitroaniline by this method resulted in failure. The conditions necessary to effect alkylation resulted in decomposition.

When branched chain alkyl orthophosphates such as isopropyl phosphate were used, practically pure isopropylaniline was obtained.

The authors wish to thank the Commercial Solvents Corporation for some of the phosphate esters used in this work.

Experimental

Preparation of Orthophosphate Esters.—The *n*-propyl and the isopropyl esters of orthophosphoric acid were prepared from phosphorus oxychloride and the proper alcohol similar to the method described in "Organic Syntheses."[7] The yield of *n*-propyl phosphate was 54%, while that of the isopropyl phosphate was 65%.

Procedure for Alkylation of Amines.—A mixture of 0.3 mole of the amine and 0.2 mole of trialkyl phosphate in a 500-cc. flask provided with a condenser and boiling chips was refluxed at a moderate rate for two hours. In most cases, during the early stages of heating, the reaction became vigorous and the temperature rose sharply. As soon as rapid boiling ceased the stream of water in the condenser jacket was replaced by one of air. The mixture was then cooled to 50°, 25 g. of sodium hydroxide in 100 ml. of water added and the whole refluxed one hour, and then poured into a 400-cc. beaker where it was allowed to cool to room temperature. The oily layer of amine, which formed on top, was poured off from the solid sodium phosphate. The latter was extracted with ether and the combined extracts and oil dried over anhydrous sodium sulfate. The ether was then removed, the residue treated with an equal volume of acetic anhydride and allowed to stand overnight.

(1) Original manuscript received April 13, 1942.

(2) Claesson and Lundwall, *Ber.*, **13**, 1700 (1880); Ullmann and Wenner, **33**, 2476 (1900); Cade, *Chem. Met. Eng.*, **29**, 319 (1923).

(3) Voss and Blanke, *Ann.*, **485**, 258 (1931).

(4) Marvel and Sekera, THIS JOURNAL, **55**, 345 (1933).

(5) Commercial Solvents Corporation, Terre Haute, Indiana.

(6) Noller and Dutton, THIS JOURNAL, **55**, 424 (1933).

(7) *Organic Syntheses*, **16**, 10 (1936).

Ester	Primary amine	Tertiary amine	Yield, %
Methyl phosphate	Aniline	Dimethylaniline	67.9
Methyl phosphate	β-Naphthylamine	Dimethyl-β-naphthylamine	64.4
Ethyl phosphate	Aniline	Diethylaniline	99.0
Ethyl phosphate	α-Naphthylamine	Diethyl-α-naphthylamine	60.0
n-Propyl phosphate	Aniline	Di-*n*-propylaniline	78.1
Butyl phosphate	Aniline	Di-*n*-butylaniline	78.5

The mixture was treated with 20 ml. of concd. hydrochloric acid dissolved in 30 ml. of water and shaken until the base dissolved. The solution was extracted with two 30-ml. portions of ether and the water layer treated with a 25% sodium hydroxide solution to free the base. The oil which formed was collected by extracting the mixture with ether. The ether was dried over anhydrous sodium sulfate and distilled to recover the tertiary amine.

The yield of isopropylaniline from isopropyl phosphate and aniline was 80.5%.

The boiling points of the amines and the melting points of their solid derivatives corresponded to those found in the literature.

Summary

A method has been developed for the preparation of tertiary amines by treating an aromatic amine with alkyl esters of orthophosphoric acid. Six tertiary amines have been prepared in 60 to 99% yield by this procedure.

BLOOMINGTON, INDIANA RECEIVED OCTOBER 16, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF FLORIDA]

Physical Properties of Terpenes. I. The System α- and β-Pinene[1a]

BY ROBERT E. FUGUITT, W. DAVID STALLCUP[1b] AND J. ERSKINE HAWKINS

A knowledge of the physical properties of binary mixtures of α- and β-pinene is necessary for some phases of study of American gum turpentine which is composed largely of these two substances.[1c]

Data in the literature show a wide variation in the values for the physical constants for α- and β-pinene. Since it was desired to make a study of binary mixtures of these compounds, it was necessary first to establish constants for the pure substances.

With efficient fractionating columns it is possible to obtain α- and β-pinenes which, the authors believe, are of a higher degree of purity than has been reported heretofore. In a previous publication[2] the authors have shown that the spiral screen type of column developed by Lecky and Ewell[3] is well suited for the purification of α- and β-pinene.

Preparation of α-Pinene and β-Pinene

α-Pinene was prepared by the careful fractionation of four liters of commercial α-pinene,[4] from gum turpentine, through a spiral screen column[2] at 20-mm. pressure and a reflux ratio of 40 to 1. This column exerted 75 plates upon a mixture of *n*-heptane–methylcyclohexane at total reflux and atmospheric pressure. Fractions were collected at 75-cc. intervals. All fractions with a refractive index in the range 1.4631–1.4633 at 25.0° were combined and refractionated through the same column. Fractions were then collected at 50-cc. intervals and their refractive indices and optical rotations were measured at 25.0°. The fractions which had constant values of refractive index and optical rotation were combined and were considered to be pure α-pinene. In verification, a 100-cc. portion of the latter was fractionated through a column which had 60 plates determined as above. No change in these two physical constants was noted at any point during collection of the distillate.

For comparison, α-pinene from wood turpentine was desired. The preparation of this pure component from wood turpentine involved its separation from a small amount of camphene which boils about 3° higher. The intermediate fractions having constant refractive indices and optical rotations at 25.0° were then combined and refractionated. The material thus obtained had constant physical properties and was of the same purity as the α-pinene from gum turpentine.

The β-pinene used was prepared in an analogous manner from commercial β-pinene[4] obtained from gum turpentine.

These purified pinenes had the following constants

	B. p., °C. (20.0 mm.)	$n^{25.0}_D$	$d^{25.0}_4$	$[\alpha]^{25.0}_D$
α-(gum)	52.2	1.4631	0.8542	− 3.83
α-(wood)	52.2	1.4631	.8542	+34.07
β-(gum)	59.7	1.4768	.8666	−21.49

These constants are in close agreement with unpublished

(1a) Original manuscript received April 11, 1942.

(1b) Present address, American Cynamid Co., Stamford, Conn.

(1c) Palkin and co-workers, U. S. D. A. Technical Bulletin No. 276, January, 1932.

(2) Stallcup, Fuguitt and Hawkins, *Ind. Eng. Chem., Anal. Ed.*, **14**, 503 (1942).

(3) Lecky and Ewell, *ibid.*, **12**, 544 (1940).

(4) Furnished through the courtesy of Southern Pine Chemical Company, Jacksonville, Florida.

data of J. P. Bain,[5] with much of the data of S. Palkin and co-workers,[1,6] with data of Waterman, Van't Spijker and Van Westen[7] and some of the data of Dupont.[8]

Experimental

Density Measurements.—These were made with a 25-ml. density bottle. In all cases values were obtained at least in duplicate which checked to the fourth decimal place. The thermostat was controlled by means of an Aminco Metastatic Thermoregulator connected to a vacuum tube relay circuit developed by Hershberg and Huntress.[9] The thermoregulator controlled the temperature within a limit of ±0.02°.

Mixtures of α- and β-pinene were made up to known concentrations by weight. Measurements of the variation of density with concentration were made using α-pinene from both gum and wood turpentine. The densities of the mixtures were independent of the source of the α-pinene used. The average deviation of the density determinations was 0.00004. These data may be expressed at 25.0° by the equation

$$d^{25}_4 = 0.8542 + 0.0129X - 0.0005X^2 \qquad (1)$$

in which X is the mole fraction of β-pinene.

Refractive Index Measurements.—These were obtained with the pure substances and their mixtures by means of an Abbé refractometer calibrated against a known glass. Constant temperature was maintained by circulating water through the refractometer from the thermostat described above. The average deviation of the determinations was 0.00006.

Refractive index measurements of the two pure substances for the temperature range 15–35° show that both α- and β-pinene have a coefficient of 0.00045 unit per degree. Observations were made every two degrees, but since the relation is linear only the limiting points are given: α-pinene, $n^{15.0}_D$ 1.4676, $n^{35.0}_D$ 1.4586; β-pinene, $n^{15.0}_D$ 1.4813, $n^{35.0}_D$ 1.4723.

The variation of the refractive index with concentration for mixtures of β-pinene and either gum or wood α-pinene at 25.0° may be expressed by the equation

$$n^{25.0}_D = 1.4631 + 0.0144X - 0.0007X^2 \qquad (2)$$

where X is the mole fraction of β-pinene.

The molar refractions of the pure components were calculated using the standard atomic refraction values of Auwers and Eisenlohr and also a value of 0.48 for the cyclobutane ring. In this manner the value of 43.99 was obtained for both α- and β-pinene. From the observed data the values of 43.93 and 44.40 were calculated for α- and β-pinene, respectively, by use of the Lorenz–Lorentz equation. The exaltation of 0.41 for β-pinene is probably due to the presence of the exocyclic double bond. Auwers[10] has proposed that values of from 0.32 to 0.52 be added to correct for the exocyclic double bond.

Polarimetric Measurements.—Since α-pinene has a rotation that varies with its source, sample, and time of year collected from the tree, the value of this constant has no diagnostic significance.[11] It has been pointed out by Darmois[12] that β-pinene has a constant specific rotation regardless of its source, and that this value is −22.44° for the j-line of mercury. Dupont[8] reported a value of −22.48°.

All rotations were observed at 25.0° in a jacketed two-decimeter tube. A Duboscq polarimeter, reading by vernier to 0.01° of arc and equipped with suitable filters, depending on the wave length of light, was used. Readings on the same tube could be made with an average deviation of 0.02° using the sodium light and 0.03° using a less intense mercury arc.

Listed in Table I are rotations of α- and β-pinene and their mixtures for the Na_D (589 μμ), Hg_j (578 μμ) and Hg_v (546 μμ) lines. Also given are the observed rotatory dispersions. Biot's law for the linearity of specific rotations of mixtures does not hold exactly. The maximum deviation is about 0.3° at a mole fraction of 0.5. The data could be expressed by a second degree equation. However, this relation would change with the variation in the value of the rotation of the pure α-pinene used.

Also, listed in column 3, Table I, are the mole fractions of β-pinene calculated by Biot's law from the observed data using the Na_D line. The deviations for the Hg_j and Hg_v lines are about the same.

Biot's law may be applied, to express rotatory dispersion for a given mixture, in the form

$$\frac{[\alpha]_v}{[\alpha]_D} = \frac{n_{\beta\text{-}}[\alpha_{\beta\text{-}}]_v + (1 - n_{\beta\text{-}})[\alpha_{\alpha\text{-}}]_v}{n_{\beta\text{-}}[\alpha_{\beta\text{-}}]_D + (1 - n_{\beta\text{-}})[\alpha_{\alpha\text{-}}]_D}$$

in which $n_{\beta\text{-}}$ is the mole fraction of β-pinene in the mixture, $[\alpha_{\beta\text{-}}]_v$ and $[\alpha_{\beta\text{-}}]_D$ are the specific rotations of β-pinene with the v-line and D-line, respectively, and $[\alpha_{\alpha\text{-}}]_v$ and $[\alpha_{\alpha\text{-}}]_D$ are the specific rotations of α-pinene with the v-line and D-line, respectively. When the values of dispersion are calculated on this basis only slight variations from the observed dispersions are noted. This deviation is illustrated for the $[\alpha]_v/[\alpha]_D$ dispersion by the data in column 7, Table I.

Dupont[12] observed that for high α-pinene con-

(5) Private communication.

(6) U. S. D. A. Technical Bulletin No. 596, December, 1937.

(7) Waterman, Van't Spijker and Van Westen, *Rec. trav. chim.*, **48**, 1191 (1929).

(8) Dupont, Beilstein Suppl., Vol. V, pp. 77–79 (1930 ed.).

(9) Hershberg and Huntress, *Ind. Eng. Chem., Anal. Ed.*, **5**, 344–6 (1933).

(10) Auwers, *Ann.*, **387**, 240 (1912).

(11) Black and Thronson, *Ind. Eng. Chem.*, **26**, 66 (1934).

(12) G. Dupont, "Les Essences de Terebenthine," Gauthier Villars and Co., Paris, 1926.

TABLE I

SPECIFIC ROTATIONS AND DISPERSIONS OF MIXTURES OF α- AND β-PINENE

Mole fraction β-pinene	$[\alpha]^{25.0}_D$	Mole fraction β-pinene Biot	$[\alpha]^{25.0}_j$	$[\alpha]^{25.0}_V$	$[\alpha]_V/[\alpha]_D$	Dev. × 10³	$[\alpha]_V/[\alpha]_j$
0.000	− 3.83	...	− 4.03	− 4.57	1.193	...	1.134
.110	− 5.69	0.105	− 5.96	− 6.59	1.158	−9	1.106
.205	− 7.32	.198	− 7.61	− 8.29	1.132	−4	1.091
.290	− 8.71	.276	− 9.02	− 9.77	1.121	−4	1.084
.394	−10.53	.379	−10.85	−11.67	1.107	0	1.076
.495	−12.26	.477	−12.61	−13.53	1.103	−2	1.074
.581	−13.84	.567	−14.19	−15.17	1.097	−1	1.070
.680	−15.67	.671	−16.05	−17.13	1.093	−1	1.067
.806	−17.90	.796	−18.32	−19.50	1.089	−1	1.064
.887	−19.44	.884	−19.86	−21.09	1.085	0	1.062
1.000	−21.49	...	−21.98	−23.28	1.083	...	1.059

tent (approximately 70 mole per cent. or greater) the dispersion is a good indication of the α-pinene content. Ordinarily the $[\alpha]_V/[\alpha]_j$ ratio is used, probably because the two lines are obtained from the same source. However, the data show that $[\alpha]_V/[\alpha]_D$ gives a wider dispersion range and therefore should be a more satisfactory indication of α-pinene content.

Vapor Pressure Measurements.—These were determined in the pressure range from 15 to 80 mm. by use of a distillation column in which the vapors were allowed to come to equilibrium with the liquid. The column temperature was adjusted to within 1.5° of the temperature recorded by the condensing vapors in the head. The temperatures of the vapors were measured by the use of a calibrated mercury thermometer that could be read to ±0.05°. The bulb of the thermometer was wrapped with a single layer of cotton gauze.

The pressure was regulated by a manostat of the Hershberg–Huntress type.[9] The action of the vacuum pump on the manostat was partially checked by placing a stopcock between the pump and the manostat. The pressure fluctuations were minimized by including a five-gallon bottle in the system between the manostat and the column.

The manometer was connected to the head of the column so that the pressure of the condensing vapors would be recorded. The vapor pressures were measured with a Germann barometer,[13] using a cathetometer which could be read to 0.01 mm. The observed pressure readings were corrected to 0° for the difference in the expansion of the mercury and the brass scale at different temperatures[14] and were corrected to 45° latitude and sea level.[15] At each recorded temperature about 2 cc. of liquid was collected at a reflux ratio of 20 to 1.

Equations were obtained by applying the method of averages to the corrected data. It was found that the equation

$$\log p = 8.1020 - 2213/T \qquad (3)$$

represents the data for α-pinene for the stated pressure range. The experimentally determined values agree with the values calculated by the empirical equation with an average deviation of 0.08 mm. and a maximum deviation of 0.2 mm. Similarly, the equation

$$\log p = 8.1504 - 2280/T \qquad (4)$$

represents the data of β-pinene for the same pressure range. The experimentally determined values agree with the values calculated by the empirical equation with an average deviation of 0.11 mm. and a maximum deviation of 0.4 mm. From the slopes of the plots the latent heat of vaporization for the stated pressure range may be shown to be 10,130 cal./mole or 74.35 cal./g. for α-pinene and 10,430 cal./mole or 76.60 cal./g. for β-pinene.

The isobaric vapor–liquid compositions at 20.0 mm. were determined using a modified Sameshima apparatus.[16] About 100 cc. of mixture was placed in the flask and then brought to equilibrium, which was generally attained within two hours but four hours were allowed before a final measurement was made. Samples were then withdrawn from the flask and from the vapor receiver. The rate of flow, which averaged 1.5 cc./min., was regulated by the voltage applied to the internal heater. The thermostat temperature was kept about 2–4° above the estimated boiling temperature of the liquid. Cold brine solution was circulated through the two condensers, each of which contained a condensing coil made from a four-foot length of glass tubing. Experiments showed that there was no detectable vapor loss four hours after reaching equilibrium between liquid and vapor. The pressure control system was the same one described for the measurements of vapor pressures of the pure compounds. Samples were withdrawn by means of capillary

(13) Germann, THIS JOURNAL, **36**, 2456 (1914); built by G. T. Armstrong of this Laboratory.

(14) Lange, "Handbook of Chemistry," Handbook Publishers Co., Sandusky, O., 4th Ed., 1941, p. 1430.

(15) Lange, *ibid.*, pp. 1445–1446.

(16) Sameshima, THIS JOURNAL, **40**, 1489 (1918).

TABLE II

LIQUID–VAPOR COMPOSITION AT 20 MM.

$n^{25.0}D$ liquid	Mole fraction α-pinene in liquid	$n^{25.0}D$ vapor	Mole fraction α-pinene in vapor
1.4759	0.070	1.4757	0.085
1.4758	.075	1.4756	.090
1.4754	.105	1.4751	.130
1.4751	.130	1.4747	.160
1.4747	.160	1.4742	.195
1.4745	.175	1.4740	.215
1.4731	.280	1.4722	.345
1.4727	.310	1.4718	.375
1.4722	.345	1.4712	.420
1.4718	.375	1.4708	.450
1.4713	.415	1.4702	.495
1.4710	.435	1.4699	.515
1.4706	.465	1.4694	.555
1.4698	.525	1.4686	.610
1.4691	.575	1.4680	.655
1.4689	.590	1.4678	.670
1.4680	.655	1.4671	.720
1.4676	.680	1.4667	.745
1.4668	.740	1.4661	.790
1.4662	.780	1.4656	.825
1.4653	.845	1.4649	.875
1.4650	.865	1.4647	.890
1.4648	.880	1.4645	.905
1.4647	.890	1.4644	.910
1.4641	.930	1.4639	.945
1.4637	.955	1.4636	.965

pipets. Data were observed by starting with mixtures rich in α-pinene and going to mixtures rich in β-pinene and also by starting with mixtures rich in β-pinene and going to mixtures rich in α-pinene. The compositions were determined by means of refractive index measurements and application of equation (2). The data obtained by this method are recorded in Table II.

In order to compare the observed values with those of an ideal system, pressures, $p_{\alpha\text{-}}$ and $p_{\beta\text{-}}$, of the pure components were calculated by equations (3) and (4) for the temperatures listed in Table III. Then for each temperature was calculated a liquid mixture composition at 20.0 mm. by applying Raoult's law in the form

$$20.0 = x_{\alpha\text{-}}p_{\alpha\text{-}} + (1 - x_{\alpha\text{-}})p_{\beta\text{-}}$$

where $x_{\alpha\text{-}}$ is the mole fraction of α-pinene in the liquid phase. The corresponding vapor composition was calculated from the relation

$$y_{\alpha\text{-}} = \frac{x_{\alpha\text{-}}p_{\alpha\text{-}}}{20.0}$$

where $y_{\alpha\text{-}}$ is the mole fraction of α-pinene in the vapor phase. The observed mole fraction of α-pinene in the vapor, corresponding to liquid composition $x_{\alpha\text{-}}$, in column 4, Table III, was obtained from a plot of the vapor–liquid relations at 20.0 mm., using the data in Table II. The difference between the observed and calculated vapor composition is a measure of the deviation from ideality of the mixtures. These deviations are listed in the last column of Table III.

From the plot of the data in Table II it can be seen that a minimum of 24 theoretical plates at total reflux are required to go from a mixture of 95 mole per cent. to 5 mole per cent. α-pinene. The same diagram shows a minimum of 50 plates between pure α- and pure β-pinene under total reflux conditions.

TABLE III

DEVIATION OF VAPOR CONCENTRATION AS CALCULATED BY RAOULT'S LAW

t, °C.	$p_{\alpha\text{-}}$, calcd.	$p_{\beta\text{-}}$, calcd.	$x_{\alpha\text{-}}$ Mole fraction α-pinene in liquid calcd.	$y_{\alpha\text{-}}$ Mole fraction α-pinene in vapor calcd.	$y_{\alpha\text{-}}$ Mole fraction α-pinene in vapor obs.	Vapor deviation
52.6	20.39	14.20	0.937	0.955	0.950	0.005
53.0	20.79	14.48	.875	.909	.900	.009
54.0	21.80	15.21	.727	.792	.780	.012
55.0	22.87	15.98	.583	.667	.662	.005
55.5	23.41	16.37	.516	.603	.601	.002
56.0	23.97	16.77	.449	.538	.533	.005
57.0	25.12	17.60	.319	.401	.388	.013
58.0	26.32	18.47	.195	.256	.238	.018
59.0	27.56	19.37	.077	.106	.095	.011
59.4	28.14	19.74	.031	.044	.039	.005

Summary

The densities, refractive indices and optical rotations for α- and β-pinene and their mixtures have been determined.

The vapor pressure–temperature relations of α- and β-pinene were measured in the range of 15 to 80 mm.

The vapor–liquid equilibrium composition data for mixtures of α- and β-pinene at 20 mm. pressure have been determined.

GAINESVILLE, FLA. RECEIVED OCTOBER 10, 1942

[A COMMUNICATION FROM THE CENTRAL RESEARCH DEPARTMENT, MONSANTO CHEMICAL CO.]

An Improved Method of Preparation of *bis*-Arylphosphonic Acids

BY GENNADY M. KOSOLAPOFF

The usual method of preparation of phosphonic acids, $RPO(OH)_2$ and R_2POH, involves the preparation of the corresponding halophosphines by the Friedel–Crafts reaction of the corresponding hydrocarbon with phosphorus trichloride, followed by oxidation and hydrolysis. Generally, the preparation of the halophosphines is quite unsatisfactory because of meager yields. At the same time, the odor and the vapor toxicity of the halophosphines frequently make them rather inconvenient to handle. Particularly unsatisfactory are the methods of preparation of the *bis*-arylphosphonic acids. The necessary halophosphines form only as by-products in the usual Friedel–Crafts reaction of the hydrocarbons with phosphorus trichloride, with the consequently very low yields. Some improvement in this respect was introduced by Pletz[1] who obtained fair yields of R_2PCl by the thermal decomposition of *tris*-arylphosphine dichlorides. However, this method of preparation of the phosphonic acids involves at least four steps, with the consequently lowered over-all yields and necessitates operations with the objectionable halophosphines.

It is felt that a direct, preferably one-step, method of preparation of *bis*-arylphosphonic acids was needed as a stimulus for investigations of this relatively little studied class of organic compounds of phosphorus. The elimination of the actual operations with the halophosphines was also highly desirable.

The most convenient method of attack appeared to be the Grignard reaction, which has been used with success in the preparation in good yields of tertiary phosphine oxides by the addition of phosphorus oxychloride into an excess of the desired Grignard reagent.[2] The reaction probably occurs in three stages, *i. e.*

$$POCl_3 + RMgX \longrightarrow RPOCl_2 + MgXCl$$
$$RPOCl_2 + RMgX \longrightarrow R_2POCl + MgXCl$$
$$R_2POCl + RMgX \longrightarrow R_3PO + MgXCl$$

the high order of reactivity of the intermediate halophosphines making the over-all reaction very rapid.

It was felt that it should be possible to separate the component reactions and to obtain the intermediate products by the proper choice of conditions. In the usual procedure for the preparation of R_3PO, the reaction is run with the phosphorus oxychloride always in position to react with an excess of the Grignard reagent. By reversing the addition order, it was thought to be possible to arrest the reaction at the desired stage of having the Grignard reagent always in position to react with an excess of the phosphorus oxychloride. The utilization of as dilute a solution as practicable and the employment of low temperatures were the remaining factors.

In preliminary experiments, solutions of Grignard reagents were added slowly to ether solutions of phosphorus oxychloride with vigorous stirring, with or without cooling. The drops of the Grignard reagent produced an immediate turbidity of the solution and as the reaction proceeded there was a gradual deposition of a white, or pale-yellow, solid on the flask walls. On working up the ether solutions they were found to be essentially free of magnesium compounds and to contain only the normal amounts of R–R and R–X, with very small amounts of the tertiary phosphine oxides. The solid precipitate, on hydrolysis, gave satisfactory yields (usually over 50%) of *bis*-arylphosphonic acids. No appreciable amounts of the mono-arylphosphonic acids were detected in the temperature range studied: 0° to the reflux temperature of the ether solution. A slight improvement of the yield of the phosphonic acid was found at the higher temperature, while dilution of the reagents also had a beneficial effect for dilutions up to approximately one liter total volume for 0.2-mole runs, which was regarded as a practical limit for dilution. The maximum molar ratio of phosphorus oxychloride to RMgX used was 1:1.

The above results indicate that the halophosphines, as formed, combine with MgXCl forming an ether-insoluble addition complex, probably of the type $R_2POCl{\cdot}MgXCl$. Generally, this is a crystalline solid, although in some cases gummy solids are formed.

The procedure probably can be extended to the aliphatic series.

(1) V. M. Pletz, "Secondary Chlorophosphines," Dissertation, Kazan (1938).

(2) Grignard and Savard, *Compt. rend.*, **192**, 592 (1931)

Experimental

Diphenylphosphonic Acid.—Phenylmagnesium bromide (from 31.4 g. of bromobenzene and 4.86 g. of magnesium in 200 cc. of absolute ether) solution was diluted to 500 cc. by absolute ether, filtered with exclusion of air and added slowly (three and one-half hours) to a gently refluxing stirred solution of 30.6 g. of phosphorus oxychloride in 500 cc. of absolute ether; after standing overnight the ether solution was decanted from the solid precipitate and the latter treated with 200–300 g. of ice-water. The white solid which was insoluble in water was washed with water and triturated with 1 l. of warm dilute sodium hydroxide solution, filtered and filtrate acidified with dilute hydrochloric acid. The precipitated diphenylphosphonic acid was filtered, dried and recrystallized from dilute alcohol; m. p. 190–192°; yield 12 g., 55%. The sodium hydroxide-insoluble solid on repeated recrystallization yielded 4 g. of triphenylphosphine oxide, m. p. 152–153° (from dilute alcohol).

bis-p-**Chlorophenylphosphonic Acid.**—The Grignard reagent from 39 g. of *p*-chlorobromobenzene was diluted to 400 cc. with absolute ether and added in the course of one and one-half hours to a gently refluxing stirred solution of 30.6 g. of phosphorus oxychloride in 500 cc. of absolute ether. After standing overnight, the reaction mixture was worked up as above, yielding 15 g. (51%) of *bis-p*-chlorophenylphosphonic acid, m. p. 133–135° (from dilute alcohol) and 4.5 g. of *tris-p*-chlorophenylphosphine oxide, m. p. 171–2.5° (from dil. alcohol).

Anal. Calcd. for $C_{12}H_9O_2PCl_2$: eq. wt., 287; Cl, 24.7. Found: eq. wt., 283; Cl, 24.58.

Summary

An improved method for the preparation of *bis*-arylphosphonic acids has been devised in which phosphorus oxychloride is treated with Grignard reagents in dilute solution.

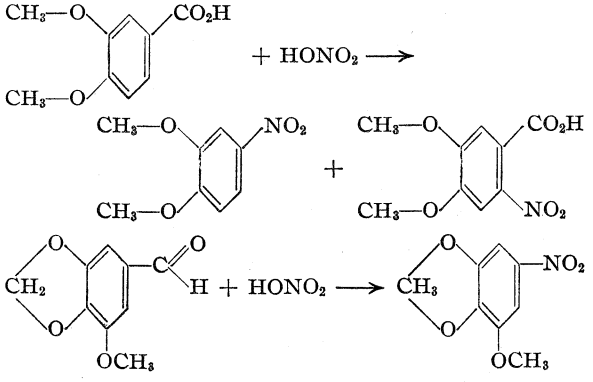
DAYTON, OHIO RECEIVED AUGUST 13, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

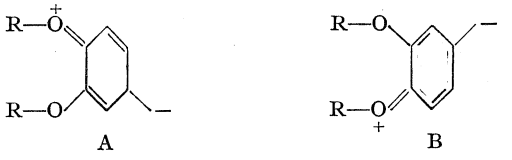
Studies in the Veratrole and Methylenedioxybenzene Series

BY RICHARD T. ARNOLD AND FREDERICK BORDWELL[1]

Interest in the veratrole (*o*-dimethoxybenzene) and methylenedioxybenzene (1,3-benzodioxole) compounds has been aroused largely for two reasons. First, these nuclei frequently make up important component parts of well known naturally occurring substances (opium alkaloids, apioles, etc.); and, second, the parent substances have exceedingly reactive benzenoid rings which orient incoming substituents in a unique and (according to the classical orientation rules) unpredictable manner. Two typical examples may be cited to illustrate the latter point.[2,3]



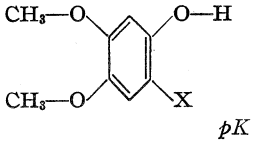
The remarkable susceptibility of these aromatic rings to attack by electrophilic reagents at the positions para to the oxygen atoms can be accounted for by resonance contributing structures of the type A and B.

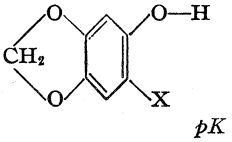


A B

In spite of the easily recognizable similarities, it is well established that the benzenoid ring of methylenedioxybenzene is more reactive than that of veratrole.[4]

To enable us to make a comparative study of the aromatic bond types in these two series we have prepared a number of substituted phenols (I–IX below) and have measured their *pK* values under identical circumstances. These values were determined by measuring the *p*H of half-





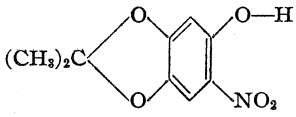
	pK		*pK*
I, X = —CHO	9.12	V, X = —CHO	8.90
II, X = —CN	8.69	VI, X = —CN	8.41
III, X = —NO_2	8.33	VII, X = —NO_2	8.17
IV, X = —CO_2H	4.60	VIII, X = —CO_2H	4.58

(1) Abstracted from a Ph.D. thesis submitted to the Graduate School in July, 1941.

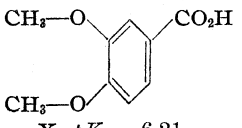
(2) Tiemann and Matsumoto, *Ber.*, **9**, 937 (1876).

(3) Salway, *J. Chem. Soc.*, **95**, 1155 (1909).

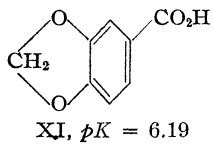
(4) Hudson and Robinson, *J. Chem. Soc.*, 715 (1941).



IX, pK = 8.68
(8.28 calcd. for 50% ethanol)



X, pK = 6.21



XI, pK = 6.19

neutralized solutions of the phenols in ethanol solutions (50% by volume). The value for compound IX was measured in 67% ethanol because of its relative insolubility.

It will be noticed that the pairs of related compounds X and XI, as well as IV and VIII, have the same acidity. The high acidity of *o*-hydroxy acids has been adequately explained by Branch and Yabroff.[5]

A comparison of I, II and III with V, VI and VII reveals that the methylenedioxy derivatives are more acidic than those of the veratrole series by 0.2–0.3 pK units. Such slight differences may be due to a combination of factors: a slight increased double bond character in the methylenedioxybenzene ring between the carbon atoms attached to groups OH and X,[6] dipolar effects and resonance effects.[7]

Nevertheless, the above discussed differences are so small that one must conclude that the benzenoid rings in the two series under consideration are very much alike. As Sutton and Pauling[8] have pointed out, however, "a small influence exerted on the benzene ring can produce important changes in reaction velocity."

Failures to prepare a number of the compounds described here have been reported.[9,16] In several other cases worthwhile modifications of reported syntheses are described.

Experimental

Methyl Veratrate.—Veratraldehyde was oxidized by a procedure similar to that used for the oxidation of piperonal[10]; the yield of veratric acid was 88%. This material was dissolved in ten times its weight of methanol and saturated with hydrogen chloride. After standing overnight the solution was distilled and yielded 73% of the ester; b. p. 165° (15 mm.); m. p. 58–59°.

Methyl 5-Nitroveratrate.—Since the method of Zincke and Francke[11] gave poor results in our hands, the following procedure was employed. Twenty-one grams of methyl veratrate was dissolved in 50 cc. of glacial acetic acid and while this solution was being stirred and cooled in an ice-bath, 100 cc. of nitric acid (d. 1.59) dissolved in 50 cc. of acetic acid was added during the course of one hour. Stirring was continued for two hours and the solution was then poured into ice water. The nitro ester was recrystallized from 600 cc. of methanol; yield 23.2 g.; m. p. 144–145°.

Methyl 5-Aminoveratrate.—The corresponding nitro compound dissolved in five times its weight of methanol was reduced at 110° with Raney nickel and hydrogen at 1000 pounds pressure; yield 80%; m. p. 128–129°. Zincke and Francke,[11] using stannous chloride, report a melting point of 133°.

Methyl 5-Hydroxyveratrate.—This substance has been obtained by direct esterification of the hydroxy acid[12] and from the amino ester.[11] Zincke and Francke[11] claimed poor yields and did not describe their procedure.

The amino ester (11.9 g.) was powdered and added to a warm solution of 13 cc. of sulfuric acid in 60 cc. of water. Cooling gave a thick paste of the amine salt which was diazotized with 4.0 g. of sodium nitrite in 15 cc. of water. The hydroxy ester was obtained pure by adding the diazonium solution dropwise to boiling copper sulfate solution. The yield of ester which steam distilled was 8.7 g.; m. p. 95–96° after one recrystallization from methanol.

5-Hydroxyveratric Acid.—The acid was obtained from the ester by refluxing the latter with sodium hydroxide (5%) until solution was effected. Acidification gave a white solid; m. p. 204–205° (dec.). Clark[13] reports 201–202°.

5-Hydroxyveratraldehyde.—Six grams of aminoveratraldehyde[14] was added to 400 cc. of water and treated with 6.0 g. of sulfuric acid in 100 cc. of water to form a suspension. Two grams of sodium nitrite in a saturated solution was added to the cold, well-stirred suspension. After one and one-half hours the solution was filtered and decomposed in boiling copper sulfate solution. The steam distillate was extracted with ether and there was obtained 2.8 g. of hydroxyaldehyde. Recrystallization from ethanol gave a product melting at 106–107°. Robertson[15] reports 107°.

Methyl 6-Aminopiperonylate.—The method described below is a modification of Bogert and Elder's[9] procedure which gave a much more pure product.

The amino ester (9.3 g.) was suspended in a mixture of 10 cc. of sulfuric acid and 50 cc. of water. Diazotization was accomplished with 3.4 g. of sodium nitrite dissolved in 20 cc. of water. The diazonium solution was diluted with four times its volume of water and added dropwise to a boiling solution of copper sulfate (50%). The steam distilled ester was perfectly white and weighed 6.9 g. after recrystallization from aqueous methanol solutions; 100–101°. The over-all yield to this point is 36% as compared to 18% reported earlier.[9]

6-Hydroxypiperonal.—The diazotization of aminopiperonal proved difficult and the use of dilute solutions was found to be distinctly advantageous.

(5) Branch and Yabroff, THIS JOURNAL, **56**, 2568 (1934).
(6) Arnold and Sprung, *ibid.*, **61**, 2475 (1939).
(7) Kossiakoff and Springall, *ibid.*, **63**, 2223 (1941).
(8) Sutton and Pauling, *Trans. Faraday Soc.*, **31**, 939 (1935).
(9) Bogert and Elder, THIS JOURNAL, **51**, 534 (1929).
(10) Shriner and Kleiderer, "Organic Syntheses," Vol. 10, J. Wiley and Sons, New York, N. Y., 1930, p. 82.
(11) Zincke and Francke, *Ann.*, **293**, 190 (1896).
(12) Hemmelmayr, *Monatsh.*, **35**, 6 (1914).
(13) Clark, THIS JOURNAL, **53**, 3434 (1931).
(14) Rilliet, *Helv. Chim. Acta*, **5**, 547 (1922).
(15) Robertson and Head, *J. Chem. Soc.*, 2434 (1930).

The aminoaldehyde (10.6 g.) was powdered and suspended in 300 cc. of water. To this mechanically stirred suspension was added 10 cc. of sulfuric acid in 80 cc. of water. To the cool well-stirred suspension 4.5 g. of sodium nitrite in 50 cc. of water was added dropwise. After standing for thirty minutes the solution was filtered and slowly decomposed with copper sulfate solution as described above. Six to eight liters of distillate was collected; yield 5.2 g.; m. p. 125–126°.

Anal. Calcd. for $C_8H_6O_4$: C, 57.82; H, 3.64. Found: C, 57.68; H, 3.69.

6-Hydroxypiperonal Oxime.—The oxime was obtained quantitatively by treating 1.0 g. of the aldehyde in 7 cc. of ethanol with 0.8 g. of hydroxylamine hydrochloride and 0.6 g. of sodium carbonate in a few cubic centimeters of water. The mixture was warmed on a steam-bath for thirty minutes and then poured into water. After recrystallization from benzene the compound melted at 142.5–143.5°.

Anal. Calcd. for $C_8H_7O_4N$: C, 53.02; H, 3.90. Found: C, 53.17; H, 3.86.

6-Hydroxypiperononitrile.—6-Hydroxypiperonal oxime (3.1 g.) was refluxed for twenty minutes with 15 cc. of acetic anhydride and the solution was poured into 50 cc. of cold water. In one hour the solution was filtered and the solid product was gently refluxed with 15 cc. of sodium hydroxide (10%). About 15 cc. of water was added to keep the sodium salt in solution. After ten minutes the solution was neutralized with hydrochloric acid. The precipitate tenaciously held water and was dried overnight in a vacuum desiccator. Several recrystallizations from alcohol and a final one from benzene gave a substance (2.0 g.) melting at 220–225° (dec.).

Anal. Calcd. for $C_8H_5O_3N$: C, 58.87; H, 3.09. Found: C, 59.02; H, 3.00.

5-Hydroxyveratraldehyde Oxime.—This oxime was prepared as described above for the corresponding piperonal derivative; yield 90%; m. p. 146–147°.

Anal. Calcd. for $C_8H_5O_3N$: C, 54.82; H, 5.58. Found: C, 55.01; H, 5.79.

5-Hydroxyveratronitrile.—This compound was obtained in a 90% yield as described above for 6-hydroxypiperononitrile. The nitrile sinters at 120° and melts with decomposition at 142–145°.

Anal. Calcd. for $C_9H_9O_3N$: C, 60.33; H, 5.02. Found: C, 60.18; H, 4.99.

6-Acetoxypiperonal.—Following the directions given by Robertson and Head[15] in their preparation of 5-acetoxyveratraldehyde, 1.0 g. of hydroxypiperonal was dissolved in 4 cc. of pyridine and the solution was cooled until the whole solidified. To this was added 12 cc. of acetic anhydride and the mixture was kept at 35–40° for twenty hours before pouring into 125 cc. of water. The precipitate was recrystallized from aqueous alcohol and appeared as beautiful needles; yield 4.4 g.; m. p. 126–127°. A mixed melting point determination with the original aldehyde gave a value of 100° with considerable range.

Anal. Calcd. for $C_{10}H_8O_5$: C, 57.69; H, 3.85. Found: C, 57.36; H, 3.92.

6-Acetoxypiperonylic Acid.—While the phenolic hydroxyl group of the hydroxy acid could be acetylated readily in the presence of sulfuric acid and acetic anhydride, a pure product could be obtained only after numerous recrystallizations. The difficulties encountered by Bogert and Elder[9] are readily understandable. The oxidation of the corresponding aldehyde proved most satisfactory.

One gram of the acetoxyaldehyde was dissolved in 25 cc. of acetone and to this was added 1.3 g. of potassium permanganate in 30 cc. of water. After warming on a water-bath for fifteen minutes the mixture was treated with sulfur dioxide. The acetone was evaporated and the acetoxy acid was filtered immediately. The product was thoroughly dried in a vacuum desiccator and recrystallized from benzene; yield 0.67 g.; m. p. 149–150° (dec.).

Anal. Calcd. for $C_{10}H_8O_6$: C, 53.55; H, 3.60. Found: C, 53.78; H, 3.78.

5-Hydroxy-6-nitro-1,3-benzodioxole.—One gram of the nitroamine was added to a mixture of 25 cc. of water and 5 cc. of concentrated sulfuric acid. The cold solution was diazotized with a slight excess of sodium nitrite and the resulting diazonium salt was decomposed by boiling copper sulfate solution. The yellow nitrophenol steam distilled as it was formed; yield 0.4 g.; m. p. 82.5–84°.

Balaban[16] has reported an unsuccessful attempt to prepare this substance.

Anal. Calcd. for $C_7H_5O_5N$: C, 45.90; H, 2.73. Found: C, 46.24; H, 2.65.

4-Hydroxy-5-nitroveratrole.—This phenol is best prepared from 4-acetamido-5-nitroveratrole.[17]

The acetanilide (2.6 g.) was refluxed with 10 cc. of sulfuric acid in 24 cc. of water for fifteen minutes. The deep red solution was cooled and diazotized with 0.8 g. of sodium nitrite dissolved in a few cubic centimeters of water. Decomposition by the copper sulfate method followed by steam distillation gave 1.4 g. of the nitrophenol; m. p. 142–143°.

Anal. Calcd. for $C_8H_9O_5N$: C, 48.24; H, 4.55. Found: C, 48.58; H, 4.68.

5-Acetamido-2,2-dimethyl-1,3-benzodioxole.—From 5-nitro-2,2-dimethyl-1,3-benzodioxole[18] dissolved in two volumes of ethanol there was obtained an 85% yield of amine by reduction with hydrogen and Raney nickel. Acetylation in the usual way with acetic anhydride and a trace of sodium acetate gave a 95% yield of the acetanilide derivative; m. p. 108.5–109.5°.

Anal. Calcd. for $C_{11}H_{13}O_3N$: C, 63.77; H, 6.47. Found: C, 63.68; H, 6.40.

5-Hydroxy-6-nitro-2,2-dimethyl-1,3-benzodioxole.—Four grams of the above described nitroacetanilide was hydrolyzed by warming for twenty minutes with 35 cc. of methanol containing 2.0 g. of potassium hydroxide. The nitroamine weighed 3.0 g.; m. p. 127–128°. Sloof[18] reports 127°.

Diazotization of the amine was exceedingly slow. Approximately 0.8 g. of amine was suspended in a mixture containing 6 cc. of sulfuric acid (d. 1.84) and 50 cc. of water. The cooled suspension was diazotized with 0.33 g. of sodium nitrite in a few cubic centimeters of water, and after standing for one hour the solution was decomposed

(16) Balaban, *J. Chem. Soc.*, 1088 (1929).
(17) Jones and Robinson, *ibid.*, **111**, 903 (1918).
(18) Sloof, *Rec. trav. chim.*, **54**, 995 (1935).

with boiling copper sulfate; yield 0.1 g.; m. p. 148–149°. All attempts to raise this yield by a variation of conditions failed.

Anal. Calcd. for $C_9H_9O_5N$: C, 51.18; H, 4.26. Found: C, 51.24; H, 4.00.

Summary

1. Nine negatively substituted phenols in the veratrole and methylenedioxybenzene series have been prepared.

2. A measure of the relative acidities of these compounds strongly indicates that the benzenoid rings in the two series are very comparable in structure.

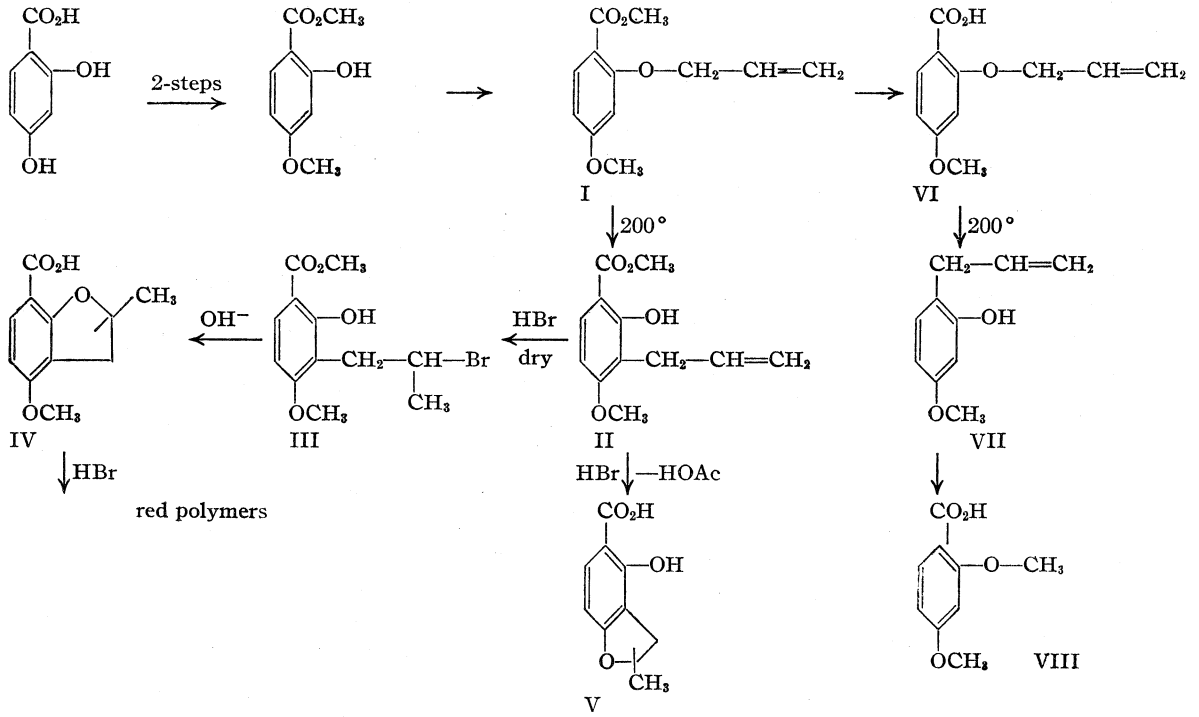
MINNEAPOLIS, MINN. RECEIVED SEPTEMBER 21, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Studies in the Coumaran Series

BY RICHARD T. ARNOLD AND JOHN MORAN

In an attempt to ascertain whether or not the coumaran heterocyclic ring is partially cleaved to an opened chain intermediate in the presence of reagents which split ordinary ethers, we have prepared 2-methyl-4-methoxy-7-carboxycoumaran IV and subjected this molecule to treatment with concentrated solutions of hydrobromic acid. Unfortunately no successful conditions were found for effecting this transformation directly. All experiments dealing with the cleavage of IV gave unidentifiable red polymers.[1,2] We wish to describe, however, a number of syntheses carried out during the course of this investigation. These can be summarized as follows



If during the cleavage of the methoxyl group the cyclic ether does form an opened chain derivative, it is to be expected that recyclization would involve the hydroxyl group para to the carboxyl group rather than that in the ortho position since the latter is rather firmly held in a chelate ring structure.

Substitution studies have repeatedly shown that the resorcinol nucleus is preferentially attacked at that position ortho to one hydroxyl group and para to the other. The thermal rearrangement of monoallylresorcinol[3] leads to the 1,2,4 configura-

(1) Schales, *Ber.*, **70**, 116 (1937).
(2) Niederl and Storch, THIS JOURNAL, **55**, 4549 (1933).
(3) Hurd, Greengard and Pilgrim, *ibid.*, **52**, 1700 1930).

tion. In this respect it is of interest that compound VI rearranges completely with decarboxylation to give 2-hydroxy-4-methoxyallylbenzene.[4] It may well be that decarboxylation precedes the rearrangement. The fact must not be overlooked, however, that below 160° the acid VI appears to be perfectly stable and above this temperature the carboxyl group may be eliminated through substitution by the allyl fragment.

When treated with hydrobromic acid, compound II did not cyclize easily but first underwent an ether cleavage followed then by ring closure to give a coumaran *o*-hydroxy acid (V). The relative position of the hydroxyl and carboxyl groups in V was established by the fact that the phenolic hydroxyl group was not attacked by diazomethane in twenty-four hours.[5,6,7]

Compound II reacted readily with anhydrous hydrogen bromide in the presence of catalytic amounts of ferric chloride to give a solid addition product (III) which in turn was converted to a methoxycoumaran acid IV when treated with alkali.[8]

Experimental

Methyl 2-Hydroxy-4-methoxybenzoate.—Seventy grams of 2-hydroxy-4-methoxybenzoic acid was dissolved in 140 cc. of methanol and to this was added a cooled solution of 16 cc. of sulfuric acid in 16 cc. of methanol. The mixture was refluxed for forty-eight hours. Crystals of ester separated when the solution was cooled but were not filtered. An excess of cold water was added and the whole was extracted with ether. Bicarbonate extraction of the ether layer yielded 2 g. of the starting acid. Removal of the ether and crystallization from ether–petroleum ether gave 62 g. of the ester; m. p. 49–51°.[9]

Methyl 2-Allyloxy-4-methoxybenzoate (I).—Sixty grams of methyl 2-hydroxy-4-methoxybenzoate was dissolved in 500 cc. of anhydrous acetone and treated with 46 g. of potassium carbonate, 50.5 g. of allyl chloride, and 25 g. of sodium iodide. The solution was refluxed while being efficiently stirred for fifty-two hours. The cooled solution was filtered and the bulk of the acetone was separated from the filtrate by distillation on a steam cone. The residue was taken up in ether and successively extracted with water, sodium hydroxide solution (5%), and a solution of sodium thiosulfate. The resulting ether layer was dried with sodium sulfate and warmed on a water-bath to remove the ether. Recrystallization of the residue from petroleum ether gave 49 g. of the expected product which gave no color reaction with ferric chloride; m. p. 49–50°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.90; H, 6.20.

(4) Tarbell, *Chem. Rev.*, **27**, 529 (1940).
(5) Herzig and Tichatschel, *Ber.*, **39**, 1558 (1906).
(6) Spath and Jeschki, *ibid.*, **57**, 471 (1924).
(7) Homeyer and Wallingford, THIS JOURNAL, **64**, 798 (1942).
(8) Stoermer, *Ber.*, **34**, 1810 (1901).
(9) Hersig and Wenzel, *Monatsh.*, **24**, 887 (1903).

Methyl 2-Hydroxy-3-allyl-4-methoxybenzoate (II).—Fifty grams of I was dissolved in 130 cc. of redistilled N,N-dimethylaniline and placed in a 200-cc. flask to which an air condenser was attached. The solution was refluxed in a nitrogen atmosphere for six hours. During this time the solution darkened but little. The dimethylaniline was largely removed by vacuum distillation. The residue was dissolved in ether and extracted with dilute hydrochloric acid. The dried ether solution was evaporated on a steam cone, and when cooled in a salt-ice bath the residue crystallized. Recrystallization from methanol solutions gave 34 g. of product melting at 57–59°. This substance gave a red-violet color with alcoholic ferric chloride.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.70; H, 6.59.

Hydrobromic Acid Treatment of Compound II.—Ten and one-half grams of methyl 2-hydroxy-3-allyl-4-methoxybenzoate was dissolved in 40 cc. of glacial acetic acid and treated with 13 cc. of hydrobromic acid (40%). The mixture was warmed on a steam-bath for twelve hours then poured into cold water. The residue was completely saponified by refluxing with 50 cc. of sodium hydroxide solution (10%). The hot solution was partially decolorized with charcoal, filtered, cooled, and acidified. A crude mixture of acids melting at 150–190° was obtained and separated by fractional crystallization into two pure components m. p. 155–156° and m. p. 203–205°. The lower melting compound was assigned formula V. It gave a positive (red) color test with ferric chloride. In the presence of a four-fold excess of diazomethane a methyl ester was obtained which liberated the hydroxy acid on basic hydrolysis.

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.83; H, 5.19. Found: C, 61.63; H, 5.06.

The high melting compound (203–205°) was assigned formula IV and was obtained in a more pure condition as described below.

Methyl 2-Hydroxy-3-(β-bromo-*n*-propyl)-4-methoxybenzoate.—Eight grams of compound II was dissolved in 20 cc. of anhydrous chloroform, cooled to 0° and treated with a few milligrams of black anhydrous ferric chloride. Dry hydrogen bromide was passed through the solution for thirty minutes and the solution was allowed to stand at room temperature for twenty-seven hours. The solvent was removed under diminished pressure and the residue immediately crystallized. When treated with ether, one gram of the residue remained undissolved and was filtered. After recrystallization from benzene–ethanol, it melted at 207–208° and proved to be a pure sample of the compound (IV) reported above as melting at 203–204°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.40; H, 5.81. Found: C, 63.13; H, 5.96.

The ether solution was evaporated and 5 g. of a bromo derivative (III) was obtained after recrystallization from petroleum ether; m. p. 73–74°.

Anal. Calcd. for $C_{12}H_{15}O_4Br$: C, 47.54; H, 4.99. Found: C, 47.82; H, 5.50.

2-Methyl-4-methoxy-7-carboxycoumaran.—Five grams of the bromo compound (III) was shaken with 20 cc. of sodium hydroxide for fifteen minutes and was refluxed for an additional fifteen minute interval. The resultant solu-

tion was cooled, filtered, and carefully acidified. The precipitate was recrystallized from benzene–ethanol and melted at 207–208°. Mixed melting point determinations showed this substance to be identical with samples obtained in earlier experiments as described above.

2-Hydroxy-4-methoxyallylbenzene.—One and three-tenths grams of 2-allyloxy-4-methoxybenzoic acid dissolved in 12 cc. of N,N-dimethylaniline was refluxed for six hours, cooled, and poured into ether. The amine was removed from the ether layer by extraction with hydrochloric acid. Evaporation of the ether gave an oil which was soluble in sodium hydroxide and completely insoluble in sodium bicarbonate. A positive ferric chloride test was obtained. The structure of this oil was established by methylation, isomerization with alkali, and oxidation to 2,4-dimethoxybenzoic acid; m. p. and mixed m. p. 108°.

Summary

A number of reactions leading to the formation of substituted coumarans have been described.

MINNEAPOLIS, MINN. RECEIVED SEPTEMBER 21, 1942

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

Solvent Polarization Error and its Elimination in Calculating Dipole Moments

BY I. F. HALVERSTADT[1,2] AND W. D. KUMLER

An old idea in dipole moment literature is that P_{12}–N_2 (or p_{12}–ω_2) curves would be straight lines in the absence of intermolecular action[3] or molecular association. This idea is implicit in the usual methods of calculating the degree of molecular association from polarization concentration curves, and in the calculation of dipole moments by a linear extrapolation of P_2–N_2 curves, a method still used by a number of authors.

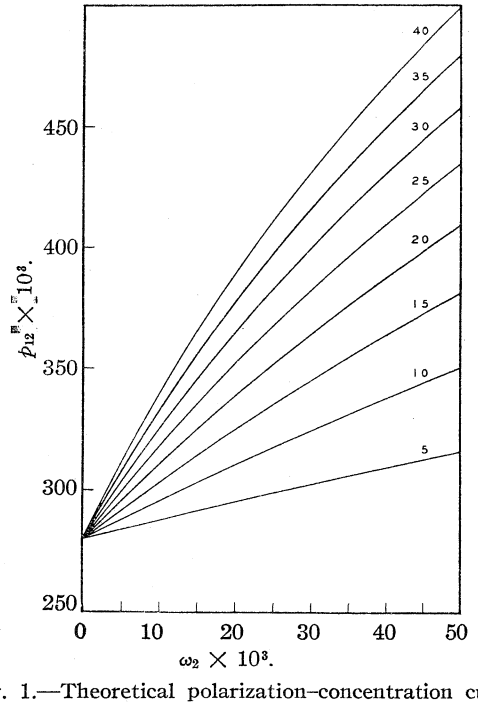


Fig. 1.—Theoretical polarization–concentration curves calculated by use of the Debye–Clausius–Mosotti equation for solutions in which ϵ_{12} is taken as linear with ω_2 (absence of association). β is taken in all cases as -0.2 and α has been varied from 5 to 40.

Considerable evidence has accumulated which indicates that the dielectric constant ϵ_{12} is a linear function of the weight fraction of solute ω_2[4,5,6,7] in dilute solutions.

We have examined over fifty compounds of widely different nature and have found ϵ_{12} to be linear with ω_2 in every case as long as ω_2 is less than 0.01. Now it can be shown from the nature of the relation

$$p_{12} = \frac{\epsilon_{12} - 1}{\epsilon_{12} + 2} \frac{1}{d_{12}}$$

that if ϵ_{12} is linear with respect to ω_2, p_{12} is not linear with ω_2. The extent of this deviation is shown in Fig. 1. The corresponding p_2–ω_2 curves are given in Fig. 2 and it is to be observed that the latter curves are neither horizontal nor straight. It is thus obvious that a linear extrapolation of p_2–ω_2 or P_2–N_2 curves introduces an error which is small in case of compounds with a low dipole moment and comparatively larger with compounds of high dipole moment.

This error is eliminated by the method of extrapolation proposed by Hedestrand.[8] However, serious errors may result even with the use of Hedestrand's method if it is not realized that the dielectric constant of the solvent in the solution sometimes differs considerably from the measured dielectric constant of the pure solvent.

(1) Abraham Rosenberg Fellow in Pharmaceutical Chemistry, 1941–1942.

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

(3) Smyth, "Dielectric Constant and Molecular Structure," Chemical Catalog Co., New York, N. Y., 1931, p. 176.

(4) Muller, *Physik. Z.*, **35**, 346 (1934).

(5) Rodebush and Eddy, *J. Chem. Phys.*, **8**, 424 (1940).

(6) McCusker and Curran, THIS JOURNAL, **64**, 614 (1942).

(7) Wyman, *ibid.*, **58**, 1482 (1936).

(8) Hedestrand, *Z. physik. Chem.*, **B2**, 428 (1929).

Solvent Polarization Error

Two considerations are involved here. First, with the usual methods of handling, the solutions are exposed longer to air than is the pure solvent and consequently the solutions may absorb more water vapor than the solvent. Second, even if rigid methods are used to exclude moisture each $\Delta\epsilon$ value for the different solutions depends on a single solvent measurement of ϵ_1 and consequently the latter is much more heavily weighted than any single solution measurement of ϵ_{12}. Now since the ϵ_{12}–ω_2 curves are straight lines both of the factors giving rise to solvent polarization error can be essentially eliminated if the dielectric constant of the pure solvent is obtained by extrapolating the ϵ_{12}–ω_2 curves for the solution to $\omega_2 = 0$. By comparing the extrapolated value of ϵ_1 with the measured value one can also tell if there has been appreciable contamination of the solvent in handling the solutions. The method used to calculate p_{2_0} making use of the extrapolated value of ϵ_1 is as follows:

A Method of Calculating p_{2_0}[9]

In calculating p_{2_0} we use the equation

$$p_{20} = \frac{3\alpha v_1}{(\epsilon_1 + 2)^2} + (v_1 + \beta)\frac{(\epsilon_1 - 1)}{(\epsilon_1 + 2)} \qquad (1)$$

which is derived from the expressions

$$p_{12} = \frac{(\epsilon_{12} - 1)}{(\epsilon_{12} + 2)} v_1 \qquad (2)$$

$$\epsilon_{12} = \epsilon_1 + \alpha\omega_2 \qquad (3)$$

$$v_{12} = v_1 + \beta\omega_2 \qquad (4)$$

The corresponding equation in N_2 is

$$P_{20} = \frac{3\alpha' v_1}{(\epsilon_1 + 2)^2} M_1 + (M_2 v_1 + M_1\beta')\frac{(\epsilon_1 - 1)}{(\epsilon_1 + 2)} \qquad (5)$$

This is essentially the same as the equation proposed by Hedestrand.[8]

The ϵ_{12}–ω_2 and v_{12}–ω_2 curves are plotted. If one point is considerably off the curve and all other points on, it suggests an experimental error and that point is rechecked. If the plots show curvature, they suggest some abnormal behavior and this method is not used, or the method is applied to the points in dilute solutions where they are linear. A straight line equation is fitted to the data by the method of least squares using the points for the solutions and omitting those for the pure solvent.[10] The constants of these equations give the values of ϵ_1, v_1, α and β which are substituted in equation (1).

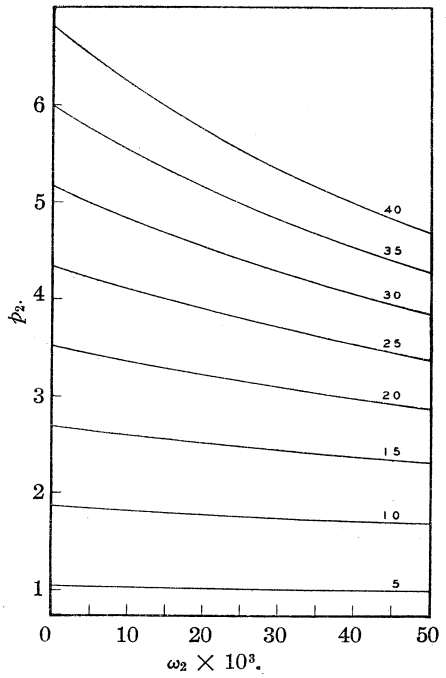


Fig. 2.—The theoretical p_2–ω_2 curves corresponding to the p_{12}–ω_2 curves in Fig. 1.

This calculation can be done graphically by plotting the ϵ_{12}–ω_2 and v_{12}–ω_2 curves. These are straight lines and can easily be extrapolated to $\omega_2 = 0$. The intercept of the ϵ_{12}–ω_2 line gives ϵ_1 and its slope is α. The intercept of the v_{12}–ω_2 line gives v_1 and its slope is β.

The advantages of this method of calculation are: first, it eliminates errors due to a difference in the dielectric constant of the solvent in the solution and the measured dielectric constant of the pure solvent. Second, it is objective and does

(9) The symbols used are: subscripts 1, 2, and 12 refer to solvent, solute and solution, respectively; ϵ, dielectric constant; d, density; v, specific volume, $1/d$; V, molecular volume; M, molecular weight; p, specific polarization; p_{2_0}, specific solute polarization at infinite dilution; P, molar polarization; P_{2_0}, solute molar polarization at infinite dilution; P_{E_2}, solute molar electronic polarization; ω, weight fraction; W, weight; m, moles; N, mole fraction; $\alpha = d\epsilon_{12}/d\omega_2$; $\beta = dv_{12}/d\omega_2$; $\alpha' = d\epsilon_{12}/dN_2$; $\beta' = dv_{12}/dN_2$; μ, dipole moment in Debye units; T, absolute temperature.

(10) The usual statistical method of least squares was used; for example, to fit the straight line $\epsilon_{12} = \epsilon_1 + \alpha\omega_2$ to the dielectric constant data, the equations

$$\Sigma\epsilon_{12} = N\epsilon_1 + \alpha\Sigma\omega_2$$

$$\Sigma(\omega_2\epsilon_{12}) = \epsilon_1\Sigma\omega_2 + \alpha\Sigma(\omega_2)^2$$

in which N represents the number of observations, were set up and solved for ϵ_1 and α. In this method if the data are accurate to five places, the summations need to be carried only to five places, but all numbers derived from these during the solutions of the equations should be taken to eight or nine places if anomalous solutions are to be avoided. This is necessary because ϵ_1 and α are obtained as the ratios of small differences between relatively large numbers and if these large numbers are given only to five places the differences will very often be given only to three places, which, of course, will lead to incorrect results. The calculation of the dipole moment of a compound by this method requires less than an hour if an electric calculating machine is used.

not involve the judgment of the calculator. Third, all extrapolations are carried out with straight line functions. Fourth, if the solutions are absorbing water this is easily detected because the extrapolated and measured dielectric constants for the solvent will be different.

If a contaminant such as water gets into the solutions it will cause the p_2 values to be too high and the magnitude of the error thus introduced will be greater the higher the dilution.

An examination of the literature reveals a number of cases of an abnormal rise in p_2 or P_2 values at high dilution. The effect is usually either ignored, attributed to experimental error, or to that convenient explanation of anomalous behavior—molecular association. Application of our method of calculation to some of these cases reveals a solvent polarization error and the abnormality in the moment disappears when our method is applied. For example, a case of a very marked upward trend at high dilution is found in the paper of Svirbely, Ablard and Warner.[11] They obtain the following values: *d*-pinene 2.67, *d*-limonene 1.56, methyl benzoate 2.52, ethyl benzoate 2.43. The first two values are much too high (1 to 2 units) for hydrocarbons with one and two double bonds. The last two values are about half a unit high for esters. We have recalculated their data using our method and obtained the following values which are consistent with those obtained by other authors[12] for the same compounds. The recalculated values are as follows: *d*-pinene 0.80, *d*-limonene 0.61, methyl benzoate 1.86, ethyl benzoate 1.94. No correction has been made for atomic polarization which will have an appreciable effect on the moments of the first two compounds. These are still probably high by about 0.2 of a unit.

The high values obtained by the above authors in very dilute solutions we believe are without significance and result most probably from solvent polarization errors.

Lewis, Oesper and Smyth[13] have measured trimethyl- and triethyllead chloride at high dilutions and obtain a higher value, 4.47, for the trimethyl compound than for the triethyl compound, 4.39. This is contrary to expectation because the ethyl groups are more polarizable than methyl groups and the large lead–chlorine moment should have a large polarizing effect. The trimethyl compound was measured in solutions about ten-fold more dilute than the triethyl compound so the effect of a small solvent polarization error on P_2 would be much greater for the trimethyl compound. A recalculation by our method gives values of the expected order, 3.81 for trimethyllead chloride and 4.27 for triethyllead chloride.

That solvent polarization errors can have an enormous effect on the observed moment of a compound as determined in very dilute solution is illustrated in the cases of urea and thiourea. The moments of these compounds as given in the literature were 8.6 and 7.6, respectively.[14] A redetermination of these moments under conditions in which solvent contamination was reduced and solvent polarization errors essentially eliminated by using our method of calculation gave values of 4.56 for urea and 4.89 for thiourea.[15]

Theoretically the dielectric constant of the solvent should be increased slightly[16] by the presence of a polar solute and the possibility exists that this effect is responsible for the abnormal increase of P_2 at high dilutions. There are, however, some serious objections to such an interpretation. First, the effect of the solute in increasing the dielectric constant of the solvent would be greater the higher the concentration of the solute. The observed effect is just the reverse, the P_2 values become more abnormal as the solutions become more dilute. Second, many investigators including ourselves do not always obtain the same measured value for the dielectric constant of the pure solvent and these variations are most noticeable with the very hygroscopic solvent dioxane and least noticeable with hexane. Third, where special precautions are taken to eliminate water[17] this sharp rise in P_2 curves at high dilutions is not present. The evidence thus points very strongly to absorption of water as the cause of the abnormally high P_2 values in dilute solutions.

A Test of Our Method of Calculation

A wide variation of dipole moment values in the literature is difficult to reconcile with the accuracy of the dielectric constant and density

(11) Svirbely, Ablard and Warner, THIS JOURNAL, **57**, 652 (1935).

(12) Estermann, *Z. physik. Chem.*, **B1**, 422 (1928); Bergmann and Weizmann, THIS JOURNAL, **57**, 1755 (1935).

(13) Lewis, Oesper and Smyth, THIS JOURNAL, **62**, 3243 (1940).

(14) Bergmann and Weizmann, *Trans. Faraday Soc.*, **34**, 783 (1938).

(15) Kumler and Fohlen, THIS JOURNAL, **64**, 1944 (1942).

(16) Onsager, *ibid.*, **58**, 1486 (1936).

(17) Linton, THIS JOURNAL, **62**, 1945 (1940); Maryott, *ibid.*, **63**, 3079 (1941).

TABLE I

Dielectric constants and specific volumes in Table I were plotted against N_2 the mole fraction of the solute, and total polarizations were calculated according to equation (5). All of these compounds were measured in benzene.

Compound	ϵ_1 measured	ϵ_1 calculated	v_1 calculated	α'	β'	P_{20} old	P_{20} new	P_{E_2}	μ old	μ new
d-Pinene[a]	2.2830	2.2872	1.14504	0.660	0.0377	192	57.4	44.0	2.67	0.80
d-Limonene[a]	2.2750	2.2767	1.15199	.233	.1160	95	53.0	45.3	1.56	.61
Methyl benzoate[a]	2.2830	2.2876	1.14509	4.945	.3880	170	109.9	37.8	2.52	1.86
Ethyl benzoate[a]	2.2830	2.2866	1.14505	5.518	.3626	166	123.7	45.5	2.43	1.94
Trimethyllead chloride[b]	2.276	2.2777	1.14521	20.78	2.618	455	343.0	41	4.47	3.81
Triethyllead chloride[b]	2.276	2.2776	1.14491	26.13	2.667	455	434.0	55	4.39	4.27
Nitrobenzene[c]	2.2825	2.2818	1.13879	23.11	0.483	366	367.0	32.7	3.97	3.98
Nitrobenzene[d]	2.2826	2.2873	1.13916	23.20	.510	382	367.0	32.7	4.08	3.98
Nitrobenzene[e]	2.280	2.2752	1.14094	23.09	.488	348	368.2	32.7	3.93	4.00
Nitrobenzene[f]	2.2727	2.2704	1.14385	22.87	.476	354	367.0	32.6	3.94	4.01

[a] Data from Svirbely, Ablard and Warner, THIS JOURNAL, **57**, 652 (1935). [b] Data from Lewis, Oesper and Smyth, *ibid.*, **62**, 3243 (1940). [c] Data from Tiganik, *Z. physik. Chem.*, **B13**, 440 (1931). [d] Data from Bergmann, Engel and Sandor, *ibid.*, **B10**, 397 (1930). [e] Data from Plotz, *ibid.*, **B20**, 351 (1933). [f] Data from Jenkins, *J. Chem. Soc.*, 480 (1934).

measurements. Differences of 0.1–0.2 which represent errors of several per cent. are quite common. Most dielectric constant and density measurements are accurate to at least 0.5% when the total polarization is several times the electronic polarization, and measurements are made in solutions that are not too dilute. This discrepancy is evidently due to an error in the solvent polarization plus errors in extrapolation. If this is the case an application of our method to the data should reveal and correct such errors.

Nitrobenzene was chosen to test this point because it has been measured a number of times in benzene. Four sets of data were found in the literature in which the solutions were sufficiently dilute so that the dielectric constant values were linear with concentration. As seen in Table I the dipole moment values vary by 0.15 from 3.93 to 4.08. A recalculation by our method reduces the variation to 0.03. Part of this difference may be due to the decrease in the dielectric constant of the solvent with increase of temperature.

TABLE II

MEASUREMENTS IN DIOXANE AT 25°

Compound	ϵ_1 measured	ϵ_1 extrapolated	v_1 extrapolated	α	β	P_{20} old	P_{20} new	P_{E_2}	μ old	μ new
Tetronic acid	2.2023	2.2015	0.97379	28.98	0.2909	485	499.5	22.1	4.72	4.80
α-Chlorotetronic acid	2.2104	2.2086	.97364	32.09	.4244	700	733.1	26.0	5.69	5.83
α-Bromotetronic acid	2.2023	2.2029	.97393	26.01	.5162	777	793.6	28.5	6.00	6.07
Methyl α-bromotetronate	2.2023	2.2037	.97406	25.06	.4230	830	830.3	32.4	6.19	6.19
α-Iodotetronic acid	2.2023	2.2043	.97366	17.41	.4850	689	681.9	36.9	5.59	5.57
Methyl α-iodotetronate	2.2163	2.2188	.97363	19.71	.5069	820	834.4	39.7	6.12	6.22
l-Ascorbic acid	2.2137	2.2110	.97360	12.20	.4122	360	382.3	38.2	3.93	4.07
Aniline	2.2095	2.2120	.97383	4.412	.0129	106	93.4	31	1.90	1.73
Xenylamine	2.2099	2.2117	.97387	3.615	.0853	148	144.0	59	2.07	2.02
Xenylamine (in benzene)	2.2760	2.2746	1.14618	2.556	.2702	122	125.6	59	1.74	1.79
Benzenesulfonamide	2.2095	2.2074	0.97386	21.68	.2720	577	594.1	39	5.09	5.17
p-Phenylbenzenesulfonamide	2.2099	2.2089	.97394	15.41	.2395	630	642.2	68	5.20	5.25
Sulfanilamide (operator 1)	2.2067	2.2065	.97367	32.75	.3059	960	964.1	45	6.63	6.65
Sulfanilamide (operator 2)	2.2104	2.2071	.97391	32.73	.3306	929	962.1	45	6.52	6.64
Metanilamide	2.2104	2.2097	.97375	24.48	.3070	705	728.0	45	5.63	5.73
p-(*p*-Aminophenyl)-benzenesulfonamide	2.2099	2.2076	.97378	24.78	.2552	1012	1066	75	6.71	6.90
Desoxycholic acid	2.2067	2.2053	.97385	3.493	.1015	314	324.7	108.8	3.15	3.22

Data from: Kumler, THIS JOURNAL, **62**, 3292 (1940); Kumler and Halverstadt, *ibid.*, **63**, 2182 (1941); Kumler and Halverstadt, *ibid.*, **64**, 1941 (1942).

Rau and Narayanaswamy[18] found experimentally that the apparent moment of nitrobenzene in benzene increases about 0.01 for an increase of 5°. Since the temperatures of the measurements we used range from 20 to 25° this would reduce the variation to 0.02 which is about the magnitude expected. Taking an average of the values corrected to 25° the dipole moment of nitrobenzene in benzene appears to be 4.00 ± 0.01, no correction being made for the atomic polarization.

In Table II the dipole moment values from two previous papers have been recalculated by the new method. There appear to have been no serious solvent polarization errors with the exception of aniline where the old moment value is high by 0.17. In thirteen of the seventeen cases the old values are lower by 0.02–0.19 than the new values. This we attribute to the linear extrapolation of the P_2-concentration curves which we have previously shown are concave upward, and to solvent polarization errors. The conclusions that were originally drawn from the old data hold for the new more accurate values.

To show further how the new method of calculation avoids exaggeration of experimental error we have included in Table II two measurements on sulfanilamide carried out by different operators using different samples of solute and solvent. The moment values calculated by the old method are 6.63 and 6.52, a difference of 0.11, while the new method gives 6.65 and 6.64, a difference of 0.01.

Summary

The available data indicate that the dielectric constant–weight fraction, ϵ_{12}–ω_2 curves for polar solutes in non-polar solvents are straight lines in dilute solutions. If this is the case it follows that the polarization p_{12} as defined by the Debye–Clausius–Mosotti (D-C-M) equation cannot be a linear function of the concentration. The p_2-ω_2 curves are neither horizontal nor straight and their curvature increases as ω_2 decreases. As a result, dipole moments calculated by a linear extrapolation of p_2 or P_2 to zero concentration are in error although the error is small for compounds with small moments. Per cent. association calculated by the assumption that p_{12}–ω_2 or p_2–ω_2 curves are linear in the absence of association is likewise in error.

A new method of calculating polarizations at infinite dilutions has been devised which, first, eliminates solvent polarization error, second, is objective and does not involve the judgment of the calculator, third, all extrapolations are made either statistically or graphically with straight line functions.

Evidence is presented to show that solvent polarization errors are responsible for some erroneous dipole moment values in the literature.

Our method of calculation has been applied to some of the anomalous cases and values are obtained which are more consistent with other determinations on the compounds or with the moment expected theoretically.

A test of this method of calculation has been applied to four sets of accurate data in the literature on nitrobenzene in benzene. The dipole moment values given by the authors have a variation of 0.15; our method gives a variation of 0.02. Another test was made on sulfanilamide measured by two operators and calculated by both methods. The linear P_2 extrapolation gave a variation of 0.11; our method, a variation of 0.01.

SAN FRANCISCO, CALIFORNIA RECEIVED JANUARY 5, 1942

(18) Rau and Narayanaswamy, *Proc. Indian Acad. Sci.*, **1A**, 489 (1935). These authors obtained a value of 3.99 for the moment of nitrobenzene at 30° using Hedestrand's method of calculation. We did not recalculate their data because they measured only three solutions and one of these was at too high a concentration.

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

The Dipole Moment of *ms*-Tetraphenylporphine

BY W. D. KUMLER

The configuration of the porphine ring system is of much interest because of its presence in chlorophyll and hemoglobin. A dipole moment study of a compound such as *ms*-tetraphenylporphine appeared to offer a way to tell whether the compound and, hence, the ring system was symmetrical or unsymmetrical.

The *ms*-tetraphenylporphine used in these studies was the more abundant isomer with a hydrochloric acid number of 13.5.[1] The compound is highly colored and absorbs appreciably in the yellow, hence, the usual method of determining the electronic polarization by measuring the refractive index with the D sodium line could not be used. However, it appeared if light were used of a wave length that was not absorbed by the compound the refractive index might be measured despite the fact that the compound is highly colored. The orange 6143 line in a neon tube was found to be a suitable source. Abnormalities in the refractive index, which might have been expected had the wave length of light used been too near an absorption band, were not observed.

Results

The results are given in Table I.

TABLE I

MEASUREMENTS IN BENZENE AT 25°

ω_2	ϵ_{12}	v_{12}
0.002010	2.2777	1.1454
.004458	2.2807	1.1447
.005595	2.2816	1.1442
.006762	2.2834	1.1436
.007916	2.2851	1.1435

ϵ_1	v_1	α	$-\beta$	P_{2_0}	$P_{E_{2_0}}$
2.2742	1.1460	1.355	0.311	310	293

The P_{2_0} value was calculated by using the equations

$$p_{2_0} = \frac{3\alpha v_1}{(\epsilon_1 + 2)^2} + (v_1 + \beta)\frac{(\epsilon_1 - 1)}{(\epsilon_1 + 2)}$$

$$P_{2_0} = p_{2_0} M_2$$

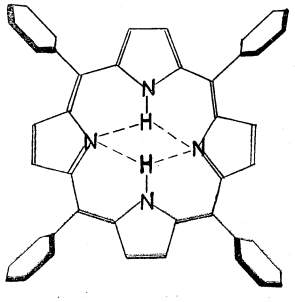
where the symbols have the same significance as in the previous paper.[2]

The values of α, β, v_1, and ϵ_1 were determined graphically. A combination of three factors, namely, the large size of the molecule, its low solubility, and the fact that its moment is small or zero, result in a very small difference in the dielectric constant of the various solutions. As a result the experimental error in both P_{2_0} and $P_{E_{2_0}}$ is probably about 7 cc.

The value of 310 for P_{2_0} and 293 for $P_{E_{2_0}}$ indicates that the compound has a small or zero moment. The experimental error is of such magnitude that a moment of a few tenths cannot be distinguished from a moment of zero. It is probable that this large highly resonating molecule has a comparatively large atomic polarization of the order of the difference between P_{2_0} and $P_{E_{2_0}}$.

The polarization of the compound was also determined at 5° intervals between 25° and 45° but no decrease in polarization with increasing temperature was observed which likewise indicates the compound has zero moment.

With zero moment the molecule must be arranged in some symmetrical fashion. A symmetrical structure might exist with the giant ring either puckered or flat. The giant ring is, however, a highly resonating system and the atoms must get into such a position that the alternate single and double bonds can shift their position without involving an appreciable movement of the atoms. This demands a flat structure with the giant ring, the pyrrole rings and the 1 and 4 carbon atoms of each benzene ring all in one plane. The two hydrogen atoms in the center can conceivably be arranged symmetrically in a number of ways. First, on opposite nitrogen atoms with one hydrogen above and one below the plane of the main ring. Second, as above but forming hydrogen bonds to one of the adjacent nitrogen atoms. Third, in the plane of the main ring and forming a bifurcated hydrogen bond with both adjacent nitrogen atoms (as in the figure). Fourth, the same as in the second case except the covalence to each hydrogen shifts (resonates), being attached first to one and then to the other nitrogen atom. Fifth, the same as in the third case except the covalence to



ms-Tetraphenylporphine.

(1) Rothemund and Menotti, THIS JOURNAL, **63**, 267 (1941).
(2) Halverstadt and Kumler, *ibid.*, **64**, 2988 (1942).

each hydrogen shifts among three nitrogen atoms. Case one is unlikely because it appears highly probable that hydrogen bonds are present.[3,4,5] If the actual situation is that of case four or five, which does not appear at all unlikely, there would be no isomerism due to the position of the hydrogen atoms.

It appears from a study of the Fisher models that a flat giant ring of this type can be constructed without undue strain. However, there is much interference between the pyrrole rings and the benzene rings if an attempt is made to place the latter in the same plane as the rest of the molecule. This suggests that the benzene rings do not have free rotation and are probably oscillating about a position perpendicular to the plane of the main ring. The general shape of the molecule would then be that of a flat disc with the four benzene rings cutting it at about right angles. If the benzene rings do not have free rotation then derivatives of *ms*-tetraphenylporphine having ortho or meta substituents should exist in a number of stereoisometric forms depending on whether the substituents are above or below the plane of the giant ring.

Experimental

The dielectric constant measurements were carried out with the same apparatus and in the same manner as described previously.[6] The refractive indices were measured with a Pulfrich refractometer using a neon Geissler tube as a light source.

The *ms*-tetraphenylporphine was recrystallized twice from benzene.

Acknowledgment.—We are indebted to Dr. O. L. Inman and Dr. Paul Rothemund of the C. F. Kettering Foundation at Antioch College for the sample of *ms*-tetraphenylporphine.

Summary

The more abundant isomer of *ms*-tetraphenylporphine was found to have a polarization of 310 and an electronic polarization of 297. Measurement of polarizations at different temperatures gave no evidence of a decrease of polarizations with increasing temperatures. Both methods indicate the compound has zero moment although the data do not enable one to distinguish between a moment of a few tenths and a zero moment.

The electronic polarization of the compound was obtained by measuring the refractive index of the solutions although they were highly colored. This was accomplished by using the orange line of a neon tube. This light had a wave length that was not absorbed by the solution.

The zero moment indicates the compound is symmetrical. The resonance demands that the giant ring and the pyrrole rings be in one plane. A study of the Fisher models suggests the benzene rings do not have free rotation and are perpendicular to this plane. With ortho or meta substituents on the benzene rings this hindered rotation will give rise to a number of stereoisomers.

SAN FRANCISCO, CALIF. RECEIVED SEPTEMBER 24, 1942

(3) Corwin and Quattlebaum, THIS JOURNAL, **58**, 1081 (1936).
(4) Vestling and Downing, *ibid.*, **61**, 3511 (1939).
(5) Aronoff and Weast, *J. Org. Chem.*, **6**, 550 (1941).
(6) Kumler, THIS JOURNAL, **62**, 3292 (1940).

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 885]

The Serological Properties of Simple Substances. I. Precipitation Reactions between Antibodies and Substances Containing Two or More Haptenic Groups

BY LINUS PAULING, DAVID PRESSMAN, DAN H. CAMPBELL, CAROL IKEDA, AND MIYOSHI IKAWA

The study of serological precipitation reactions is complicated by the fact that ordinarily these reactions involve two proteins, the antigen and the antibody. The understanding of these reactions was greatly advanced by the introduction into their study of precise microanalytical methods and a further simplification involving the use of a nitrogen-free multivalent hapten of pneumococcus polysaccharide.[1] A few years ago it was reported by Landsteiner and van der Scheer[2a] that the precipitin reaction and anaphylaxis could be produced by simple substances formed by coupling two haptenic groups with resorcinol or tyrosine, in place of the azoprotein (containing the same haptenic group) which has been used as the antibody-producing antigen. Landsteiner[2b] suggested that "the ready precipitability of these

(1) M. Heidelberger and F. E. Kendall, *J. Exptl. Med.*, **50**, 809 (1929); **61**, 559, 563 (1935).

(2) (a) K. Landsteiner and J. van der Scheer, *Proc. Soc. Exptl. Biol. Med.*, **29**, 747 (1932); *J. Exptl. Med.*, **56**, 399 (1932); **57**, 633 (1933); **67**, 79 (1938). (b) K. Landsteiner, "The Specificity of Serological Reactions," Charles C Thomas, Baltimore, Md., 1936, p. 120.

dyes is dependent upon peculiarities in constitution which, like those of fatty groups, diminish solubility in water and favor the formation of colloidal solutions." However, it seemed probable to us, on the basis of a theory of the structure of antibodies and the nature of the precipitin reaction,[3] that simple substances containing two or more haptenic groups would react with antibodies in essentially the same way as the homologous protein antigens containing the same haptenic groups; we accordingly prepared a half-dozen simple substances of this sort, each with two or more phenylarsonic acid groups per molecule, and observed each to precipitate antisera homologous to phenylarsonic acid azoprotein,[4] thus obtaining evidence for the generality of the phenomenon discovered by Landsteiner and van der Scheer.

The problem of obtaining from precipitation experiments evidence about the structure of antibodies and the nature of serological reactions is obviously greatly simplified by the replacement of protein antigens by simple substances of known structure. For this reason we began and are carrying on an extensive program of investigation of the reactions of simple substances with antisera. In this paper we report the quantitative study of the precipitin reaction for twenty simple substances containing two or more haptenic groups, and the results of tests of seven substances containing one group. It is found that the observations support the framework theory of serological precipitates.[5]

Discussion of Experimental Methods

Simple Antigens.—The simple antigens and haptens used in the investigation are listed in Table I; methods of preparations of these substances and the intermediates used are described in the following section.

Protein Antigens.—The immunizing antigens used for inoculations were made from diazotized arsanilic acid and sheep serum by the method described by Landsteiner and van der Scheer.[6] The ratio of arsenic to protein in these antigens ranged from 2 to 3%.

Test antigens were similarly made from purified ovalbumin by treatment with diazotized arsanilic acid, diazotized *p*-(*p*-aminophenylazo)-phenylarsonic acid, or diazotized *p*-aminobenzanilide-*p'*-arsonic acid. The azo-ovalbumins contained, respectively, 0.16, 4.0, and 2.0% arsenic.

Arsanilic acid was diazotized in hydrochloric acid solution by the addition of sodium nitrite solution at 0° to the starch–iodide end-point. The diazotizations of *p*-(*p*-aminophenylazo)-phenylarsonic acid and of *p*-aminobenzanilide-*p'*-arsonic acid were similarly carried out at 10° with end-point the disappearance of the slightly soluble amine hydrochlorides.

Preparation of Antisera.—Twenty-five rabbits were injected intraperitoneally or intravenously with 1- or 2-ml. portions of the atoxylazo-sheep-serum antigen described above, containing 0.5% protein. Several weekly courses of 3 to 5 injections were given, with intervening rest periods of a week or more. The rabbits were bled from the ear on the eighth, ninth, and tenth days after the last injection, 40 ml. of blood being taken from each rabbit each day. The blood was permitted to clot, and the antisera were pooled according to titer. The courses of injections and subsequent bleedings were repeated to obtain more pools of serum.

A measure of the total amount of antibody homologous to the atoxyl hapten (the phenylarsonic acid group) was made by determining the maximum amounts of antibody precipitated by the azo-ovalbumin test antigens. The most effective test antigen, that made from *p*-(*p*-aminophenylazo)-phenylarsonic acid, precipitated 2 mg. of antibody per ml. of antiserum A, 4 mg. per ml. of B, 1.5 mg. per ml. of C, and 4 mg. per ml. of D.

The Reaction of Antigen and Antiserum.—The precipitation tests were carried out by mixing portions of undiluted antiserum, usually 2 ml., with equal volumes of saline solution containing dye; usually four to six dye concentrations were tested, differing by powers of 2. The tubes were allowed to stand for one hour at room temperature and then overnight in the refrigerator. The precipitates were then centrifuged down, washed with three or four 10-ml. portions of normal saline, and analyzed for nitrogen. In some experiments colorimetric determinations were made of the amount of dye in the redissolved precipitates. In the tests with serum A the customary visual estimates of cloudiness were made one-half hour after the solutions were mixed.

Methods of Analysis.—Analyses for nitrogen were made by the semimicro Kjeldahl method, using the apparatus described by Redemann.[7] Sulfuric acid, copper sulfate, and potassium sulfate were used in the digestion mixture; hydrogen peroxide was found not to be needed.

The arsenic determinations were carried out by the method of Haurowitz and Breinl.[8] Carbon and hydrogen analyses were made with the usual semimicro technique. Colorimetric determinations of dye and azoprotein were made with a Klett photoelectric colorimeter after dissolving the precipitates in a few drops of 2 *N* sodium carbonate solution.

The reported values of antibody in precipitates are the values of antibody nitrogen multiplied by the factor 6.25, the antibody nitrogen being the difference between total nitrogen in the precipitate and antigen nitrogen calculated

(3) L. Pauling, THIS JOURNAL, **62**, 2643 (1940). J. R. Marrack and F. C. Smith, *Brit. J. Exptl. Path.*, **13**, 394 (1932), had made the tentative suggestion that precipitation by azohaptens depends upon the presence in the molecule of two or more haptenic groups.

(4) L. Pauling, Dan H. Campbell and D. Pressman, *Proc. Nat. Acad. Sci.*, **27**, 125 (1941).

(5) R. J. Marrack, "The Chemistry of Antigens and Antibodies," His Majesty's Stationery Office, London, 1938; M. Heidelberger, *Chem. Rev.*, **24**, 323 (1939); *Bact. Rev.*, **3**, 49 (1939); L. Pauling, ref. 3.

(6) K. Landsteiner and J. van der Scheer, *J. Exptl. Med.*, **55**, 781 (1932).

(7) C. E. Redemann, *Ind. Eng. Chem., Anal. Ed.*, **11**, 635 (1939).

(8) F. Haurowitz and F. Breinl, *Z. physiol. Chem.*, **205**, 259 (1932).

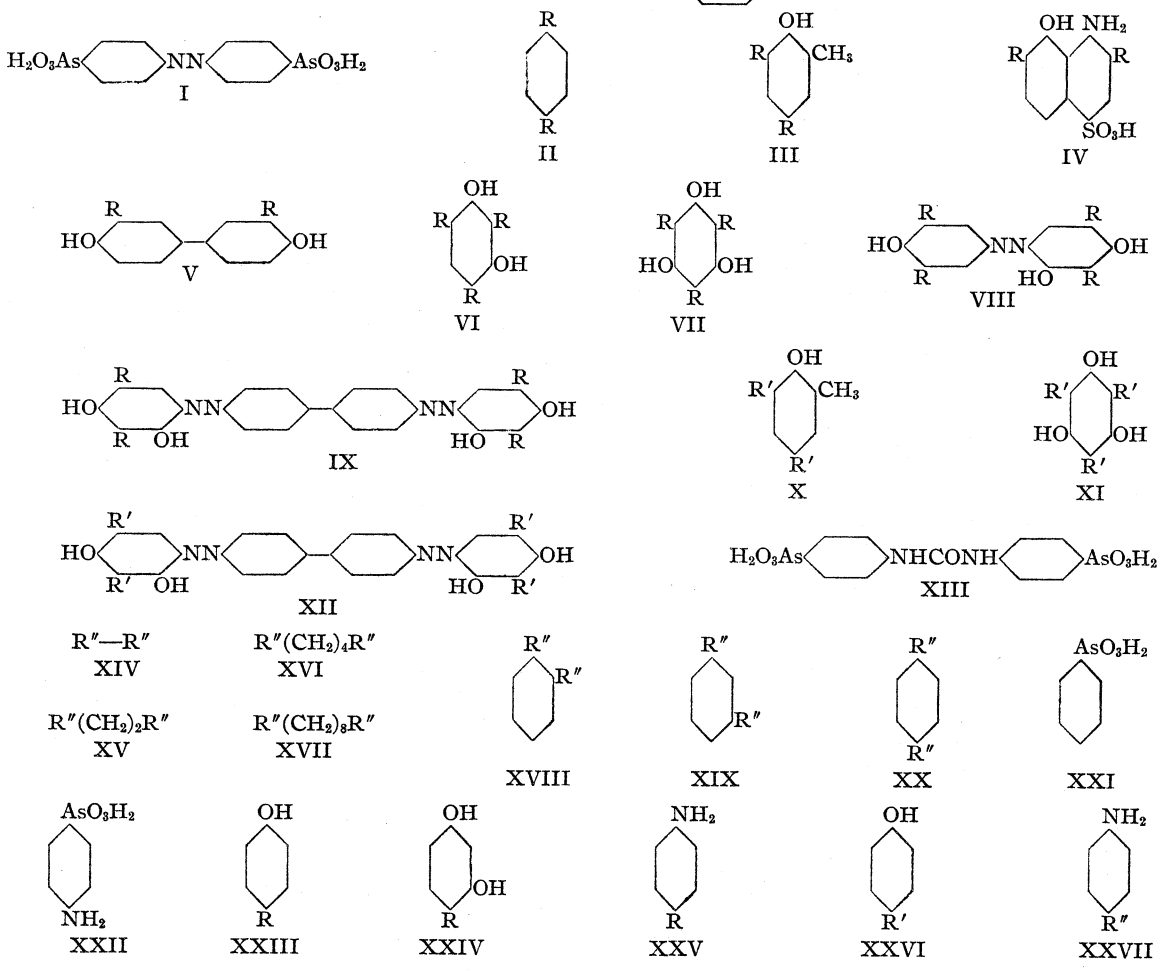
TABLE I

SUBSTANCES USED IN PRECIPITATION TESTS

R = *p*-azophenylarsonic acid, —NN⟨⟩AsO_3H_2

R′ = *p*-(*p*-azophenylazo)-phenylarsonic acid, —NN⟨⟩NN⟨⟩AsO_3H_2

R″ = phenylcarbamyl-*p*-arsonic acid, —CONH⟨⟩AsO_3H_2



from the amount of antigen as determined colorimetrically (for simple antigens this correction is very small).

The Preparation of Compounds

XXI, Phenylarsonic acid was prepared by Mr. David Brown by the Bart reaction.[9]

XXII, Arsanilic acid was prepared by the method of Bechamp.[10]

XXV, *p*-(*p*-Aminophenylazo)-phenylarsonic acid was made (a) by the hydrolysis in 2 *N* sodium hydroxide of the acetyl derivative made by condensing *p*-nitrosophenylarsonic acid with *p*-aminoacetanilide (20% excess) in glacial acetic acid by refluxing for three hours, and (b) by the hydrolysis for twenty minutes in boiling 1 *N* sodium hydroxide of the ω-methylsulfonate formed by reaction in 0.3 *N* sodium carbonate of diazotized arsanilic acid and aniline-ω-methylsulfonate (20% excess).[11] The two products, purified as the sodium salts, appeared to be identical.

Anal. Calcd. for $C_{12}H_{11}O_3N_3AsNa$: C, 42.04; H, 3.12. Found: (a) C, 41.98; H, 3.23; (b) C, 42.12; H, 3.40.

Nitrosophenylarsonic acid was made by the method of Karrer[12] from arsanilic acid and Caro's acid.

I, Azobenzene-*p*,*p*′-diarsonic acid was prepared by the method of Karrer[12] from *p*-nitrosophenylarsonic acid and arsanilic acid and was purified by repeated precipitation with acid from alkaline solution.

Anal. Calcd. for $C_{12}H_{12}O_6N_2As_2$: C, 33.50; H, 2.79 Found: C, 33.50, 33.56; H, 2.83, 2.97.

(9) H. Gilman, "Organic Syntheses," John Wiley and Sons, New York, N. Y., 1935, Vol. XV, p. 59.

(10) *Ibid.*, 1932, Coll. Vol. I, p. 63.

(11) F. G. Pope and W. I. Willett, *J. Chem. Soc.*, 1259 (1913); H. Bucherer and A. Schwalbe, *Ber.*, **39**, 2798 (1906).

(12) S. Karrer, *ibid.*, **45**, 2066, 2376 (1912).

TABLE II

Compound	Reactant	Excess of diazo compound	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Color in alkali	Color in H_2SO_4
III	*o*-Cresol	50%	$C_{19}H_{16}O_7N_4As_2$	40.07	3.09	40.17	3.20	Orange	Purple
IV	1-Amino-8-naphthol-4-sulfonic acid	100%	$C_{22}H_{19}O_{11}N_5As_2S$					Purple	Green
V	*p,p*-Dihydroxybiphenyl	150	$C_{24}H_{20}O_8N_4As_2$	44.85	2.74	45.43	2.93	Light	Light
						45.47	2.83	yellow	yellow
VI	Resorcinol	33	$C_{24}H_{21}O_{11}N_6As_3$	36.27	2.67	36.52	2.62	Orange	Pink
						36.67	2.62		
VII	Phloroglucinol	33	$C_{24}H_{21}O_{12}N_6As_3$	35.55	2.61	35.58	2.91	Yellow	Pink
						35.65	2.91		
VIII	2,4,4′-Trihydroxyazobenzene	30	$C_{36}H_{30}O_{15}N_{10}As_4$	37.85	2.64	38.62	2.98	Brown	Pink
						38.80	3.18		
IX	4,4′-Bis-(azo-2,4-dihydroxy)-biphenyl	25	$C_{48}H_{36}O_{16}N_{12}As_4$	43.07	2.86	43.17	3.40	Brown	Purple
X	*o*-Cresol	50	$C_{31}H_{26}O_7N_8As_2$	48.21	3.37	48.42	3.64	Violet-	Purple
						48.27	3.64	red	
XI	Phloroglucinol	33	$C_{42}H_{33}O_{12}N_{12}As_3$	44.92	2.96	44.71	2.96	Violet	Blue
XII	4,4′-Bis-(azo-2,4-dihydroxy)-biphenyl	10	$C_{72}H_{54}O_{16}N_{30}As_4$	49.27	3.10	49.85	3.66	Brown	Violet
XXIII	Phenol	20[a]	$C_{12}H_{11}O_4N_2As$	44.60	3.42	44.68	3.42	Yellow	Yellow
XXIV	Resorcinol	100[a]	$C_{12}H_{11}O_5N_2As$	42.59	3.28	42.65	3.26	Orange	Yellow
XXVI[b]	Phenol	20[a]	$C_{18}H_{14}O_4N_4As$-Na	48.20	3.16	48.20	3.42	Red-orange	Blue-violet

[a] Excess of phenol (per cent.). [b] Sodium salt.

II, *p*-Di-(*p*-azophenylarsonic acid)-benzene was similarly made from *p*-nitrosophenylarsonic acid and *p*-phenylenediamine and similarly purified.

Anal. Calcd. for $C_{18}H_{16}O_6N_4As_2$: C, 40.46; H, 2.94. Found: C, 38.85, 38.81; H, 3.12, 3.19.

III, 2-Methyl-4,6-di-(*p*-azophenylarsonic acid)-phenol; IV, 1-Amino-2,7-di-(*p*-azophenylarsonic acid)-4-sulfo-8-naphthol; V, 3,3′-Di-(*p*-azophenylarsonic acid)-4,4′-dihydroxybiphenyl; VI, 1,3-Dihydroxy-2,4,6-tri-(*p*-azophenylarsonic acid)-benzene; VII, 1,3,5-Trihydroxy-2,4,6-tri-(*p*-azophenylarsonic acid)-benzene; VIII, 2,4,4′-Trihydroxy-3,5,3′,5′-tetra-(*p*-azophenylarsonic acid)-azobenzene; IX, 4,4′-Bis-(azo-2,4-dihydroxy)-3,5-di-(*p*-azophenylarsonic acid)-biphenyl; X, 2-Methyl-4,6-di(*p*-(*p*-azophenylazo)-phenylarsonic acid)-phenol; XI, 1,3,5-Trihydroxy-2,4,6-tri-(*p*-(*p*-azophenylazo)-phenylarsonic acid)-benzene; XII, 4,4′-Bis-(azo-2,4-dihydroxy)-3,5-di-(*p*-(*p*-azophenylazo)-phenylarsonic acid)-biphenyl; XXIII, *p*-(*p*-Azophenylarsonic acid)-phenol; XXIV, 1,3-Dihydroxy-4-(*p*-azophenylarsonic acid)-benzene; XXVI, *p*-(*p*-(*p*-azophenylazo)-phenylarsonic acid)-phenol.—Compounds III to XII, XXIII, XXIV, and XXVI were made by coupling diazotized arsanilic acid or diazotized *p*-(*p*-aminophenylazo)-phenylarsonic acid with the appropriate phenolic nucleus in dilute sodium carbonate solution or (for XXVI) in sodium acetate–acetic acid solution. For III, X, and XI pyridine was added[13] in amount about 10% of the volume of the reaction mixture. The reaction mixtures were allowed to stand for a few days (1 to 4) and the products were then precipitated with hydrochloric acid and purified by repeated solution in dilute sodium hydroxide and reprecipitation with acid. Compounds X, XI, and XII were in addition purified by dialysis through Visking sausage casing against dilute borax solution with *p*H 10; this membrane permits passage of molecules containing only one haptenic group R′ but not those containing two or more of these groups. The compounds were washed free of sodium chloride and dried *in vacuo*. Experimental details, analytical results, and colors of solutions in alkali and in concentrated sulfuric acid are given in Table II.

A chromatographic method of analysis of the purity of these compounds was developed and applied by Mr. A. Pardee. The column packing used was a mixture of 30% Celite and 70% Neutrol Filtrol. A dilute solution of the dye was poured into the packed column and the chromatogram was developed with phosphate buffer of *p*H varying from 8 to 12 in different cases. The rate of passage of the dyes was greater the higher the *p*H. Compounds VI, VII, X, XI, XXIII, XXIV, and XXVI appeared to be quite pure, having at most only a slight trace of a second band. On the other hand, compounds I, II, III, V, VIII, IX, and XII contain appreciable colored impurity, as shown by the appearance of more than one band on the column. Compounds V, VIII, IX, and XII might be expected to be impure from the large number of steps in their preparation. The impurity in compound II was identified as XXV from a mixed chromatogram.

2,4,4′-Trihydroxyazobenzene was prepared by coupling diazotized *p*-aminophenol with resorcinol (100% excess) in the presence of sodium hydroxide. The product was purified by dissolving it in sodium hydroxide and reprecipitating with acid and finally by two crystallizations from 70% alcohol.

Anal. Calcd. for $C_{12}H_{10}O_3N_2$; C, 62.60; H, 4.38. Found: C, 62.39; H, 4.46.

4,4′-Bis-(azo-2,4-dihydroxy)-biphenyl was prepared by adding bisdiazotized benzidine to resorcinol (100% excess) in a sodium acetate buffered solution. The mixture finally was made alkaline with sodium hydroxide. The product was purified by washing.

Anal. Calcd. for $C_{24}H_{18}O_4N_4$; C, 67.60; H, 4.25. Found: C, 66.37; H, 4.62.

XXVII, *p*-Aminobenzanilide-*p*′-arsonic acid was prepared by the method of King and Murch[14] by the hydrolysis of the carbethoxyamino compound obtained by coupling *p*-arsanilic acid with *p*-carbethoxyaminobenzoyl chloride.

(13) K. H. Saunders, "The Aromatic Diazo-Compounds," Edward Arnold and Company, London, 1936, p. 115.

(14) H. King and W. O. Murch, *J. Chem. Soc.*, 2595 (1924).

TABLE III

Compound	Reactant	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
XIII	Phosgene	$C_{13}H_{14}O_7N_2As_2$	33.93	3.07	33.83	3.09
XIV	Oxalyl chloride	$C_{14}H_{14}O_8N_2As_2$	34.45	2.89	34.30	3.05
XV	Succinic anhydride	$C_{16}H_{18}O_8N_2As_2$	37.23	3.52	37.15	3.70
XVI	Adipyl chloride	$C_{18}H_{22}O_8N_2As_2$	39.72	4.08	39.69	4.24
XVII	Sebacyl chloride	$C_{22}H_{30}O_8N_2As_2$	44.01	5.04	43.97	5.03
XVIII	*o*-Phthalyl chloride	$C_{20}H_{18}O_8N_2As_2$	42.57	3.22	42.55	3.53
XIX	Isophthalyl chloride	$C_{20}H_{18}O_8N_2As_2$	42.57	3.22	42.42	3.28
XX	Terephthalyl chloride	$C_{20}H_{18}O_8N_2As_2$	42.57	3.22	42.76	3.43

Anal. Calcd. for $C_{13}H_{13}O_4N_2As$; C, 46.44; H, 3.90. Found: C, 46.91, 46.74; H, 4.08, 3.97.

XIII, Carbanilide-*p,p'*-diarsonic Acid; XIV, Oxanilide-*p,p'*-diarsonic Acid; XV, Succinanilide-*p,p'*-diarsonic Acid; XVI, Adipanilide-*p,p'*-diarsonic Acid; XVII, Sebacanilide-*p,p'*-diarsonic Acid; XVIII, Phthalanilide-*p,p'*-diarsonic Acid; XIX, Isophthalanilide-*p,p'*-diarsonic Acid; XX, Terephthalanilide-*p,p'*-diarsonic Acid.—These dianilide compounds were prepared by essentially the methods of King and Murch[14] and Morgan and Walton,[15] involving the reaction of arsanilic acid with the required acid chloride or anhydride in a basic or buffered aqueous solution. The compounds were purified by repeated solution in sodium hydroxide and precipitation with hydrochloric acid followed by a thorough washing with hot water. The reactants used and the results of analyses are given in Table III.

Results of the Precipitation Experiments

The Precipitation Reactions between Multivalent Compounds and Antisera.—Precipitation tests were carried out between the antisera A, B, C, and D homologous to atoxylazoprotein and the twenty compounds I to XX, each of which contains in its molecule two or more haptenic groups R, R′, or R″. *In every case precipitation occurred.* The amount of precipitate was found to vary with concentration of the antigen in the same way as for ordinary antigens. There is an optimum antigen concentration (or amount while the volume of antigen solution is held constant) at which the amount of precipitate reaches a maximum.

The amounts of precipitated antibody found by analysis are given in Tables IV, V, VI, VII, and VIII and are represented graphically in Figs. 1, 2, 3, 4, and 5.

Errors in the determination of the amounts of precipitated antibody may arise in the separation and washing of the precipitate or in the nitrogen analysis. Examination of the reported results of duplicate determinations indicates a probable error of about 5% for individual determinations.

(15) G. T. Morgan and E. Walton, *J. Chem. Soc.*, 615 (1931); 91 (1933). 902 (1936).

TABLE IV

AMOUNTS OF ANTIBODY PRECIPITATED FROM ANTISERUM A BY ANTIGENS I TO XII

Amounts of solutions used: 2 ml. antiserum, 3 ml. saline-antigen. The *p*H of the supernatant solutions was between 8.3 and 8.5. In Tables IV to VIII, inclusive, the amount of antigen used, in micrograms per ml. of antiserum, is given at the top of each column. The numbers in the columns are the amounts of precipitated antibody, in micrograms per ml. of antiserum. The meaning of the other symbols is given in the text.

Amount of antigen	3.13	6.25	12.5	25	50
I	−+	−+	−++	−+	−−
II	−++	−84	++134	+119	−53
III	−47	±103	++150	+100	−22
IV	−69	+138	++225	++213	±75
V	±106	+222	++322	+213	−63
VI	±100	+188	++222	+135	− ↓
VII	−48	+116	++128	+94	− ↓
VIII	+141	++185	+++338	++250	±110
IX	±106	+141	++291	+++347	−69
X	±66	+144	++188	+++397	↓ 660
XI	++232	↓ 425	↓ 920	↓ 1560	↓ 1690
XII	+128	+197	+++456	↓ 890	↓ 1210

TABLE V

AMOUNTS OF ANTIBODY PRECIPITATED FROM ANTISERUM B BY ANTIGENS II TO IX

Amounts of solutions used: 2 ml. antiserum, 3 ml. saline-antigen. The *p*H of the supernate was in each test 8.3.

Amount of antigen	6.25	12.5	25	50	100
II	270	520	660	470	300
	250	490	670	460	280
III	120	290	470	120	0
	110	350	490	140	9
IV	100	440	950	330	80
	200	490	850	330	100
V	330	760	1330	520	80
	270	840	1120	460	
VI	330	920	(1600)[a]	230	60
	310		(1490)	180	20
VII	180	350	770	300	100
	180	370	710	190	50
VIII	330	840	1590	340	20
	310	860	1400	280	10
IX	110	160	650	920	260
	110	130	690	670	260

[a] There is strong evidence that these values are in error.

TABLE VI

AMOUNTS OF ANTIBODY PRECIPITATED FROM ANTISERUM C BY ANTIGENS VI, IX, X, XI, AND XII

Amounts of solutions used: 2 ml. antiserum, 2 ml. saline-antigen for VI and IX; 1 ml. antiserum, 1 ml. saline-antigen for X, XI, and XII. The *p*H of the supernate was 8.4 for VI and IX, 8.5 for X, XI, and XII.

Amount of antigen	6.25	12.5	25	50	100	200
VI	290	460	270	160		
	290	380	270	150		
IX	220	440	400	230		
	180	430	390	220		
X	110	220	380	540	640	600
	110	220	350	530	650	710
XI	310	710	1360	1330	1000	660
	320	610	1350	1360	1190	750
XII	310	440	900	910	640	350
	320	440	840	990	680	360

TABLE VII

AMOUNTS OF ANTIBODY PRECIPITATED FROM ANTISERUM B BY ANTIGENS XIII TO XX

Amounts of solutions used: 3 ml. antiserum, 3 ml. saline-antigen. The *p*H of the supernate was 8.2 for each antigen.

Amount of antigen	6.25	12.5	25	50	100
XIII	50	75			10
	25	75			50
XIV	180	385	440	340	265
	165	355	475	340	270
XV	130	345	315	200	150
	150	255	325	225	140
XVI	15	35	55	35	15
	35	50		35	
XVII	35	35	50	45	30
	35	50	50	40	40
XVIII	10	10	60	85	50
	0	0	55	65	55
XIX	65	305	465	200	75
	65	300		215	
XX	120	505	695	440	195
	120	435	735	500	175

Test of the Customary Visual Estimation Method.—For the series reported in Table IV we took advantage of the opportunity of testing the customary visual-estimation method of studying antigen-antibody precipitation reactions. The tubes were inspected one-half hour after the solutions were mixed, and a record made of their appearance; this is given by the symbols in the table, which have the following meanings: −, no apparent cloudiness; ±, slight cloudiness; +, ++, +++, increasingly pronounced cloudiness; ↓, formation of clumps of precipitate. Comparison of these with the amounts of antibody precipitated in twenty-four hours shows that the correlation is reasonably good, and suggests that visual estimates of the amount of precipitate may be trusted to within about ± 30%. In this case each symbol represented about 60% more precipitate than the preceding one, as follows: −, 75; ±, 100; +, 150; ++, 250; +++, 400; ↓, 500 μg/ml.

TABLE VIII

AMOUNTS OF ANTIBODY PRECIPITATED FROM ANTISERUM D BY ANTIGENS II AND XIII TO XX

Amounts of solutions used: 2 ml. antiserum, 3 ml. saline-antigen.

Amount of antigen	3.13	6.25	12.5	25	50	100
II	140	280	780	1160	1150	930
XIII			20	20		
XIV			570	690	700	570
			460	640	640	510
				740	760	
XV	60	190	440	600	480	
				700	660	
XVI	10	10	50	110	90	
XVII	10	60	80	100	120	100
			80	90	110	90
			80	90	110	
XVIII	20	30		50	40	
XIX	10	180		1060	420	
XX	120	250	610	1170	800	

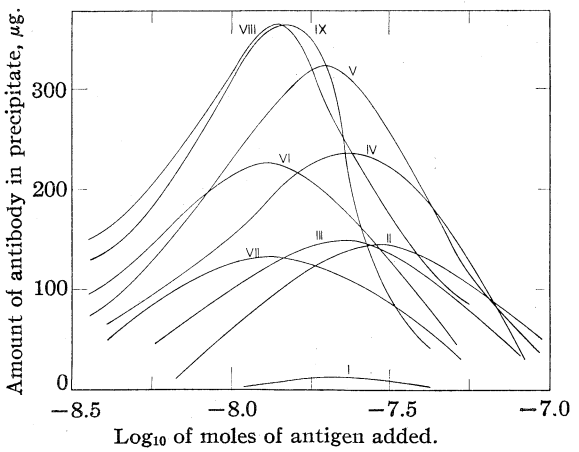


Fig. 1.—Amounts of antibody precipitated from antiserum A (per ml.) by antigens I to IX as functions of log of molal antigen concentration (Table IV). The curve for I represents an estimate. Smooth curves have been drawn through the experimental points, which are not shown.

Comparison Tests with Normal Serum.—Similar tubes were set up for each of the twenty antigens with normal rabbit serum in place of antiserum. In none did precipitation occur.

The Failure of Monohaptenic Compounds to Produce Precipitates with Antisera.—The seven

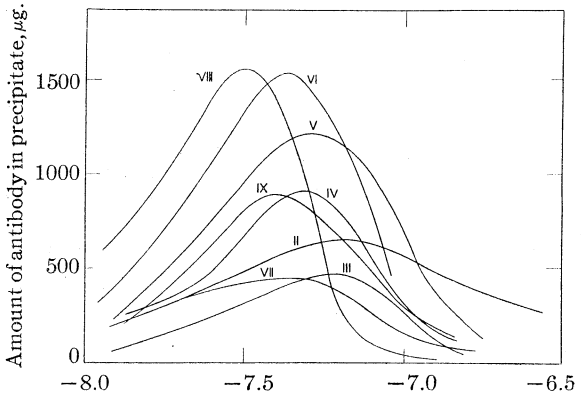


Fig. 2.—Amounts of antibody precipitated from antiserum B (per ml.) by antigens II to IX (Table V).

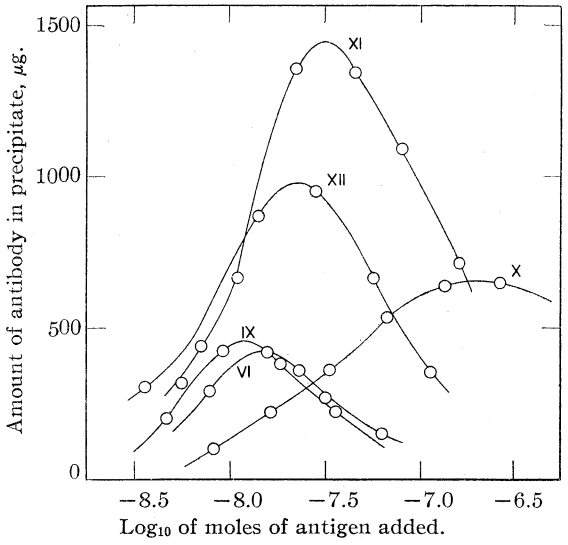


Fig. 3.—Amounts of antibody precipitated from antiserum C (per ml.) by antigens VI, IX, X, XI, and XII (Table VI).

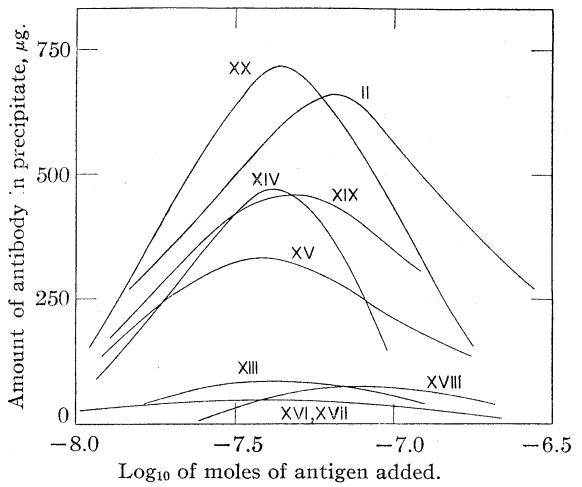


Fig. 4.—Amounts of antibody precipitated from antiserum B (per ml.) by antigens XIII to XX (Table VII) with antigen II for comparison (Table V).

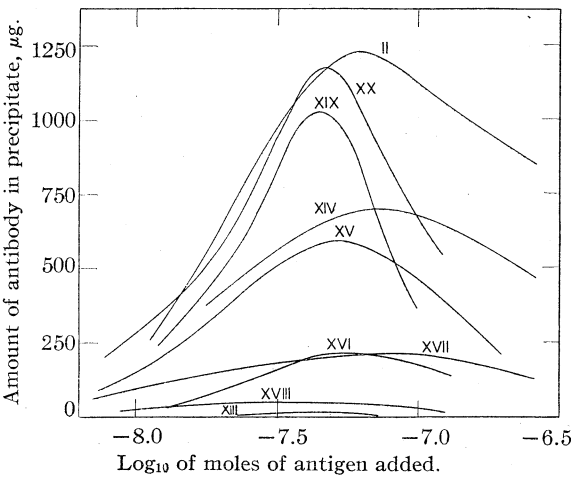


Fig. 5.—Amounts of antibody precipitated from antiserum D (per ml.) by antigens II and XIII to XX (Table VIII).

compounds XXI to XXVII, each of which contains one haptenic group per molecule, were tested with the antisera in the same way as the twenty compounds I to XX; no precipitate was formed by any of these "univalent" substances. This result is, of course, to be expected, in view of the failure of Landsteiner[16] to obtain precipitates between haptens and homologous antisera during his extensive experiments on the inhibition by homologous haptens of the azoprotein-antibody precipitation reaction.

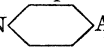
Discussion

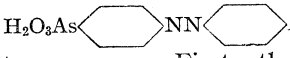
The fact that each of the twenty polyhaptenic substances precipitates hapten-homologous antibody, whereas substances containing only one haptenic group do not have this effect, provides strong support for the Marrack–Heidelberger framework theory (lattice theory) of the structure of serological precipitates, inasmuch as the framework theory gives a simple explanation of the phenomenon, and no other reasonable explanation has been proposed. Multivalent antibody molecules, whose existence is postulated in the framework theory, would be expected to combine with polyhaptenic molecules to form infinite aggregates, which would grow into visible precipitates, whereas with monohaptenic molecules they would form soluble small complexes containing one antibody molecule.

The general shape of all the curves of Figs. 1 to

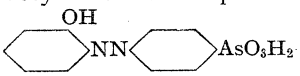
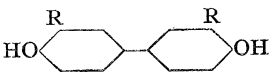
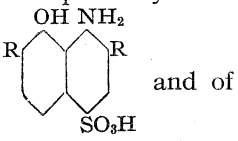
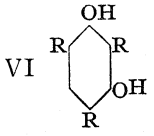
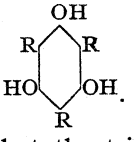
(16) K. Landsteiner, "The Specificity of Serological Reactions," Charles C. Thomas, Baltimore, 1936, p. 118.

5, showing the dependence of amount of antibody precipitated on the amount of added antigen, is the same; the amount of precipitated antibody first increases, then reaches a maximum, and finally decreases, reaching zero for large amounts of antigen. This inhibition of precipitation by excess antigen, which occurs also for protein antigens, is explained as resulting from the formation of soluble complexes, such as A–B–A (A_2B) for a bivalent antibody (A = antigen, B = antibody). There may also be formed soluble complexes AB_2, A_2B_3, etc., which contain an excess of antibody, saturating the effective valences of the antigen molecules. The interpretation of the precipitation data in terms of the strength of the antigen-antibody bond is complicated not only by the necessity of considering these soluble complexes but also by the heterogeneity of antibody molecules.

The data for nine compounds I to IX which contain the group  used in the immunizing azoprotein are reproduced in Figs. 1 and 2. It is seen that there is agreement between the results obtained with the two antisera in most respects. From Fig. 1 we obtain the following sequence of precipitating ability of the haptens: VIII = IX > V > VI = IV > VII = III = II > I. Nearly the same sequence is given by Fig. 2. The principal difference is the interchange of VI and IX, and other data (as in Fig. 3) indicate that the order given by Fig. 1 is to be preferred. It is possible that some gross error was made in the work; on the other hand, the difference between Figs. 1 and 2 may well be real, resulting from difference between the two antisera.

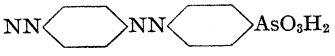
The smallness of the amount of precipitate given by I  we attribute to two causes. First, the molecule contains only one azo group, so that in holding two antibody molecules the molecule cannot exert toward each the influence of the complete haptenic group  (present in the immunizing azoprotein); and second, two large antibody molecules clasping the two end halves of this very small antigen would be expected to interfere sterically with each other, and be prevented by this steric interference from forming as strong an antigen-antibody bond as would otherwise be possible.

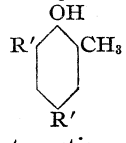
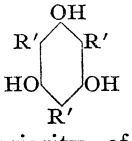
Of the five dihaptenic compounds I to V the two most effective, IV and V, are those with the greatest hapten-hapten distance. We attribute their relative effectiveness to the resultant diminution in steric interaction of the attached antibodies.

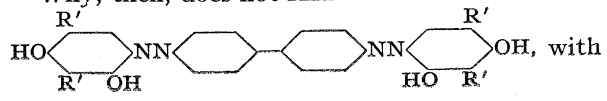
Since in the immunizing azoprotein the azophenylarsonic acid groups are attached in part to tyrosine residues, a very effective haptenic group is expected to be  with one hydroxyl adjacent to the azo group. By considering this we explain the superiority of V  to IV  and of VI  to VII  .

It is interesting that the trihaptenic (VI and VII) and tetrahaptenic (VIII and IX) compounds are superior but not greatly superior to the dihaptenic compounds of similar size and structure. It was expected[3] that dihaptenic compounds would be inferior in precipitating ability because of the formation with bivalent antibody of soluble strings A–B–A–B–A–B– rather than insoluble frameworks. The observation that good precipitates are obtained with dihaptenic compounds indicates either that the long strings themselves precipitate easily or that enough trivalent antibody molecules are present to link the strings together.

The compounds X, XI, and XII, which contain the long haptenic group

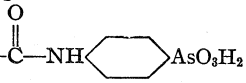
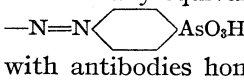
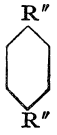
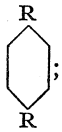


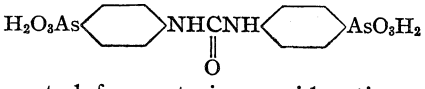
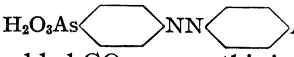
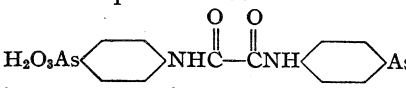
are much more effective than the corresponding compounds III, VII, and IX; this increased effectiveness we attribute to decreased steric interference between the attached antibodies. The comparison of X  and XI  is especially interesting. The superiority of the latter is clearly to be attributed to its having three haptenic groups instead of two.

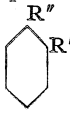
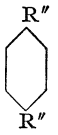
Why, then, does not XII  , with

four, precipitate still more antibody? The answer may be that little gain is to be expected from increasing the number of haptenic groups from three to four, since three are enough to tie the strings together into a framework. In fact, XII is as effective as XI at low concentrations, and its later inferiority may be due to greater ability to form soluble complexes.

There is a striking relation between the number of haptenic groups per antigen molecule and the optimum antigen concentration for precipitation; a great change occurs from dihaptenic to trihaptenic antigens, and a much smaller change on addition of a fourth haptenic group. This is seen clearly in Fig. 3; the logarithm of the optimum molal concentration of X is −6.8, of XI −7.5, and of XII −7.65. Similarly the five dihaptenic antigens of Fig. 1 are grouped together at −7.6, and the others at −7.9.

The data represented in Figs. 4 and 5 show that the amide haptenic group  is essentially equivalent to the azo haptenic group  in its power to combine with antibodies homologous to the azo haptenic group. A straightforward comparison can be made between the amide compound XX  and the azo compound II  ; it is seen from the corresponding curves in Figs. 4 and 5 that these compounds are nearly equal in precipitating power.

The compound XIII  would be expected from steric considerations to be somewhat more effective than I  , because of the added CO group; this is borne out by experiment. The compound XIV  , containing two complete haptenic groups, should be still more effective. It is in fact surprisingly effective, with nearly the precipitating power of XX.

The compounds XVIII  , XIX  and XX  are increasingly effective in this order, with XVIII by far the weakest of the three. This is reasonably interpreted as due to steric interference of the attached antibody molecules.

This explanation cannot be extended, however, to the sequence XIV R″—R″, XV R″$(CH_2)_2$R″, XVI R″$(CH_2)_4$R″, XVII R″$(CH_2)_8$R″, since these compounds decrease in precipitating power in this order. A structural interpretation of this result in terms of the lack of rigidity of the polymethylene chain might be developed, but it is not very convincing.

The curves for compounds XIV and XV differ in shape from those for XIX and XX; no reasonable explanation of this has occurred to us.

It is important to note that the polyhaptenic simple antigens are not greatly inferior in precipitating power to azoproteins. Indeed, the best of the simple antigens, XI, was found to precipitate as much antibody as the test azoprotein.

Boyd[17] has recently reported failure to obtain precipitates between antisera and a number of simple substances containing two or more haptenic groups (including several substances also studied by us), and on the basis of this negative evidence he has drawn conclusions contrary to those which we have reached. In view of our observations, we consider it likely that his experiments were carried out under conditions unfavorable to precipitation—his antisera may have been weak, or his antigens may have contained monohaptenic impurities.

We are grateful to the Rockefeller Foundation for financial support of this work. We wish to thank Mr. Paul Faust and Mr. Shelton Steinle for their assistance in carrying out analyses, and Mr. David Brown for the preparation of phenylarsonic acid.

Summary

Twenty-seven simple substances containing the phenylarsonic acid group as haptenic group were prepared and used in precipitin tests with antisera made by injecting rabbits with azophenylarsonic acid sheep serum.

The twenty simple antigens containing two or more haptenic groups per molecule were found to give precipitates with the antisera, whereas

(17) W. C. Boyd, *J. Exptl. Med.*, **75**, 407 (1942); S. B. Hooker and W. C. Boyd, *J. Immunol.*, **42**, 419 (1941).

the seven monohaptenic substances failed to precipitate. It is pointed out that these results provide strong support of the framework theory of the precipitin reaction.

Data on the amounts of precipitate formed are discussed in relation to the structure of the simple antigens.

PASADENA, CALIFORNIA RECEIVED JULY 6, 1942

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 886]

The Serological Properties of Simple Substances. II. The Effects of Changed Conditions and of Added Haptens on Precipitation Reactions of Polyhaptenic Simple Substances

BY LINUS PAULING, DAVID PRESSMAN, DAN H. CAMPBELL, AND CAROL IKEDA

During the course of the investigation of precipitation reactions of polyhaptenic simple substances reported in the preceding paper of this series[1] we found it desirable to carry out a study of the effects of changed conditions of precipitation and washing on the amount of residual precipitate. We also made some experiments on the inhibition of precipitation by added haptens, in order to see how great would be the effects of monohaptenic impurities possibly present in the substances studied. The results obtained are presented and discussed in this paper.

Experimental Methods.—The experiments were carried out in the way described in the preceding paper (I). In addition to antisera C and D mentioned in paper I, three antisera, E, F, and G, were used. E and G contained amounts 0.6 and 3.2 mg. per ml., respectively, of antibody precipitable by azo-ovalbumin test antigen; the strength of F was not determined.

The borate buffer solutions were made by adding suitable amounts of 0.16 *N* sodium hydroxide solution to 0.2 *M* boric acid solution containing 0.9% sodium chloride.

The Effect of Changed Conditions of Precipitation and Washing on the Amount of Precipitate.—It is seen from the data reported in Tables I, II, and III, obtained with two antigens (VI and X) and three antisera (C, E, and F), that the antigen-antibody precipitate is either dissolved slightly or carried away mechanically by the saline or borate buffer solutions with which it is washed. The loss in this way is, however, small, amounting to about 5 to 15% for eight or ten extra washings with 10-ml. portions of solution.

A few experiments were made (Tables II and III) to test the effects of changing the time and temperature of precipitation. It was found that increasing the precipitation time from one day to two days increases the amount of precipitate by about 10%. The amount of precipitate formed seems to increase with increase in temperature of

TABLE I

EFFECT OF NUMBER OF WASHINGS ON AMOUNT OF RESIDUAL PRECIPITATE

3 ml. antigen VI, 25 μg./ml. in saline solution, plus 3 ml. antiserum C						2 ml. antigen VI plus 2 ml. antiserum E		
	Composition of precipitate			Composition of precipitate			Composition of precipitate	
Washings	Antibody[a]	Antigen[a]	Washings	Antibody[a]	Antigen[a]	Washings	Antibody[a]	Antigen[a]
2	1665	8.9	6	1600	8.7	3	1110	5.7
	1660	8.4		1540	8.7		1125	6.2
	1660	8.9		1590	8.7	10	970	5.7
3	1600	8.7	7	1590	8.7		930	6.0
	1600	8.9		1530	8.9	15	960	6.0
	1545	8.7		1510	8.9			
4	1545	8.7	8	1510	9.2			
	1570	8.9		1530	8.7			
	1660	8.7		1480	8.1			
5	1570	8.9	10	1520	9.5			
	1570	8.9		1510	7.6			
	1570	9.5		1320	9.5			

[a] Amounts of precipitated antibody and antigen in micrograms. *p*H of all supernates 8.1.

(1) Linus Pauling, David Pressman, Dan H. Campbell, Carol Ikeda, and M. Ikawa, THIS JOURNAL, 64, 2994 (1942). We shall refer to this as paper I.

TABLE II

EFFECT OF CHANGED CONDITIONS ON AMOUNT OF PRECIPITATE

3 ml. antigen VI, 12.5 μg./ml., in saline solution, plus 3 ml. antiserum E. *p*H of supernates 8.0 to 8.3.

Conditions of precipitation	Washings	Composition of precipitate: Antibody, μg.	Antigen, μg.
Room 1 hr., refrigerator 24 hr.	3	1600	9.2
		1610	8.9
	10	1190	8.4
		1310	8.1
		1140	8.7
	15	1140	9.2
Room 1 hr., refrigerator 48 hr.		1780	9.2
	3	1590	8.9
Refrigerator 24 hr.	3	1590	8.9
		1640	9.2
Refrigerator 48 hr.	3	1610	8.9
		1690	8.9
Room 24 hr.	3	1080	7.0
		980	7.0

TABLE III

EFFECT OF CHANGED CONDITIONS ON AMOUNT OF PRECIPITATE

5 ml. antigen X, 20 μg./ml. in saline solution, 2.5 ml. antiserum F, and 7.5 ml. borate buffer of *p*H 9.0.

Conditions of precipitation	Washing solution	Washings	Composition of precipitate: Antibody, μg.	Antigen, μg.
Room 1 hr., refrigerator 24 hr.	Saline	3	520	3.3
			520	3.3
	Saline	10	525	3.1
			530	3.1
	Saline, iced	3	585	3.3
			520	2.9
	Buffer,	3	600	3.3
	Buffer, iced	3	630	2.9
			600	2.9
Room 1 hr., refrigerator 48 hr.	Saline	3	580	2.9
			595	2.9
Room 3 hr., refrigerator 22 hr.	Saline	3	610	3.1
			550	3.1
Room 24 hr.	Saline	3	675	3.1
			605	3.1
35° 1 hr., refrigerator 24 hr.	Saline	3	560	2.9
			555	2.9

the tube during the first few hours of the precipitation period (Table III). However, the evidence is inconclusive as to whether the final amount of precipitate is increased or not by refrigeration during the later part of the precipitation period.

The data reported in Table IV show that the amount of precipitated antibody is decreased by the addition of buffer solution to the antigen-antibody mixture. The decrease is not proportional to the volume of buffer added, so that the phenomenon is not analogous to the solution of a

TABLE IV

THE EFFECT OF DILUTION WITH BUFFER SOLUTION ON AMOUNT OF PRECIPITATED ANTIBODY

2.5 ml. antigen VI, varying volume of borate buffer solution with *p*H 8.0, 2.5 ml. antiserum C.

Volume of buffer solution	Amount of antigen used (μg.): 15.6	31.3	62.5
	Amount of precipitated antibody (μg.)		
0	750	1375	775
2.5	600	1030	990
5	480	845	525
10	470	655	450

well-defined compound. These observations provide further evidence of the heterogeneity of the antibodies in immune sera.

The Effect of Hydrogen-ion Concentration on Amount of Precipitate.—The results of experiments to test the effect of change in *p*H on the amount of precipitate are given in Table V. It is seen that for this antigen-antibody system the optimum *p*H is about 8.1, the amounts of precipitate in this region being greater than for either more acidic or more basic solutions. Evidence that the buffering substances do not have a large direct influence on the reaction is given by the agreement of the values at *p*H 8.1 for added saline solution and added borate buffer.

The optimum antigen concentration is seen to be changed only slightly by change in *p*H.

Less extensive experiments were also carried out with the amide antigen XIV (R″–R″) in place of the azo antigen; the results obtained, given in Table VI, are similar.

The Effect of Dilution with Normal Serum or Buffer Solution.—In order to determine the effect of change in the strength of a serum of fixed antibody composition on the position of the optimum zone, identical experiments were made with sera obtained by mixing antiserum G and normal serum. The results are given in Table VII. It is seen that for both antigens (III and VI) the maximum precipitation occurs at an amount of antigen about midway between 25 and 50 μg. (for 2 ml. of antiserum), and that on two-fold dilution of the antiserum, decreasing its antibody concentration by the divisor 2, the optimum amount of antigen is also decreased by about the divisor 2. The effect of diluting the antiserum is hence to cause the optimum zone to shift in such a way as to keep constant the ratio of antigen to antibody.

The same result is given by experiments on the effect of dilution with buffer solution, reported

TABLE V

EFFECT OF HYDROGEN-ION CONCENTRATION ON AMOUNT OF PRECIPITATE

3 ml. saline solution VI, 3 ml. antiserum E, and 3 ml. saline or buffer solution; 48 hrs. in refrigerator. B = antibody in precipitate, micrograms. A = antigen in precipitate, micrograms.

Amount of antigen (μg.) Added solution	pH of supernate	22.2 B	22.2 A	33.3 B	33.3 A	50 B	50 A	75 B	75 A
Boric acid	7.6–7.7	640	4.9	820	5.9	820	5.7	610	4.1
		640	4.6	820	5.7	820	5.7	620	5.4
Saline	8.1–8.2	890	4.6	1140	6.5	1020	6.2	610	3.0
		840	4.6	1140	6.5		6.2	550	3.8
Borate buffer,	8.1	820	5.7	1080	8.4	940	7.0	650	4.9
*p*H 8.0		790	5.7	1080	7.3	920	6.0	590	5.4
Borate buffer,	8.8–8.9	680	5.1	780	5.9	640	6.2	520	5.4
*p*H 9.0		650	4.6	820	6.5	720	6.2	520	4.3

TABLE VI

EFFECT OF HYDROGEN-ION CONCENTRATION ON AMOUNT OF PRECIPITATED ANTIBODY

1 ml. antigen XIV, 1 ml. antiserum G, 2 ml. saline or buffer solution.

Amount of added antigen (μg.) Added solution	pH of supernate	12.5 Amount of precipitated antibody (μg.)	25 Amount of precipitated antibody (μg.)	50 Amount of precipitated antibody (μg.)
Boric acid	7.6	200	275	260
		250	290	240
Saline	8.0–8.2	270	305	270
		290	345	265
Borate buffer,	8.1	270	290	225
*p*H 8.0		290	375	325
Borate buffer,	8.8–9.0	215	290	240
*p*H 9.0		280	295	270

TABLE VII

THE EFFECT OF DILUTION WITH NORMAL SERUM ON AMOUNT OF PRECIPITATED ANTIBODY

3 ml. of antigen III or VI plus 2 ml. of mixture of normal serum and antiserum G.

Amount of antigen used (μg.) Antigen	Antiserum	Normal serum	12.5 Amount of precipitated antibody (μg.)	25 Amount of precipitated antibody (μg.)	50 Amount of precipitated antibody (μg.)	100 Amount of precipitated antibody (μg.)
III	2	0	230	495	495	265
			215		555	230
	1	1	305	340	200	105
			305	280	215	55
	0.5	1.5	225	170	105	10
			230	170	105	0
VI	2	0	395	1150	1070	170
			400	1100	1240	170
	1	1	495	455	195	65
			425	510	205	70
	0.5	1.5	290	120	40	0
			330	200	45	0
*p*H of supernate	antigen III		8.1	8.1	8.1	8.1
	antigen VI		8.2	8.3	8.4	8.5

in Table IV. In these experiments, in which the amount of antibody is kept constant, the position of the optimum zone does not change significantly.

These conclusions agree with those reached by many earlier investigators with protein antigens.

The Inhibition of Precipitation by Hapten.—It was discovered by Landsteiner[2] that a hapten such as arsanilic acid present in reasonable concentration in a mixture containing an azoprotein (made from this hapten) and the hapten-homologous antiserum decreases the amount or inhibits the formation of the antigen-antibody precipitate. It has also been found[3] that this phenomenon occurs with polyhaptenic simple substances replacing the azoprotein. Quantitative results were obtained by us with antigens VI, X, and XX, containing the groups R, R′, and R″, respectively, and haptens XXI, XXII, XXIII, and XXVII. These are given in Tables VIII to XI and Figs. 1 and 6. It is seen (Table VIII) that addition of hapten decreases the amount of precipitate without noticeable shift in the equivalence zone, and (Tables X, XI) that haptens differ in their inhibiting power.

TABLE VIII

THE INHIBITION OF PRECIPITATION BY HAPTEN

3 ml. antigen VI, 1 ml. hapten XXI, 3 ml. antiserum E. *p*H of supernates 8.2.

Amount of antigen (μg.) Amount of hapten (μg.)	15	22.2	31.3	50	75
	Amount of precipitated antibody (μg.)				
0	540	790	1280	1020	560
12.5	520	740	910	850	540
25	520	580		780	530
50	340	560	630	640	530
100	330	360	610	550	450
200	290	340	430	440	360
400	200	270	290		270

TABLE IX

INHIBITION BY HAPTEN

1 ml. antigen VI (12.5 μg.), 0.5 ml. hapten XXIII, 1 ml. antiserum D. *p*H of supernates 8.1.

Amount of hapten, μg.	Amount of precipitated antibody, μg.
0	505 470
3.13	505
6.25	480
12.5	355
25	220
50	70

(2) K. Landsteiner, *Biochem. Z.*, **93**, 117 (1919); **104**, 280 (1920); K. Landsteiner and J.v an der Scheer, *J. Exptl. Med.*, **48**, 315 (1928); **50**, 407 (1929); **54**, 295 (1931); **55**, 781 (1932).

(3) K. Landsteiner and J. van der Scheer, *ibid.*, **56**, 399 (1932).

TABLE X

INHIBITION BY HAPTEN

0.5 ml. antigen X (25 μg.), 0.2 ml. hapten XXII or XXIII, 0.5 ml. antiserum D.

Amount of hapten, μg.	Amount of precipitated antibody, μg. Hapten XXII	XXIII
0	570	565
1.25	505	565
2.50	495	530
5	420	390
10	455	315
20	295	125
40	210	65
*p*H of supernates	8.5	8.8

TABLE XI

INHIBITION BY HAPTEN

1 ml. antigen XX (25 μg.), 0.5 ml. hapten XXII or XXVII, 1 ml. antiserum D.

Amount of hapten, μg.	Amount of precipitated antibody, μg. Hapten XXII	XXVII
0	1305	1200
3.13	1295	1120
6.25	1225	845
12.5	1075	590
25	960	215
50	650	
100	475	40
*p*H of supernates	8.2	8.3

The results obtained show that no significant error would be introduced in the experiments by the presence of haptens as impurities in the polyhaptenic antigens in amounts as great as 5%. It is improbable that any of the substances used contained this much monohaptenic impurity.

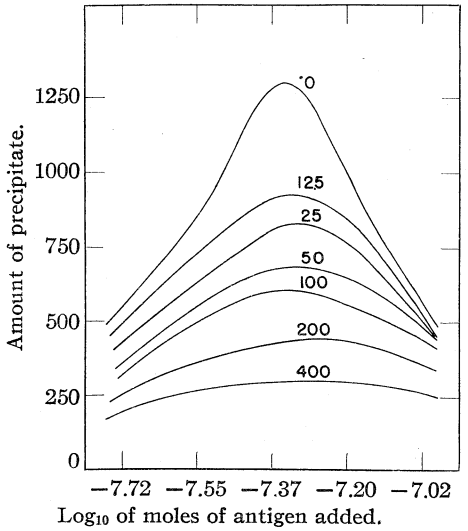


Fig. 1.—Effect of added hapten (in amounts given) on amount of antigen-antibody precipitate (Table VIII).

The data reported in Table XII indicate that the same final equilibrium is reached by the system antigen-antibody-hapten when the order of combining the reactants is changed.

TABLE XII

EFFECT OF ORDER OF COMBINATION OF REACTANTS

Reactants combined as indicated and allowed to stand indicated times at room temperature, then 24 hours in refrigerator: A, 3 ml. solution of antigen VI (37.5 μg.); H, 1 ml. solution of hapten XXI (100 μg.); S, 3 ml. antiserum E. *p*H of supernates 8.1.

	Amount of precipitated antibody, μg.
1. A + S + 1 ml. saline solution, 1½ hours	1200 1090
2. A + S + H, 1½ hours	520 520
3. S + H, ½ hour, + A, 1 hour	550 525
4. A + S, ½ hour, + H, 1 hour[a]	550 520
5. Same as 4, with shaking.[a]	550 525

[a] A precipitate formed before hapten was added.

Discussion

A reasonable interpretation of these results and those of the preceding paper can be given in terms of the multivalent-antibody theory. This interpretation is conveniently presented with the aid of a simplified model susceptible to easy mathematical treatment.[4]

Let us assume that our idealized antigen–antibody system consists of a solution containing antigen molecules A, antibody molecules B, soluble complex molecules A_2B, and molecules AB in equilibrium with a precipitate AB. We ignore other complexes A_3B_2, A_4B_3, AB_2, etc., and the known heterogeneity of antibody molecules in a serum.

For simplicity we assume that each of the two bonds in A–B–A is equal in strength to the bond in A–B, and that the equilibrium constants for the two reactions

$$A + B = AB$$

and

$$A + AB = A_2B$$

differ only by the entropy factor 4. We represent these by $4K$ and K, respectively, with K the equilibrium constant for combination of a single haptenic group of an antigen molecule and a single complementary region of an antibody molecule, and derive the equation

$$AB(\text{pp}) = A_{\text{total}} - s - \frac{1 + 2Ks}{2 + 2Ks}\{A_{\text{total}} - B_{\text{total}} + [s(1 + Ks)/K + (A_{\text{total}} - B_{\text{total}})^2]^{1/2}\} \quad (1)$$

(4) Somewhat similar quantitative theories of the precipitin reaction have been published by M. Heidelberger and F. E. Kendall, *J. Exptl. Med.*, **61**, 563, **62**, 467, 697 (1935); **66**, 229 (1937); F. E. Kendall, *Annals N. Y. Acad. Sci.*, 153, 85 (1942); and A. D. Hershey, *J. Immunol.*, **42**, 455 (1941). These theories are designed to apply more broadly than ours, which is based on postulates suited to the special antigens and haptens which we are studying.

in which AB (pp) is the amount of precipitated compound, with solubility s, and A_{total} and B_{total} are the total amounts (per unit volume) of antigen and antibody in all molecular species, including the precipitate.

The curves of amount of precipitate for a given antiserum with varying amounts of antigen calculated with this equation have the general shape indicated by the experimental points.

Curves for the arbitrary values $s = 1$, $K = 1/2$ are plotted against A_{total} in Figure 2 for each of several values of B_{total}, corresponding to the strength of the serum. It is seen that in each case the maximum amount of precipitate is produced by an amount of antigen approximately equal to the amount of antibody. This is in agreement with the results obtained with diluted serum (Tables IV and VII).

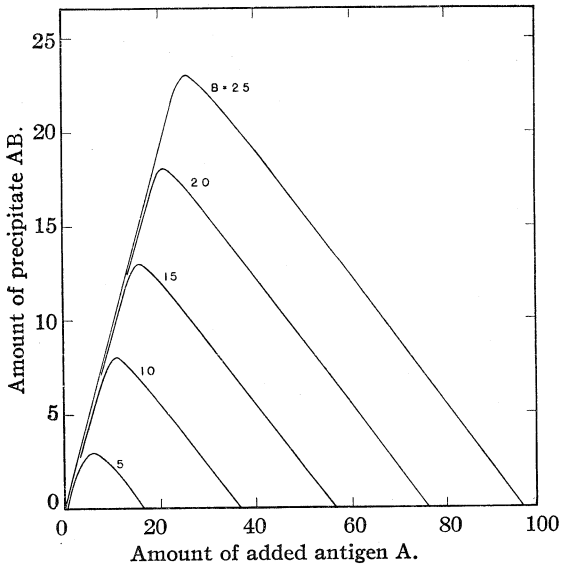


Fig. 2.—Theoretical curves showing amount of precipitate AB as function of amount of antigen A for antisera with varying antibody concentration $B = 5$ to 25. Values of constants used are $s = 1$, $K = 1/2$.

The observation, reported in the preceding paper, that different polyhaptenic antigens containing the same haptenic group have the same molal concentration for maximum precipitation with a given serum, although the amount of precipitable antibody in the serum varies with the antigen, requires explanation, since it might well be expected that the optimum antigen concentration would be proportional to the amount of precipitate. Let us assume that for antigens containing the same haptenic group the A–B bond constant K has the same value, but that the solubility s of the precipitate may vary. This might reasonably result from steric interference of the large antibody molecules in the chains –A–B–A–B–A–B- in the precipitate, which might cause a second bond formed by a bivalent antigen molecule to be much weaker than the first bond. The curves in Fig. 3, with K constant and s varying, represent this situation. We see that, as the result of the consecutive equilibria A + B = AB and AB + A = A_2B, the position of the maximum is constant when K is constant and the solubility s varies. It is found from the equation, in fact, that the maximum occurs at the point $A_{total} - B_{total} = 1/2K$, and is independent of s.

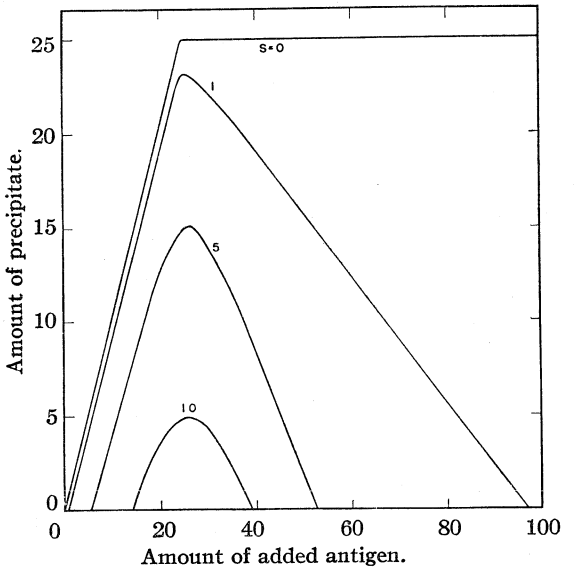


Fig. 3.—Calculated effect of variation of solubility of antigen-antibody precipitate on amount of precipitate; all curves for initial antibody concentration $B = 25$ and $K = 1/2$.

It is also found (Fig. 4) that variation in K produces little change in the optimum antigen concentration, except when the value of K becomes very small. It accordingly seems probable that the difference of the optimum concentration for antigens containing the haptenic group R and those containing the longer group R′, as shown in Fig. 3 of paper I, is evidence that the effective strength of the serum for groups R′ is greater than that for R, because of the presence of antibodies capable of combining with R′ and not with R.

The maximum amount of precipitate is independent of K; its value, as found from Equation 1, is $B_{total} - 2s$.

The fact that change in effective strength of a serum with change in pH is not accompanied by

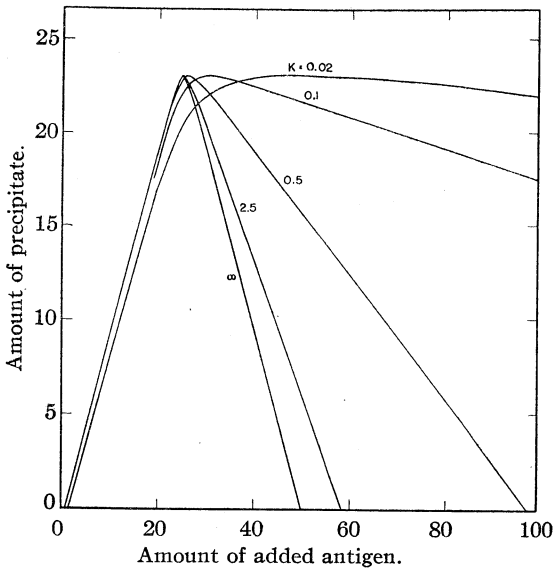


Fig. 4.—Calculated effect of variation of A–B bond-strength constant K on amount of precipitate; all curves for initial antibody concentration $B = 25$ and AB solubility $s = 1$.

shift of the optimum antigen concentration indicates that the effect is not due simply to change in the concentration of effective antibody molecules. Further experiments on the *p*H effect are under way.

The phenomenon of hapten inhibition has been explained by Landsteiner as resulting from combination of hapten and antibody to form a soluble complex, thus effectively neutralizing the antibody. The formation of soluble complex instead of a precipitate by antibody and hapten is explained by the framework theory as the result of the univalence of the hapten. It might be expected that as the maximum amount of precipitate which can be obtained from a serum is decreased by addition of hapten there would occur a corresponding decrease in the optimum antigen concentration, as was observed in the dilution experiments.

It is seen from Fig. 1, however, that the optimum antigen concentration is not shifted very much by addition of hapten. A small shift can be predicted by an extension of our simple theory. If we consider a system containing in solution the molecular species H, BH, BH_2, and ABH (H = hapten) as well as A, B, AB, and A_2B, and assume the B—H bond strength to be such that the equilibrium constants for the reactions

$$B + H = BH$$
$$BH + H = BH_2$$

and

$$AB + H = ABH$$

are $2K'$, $K'/2$, and K', respectively, we obtain the set of equations

$$AB(\text{pp}) = A_{\text{total}} - s - \alpha\{1 + 2K(s + z)\} \quad (2)$$

$$A_{\text{total}} - B_{\text{total}} = \alpha - \frac{s}{4K\alpha} + \alpha Ks - z - \frac{\alpha K z^2}{s} \quad (3)$$

$$z = -\frac{1}{2}\left(\frac{s}{2K\alpha} + s + \frac{1}{K'}\right) \pm \left\{\frac{1}{4}\left(\frac{s}{2K\alpha} + s + \frac{1}{K'}\right)^2 + \frac{sH_{\text{total}}}{2K\alpha}\right\}^{1/2} \quad (4)$$

in which H_{total} is the total hapten concentration. The auxiliary variables α (the concentration of the molecular species A in solution) and z (the concentration of the molecular species HB in solution) are related by Equation 4, by means of which z can be calculated for an assumed value of α. Then by use of Equation 2 the amount of precipitate can be found, and by Equation 3 the variable α can be replaced by A_{total} and B_{total}.

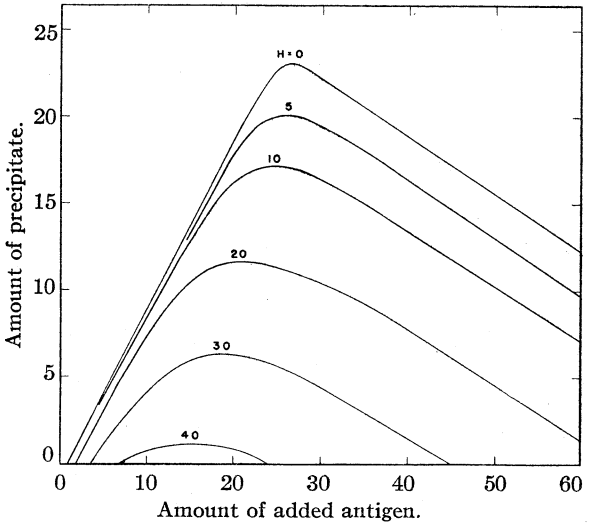


Fig. 5.—Calculated effect of addition of hapten on amount of antigen-antibody precipitate, for $B_{\text{total}} = 25$, $K = 1/2$, and $K' = s = 1$.

In Fig. 5 there are shown curves calculated in this way for $K = 1/2$, $K' = s = 1$, $B_{\text{total}} = 25$, and $H_{\text{total}} = 0$, 5, 10, 20, 30, and 40. It is seen that there is a small shift of the maxima toward lower antigen concentrations. In the region of the equivalence zone, where A_{total} equals B_{total}, the amount of precipitate formed is proportional to the hapten concentration, as is given by Equation 5, which is derived from Equations 2, 3, and 4.

$$\frac{dAB(\text{pp})}{dH_{\text{total}}} = -\frac{1/2 + Ks + (K^2s^2 + Ks)^{1/2}}{1 + Ks + \left(1 + \frac{1}{K's}\right)(K^2s^2 + Ks)^{1/2}} \quad (5)$$

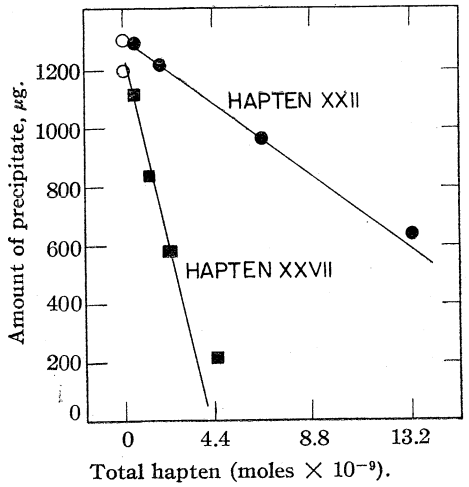


Fig. 6.—Observed effect of haptens XXII and XXVII on amount of precipitate between antigen XX and antiserum (Table XI).

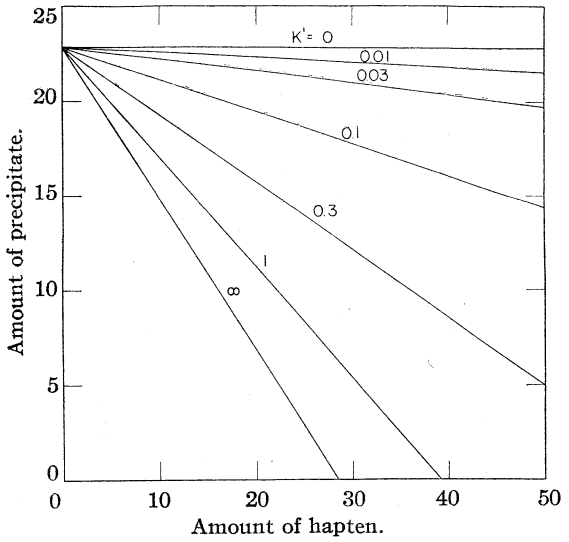
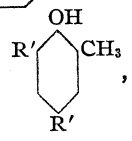


Fig. 7.—Calculated dependence of amount of antigen-antibody precipitate on hapten-antibody bond-strength constant K', for $A_{total} = B_{total} = 25$, $K = 1/2$, $s = 1$.

The experimental data at low hapten concentrations are in rough agreement with the straight-line relation, as shown in Fig. 6 for the data of Table XI.

In Fig. 7 there is shown the predicted effect of variation of the hapten-antibody bond-strength constant K'.

It might be expected from its similarity in structure with the antigen that hapten XXVII, NH_2⬡R″, would be much more effective than hapten XXII, arsanilic acid, in inhibiting precipitation by antigen XX, R″⬡R″; that this expectation is borne out can be seen from the slopes of the curves of Fig. 6. The data of Table X show that hapten XXIII, HO⬡R, has greater inhibiting effect for antigen X,



than has hapten XXII.

The data of Tables VIII and IX cannot be interpreted so reliably, since the antigen used (VI) is trihaptenic. The observation that hapten XXIII is very much more effective than hapten XXI, phenylarsonic acid, is however to be expected from the structures. We are planning to continue work on hapten inhibition, with the hope of obtaining quantitative information about the relative bond strengths of different haptenic groups with antibody.

We thank the Rockefeller Foundation for financial support of this work. We are indebted also to Dr. Verner Schomaker for helping with the theoretical treatment of antibody-antigen-hapten interactions, and to Mr. Shelton Steinle for carrying out analyses.

Summary

The results are reported of experimental studies of the effect of changed conditions, including time and temperature of precipitation, washing, addition of buffer solution and normal serum, hydrogen-ion concentration, and addition of hapten, on amount of precipitate formed by antisera and simple polyhaptenic antigens of known structure.

A simple theory of antibody-antigen-hapten interaction is formulated on the assumption of the bivalence of antibodies. It is found that this theory provides a reasonable interpretation of the experiments.

PASADENA, CALIFORNIA RECEIVED JULY 6, 1942

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 887]

The Serological Properties of Simple Substances. III. The Composition of Precipitates of Antibodies and Polyhaptenic Simple Substances; the Valence of Antibodies

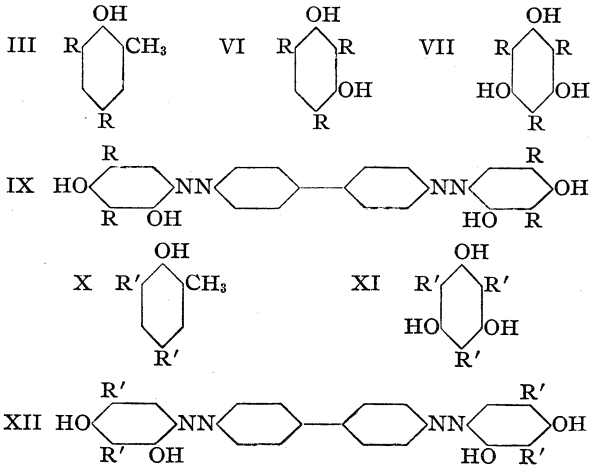
BY LINUS PAULING, DAVID PRESSMAN, AND CAROL IKEDA

The antibody–antigen mole ratio of precipitates formed by interaction of antigens and homologous antisera provides information about the relative combining powers or "valences" of antigen and antibody molecules. For protein antigens it has been found by Heidelberger and co-workers[1] and by other investigators[2] that the antibody–antigen mole ratio is greater than unity, and increases from the antigen-excess region (where the values approach unity) through the equivalence zone to the antibody-excess region, the values for the last region being nearly twice those for the equivalence zone. These results, which show that the effective valence of the protein antigen molecules is greater than that of the antibody molecules, have been accounted for in a reasonable way by the framework theory and the postulate that antibodies which act as precipitins are bivalent.[3] Since the mole ratio gives only the relative valences of antigen and antibody, and information about the valence of protein antigens is in general not at hand, these data do not directly provide information about the valence of the antibodies; but similar data for simple antigens of known structure should give this information. In this paper, the third in a series of studies of the serological properties of simple substances,[4] we present and discuss the results of about 400 analyses of precipitates formed by antibodies and polyhaptenic substances.

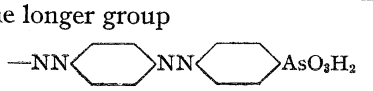
Experimental Methods.—The preparation of antigens and antisera and the techniques of precipitation and analysis have been described in the first paper of this series.

A series of tests was made to determine the extent to which the dyes used in the investigation might be non-specifically carried down with the specific precipitates. In each test 1 ml. of dye solution in borate buffer solution of *p*H 8 was added to 1 ml. of buffer solution containing 1 mg. ovalbumin; 1 ml. of antiovalbumin rabbit serum was then added, the tube was allowed to stand one hour at room temperature and overnight in the refrigerator, and the precipitate was then centrifuged down, washed three times with 10-ml. portions of saline solution, and analyzed for dye and protein. Six tests, with amount of dye increasing by threefold steps from 4 to 1000 μg., were made with each of the dyes III, VI, IX, X, XI, and XII. The amount of dye found in the precipitate was about 3 μg., exceeding this value only for the two largest amounts of added dye (1000 and 333 μg.). Since the amount of precipitated antibody in each test, about 6 mg., corresponds for specific precipitation to about 30 to 70 μg. of dye, a possible error of about 4 to 10% because of non-specific coprecipitation of dye is indicated.

Values of the Antibody-antigen Mole Ratio for Simple Antigens.—Many experiments were carried out in which equal volumes of antiserum were mixed with antigen solutions containing varying amounts of the dye. The following seven dyes were used



with R the short haptenic group —NN⟨⟩AsO_3H_2 and R′ the longer group



In most of the experiments no difference in

(1) M. Heidelberger, THIS JOURNAL, **60**, 242 (1938).

(2) See the summary of results given by J. R. Marrack, "The Chemistry of Antigens and Antibodies," His Majesty's Stationery Office, London, 1938, p. 161.

(3) L. Pauling, THIS JOURNAL, **62**, 2643 (1940).

(4) L. Pauling, *et al.*, *ibid.*, **64**, 2994 and 3003 (1942).

composition was found to within the estimated reliability of the results (about ±10%) for precipitates obtained in the entire range from antigen excess to antibody excess. Data for three series of tests are represented in Fig. 1. It is seen that in these three series, two of which cover the range from antigen excess (at the right) to antibody excess, there is evidenced no significant trend of the mole ratio.

In Tables I to VI there are given the averaged values of the mole ratio for the forty-three series of tests carried out, with a description of the conditions for each series. The mean deviation of the ratios from the average for each series is also given. The average of all tests for each antigen and the mean deviation from the average are shown at the bottom of the corresponding table. The mean deviations give an indication of the probable reliability of the results.

In three series the hydrogen-ion concentration was varied from about *p*H 7.8 to *p*H 9.2 for the supernate; no significant correlation with the mole ratio was detected, and the values were averaged for inclusion in the tables.

The mole ratio values given in Tables IV, V, and VI show especially pronounced variation. We have not detected any reliable correlation with the changed test conditions, nor found any explanation of the variation.

In a few series, notably the two for antigen IX, a pronounced decrease of the mole ratio with decrease in the amount of added antigen was found. This behavior, which is the opposite to that shown by protein antigens, is hard to understand; and we plan to study it further, checking especially the possibility of some so far undetected source of error.

Discussion.—The most extensive and consistent set of analyses, that for the trihaptenic antigen VI (Table I), gave the average value 0.85 ± 0.11 for the antibody-antigen mole ratio. The same average, 0.85, is obtained by adding to the 186 analyses for this antigen the 53 analyses made for the other trihaptenic antigens XI and VII (Tables II and III).

The interpretation of this number requires an assumption as to the number of haptenic groups of the dye which are effective in forming bonds with antibody molecules. If all three of the haptenic groups were thus effective, the valence of the antibody would be given by the observed ratio as 3/0.85 = 3.5. But the observations indicate

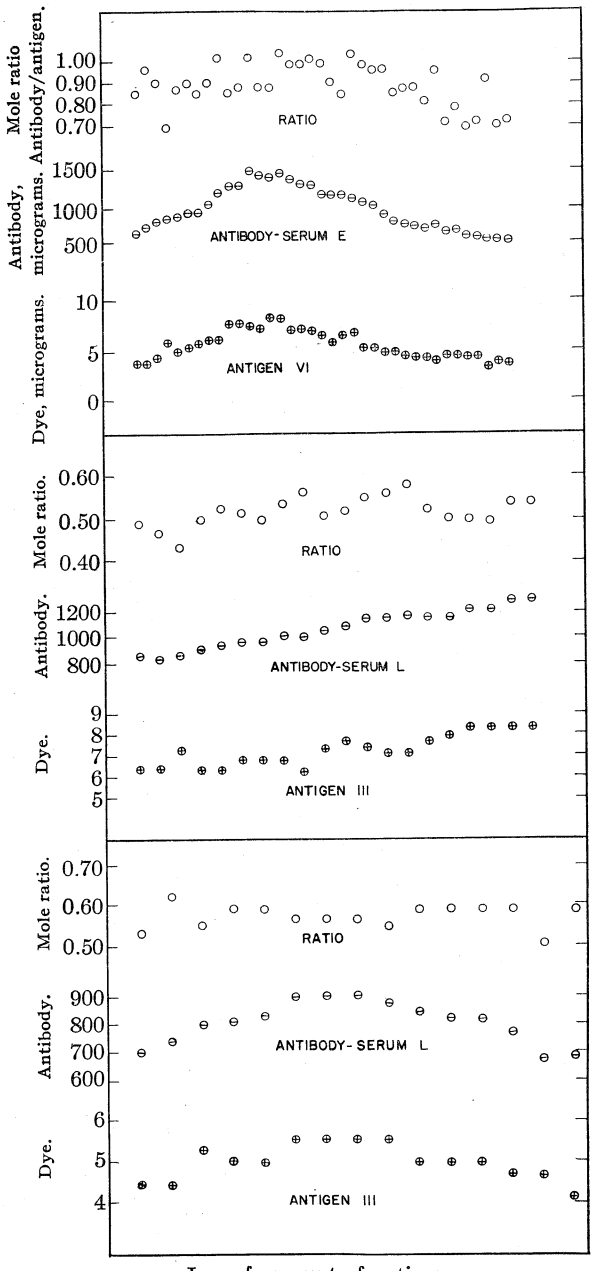


Fig. 1.—Values of (from bottom up) amount of antigen (micrograms) in precipitate, amount of antibody (micrograms) in precipitate, and antibody-antigen mole ratio. The three series of tests correspond to line 1 of Table I (top), line 6 of Table IV (middle), and line 7 of Table IV (bottom). The horizontal scale is the logarithm of the amount of antigen used, with the maximum at the left.

in several ways that the haptenic groups are not all effective. First, the average ratio from the 119 analyses for the dihaptenic dyes is 0.75, and that from the 44 analyses for the tetrahaptenic dyes is 0.83; and these numbers differ from the value for the trihaptenic dyes by much less than

TABLE I

ANTIBODY-ANTIGEN MOLE RATIO FOR TRIHAPTENIC ANTIGEN VI

Antiserum	Antigen solution[a]	Buffer	*p*H of supernate	Number of analyses	Mole ratio antibody/antigen
E, 3 ml.	3 ml., 75 to 13 μg.		8.1–8.2	37	0.88 ± 0.10
E, 3	3 ml., 110 to 14		8.2	25	.94 ± .09
H, 10	5 ml., 167 to 10	10 ml., *p*H 9.0	8.8	8	.88 ± .07
H, 7	5 ml., 75	7 ml., 7.0 to 10.0	7.8 to 9.2	7	.88 ± .06
H, 10	5 ml., 165 to 15	10 ml., 8.5	8.4	7	.79 ± .08
F, 7.5	7 ml., 105 to 21	20 ml., 9.0	8.8	4	.96 ± .01
F, 7.5	14 ml., 100 to 20	20 ml., 9.0	8.8	4	.93 ± .02
C, 2	2 ml., 100 to 12.5		8.4	8	.71 ± .08
C, 3[b]	3 ml., 75		8.1	24	.90 ± .05
E, 2[b]	2 ml., 50		8.1	5	.87 ± .07
E, 3[c]	3 ml., 38		8.0–8.3	14	.84 ± .04
E, 3[d]	3 ml., 75 to 22	3 ml., 7.0	7.6–7.7	8	.70 ± .04
E, 3[d]	3 ml., 75 to 22	3 ml. saline	8.1–8.2	7	.90 ± .07
E, 3[d]	3 ml., 75 to 22	3 ml., 8.0	8.1	8	.69 ± .05
E, 3[d]	3 ml., 75 to 22	3 ml., 9.0	8.8–8.9	8	.61 ± .06
R, 5	5 ml., 167 to 22		8.0	12	.71 ± .08
			Average of 186 analyses		**0.85 ± 0.11**

[a] In this and succeeding tables there are shown in this column the volume of solution and the amount of antigen contained in it. The notation "75 to 13 μg." in the first row, for example, indicates that these are the limiting values of the sequence of 37 differing by a constant factor (in this case 1/1.05). Unless otherwise indicated, the antigen solutions were made by dissolving the antigen in saline solution with sodium carbonate added to bring the *p*H to about 8.5. [b] From Table I of paper II. [c] From Table II of paper II. [d] From Table V of paper II.

TABLE II

ANTIBODY-ANTIGEN MOLE RATIO FOR TRIHAPTENIC ANTIGEN XI

Antiserum	Antigen solution	Buffer	*p*H of supernate	Number of analyses	Mole ratio antibody/antigen
J, 10 ml.	10 ml., 200 to 7.4 μg.	10 ml., *p*H 9.0	8.9	8	0.97 ± 0.05
J, 10	10 ml., 222 to 13	10, 9.0	8.9	9	.85 ± .13
J, 10	10 ml., 149 to 45	10, 9.0	8.9	4	.84 ± .09
J, 10	10 ml., 200 or 149	10, 7.0 to 10.0	7.7 to 9.4	8	.95 ± .10
C, 1	1 ml., 200 to 6.25		8.5	12	.87 ± .09
			Average of 41 analyses		**0.90 ± 0.07**

TABLE III

ANTIBODY-ANTIGEN MOLE RATIO FOR TRIHAPTENIC ANTIGEN VII

Antiserum	Antigen solution	Buffer	*p*H of supernate	Number of analyses	Mole ratio antibody/antigen
K, 3 ml.	3 ml., 67 to 6 μg.		7.8	6	0.72 ± 0.14
K, 3	3 ml., 67 to 9	3 ml., *p*H 9.2	8.8	6	.69 ± .11
			Average of 12 analyses		**0.71 ± 0.13**

TABLE IV

ANTIBODY-ANTIGEN MOLE RATIO FOR DIHAPTENIC ANTIGEN III

Antiserum	Antigen solution	Buffer	*p*H of supernate	Number of analyses	Mole ratio antibody/antigen
H, 20 ml.	10 ml., 360 to 105 μg.	20 ml., *p*H 8.5	8.5	4	0.99 ± 0.10
H, 10	5 ml., 167 to 33	10 ml., 9.0	8.8	5	1.19 ± .12
H, 10	10 ml., 222	10 ml., 7.0–9.5	7.7–9.1	5	0.85 ± .10
K, 5	5 ml., 67 to 11		7.9	11	.76 ± .04
K, 3	3 ml., 67 to 11[a]		8.8	11	.58 ± .05
L, 5	5 ml., 167 to 65		7.9	20	.51 ± .03
L, 5	5 ml., 167 to 65[a]		8.8	15	.57 ± .03
L, 5	10 ml., 125 and 55		7.9	2	.69 ± .01
L, 5	10 ml., 125 to 55[a]		8.8	3	.73 ± .02
M, 10	10 ml., 220 to 46		8.2	8	1.18 ± .16
N, 10	10 ml., 167	10 ml., 8.0	7.9	3	0.71 ± .02
O, 15	15 ml., 250	15 ml., 8.0	7.9	3	.60 ± .08
P, 15	15 ml., 375	15 ml., 8.0	7.9	2	.81 ± .08
Q, 5	5 ml., 158	5 ml., 8.0	7.9	3	.73 ± .00
			Average of 95 analyses		**0.73 ± 0.17**

[a] Antigen dissolved in buffer, *p*H 9.2.

TABLE V

ANTIBODY-ANTIGEN MOLE RATIO FOR DIHAPTENIC ANTIGEN X

Antiserum	Antigen solution	Buffer	pH of supernate	Number of analyses	Mole ratio antibody/antigen
F, 2.5 ml.[a]	5 ml., 100 μg.	7.5 ml., pH 9.0		17	0.93 ± 0.08
O, 2	2 ml., 200 to 19		9.0	7	.54 ± .09
			Average of 24 analyses		**0.82 ± 0.16**

[a] From Table III of paper II.

TABLE VI

ANTIBODY-ANTIGEN MOLE RATIO FOR TETRAHAPTENIC ANTIGENS IX AND XII

Antiserum	Antigen solution	pH of supernate	Number of analyses	Mole ratio antibody/antigen
C, 2 ml.	2 ml., 100 to 12.5 μg. antigen IX	8.4	8	1.20 ± 0.15
R, 5	5 ml., 167 to 22 μg. antigen IX	8.0	12	0.98 ± .25
C, 2	2 ml., 200 to 6.25 μg. antigen XII		12	.87 ± .06
R, 5	5 ml., 167 to 22 μg. antigen XII	8.0	12	.40 ± .06
		Average of 44 analyses		**0.83 ± 0.25**

the 33⅓% which could be expected if all of the haptenic groups were effective, the antibody valence remaining constant. Second, if all three haptenic groups of a trihaptenic dye were able to form bonds with different antibody molecules a pronounced change in composition of the precipitate with change of the total antibody-antigen ratio for the system would be expected, and this is not observed. For bivalent antibody and trivalent antigen the expected values of the antibody-antigen ratio are 1.0 for antigen excess, 1.5 for the equivalence zone, and 2.0 for antibody excess.[3] Such change in composition is observed for protein antigens; but it did not appear, to within the estimated probable error of the work, in any of our series (illustrated by that for antigen VI shown in Fig. 1).

It is, moreover, not unreasonable that the number of antibody molecules to which a small antigen molecule can be bonded should be limited. If, as has been postulated,[3] the bond between dye and antibody is formed by the insertion of the haptenic group into a complementary cavity in the antibody molecule (Fig. 2), then it might well occur that two antibody molecules attached to a dye molecule would by steric interference prevent others from attaching themselves to the other haptenic groups of the dye molecule. If this were to hold for every dye molecule the antibody-antigen ratio for bivalent antibodies would be 1.

Even with the minimum effective antigen valence, 2, compatible with the framework theory, the valence of the antibody molecules must be taken greater than 2 to account for the observed values less than unity for the mole ratio. The possibility that dye not specifically bonded to antibody is carried down with the precipitate was tested as described above, and it was found that about 3 μg. of dye per 6000 μg. of precipitated antibody was carried down by ovalbumin-antiovalbumin precipitates. If a corresponding 10% correction were made, the antibody-antigen ratios (for specifically precipitated dye) would become 0.83, 0.93 and 0.91, which are still less than unity. It is, of course, possible that the non-specific precipitation of dye is somewhat greater, but it seems more probable that the extra dye molecules are held by specific hapten-antibody bonds, as discussed below.

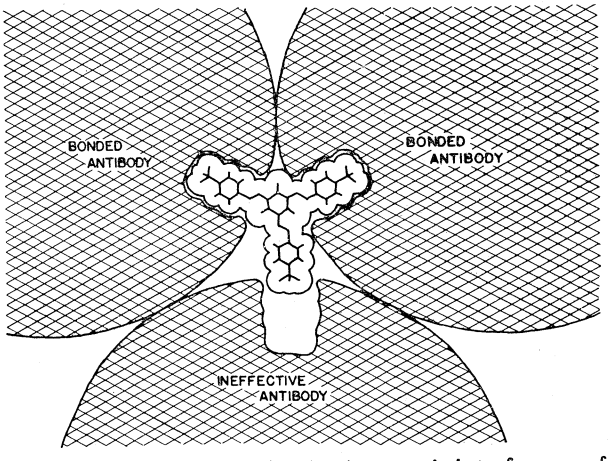


Fig. 2.—Scale drawing showing how steric interference of antibody molecules might prevent a trihaptenic dye from combining with more than two antibody molecules. The radius of curvature of the antibody molecules as drawn is 30 Å.

The calculation of the antibody valence on the basis of this assumption is not straightforward. If each dye molecule were to use two haptenic groups in bond formation the antibody valence given by the ratios would be 2/0.75 = 2.7 for

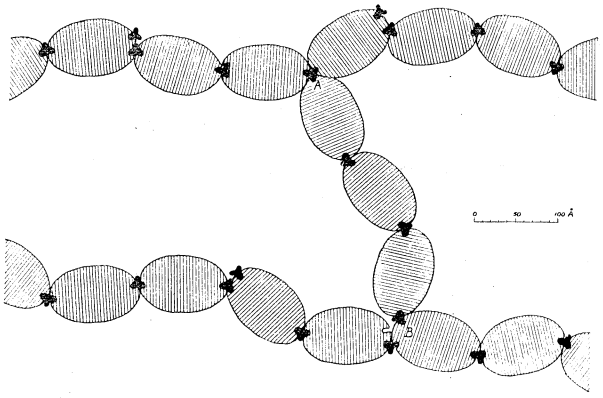


Fig. 3.—Scale drawing representing the structure of the precipitate formed by antibody and an antigen such as VI, $C_6H(OH)_2(NNC_6H_4AsO_3H_2)_3$, as indicated by the experimental results. Most of the antibody molecules are bivalent, and most of the antigen molecules use only two of their three haptenic groups for forming bonds with antibodies. Two long chains are shown, and a short connecting chain. This is attached at A to an antigen molecule bonded to three antibody molecules—a structural feature expected to be rare because of steric interference of the antibody molecules. The bond at B is to a trivalent antibody. There are four other trivalent antibodies, three with extra antigens attached, leading to the antibody-antigen ratio 0.85.

the precipitates with dihaptenic dyes, 2/0.85 = 2.3 for those with trihaptenic dyes, and 2/0.83 = 2.4 for those with tetrahaptenic dyes. If, on the other hand, extra dye molecules were held by a single bond to dye-antibody chains the increased antibody valence over 2 would need to be only one-half as great, and the antibody valence would be calculated to be 2.3, 2.2, and 2.2, respectively.

It seems not unlikely that some antibodies have more than two regions complementary to the haptenic group. Even if, as has been postulated,[3] only two parts of an antibody molecule assume configurations complementary to a portion of the surface of the immunizing antigen, this portion might include, in the case of an azoprotein, two or more haptenic groups, so that the resultant antibody molecule would be able to interact with three haptenic groups or more.

The picture of the antibody-dye precipitates indicated by our data is thus the following. Only two of the haptenic groups of a dye are ordinarily effective in reacting with antibody, others being presumably inhibited by steric interference of the attached antibody molecules. The effective valence of the antibody molecules is also usually 2, but some of these molecules, with three or more hapten-complementary regions, form bonds with additional dye molecules, causing the antibody-antigen mole ratio to fall below unity. Figure 3 illustrates various aspects of this picture.

We thank the Rockefeller Foundation for support of the work reported in this paper, and Mr. Shelton Steinle and Mrs. Elizabeth Swingle for carrying out analyses.

Summary

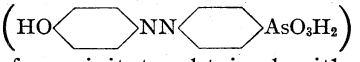
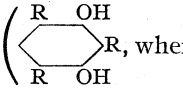
Many analyses of precipitates between dyes containing azophenylarsonic acid groups and hapten-homologous antisera have been made, leading to the average antibody-antigen mole ratios 0.75 for dihaptenic dyes, 0.85 for trihaptenic dyes, and 0.83 for tetrahaptenic dyes. The approximate equality of these values is interpreted as resulting from the limitation to 2 of the effective valence of polyhaptenic dyes by the steric interference of attached antibody molecules, and the approximation of the values to unity is taken to indicate bivalence of most of the antibody molecules.

PASADENA, CALIFORNIA RECEIVED JULY 6, 1942

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 907]

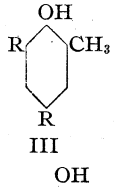
The Serological Properties of Simple Substances. IV. Hapten Inhibition of Precipitation of Antibodies and Polyhaptenic Simple Substances

BY DAVID PRESSMAN, DAVID H. BROWN, AND LINUS PAULING

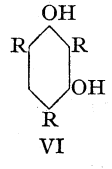
As part of a series of studies of the antigen-antibody reaction by use of polyhaptenic simple substances as antigens,[1,2,3] we have made a quantitative investigation of the ability of various substituted phenylarsonic acids to inhibit the precipitation of compounds containing two or more phenylarsonic acid groups with antiserum to sheep serum coupled with diazotized *p*-arsanilic acid.[4] The investigation included study of the effect of various concentrations of hapten XXIII  on the amount of precipitate obtained with antiserum and various concentrations of antigen VI  , where R is the *p*-azophenylarsonic acid group); the effect of changed conditions of precipitation for the same system; the effects of four haptens on the precipitation of each of five antigens and each of two pools of antiserum; and the effects of 24 different haptens on one precipitin reaction. The results are discussed in this paper.

Experimental Methods

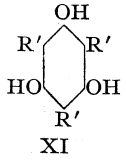
Simple Antigens and Haptens.—The substances used are the polyhaptenic compounds



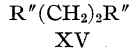
III



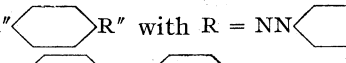
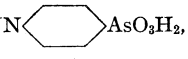
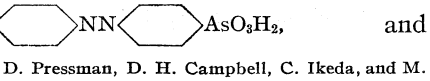
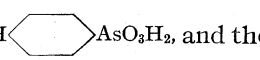
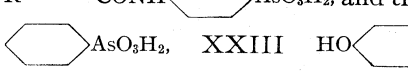
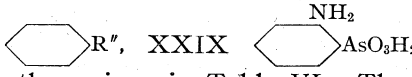
VI



XI



XV

and XX  with R =  , R′ =  , and R″ = —CONH  , and the haptens XXI  , XXIII , XXVIII  , XXIX , and twenty others given in Table VI. The preparation of most of these substances has already been described[1] or will be discussed elsewhere.[5]

***p*-Benzoylaminophenylarsonic acid** was prepared from *p*-arsanilic acid and benzoyl chloride by the Schotten–Baumann reaction. The product was precipitated with hydrochloric acid and purified by extraction with boiling ethanol.

***p*-Acetaminophenylarsonic acid** was prepared from *p*-arsanilic acid and acetic anhydride in basic solution. The compound was purified by precipitation with hydrochloric acid and recrystallization from boiling water.

Antisera to sheep serum coupled with diazotized arsanilic acid were prepared as previously described, with use of the same rabbits.

Method of Analysis.—Each precipitate was centrifuged and washed thoroughly with three 10-ml. portions of 0.9% saline solution at room temperature. The amount of protein in the precipitate was determined with the Folin–Ciocalteu reagent[6] by a modification to be discussed elsewhere.

Buffer.—The borate buffer of *p*H 8.0 was prepared by adding 0.16 *N* sodium hydroxide solution to 0.2 *M* boric acid in 0.9% sodium chloride solution. The antigen and hapten solutions were all diluted with this buffer.

TABLE I

EFFECT OF STANDING AT ROOM TEMPERATURE AND IN THE REFRIGERATOR ON AMOUNT OF PRECIPITATE OBTAINED IN THE PRESENCE OF HAPTEN

Analyses for 5-ml. aliquots of a mixture of equal volumes of serum S, antigen VI (25 μg./ml.), and hapten XXIII (60/μg.(ml.). *p*H of all supernates 8.2.

Time at room temp.	Nights in refrigerator	Amount of precipitated antibody, μg.
0	1	125 131 138
0	2	131 131 144
¾ hour	1	125 125 131
¾ hour	2	131 144 144
2 hours	1	106 106 144
2 hours	2	106 119 125 125 125 138
Overnight	0	63 63 63
Overnight	1	94 100 100 106
Hapten replaced by buffer		
2 hours	2	810

(1) L. Pauling, D. Pressman, D. H. Campbell, C. Ikeda, and M. Ikawa, THIS JOURNAL, **64**, 2994 (1942).

(2) L. Pauling, D. Pressman, D. H. Campbell, and C. Ikeda, *ibid.*, **64**, 3003 (1942).

(3) L. Pauling, D. Pressman, and C. Ikeda, *ibid.*, **64**, 3010 (1942).

(4) The first experiments on the precipitation of polyhaptenic simple substances by antisera and its inhibition by haptens were carried out by K. Landsteiner and J. van der Scheer, *J. Exp. Med.*, **56**, 399 (1932).

(5) D. Pressman and D. H. Brown, to be published.

(6) O. Folin and V. Ciocalteu, *J. Biol. Chem.*, **73**, 627 (1927).

The Effect of Changed Conditions on Amount of Precipitate.—In order to observe the effect of standing on the amount of precipitate obtained in the presence of hapten, equal volumes of serum S, antigen VI (25 μg./ml.), and hapten XXIII (60 μg./ml.) were mixed and 5-ml. aliquots of the mixture were permitted to stand zero, three-quarters, or two hours or overnight at room temperature and were then placed in the refrigerator at 3° over zero, one, or two nights. The amount of precipitate obtained in each test was about 15% of that obtained in the absence of hapten. The results are given in Table I.

Only when the tubes stood overnight at room temperature without subsequent refrigeration was a significant decrease in the amount of precipitate observed. This effect was also observed with specific precipitates in the absence of hapten.[2] A slight decrease was observed when the tubes stood overnight at room temperature and then overnight in the refrigerator.

TABLE II

INHIBITION OF PRECIPITATION OF ANTISERUM S AND ANTIGEN VI BY HAPTEN XXIII

Antigen solution, hapten solution, and antiserum, 1 ml. each; 2 hours at room temperature, overnight in refrigerator. Blanks of antiserum and buffer: 0, 0, 0 μg. *p*H of all supernates 8.2.

Amount of hapten, μg.	Amount of antigen, μg. 6.3	12.5	25	50	100
	Amount of antibody precipitated, μg.[a]				
0	122	335	660	305	(144)
4.1	(131)	262	356	181	131
8.3	125	212	285	147	106
16.5	88	163	178	109	103
31	41	94	116	72	
63	9	41	31	35	(31)
125	6	6	19	12	12
250	0	0	3	0	3
500	0	0	6	0	3

[a] Values are averages of duplicate analyses, with mean deviation of ±5% from the averages, except for the values in parentheses, which represent single analyses.

The Effect of Various Amounts of Hapten XXIII on Amount of Precipitate Obtained with Various Amounts of Antigen VI.—The results of the study of inhibition by hapten XXIII of the precipitation of antigen VI are given in Table II. As previously observed with phenylarsonic acid as the hapten,[2] the optimum zone does not shift significantly with increasing amounts of hapten.

Experiments on the Relative Inhibiting Powers of Different Haptens.—Since the effect of hapten inhibition is most easily given theoretical interpretation in the antigen–antibody equivalence zone, experiments were carried out with antiserum pools S and T to determine the optimum zones (which may be taken as the equivalence zones) for antigens III, VI, XI, XV, and XX. The results are given in Table III. It is seen that antiserum S contained much more antibody than T. As previously observed,[1] antigen XI, with long haptenic groups, gave much larger amounts of precipitate than the others. It is interesting, as an example of the variability of antisera, that antigen XX gave more precipitate than antigens III, VI, and XV with antiserum T but less with antiserum S.

Hapten inhibition experiments were then carried out with haptens XXI, XXIII, XXVIII, and XXIX and these five antigens in the optimum zones for the individual antigens with each of the antisera S and T. The results are given in Tables IV and V.

Experiments were also carried out with antiserum S and antigen VI at the optimum concentration in the presence of each of twenty-four haptens at various concentrations, with the results shown in Table VI.

Discussion

The data on hapten inhibition given in the foregoing tables can be most effectively discussed by comparison with the simple theory developed in a preceding paper of this series.[2] It was shown that for the system postulated, with both antigen and antibody assumed to be bivalent, a plot of the amount of antibody precipitated, for the case

TABLE III

PRECIPITATION OF ANTISERA S AND T AND FIVE ANTIGENS

Antigen solution 0.5 ml.; antiserum, 0.5 ml.; 1 hour at room temperature and overnight in refrigerator.

	Amount of antigen used, μg. 4.7	6.2	8.0	10.4	13.5	17.5	22.8	29.6	38.5	50
	Amount of antibody precipitated, μg.[a]									
Antiserum S										
Antigen III	194	228	303	(275)	306	226	191	169	135	(106)
VI	101	157	278	426	372	263	(156)	85	69	32
XI	147	226	291	438	603	859	1070	1410	1340	1300
XV	(138)	160	(187)	178	125	115	(75)	47	32	28
XX	(69)	100	97	107	54	47	28	28	22	22
	Blanks of antiserum and buffer: 0, 0, 0. *p*H of supernates 8.2									
Antiserum T										
Antigen III	10	16	0							
VI	47	42	10							
XI	153	(187)	253	319	438	500	460	472	469	359
XV	0	19	22	13	13					
XX	88	63	63	56	81	41	44	28	50	31
	Blanks of antiserum and buffer: 0, 0, 0. *p*H of supernates 8.3									

[a] Averages of duplicate analyses, with mean deviation ±7%; single analyses in parentheses.

TABLE IV

HAPTEN INHIBITION OF PRECIPITATION OF ANTISERUM S AND ANTIGEN

Antigen solution, hapten solution, and antiserum, 1 ml. each; overnight at room temperature and overnight in refrigerator. Blanks of antiserum and buffer: 0, 0, 0 μg. *p*H of all supernates 8.2.

Antigen, μg.	Hapten	Amount of hapten, μg. 0	1.95	3.9	7.8	15.6	31.3	62.5	125	250
		Amount of antibody precipitated, μg.[a]								
III	XXI	540	522	488	(456)	413	394	365		241
25	XXIII		468	488	(438)	285	257	181	113	50
	XXVIII		563	541	479	410	(406)	276	219	166
	XXIX		528	538	525	507	463	432	403	378
VI	XXI	556	500	432	369	266	191	147	101	97
25	XXIII		485	363	254	127	91	47	6	0
	XXVIII		457	397	319	213	122	60	28	6
	XXIX		528	519	488	441	362	294	222	197
XI	XXI	2310	2290	2160	(2070)	1935	1640	1400	1360	1090
59	XXIII		2255	2130	1955	1585	1170	794	416	194
	XXVIII		2285	2190	1860	1800	1320	970	663	435
	XXIX		2410	2330	2280	2210	2115	(2060)	1740	1490
XV	XXI	386	416		347	307	332	225	188	119
25	XXIII		366	347	228	131	79	37	16	0
	XXVIII		360	363	310	225	178	88	41	13
	XXIX		388	(400)	(419)	(425)	402	347	366	385
XX	XXI	167	194	178	178	169	147	125	94	60
16.7	XXIII		135	125	88	50	37	6		0
	XXVIII		141	125	106	63	37	6	0	0
	XXIX		190	181	181	147	141	125	116	94

[a] Averages of duplicate analyses, with mean deviation ±3%; single analyses in parentheses.

TABLE V

HAPTEN INHIBITION OF PRECIPITATION OF ANTISERUM T AND ANTIGEN

Antigen solution, hapten solution, and antiserum, 3 ml. each for antigen VI, 2 ml. for XI and XX; 2 hours at room temperature and overnight in refrigerator. Blanks of antiserum and buffer: 0, 0, 0 μg. *p*H of all supernates 7.8–7.9.

Antigen, μg./ml.	Hapten	Concentration of hapten solution, μg./ml. 0	1.95	3.9	7.8	15.6	31.2
		Amount of antibody precipitated, μg.[a]					
VI	XXI	373	353	(325)	254	197	(119)
10	XXIII		353	347	294	185	63
	XXVIII		303	178	57	22	3
	XXIX		356	344	291	244	166
XI	XXI	1320	1220	1110	832	804	581
61	XXIII		1245	1150	950	715	532
	XXVIII		1210	844	675	478	313
	XXIX		1155	1050	885	819	675
XX	XXI	491	516	472	(488)	438	485
6.3	XXIII		481	495	460	378	400
	XXVIII		485	466	422	354	222
	XXIX		479	485	479		446

[a] Averages of duplicate analyses, with mean deviation ±3%; single analyses in parentheses.

of equivalent amounts of antigen and antibody, against the amount of hapten present should be a straight line. Some examples of plots of this sort are given in Fig. 1, taken from the data of Table VI, which correspond to the optimum zones. It is seen that the curves approach the theoretical linear form only at low hapten concentrations; the deviation from linearity at higher concentration we attribute to the heterogeneity of the antiserum, which may contain antibodies with greatly varying combining powers.

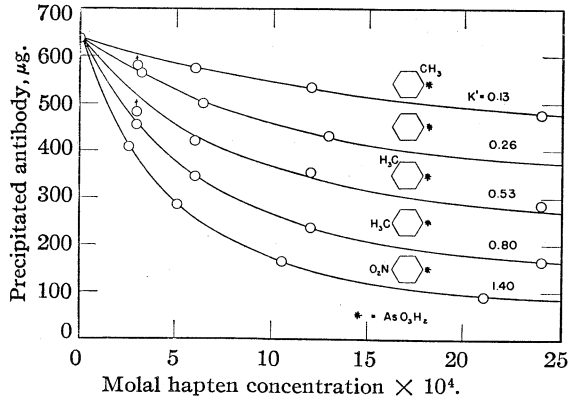


Fig. 1.—Effect of haptens in decreasing the amount of antibody precipitated by the trihaptenic antigen VI. Curves are shown for six of the twenty-four haptens for which data are given in Table VI.

Equation V of the earlier paper,[2] giving the value of the initial slope of the hapten-inhibition curve, may be rewritten in the form

$$-\frac{dH}{d\,AB(pp)} = \frac{C}{K'} + C' \qquad (1)$$

with

$$C = \frac{(Ks + K^2s^2)^{1/2}}{s\{1/2 + Ks + K^2s^2 + (Ks + K^2s^2)^{1/2}\}}$$

and

$$C' = \frac{1 + Ks + (Ks + K^2s^2)^{1/2}}{1/2 + Ks + (Ks + K^2s^2)^{1/2}}$$

Here H is the amount of hapten added, AB(pp) is the amount of antibody precipitated, s is the solubility of the antigen-antibody complex, and K and K' are the bond-strength constants for the antigen-antibody bond and the hapten-antibody bond, respectively. Both C and C' for any antiserum depend only on the antigen and are independent of the hapten. The constant K' is characteristic of the hapten, indicating the strength of the bond between the hapten and the antibody. Thus for any given antiserum and antigen the reciprocal of the rate of decrease of amount of precipitate with increasing amount of hapten is a linear function of the reciprocal of the hapten constant K'.

From the form of Equation 1 we should expect the order of inhibitory activity of various haptens for a given antiserum to be the same for various antigens. This is the case for our experiments. With serum S the order of inhibition was XXIII > XXVIII > XXI > XXIX for each of the five antigens used (Table IV). The order observed for serum T was different; XXVIII > XXIII > XXI > XXIX; but this order was again observed for each of the five antigens (data for antigens VI, XI, and XX are given in Table V; less reliable results obtained for III and XV, not included in the table, also placed the haptens in the same order).

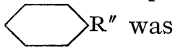
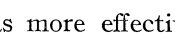
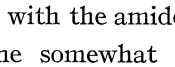
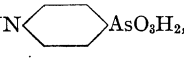
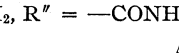
It is surprising that the amide compound  R″ was more effective in inhibition with serum T than was the azo compound HO  R, since the antibodies were produced by inoculation with an azoprotein and would accordingly be expected to combine preferentially with azo groups. Antiserum T was consistent in its greater reactivity with amide groups than with azo groups, insofar as it also gave a larger amount of precipitate with the amide antigen R″  R″ than with the somewhat similar azo antigens

TABLE VI

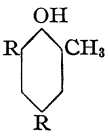
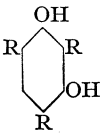
INHIBITION OF PRECIPITATION OF ANTISERUM S AND ANTIGEN VI BY HAPTENS

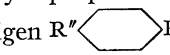
Antigen solution, 1 ml. (25 μg.); hapten solution, 1 ml.; antiserum, 1 ml.; 2 hours at room temperature and 2 nights in refrigerator. * = AsO_3H_2, R = NN  AsO_3H_2, R″ = —CONH  AsO_3H_2.

Hapten	K'	$K_{A_2}{}^a \times 10^9$	Amount of hapten, μg. 1.95	3.9	7.8	15.6	31.3	62.5	125	250
			Amount of precipitated antibody, μg.[b]							
o-$NH_2C_6H_4$*	0.13	2.2	662	550	500	(488)	(463)	375	269	200
o-$CH_3C_6H_4$*	.13	1.4	581	575	535	475	385	354	272	206
1-*-4-$NH_2C_{10}H_6$	.17	0.7	590	(588)	516	432	385	(275)	238	175
1-*-$C_{10}H_7$	.23	2.2	565	532	475	379	347	272	210	182
C_6H_5*	.26	3.3	566	501	432	325	235	169	131	91
o-$NO_2C_6H_4$*	.28	2.9	516	463	447	357	266	213	191	154
m-$NH_2C_6H_4$*	.29	2.4	566	538	387	306	(206)	181	131	119
p-$HOOCC_6H_4$*	.29	3.6	560	447	429	338	241	188	147	122
p-$NH_2C_6H_4$*	.44	1.2	538	(494)	376	276	216	172	128	116
p-$CH_3C_6H_4$*	.53	1.5	479	419	354	285	216	166	144	128
p-HOC_6H_4*	.60	3.9	475	422	372	213	173	134	103	85
2-*-$C_{10}H_7$	.66	3.4	473	388	344	250	182	(144)	116	79
m-$NO_2C_6H_4$*	.75	16	463	372	294	210	166	137	119	106
p-$CH_3C_6H_4$*	.80	2.1	457	344	238	163	144	91	63	41
p-ClC_6H_4*	.80	5.6	450	347	275	188	125	100	72	37
p-BrC_6H_4*	.80	6.5	494	400	285	216	103	106	78	66
p-IC_6H_4*	.80	5.7	(475)	404	297	194	169	131	94	50
C_6H_5R''	.80		541	454	332	225	175	101	50	6
p-$NH_2C_6H_4R''$	.89		559	457	291	194	135	78	34	10
p-$NO_2C_6H_4R''$	.89		513	419	335	216	153	88	41	13
p-HOC_6H_4R	.98		494	391	310	184	119	60	6	0
p-$NH_2C_6H_4R$	1.02		550	(438)	269	160	85	38	0	0
H_3CR''	1.02		451	341	203	141	85	50	19	0
p-$NO_2C_6H_4$*	1.40	16	407	285	163	91	44	16	0	0

Average value for no hapten 638 μg. Control, antiserum and buffer 0, 0, 0, 0 μg. *p*H of all supernates 8.1–8.2.

[a] Second acid dissociation constant.[5] [b] Averages of duplicate analyses, with mean deviation ±3%; single analyses in parentheses.


and

(Table III). This is the reverse of the behavior observed for serum S and the antisera tested previously.[1]

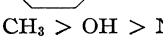
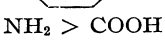
Another example of the variability in properties of the antisera is that the amide antigen  gave more precipitate than the other amide antigen $R''(CH_2)_2R''$ with serum T but less with serum S.

In order to obtain from the data of Table VI numbers representing the inhibiting power of the twenty-four haptens, the following treatment was used. Plots were made of the amount of precipitated antibody for each hapten as a function of the number of moles of hapten added, as illustrated in Fig. 1. Smoothed curves were drawn through the points, and the initial slopes were read from the curves. Some consideration was given to the course of the curve throughout the range of concentration covered by the experiment in determining the value of the initial slope, with use of a family of curves deduced from the whole set of data. Plots against the log of hapten concentration were also used. The reciprocals of the negative slopes $-\mathrm{d}\,AB(\mathrm{pp})/\mathrm{d}\,H$ are given in Table VI, under the heading K'. These reciprocals would be proportional to K' if the value of C' in Equation 1 were negligible compared to the other term. In any case these numbers would be expected to represent qualitatively the combining power of the haptens with antibody. A constant factor was introduced such that the average value of K' for the two azo haptens became unity.

Many interesting correlations of the values of K' with the molecular structure of the haptens can be observed. The effects of a substituent on the bond-strength constants of the substituted phenylarsonic acid molecules are seen to be dependent both on the position of the substituent in the benzene ring and on the nature of the substituent. It would also be expected that, aside from direct structural effects, the constituents would be of influence through their effect on the second dissociation constant of the acids. The antibodies, produced presumably in about neutral solution in the animal, probably have combining groups for both singly ionized and doubly ionized arsonic acid molecules. The combining power of the latter is probably greater than that of the former because of the stronger forces resulting from the doubled electric charge,[7] as has been pointed out by Haurowitz.[8] Accordingly it would be expected that increase in the second dissociation constant of the acid, leading to increase in the number of doubly charged ions present, would lead to increase in bond-strength constants with the antibody. There are given in Table VI values of the second ionization constant for eighteen of the haptens.[5] It is seen that the correlation with K' is not very striking.

The ortho-substituted phenylarsonic acids are seen to be, with one exception (the *o*-nitro acid), the least effective of all in combining with antibody. An α-naphthyl residue is about equivalent to an ortho-substituted benzene ring. Meta-substituted compounds are somewhat more effective in general than phenylarsonic acid, and para-substituted compounds are still more effective. β-Naphthylarsonic acid is intermediate between the meta- and para-substituted phenylarsonic acids.

All of the para-substituted phenylarsonic acids are more effective in inhibition than phenylarsonic acid itself. This increased effectiveness on replacement of the para hydrogen atom by a larger atom or group is presumably the result of increased van der Waals interaction between the substituent and the antibody. The order of effectiveness of the para substituents in increasing the value of the constant K' is

$$NO_2 > CH_3CONH > \text{  } > \text{  } > \text{Cl, Br, I, } CH_3 > OH > NH_2 > COOH > H$$

The same order holds also in the ortho and meta positions for the substituents NO_2, CH_3, and NH_2, data not having been obtained for others.

Whereas replacement of a hydrogen atom in the para position by a substituent group always leads to an increase in the value of K', this is not so for the ortho position. Both *o*-methylphenylarsonic acid and *o*-aminophenylarsonic acid, as well as the α-naphthyl compounds, are less effective in inhibition than phenylarsonic acid itself. This difference in behavior from the para-substituted compounds is attributed to steric effects. The immunizing antigen, a protein with attached *p*-azophenylarsonic acid groups, gives rise to

(7) This may be responsible for the fact that the maximum amount of precipitate with variation of *p*H is obtained at *p*H 8, instead of at about 7, which presumably prevails at the site of antibody formation.

(8) F. Haurowitz, *Z. physiol. Chem.*, **245**, 24 (1937).

antibodies which are molded to the *p*-azophenylarsonic acid group, and which in general do not allow sufficient space for a larger group than hydrogen in the ortho position. On the other hand, a para substituent may fit into the space provided for the azo nitrogen atoms, and so by increased van der Waals attraction for the antibody makes the hapten more effective than phenylarsonic acid itself.

The most striking and unexpected observation is that the nitro group in any position in the benzene ring causes a large increase in the bond-strength constant over the value for any other substituent in the same position. For the ortho compound this increase is so great as to overcome the steric effect and make the hapten more effective than phenylarsonic acid. The reason for this large effect of the nitro group is not obvious. The second acid dissociation cannot be advanced as the cause, since the value of K_{A_2} for *o*-nitrophenylarsonic acid is less than that of phenylarsonic acid, whereas its value of K' is greater. We suggest that this action of the nitro group is the result of the well-known effect of the group in aromatic compounds in causing increased van der Waals attraction for other molecules, which shows itself in the great ability of aromatic nitro compounds to form molecular compounds with other substances.

It is surprising that haptens containing the amide group —CONH— are nearly as effective as the corresponding haptens containing the azo group —NN—. As mentioned above, for antiserum T the amide group was found to be even more effective than the azo group. It will be interesting to see, by experiments with other pools of antisera, to what extent the order of combining power with antibodies of the haptens listed in Table VI varies with the antiserum used.

In the larger haptens the effect of substituents far removed from the phenylarsonic acid group is small. Thus substitution of an amino or nitro group in the para position in phenylcarbamidophenylarsonic acid leads to an increase of only 10% in the value of K', with the nitro group showing no greater effect than the amino group. Similarly *p*-hydroxyphenylazophenylarsonic acid and *p*-aminophenylazophenylarsonic acid show nearly the same value of K'.

There is now under way an investigation of the inhibition by various haptens of precipitation with simple antigens of antisera made with use of a protein with attached azophenylazophenylarsonic acid groups as the immunizing antigen.

This investigation was carried out with the aid of a grant from the Rockefeller Foundation. Mrs. Elizabeth Swingle, Mr. Frank Lanni, Mr. Stanley Swingle, and Mr. Shelton Steinle assisted with the analyses.

Summary

A study has been made of the inhibiting action of haptens (substituted phenylarsonic acids) on the precipitation of polyhaptenic simple substances containing two or more phenylarsonic acid groups by antiserum obtained by inoculating rabbits with sheep serum coupled with diazotized *p*-arsanilic acid.

It was found that the order of inhibitory activity of four haptens was the same for each of five test antigens with a given antiserum. The order depended on the antiserum used. The antiserum which showed stronger inhibition by amide haptens than by azo haptens also gave larger amounts of precipitate with amide antigens than with azo antigens.

The effect of each of twenty-four haptens on one antigen-antibody reaction was studied, and the data were interpreted to give relative values of the bond-strength constant of the haptens with the antibody. These values are shown to be correlated with the structure of the haptens.

PASADENA, CALIFORNIA RECEIVED AUGUST 10, 1942

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

The Electromotive Force of the Mercurous Bromide Electrode

BY WILLIAM R. CROWELL, RICHARD W. MERTES AND SIMPSON S. BURKE

The present paper deals with the effects of hydrogen, nitrogen, and air on the e. m. f. of the mercurous bromide electrode at 25° in 0.1002 *m* hydrobromic acid, and with measurements of the electrode e. m. f.'s in approximately 1, 2, and 3 normal hydrobromic acid solutions at 25° and 35°. The reference electrode consists of a hydrogen half cell using hydrobromic acid of the same concentration as that in the mercurous bromide compartment. Because of the differences in the values of the molal reduction e. m. f. of the mercurous bromide electrode reported by different investigators and because of the oxygen effect on the calomel electrode e. m. f. reported by Randall and Young[1] it was thought that there might also be a similar oxygen effect in the case of the mercurous bromide. While the mercurous bromide electrode is more sensitive to light than the calomel electrode, if properly prepared it is quite satisfactory in reproducibility and constancy. Although there is considerable formation of bromide complexes in solutions one normal or higher in hydrobromic acid, equilibria are easily obtained in solutions as high as three normal, and electrodes employing concentrations of acid from 0.1–3 *N* may be found to be convenient in certain cases where hydrobromic acid is used and when it is desired to eliminate unknown solution contact potentials.

Experimental

Reagents.—The hydrobromic acid was prepared from three times recrystallized potassium bromide dissolved in sulfuric acid solution. The hydrobromic acid was distilled from this solution, the portion going over between 110° and 127° again distilled and the constant boiling fraction retained.

The hydrogen was generated by electrolysis of a solution of sodium hydroxide. Tank nitrogen obtained from fractionation of liquid air was the source of the nitrogen. Both the hydrogen and the nitrogen were freed of oxygen by passage through chromous chloride solution. The mercury was passed through a dilute nitric acid tower and distilled *in vacuo*.

The mercurous bromide was prepared electrolytically by use of an apparatus which included a gas-stirred mercury anode and a platinum cathode with hydrobromic acid as the electrolyte. With this device the salt was prepared from and washed with acid which was of the same concentration as that used in the cell and which had been previously treated with the gas under investigation. The solution and mixture of mercury and mercurous bromide were then transferred to the mercurous bromide electrode chamber through which the gas being studied had been previously passed for twenty minutes to an hour. Finally the half cell was stoppered and rotated in a thermostat for several hours or until the solution was in equilibrium with the mercury and mercurous bromide. During these processes as well as during the cell measurements described later all light was excluded except that from a red light bulb which was used only when observations and experimental procedures made it necessary.

Cell Measurements.—A diagram of the complete cell is shown in Fig. 1. The mercurous bromide half cell was joined to the hydrogen electrode by means of a ground glass joint. The passages between the two half cells were flushed with hydrogen by use of the float which permitted the flow of gas before establishment of the liquid junction in the three-way stopcock. This junction was then established by sinking the float which was best accomplished by increasing somewhat the flow of hydrogen. Immediately before entering the hydrogen electrode chamber the hydrogen was bubbled through a solution of hydrobromic acid of the same concentration as that in the cell.

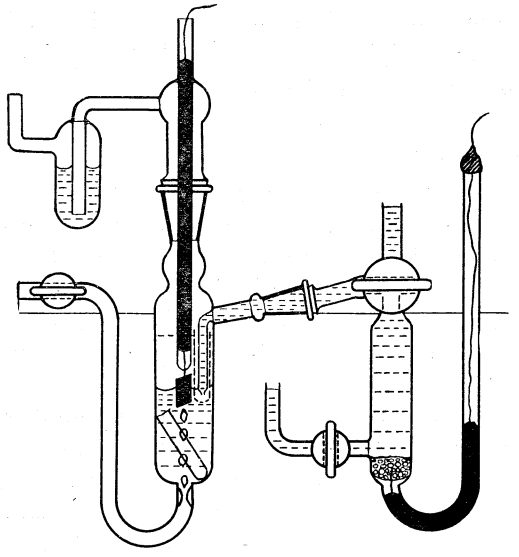


Fig. 1.—Schematic diagram of mercurous bromide–hydrogen cell.

Cell e. m. f.'s were measured by means of a Leeds and Northrup Type K potentiometer. The Weston cell used in adjusting the potentiometer current was checked against an Eppley cell which in turn had been standardized by the Bureau of Standards.

Results

Results are recorded in Tables I and II and are representative averages of several runs made over

(1) Randall and Young, THIS JOURNAL, **50**, 993 (1928).

TABLE I

EFFECT OF AIR ON THE ELECTROMOTIVE FORCE OF THE MERCUROUS BROMIDE ELECTRODE

	Cell e. m. f. at 25° in 0.1002 *m* hydrobromic acid and 1 atm. of hydrogen.			Molal reduction e. m. f. at 25°		
	Hydrogen	Nitrogen	Air	Hydrogen	Nitrogen	Air
Gerke and Geddes[4]	0.2685			−0.1392		
Ishikawa and Ueda[5]			0.26883			−0.1395
Larson[6]						− .1397
Authors	.26841	0.26841	.26889	− .1391	−0.1391	− .1396

a period of more than two years, using independently prepared reagents. Results in 0.1 *N* hydrobromic acid were reproducible within 0.05 millivolt and in the higher acid concentrations within 0.1 millivolt. The e. m. f. readings remained constant for periods ranging from twenty-four to sixty hours. Equilibrium was usually attained in less than three hours.

Table I shows results obtained from measurements made in approximately 0.1 *m* hydrobromic acid using mercurous bromide which had been prepared in an atmosphere of hydrogen, nitrogen, and air. Data of other investigators are shown for comparison with those of the authors. To put all results on the same basis they are corrected to 0.1002 *m* hydrobromic acid and one atmosphere of hydrogen. The molal reduction e. m. f., E^0, was calculated by use of the value of Harned, Keston and Donelson[2] for the mean ion activity coefficient of hydrobromic acid, namely, 0.805, employing the expression

$$E^0 = E - 0.1183 \log C\gamma^{\pm}$$

where E is the e. m. f. of the cell

$$H_2 \text{ (1 atm.)}, \text{ HBr (0.1002 } m\text{)}, Hg_2Br_2, Hg$$

C the concentration of the hydrobromic acid in moles per 1000 g. of water, and $\gamma^{\pm}$ the mean ion activity coefficient of the hydrobromic acid. In the term "molal reduction e. m. f." the sign convention and activity units were the same as those used by Latimer.[3]

A study of the procedures of the different workers indicates that Ishikawa and Ueda, and Larson probably did not insure the complete removal of all air from the solutions used in the preparation of the mercurous bromide, while Gerke and Geddes displaced all air with hydrogen. For this reason, the results of Ishikawa and Ueda and of Larson are placed in the column with the air values and the results of Gerke and Geddes are recorded in the column with the hydrogen values.

A comparison of the results in the table indicates that the electrode molal reduction e. m. f. has an accurately reproducible air free value of −0.1391 ± 0.0001 volt and an air value also accurately reproducible of −0.1396 ± 0.0001 volt. The 0.3 millivolt deviation of the results of Ishikawa and Ueda from those of Gerke and Geddes is probably due to this fact rather than because of greater experimental accuracy as claimed by the former.

Table II shows results of measurements of cell e. m. f.'s at 25 and 35° in approximately one, two, and three normal hydrobromic acid calculated on the basis of one atmosphere of hydrogen. In all these cases the mercurous bromide was prepared from and washed with hydrogen treated acid.

Since the main purpose of these measurements was to obtain data whereby the mercurous bromide electrode could be used as a reference electrode in cells requiring hydrobromic acid at these concentrations, the e. m. f. of the mercurous bromide half cell including a small solution contact e. m. f. was determined for each acid concentration. These e. m. f.'s at 25°, which are not to be confused with the molal reduction e. m. f.'s shown in Table I, are shown in Table II column 5 and were calculated by use of the cell data and hydrobromic acid mean ion activity coefficient values obtained from a curve plotted from data quoted by Harned,[7] employing the expression

$$E_{Hg,\ Hg_2Br_2\ (meas.)} = -E_{cell} - 0.05913 \log C\gamma^{\pm}$$

The values in column 6 which we term "calculated" are those for the half cell which one would obtain by use of the molal reduction e. m. f., E^0, and the activity of the hydrobromic acid, employing the expression

$$E_{Hg,\ Hg_2Br_2\ (calcd.)} = -0.1391 + 0.05913 \log C\gamma^{\pm}$$

TABLE II

E. M. F. OF MERCUROUS BROMIDE ELECTRODE AT HIGHER ACID CONCENTRATIONS

Concn. of HBr		Cell e. m. f. 1 atm. hydrogen		Electrode e. m. f. at 25°C.	
Molal	Normal	25°	35°	Measured	Calculated
1.029	1.000	0.14388	0.14310	−0.14130	−0.14168
2.117	2.002	.09058	.08867	− .11489	− .11480
3.246	2.987	.04845	.04524	− .09402	− .09353

(2) Harned, Keston and Donelson, THIS JOURNAL, **58**, 992 (1936).

(3) W. M. Latimer, "Oxidation Potentials," Prentice-Hall, Inc., New York, N. Y., 1938, pp. 2 and 3.

(4) Gerke and Geddes, *J. Phys. Chem.*, **31**, 886 (1927).

(5) Ishikawa and Ueda, *J. Chem. Soc. Japan*, **2**, 59–66 (1930).

(6) W. D. Larson, THIS JOURNAL, **62**, 765 (1940).

(7) Harned, THIS JOURNAL, **57**, 1867 (1935).

The activity coefficient values taken from the curve were 0.879 for 1.000 N acid, 1.217 for 2.002 N acid, and 1.816 for 2.987 N acid.

From the values in columns 3 and 4 the following expressions were derived for the cell e. m. f., E_t, at any temperature t from the vicinity of 25 to that of 35°

In 1.000 N hydrobromic acid E_t = $0.14388 - 0.000078(t - 25)$

In 2.002 N hydrobromic acid E_t = $0.09058 - 0.000191(t - 25)$

In 2.897 N hydrobromic acid E_t = $0.04845 - 0.000321(t - 25)$

In these acid solutions as the concentration increases there is a tendency for the mercurous bromide electrode reduction e. m. f. to become increasingly less than the calculated value because of the decrease in activity of the bromide ions due to the formation of bromide complexes. This decrease in reduction e. m. f. is more or less compensated for by an opposing liquid junction potential at the zone of contact of the hydrobromic acid solutions of the two electrodes. Such behavior probably is responsible for the fairly close agreement between the experimental and theoretical values.

Summary

Determinations of the molal reduction e. m. f. of the mercurous bromide electrode at 25° in 0.1002 m hydrobromic acid solutions show that the values obtained in solutions free from air are about 0.5 millivolt higher than those in which air is not completely removed. Both values are accurately reproducible and are −0.1391 volt in air free solutions and −0.1396 volt in solutions containing air, using hydrogen as the reference electrode. Results of e. m. f. measurements made at 25 and 35° in approximately one, two, and three normal hydrobromic acid are also shown.

LOS ANGELES, CALIF. RECEIVED SEPTEMBER 14, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

The Molar Dispersion and Refraction of Free and Bonded Ions[1]

BY NORMAN BAUER[1a] AND KASIMIR FAJANS

Introduction

This paper is a continuation of the series of "Refractometric Investigations,"[2] the main goal of which has been an understanding of the changes occurring in the electronic systems of ions, atoms and molecules when they combine with each other. Since the "valence" electrons are identical with those responsible for the optical behavior in the visible and near ultraviolet, it was justified to expect that optical properties would be especially suited to a study of this problem which is so closely connected with the nature of chemical forces. In fact, for substances having electronic systems of the noble gas type,[3] these refractometric investigations have revealed (see especially I, VII, XXX) the existence of two effects which prove to have great influence on the physical[4] and chemical behavior of substances:

(1) From a doctoral dissertation submitted by N. Bauer at the University of Michigan in June, 1941. The paper was presented in part at the 101st Meeting of the American Chemical Society, April 9, 1941.

(1a) Present address: Chemistry Department, University of New Hampshire, Durham, New Hampshire.

(2) This is paper number LV in the series. The following of the former papers will be referred to by the corresponding Roman numerals. I. K. Fajans and G. Joos, *Z. Physik*, **23**, 1 (1924); VII. K. Fajans, *Z. Elektrochem.*, **34**, 502 (1928); IX. H. Kohner, *Z. physik. Chem.*, **B1**, 427 (1928); X. W. Geffcken and H. Kohner, *ibid.*, **B1**, 456 (1928); XI. W. Geffcken, *ibid.*, **B5**, 81 (1929); XII. H. Kohner and M. L. Gressmann, *ibid.*, **A146**, 137 (1930); XIV. K. Fajans and H. Kohner, *ibid.*, **A147**, 241 (1930); XX. Z. Shibata and P. Hoelemann, *ibid.*, **B13**, 347 (1931); XXI. K. Fajans, P. Hoelemann and Z. Shibata, *ibid.*, **B13**, 353 (1931); XXIII. W. Geffcken, C. Beckmann and A. Kruis, *ibid.*, **B20**, 398 (1933); XXV. P. Wulff, *ibid.*, **B21**, 367 (1933); XXVI. A. Kruis and W. Geffcken, *ibid.*, **A166**, 16 (1933); XXVII. P. Wulff and D. Schaller, *Z. Krist.*, **A87**, 43 (1934); XXIX. W. Geffcken and A. Kruis, *Z. physik. Chem.*, **B23**, 175 (1933); XXX. K. Fajans, *ibid.*, **B24**, 103 (1934); XXXV. P. Hoelemann and H. Goldschmidt, *ibid.*, **B24**, 199 (1934); XXXVIII. P. Wulff, *ibid.*, **B25**, 177 (1934); XL. G. Damkoehler, *ibid.*, **B27**, 130 (1934); XLI. P. Wulff and T. Anderson, *Z. Physik*, **94**, 28 (1935); XLII. R. Luehdemann, *Z. physik. Chem.*, **B29**, 133 (1935); XLIII. K. Fajans and R. Luehdemann, *ibid.*, **B29**, 150 (1935); XLVII–LI. A. Kruis and W. Geffcken, *ibid.*, **B34**, 1–95 (1936).

(3) It has been shown (see, *e. g.*, K. Fajans, "Chemical Forces and Optical Properties of Substances," (Cornell Lectures), McGraw-Hill Book Co., Inc., New York, N. Y., 1931) on the basis of properties such as lattice distances, lattice energies, crystal structure, solubility, formation of complex compounds, color, etc., that deformation phenomena are more pronounced in substances formed from non-rare gas cations (Class II, *e. g.*, AgCl) than in substances derived solely from noble gas ions (Class I, *e. g.*, NaCl). However, the refractometric method has not yet given clear results for the former class of compounds (see XXX, p. 147–151); this seems to have the following reason. For most cases in Class I the refractometric effect caused by anion tightening is very much stronger than the opposite effect. In Class II, because of the deeper mutual interpenetration of the ions, and also because of the larger polarizability of non-rare gas cations, both effects are of the same order of magnitude and partly cancel each other.

(4) See, *e. g.*, K. Fajans, *Phys. Rev.*, **61**, 543 (1942).

namely, the tightening of electronic systems by neighboring positive charges and their loosening by negative charges.[5]

The existence of these two effects was first concluded on the basis of the large systematic deviations from additivity which the Lorentz–Lorenz molar refraction R shows. The analysis of these deviations was greatly aided by the derivation (I) of values of the molar refraction of individual gaseous ions, as distinguished from ions in solution or from those in molecules and crystals. Until now such a derivation has been carried out in this series of investigations only for the refraction R_D at a wave length corresponding to the sodium D line. Recent precision measurements of the refraction at various wave lengths in the visible for a number of electrolytes (XLVIII and IL), along with the accumulated data from previous work, now make it possible to obtain a set of provisional values for the molar dispersion of individual gaseous and aqueous ions.

A knowledge of the dispersion furnishes a means of extrapolating R_λ to $\lambda = \infty$. Since

$$R_\infty = \frac{4}{3}\pi N\alpha \qquad (1)$$

one can then arrive at a consistent set of values of the true electronic polarizability (α) of ions.[6] Seldom is R_D more than a few per cent. different from R_∞, and thus R_D has been a sufficiently accurate measure of α for a qualitative investigation of the role of polarizability in the physical and chemical behavior of substances. The R_∞ values should now help in developing the quantitative aspects of this problem.

However, the inclusion of the molar dispersion in this study is of importance in itself because, as this paper will show, it is a property which is even more sensitive to changes in the forces acting on the particles involved than is the molar refraction.

In the present paper we shall limit ourselves to establishing a set of values for the molar dispersion of ions and to showing by a few examples how its large deviations from additivity help in the study of electronic deformation.

1. Extrapolation to Infinite Wave Length on the Basis of Dispersion Theory.—It has been customary to define the dispersion of a substance as the difference ΔR[7] between molar refractions at two arbitrarily selected wave lengths in the visible (*e. g.*, $\Delta R = R_{H\beta} - R_{H\alpha}$).

For reasons apparent from the Introduction we have chosen the difference between the molar refraction for the sodium D line (R_D) and that for infinite wave length (R_∞) as the measure of the *molar dispersion* **D**. Extrapolations to $\lambda = \infty$ from measurements in the visible were made by the reciprocal plotting method of P. Wulff (XXV), based on the dispersion theory.

According to the dispersion theory,[8] the refraction R may be expressed as a function of the frequency $\nu = c/\lambda$ by an equation of the type

$$R_\lambda = \sum \frac{C_i}{(\nu_0)_i^2 - \nu^2} \qquad (2)$$

The summation includes one term for each of the characteristic frequencies $[(\nu_0)_i]$ of the system; the constants C_i are a measure of the probability of transition between the states which define the frequency $(\nu_0)_i$. If a single term is sufficient, then a plot of $1/R_\lambda$ *versus* ν^2 gives a straight line

$$\frac{1}{R_\lambda} = \frac{\nu_0^2}{C} - \frac{1}{C}\nu^2 \qquad (3)$$

The intercept on the $1/R_\lambda$ axis for $\nu^2 = 0$ gives the value of $1/R_\infty$. When more than one term is necessary, then, as Wulff has found, the $1/R_\lambda$ *versus* ν^2 curve is composed of straight lines and hyperbolas, the sum of which approaches a straight line for small values of ν^2.

Experience shows that when the maximum of the first principal electronic absorption band $[(\nu_0)_1]$ has a wave length less than about 250 mμ, and when infrared contributions are negligible, the plot becomes linear in the visible part of the spectrum.

In Fig. 1 several typical extrapolations are made from data of different degrees of accuracy for the molar refraction of crystals and the apparent molar refraction of aqueous electrolytes. For the case of solutions measured with the Pulfrich refractometer (see Fig. 1, part B), for which the accuracy is lower than that of the interferometric measurements in part A, the thin dashed lines show the extreme slopes of the possible straight lines which can be put through the experimental points. The errors in **D** (in Tables I, II and III) were estimated by taking half of the

(5) Concerning a theoretical treatment of the refractometric tightening and loosening effects, see Th. Neugebauer, *Physik. Z.*, **94**, 655 (1935); *ibid.*, **99**, 687 (1936); *Hungarian Acad. Sci.*, **54**, 337 (1936).

(6) For a review of other methods of obtaining α, used by M. Born and W. Heisenberg, L. Pauling, J. E. Mayer and M. G. Mayer, see *e. g.*, J. H. Van Vleck, "The Theory of Electric and Magnetic Susceptibilities," Oxford University Press, New York, N. Y., 1932, pp. 208–225, and XXX, pp. 128–133 and p. 154.

(7) The symbol Δ will be often used to denote the difference between two quantities.

(8) *Cf.* K. F. Herzfeld and K. L. Wolff, "Handbuch der Physik," Verlag Julius Springer, Berlin, 1928, XX, p. 512.

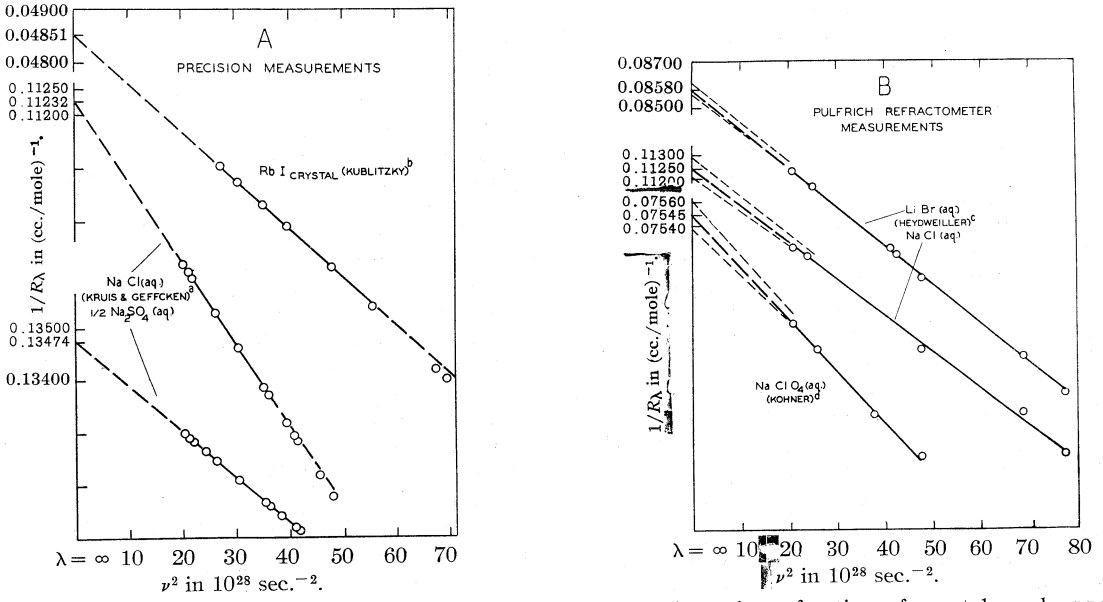


Fig. 1A and 1B.—Typical extrapolations to infinite wave length of the molar refraction of crystals and apparent molar refraction of aqueous electrolytes according to the reciprocal plotting method (P. Wulff, XXV): (a) see Table II; (b) see ref. (29); (c) see ref. (19); (d) see (IX).

difference between the values of $1/R_\infty$ given by the extension of the most probable line (*i. e.*, of the line drawn in full) and that given by the extreme possible line.

The curves in part A of Fig. 1, resulting from very accurate measurements on crystals and solutions, show departure from linearity in the direction of increasing negative slope for increasing values of ν^2. This downward curvature is to be expected on the basis of (2) for substances for which $(\nu_0)_2$ is not very much larger than $(\nu_0)_1$[9]. In general, and especially for the simple inorganic substances treated here, the experimental points fit a straight line the better, the nearer they come to the region over which extrapolation is made; thus the linear extrapolation appears to be well founded.

2. Selection of Data on the Dispersion of Simple Inorganic Substances.—The molar dispersions **D** given in Tables I, II and III were derived from the results of a large number of investigators who used various experimental techniques. Therefore, it is necessary to appraise the reliability of the various sets of data.

(a) **Gases and Vapors (Table I).**—The principal sources of data for gases were Cuthbertson and Cuthbertson,[10,11,13,16] Damkoehler (XL), Larsen,[12] Friberg[15] and Watson and Ramaswamy.[17]

We made the extrapolation to $\lambda = \infty$ for all gases except H_2Se by means of the dispersion formulas given in the original papers, which represented the experimental data (corrected to the ideal gas state) with great accuracy. The estimate of the error in dispersion was made from the relative uncertainty in the indices of refraction.

For H_2Se a plot of $1/R_\lambda$ *vs.* ν^2 was made in the usual way from the data of Frivold, Hassel and Skjulstad.[14]

(b) **Aqueous Solutions of Electrolytes at Infinite Dilution (Table II).**—Three principal series of measurements on aqueous electrolytes were used. The most accurate available data, which make the present partition into values of the molar dispersion of individual ions possible, are based on the precision measurements of Geffcken, Kruis and Beckmann (see Table II and XXIII) for five salts at 15 different wave lengths between 6678 and 4358 Å. The refractive indices and the densities of the dilute solutions

(9) An infrared contribution, corresponding to atomic polarization $[(\nu_0)_{i.r.} << (\nu_0)_1]$, would show up as a curvature of opposite sign at the red end of the spectrum when the dispersion for shorter wave lengths gives a linear $1/R_\lambda$ *vs.* ν^2 plot. Among substances included in this paper this was the case only for liquid water and was indicated by the precision measurements on aqueous Na_2SO_4 (see XXVII p. 59 and IL p. 65); the scale of Fig. 1A is too small to reproduce this indication. In such cases the linear part corresponding to the electronic contribution has to be used for the extrapolation. In general the contribution of infrared terms to the refraction in the visible is negligible. See, concerning a wide variety of crystals, *e. g.*, I p. 8, XXXVIII p. 181, and XXVII p. 59; concerning aqueous solutions of electrolytes, *e. g.*, IL p. 61.

(10) C. and M. Cuthbertson, *Proc. Roy. Soc.* (London), **A135,** 40 (1932).

(11) C. and M. Cuthbertson, *ibid.*, **A84,** 13 (1910).

(12) T. Larsen, *Z. Physik*, **111,** 394 (1938).

(13) C. and M. Cuthbertson, *Trans. Roy. Soc.* (London), **A213,** 1 (1913).

(14) O. E. Frivold, O. Hassel and T. Skjulstad, *Physik. Z.*, **37,** 134 (1936).

(15) S. Friberg, *Z. Physik*, **41,** 378 (1927).

(16) C. and M. Cuthbertson, *Proc. Roy. Soc.* (London), **A97,** 152 (1920).

(17) H. E. Watson and K. L. Ramaswamy, *Proc. Indian Acad. Sci.*, **A4,** 675 (1936).

TABLE I

MOLAR DISPERSION AND MOLAR REFRACTION OF GASES CORRECTED TO THE IDEAL GAS STATE IN CC.

Gas	R_D	D	Reference
He	0.521	0.00351 ± 0.043	(10)
Ne	1.004	.0066 ± .032	(10)
A	4.203	.064 ± .002	(11), XL
Kr	6.397	.129 ± .003	(11), XL
Xe	10.435	.298 ± .005	(11), XL
HCl	6.666	.1577 ± .032	(12)
HBr	9.161	.2745 ± .032	(12)
HI	13.73	.543 ± .003	(13)
H_2O	3.750	.085 ± .001	XXXV
H_2S	9.567	.3198 ± .032	(12)
H_2Se	12.02	.48 ± .03	(14)
H_3N	5.67	.176 ± .003	(13), (15)
H_4C	6.58	.145 ± .001	(15), (16)
H_4Si	11.34	.388 ± .002	(17)

TABLE II

APPARENT EQUIVALENT DISPERSION[a] D OF ELECTROLYTES IN INFINITELY DILUTE AQUEOUS SOLUTION IN CC.[b]

1. Interferometric Measurements of Geffcken and Kruis (XXVI, XXIX, XLVII, XLVIII)

$Na^+ + Cl^-$	0.329 ± 0.002	$NH_4^+ + NO_3^-$	0.545 ± 0.003
$K^+ + Cl^-$	.364 ± .002	$Na^+ + \frac{1}{2}SO_4^{--}$	.125 ± .003
$\frac{1}{2}Sr^{++} + Cl^-$	.336 ± .002		

2. Other Results for Noble Gas Cations[c]

	ΔD	Source
$Li^+ - Na^+$	−0.021 ± 0.008	LiOH, NaOH[18]
$Rb^+ - Na^+$	.055 ± .05	RbBr[19]
$Cs^+ - Na^+$	.09 ± .03	CsCl,[19] CsBr[20,21]
$NH_4^+ - Na^+$	.063 ± .01	NH_4F[19]
$\frac{1}{2}Ba^{++} - Na^+$	.022 ± .01	$BaClO_4$, $BaCl_2$ (IX)
$\frac{1}{2}Be^{++} - Na^+$	− .030 ± .005	$BeCl_2$[20,21]
$\frac{1}{3}Al^{3+} - Na^+$	− .024 ± .01	$Al_2(SO_4)_3$ (IX); $Al(ClO_4)_3$ (XI)

3. Non-Rare Gas Cations

	ΔD	Source
$Ag^+ - NH_4^+$	0.095 ± 0.01	$AgNO_3$[22]
$Tl^+ - Na^+$	.55 ± .15	TlF[19]
$\frac{1}{2}Zn^{++} - Na^+$	.019 ± .01	$ZnSO_4$ (XI)
$\frac{1}{2}Hg^{++} - Na^+$	.16 ± .02	$Hg(ClO_4)_2$ (XI)
$\frac{1}{2}Pb^{++} - NH_4^+$	.195 ± .02	$Pb(NO_3)_2$[20,21]
$H^+ - Na^+$	− .03 ± .05	H_2SO_4, $HClO_4$ (XII) HNO_3, HI (XLII)

4. Anions

	ΔD	Source
$F^- - Cl^-$	−0.289 ± 0.006	KF (XI)
$Br^- - Cl^-$	.28 ± .02	NaBr (XX), LiBr, CsBr[19,20,21]
$I^- - Cl^-$	1.0 ± .1	KI (XX), NaI[19]
$OH^- - Cl^-$	−0.141 ± .004	NaOH[18]
$ClO_4^- - Cl^-$	− .117 ± .007	$NaClO_4$ (IX)

[a] In part (1) of Table II the experimental values of $D_{aq.\ salt}$ are given, while in parts (2), (3) and (4) one has values of $\Delta D_{aq.\ salt}$ which represent the differences between $D_{aq.\ ion}$ and that of a reference ion (Na^+, NH_4^+, Cl^-). [b] All measurements were made at 25.0° except those at 18° by Heydweiller and Limann (see ref. 24). [c] The errors given for the differences ΔD were obtained by summing up all the estimated errors in the individual experimental values needed for the calculation of ΔD.

(18) Unpublished measurements of J. H. Faull, Jr., and P. Hoelemann.

(19) A. Heydweiller, *Physik. Z.*, **26**, 526 (1925).

(20) G. Limann, *Z. Physik*, **8**, 13 (1921).

(21) A. Heydweiller, *Z. anorg. Chem.*, **116**, 42 (1921).

(22) N. Bauer, "Dissertation," University of Michigan, 1941.

relative to that of water were determined at 25.0° with an accuracy of 0.073 (interferometric method) and 0.062 (differential buoyancy method), respectively. Usually about ten measurements were made on each salt between $2M$ and $0.01M$, so that uncertainties in the extrapolation to infinite dilution are very small.[23] Here the error in the apparent molar dispersion **D** is probably less than 1 per cent., as compared with up to 10 per cent. for measurements with the Pulfrich refractometer.

The values of **D** for some electrolytes were derived from earlier measurements in the "Refractometric Investigations" made with the Pulfrich refractometer, the use of which had been improved by Kohner and Geffcken (IX, X, XI). In this series, indices of refraction were measured for only three to five spectral lines, thereby making the extrapolation to $\lambda = \infty$ less certain.

A large number of salts was measured at 18°[24] by Heydweiller and his co-workers[19,20,21] with the Pulfrich refractometer and with the quartz spectrograph.[25] The number of spectral lines employed in the visible was two to five. For reasons discussed in XIV, the results were not always sufficiently accurate to establish the way in which the apparent molar refraction varied with concentration, thus bringing an uncertainty into the extrapolation to infinite dilution.[26]

The following values of **D** in cc./mole give examples of the best and poorest agreement between the various sets of measurements on salt solutions

NaCl	0.33 ± 0.03 (Heydweiller)	0.329 ± 0.002 (Kruis and Geffcken)
$NaClO_4$	.17 ± .02 (Heydweiller)	.212 ± .006 (Kohner)

The values of **D** for the various strong electrolytes at infinite dilution proved to be additive within the limits of experimental error; therefore it was possible to calculate values for the various ions with respect to reference ions (see footnote *a*, Table II).

(c) Alkali Halide Crystals (Table III).—The values of index of refraction given by Gyulai,[27] Spangenberg,[28] Kublitzky[29] and Wulff and Anderson (XLI) were used, some of which had already been extrapolated to $\lambda = \infty$ by

(23) The maximum which some refraction *vs.* concentration curves show (see LI and XLVIII p. 40) is not found in the corresponding dispersion curves. Therefore the extrapolation to $c = 0$ appears to be more certain for **D** than for R.

(24) The temperature coefficient of molar dispersion of aqueous electrolytes can be estimated from XX p. 351 to be less than 0.2 per cent. per degree, compared with about 0.05% per degree for refraction (XXI, p. 358). Therefore the difference between $D_{18°}$ and $D_{25°}$ is smaller than other uncertainties in Heydweiller's measurements. This result makes it also safe to use the values of $D_{cryst.}$ in Table III without a temperature correction because for refraction the values of $(dR/R)/dT$ are even smaller for crystals than for electrolytes (see XXI, p. 361).

(25) The values of R_∞ derived here from Heydweiller's data by the reciprocal plotting method differ up to 0.03 cc. from his own values, obtained by plotting R_λ against ν^2.

(26) The values of $D_{aq.}$ for rubidium and cesium salts contain an additional uncertainty because of the possible presence of impurities. Therefore even the rather large errors in Tables II and VII for these ions are only a lower limit. Thus it is uncertain whether the difference in the sequence of values shown in Fig. 3 for refraction (K, Cs, Rb) and for dispersion (K, Rb, Cs) is real.

(27) Z. Gyulai, *Z. Physik*, **46**, 84 (1927).

(28) K. Spangenberg, *Z. Krist.*, **57**, 494 (1923).

(29) A. M. Kublitzky, *Ann. Physik*, **20**, 793 (1934).

Wulff and co-workers (XXXVIII, XXVII). When no measurements of the density were made on the samples used for the refractive index determination, the molar refraction was calculated using the best density values resulting either from direct measurements (see XXVII), or from X-ray determinations given in the "Strukturbericht." Some of the salts were measured above room temperature (up to 66°; see footnote (a), Table III). Concerning the negligible temperature dependence of $D_{cryst.}$ in this interval, see ref. 24.

From Table III it can be seen that the uncertainties in $D_{cryst.}$ vary from 2 to 10%.

TABLE III

MOLAR DISPERSION OF CRYSTALS IN CC.[a]

(a) Alkali Halides

LiF	0.031 ± 0.003	(27)	NaBr	0.42 ± 0.01	(27)
NaF	.048 ± .005	(28)	KBr	.52 ± .01	(27)
KF	.080 ± .005	(29)	RbBr	.57 ± .02	(29)
NaCl	.24 ± .01		CsBr	.66 ± .05	(XXVII)
KCl	.30 ± .01	(XXXVIII)	KI	.95 ± .02	(27)
RbCl	.36 ± .02		RbI	1.06 ± .1	(29)
CsCl	.41 ± .01	(XLI)			

(b) Compounds of Doubly Charged Cations and Anions of Noble Gas Type (Haase[30])

MgO	0.09 ± 0.01	SrS	0.95 ± 0.09
CaO	.17 ± .02	CaSe	1.11 ± .06
SrO	.39 ± .04	SrSe	1.49 ± .06
BaO	.76 ± .1	BaSe	1.81 ± .08
MgS	.38 ± .02	SrTe	2.13 ± .5
CaS	.71 ± .02	BaTe	3.41 ± .5

[a] The salts measured at other than room temperature are: KF (57°), RbCl (48°), NaBr (66°), KBr (48°), RbBr (35°), RbI (35°) and KI (60°). Concerning the negligible temperature dependence of $D_{cryst.}$ between 25 and 70°, see ref. 24.

(d) **Compounds of Doubly Charged Cations and Anions of the Noble Gas Type (Table III).**—Measurements of the index of refraction by Haase[30] were used. The number of wave lengths employed varied between 2 and 5. Since, except for BaTe and MgO, the density was not measured by Haase, we have taken densities used by him on the basis of V. M. Goldschmidt's X-ray determinations. The molar dispersion could be evaluated only to within about 10 per cent.

3. Deviations from Additivity for Molar Dispersion and Refraction Based on Direct Experimental Data.—Figure 2 contains experimental data for a selection of gaseous substances isoelectronic with the noble gases. The values of R_D and **D** are based on n^*, the index of refraction corrected to the ideal gas state. The values of the Lorentz–Lorenz refraction used in Fig. 2 are thus very nearly proportional to $(n^* - 1)/d$, which is a direct measure of the interaction between free particles and the electric field associated with the light waves: *i. e.*, these R_D and **D** values are practically independent of any alleged imperfections in the Lorentz–Lorenz expression possible in the case of condensed systems.[31] The substances in Fig. 2 corresponding to the sets of connected points (*e. g.*, H_2Se, HBr, Kr) have the same number of electrons (*e. g.*, 36) and differ only by the position of the protons, two of which in H_2Se and one in HBr are within the electronic shell, while in Kr all belong to the nucleus. One observes a large change (a decrease, excepting $\mathbf{D}_{NH_3} > \mathbf{D}_{CH_4}$) in both R_D and **D** corresponding to the process of successively transferring protons from an electronic shell into the nucleus; *e. g.*, the refraction drops from 11.57 cc. in H_2Se to 9.16 in HBr and finally to 6.40 in Kr, while for dispersion the corresponding values are 0.48, 0.27 and 0.129 cc., respectively.[31a] Thus there can be no doubt that the molar refraction and dispersion are properties which depend on the forces acting on a given electronic system, and indeed are very sensitive to changes in the forces.

Because the interionic forces in crystals and gases are different from those between ions and water molecules in solution, one can understand (*cf.* I, p. 7; XXX, p. 121) that, as Fig. 3 shows, the apparent molar refraction and dispersion of aqueous alkali and hydrogen halides differ from the corresponding values in the solid and gaseous states. Here it is of especial importance to note that also for electrolytes there is a close analogy between the kind of deviations from additivity exhibited by molar dispersion and by molar refraction (concerning Cs salts, see ref. 26). The magnitude of these deviations for both **D** and R increases systematically with increase in polari-

(30) M. Haase, *Z. Krist.*, **65**, 509 (1927); for MgS see M. Haase, *ibid.*, **68**, 82 (1928).

(31) See, *e. g.*, N. F. Mott and R. W. Gurney, "Electronic Processes in Ionic Crystals," Oxford University Press, New York, N. Y., 1940, p. 18. The Lorentz–Lorenz formula is supposed to account only for that part of the internal electric field acting on a given particle which is due to the dipoles induced in surrounding particles by the external electric field of the light waves; the formula does not attempt to include the effect of forces acting between the particles in the absence of the external field. In fact the results of the "Refractometric Investigations" demonstrate that the Lorentz–Lorenz expression fulfills its purpose excellently. The systematic deviations from additivity observed for a wide variety of gaseous, liquid and cubic-solid systems can be understood as a result of known forces acting between particles independently of the light wave. Only the minute deviations from additivity in mixtures of non-ionized liquids cannot yet be explained from this point of view (*cf.* XXX, p. 108).

(31a) *Note added on November 30, 1942.* The gradation of molar refraction and dispersion of isoelectronic molecules shown in Fig. 2 proves to be in line with a general principle: The tightness of a given electronic shell decreases (R and **D** increase) when the positive charges within the shell split or when their distribution becomes less symmetrical. The apparently exceptional gradation $\mathbf{D}_{H_3N} > \mathbf{D}_{H_4C}$ is due, as is also indicated by the peculiarities of the slopes of the lines leading to H_4Si, to the competition between two factors. In the transition from H_3N to H_4C the splitting of the core N^{5+} into C^{4+} and H^+ causes a loosening, the higher symmetry of H_4C a tightening of the electronic shell. See K. Fajans, *J. Chem. Phys.*, December, 1942.

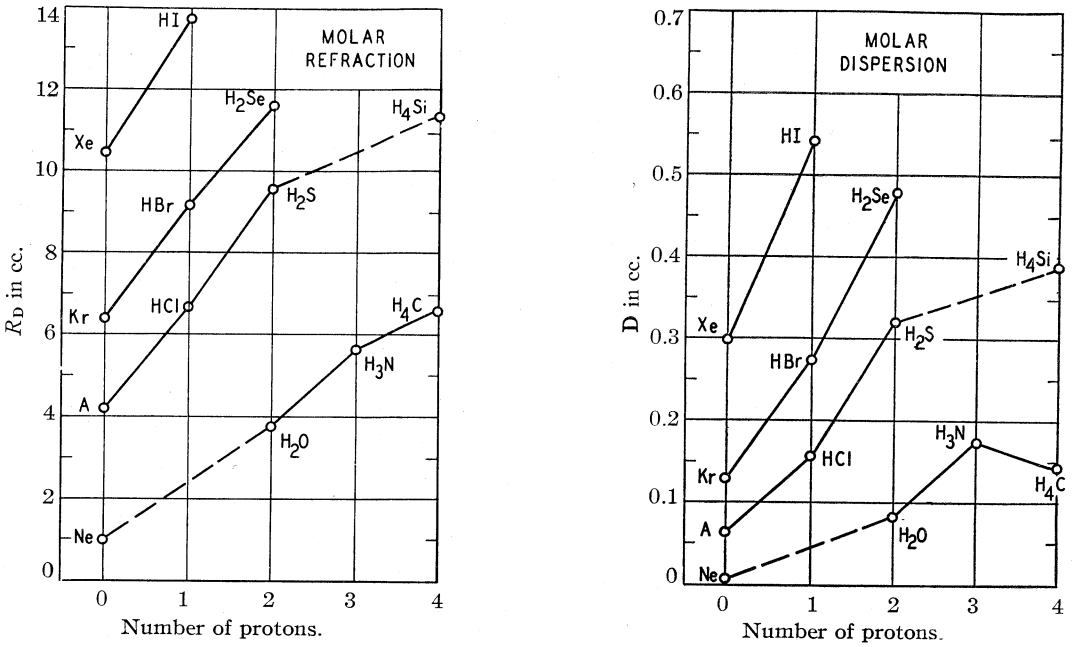


Fig. 2A and 2B.—Analogy between the changes of molar refraction and dispersion of gases due to a successive transfer of protons from the nucleus of the noble gases into the electronic shell.

zability and polarizing power of the particles involved, as has been discussed in former papers for the case of refraction, and as will be shown in Section 8 for dispersion.

4. Square Relation between Molar Refraction and Dispersion.—The similarities between the deviations from additivity of the molar refraction and dispersion noted in Section 3 lead one to expect a simple quantitative relation between these two phenomena. The dispersion theory leads to the following results.

If one assumes that a single term dispersion formula is adequate for representing the experimental data (which is the case, *e. g.*, for noble gases in the visible) one has $R_D = C/(\nu_0^2 - \nu_D^2)$, and $R_\infty = C/\nu_0^2$. From $\mathbf{D} = R_D - R_\infty$, $\mathbf{D} = (\nu_D^2/C)R_D R_\infty$. Since $R_D \approx R_\infty$ (in general within considerably less than 5%), one has

$$\mathbf{D} \approx \frac{\nu_D^2}{C} R_D^2 \qquad (4)$$

Considering the changes occurring in the molar refraction and dispersion of a given particle when it is subjected to an external influence (*e. g.*, when one ion combines with another), and assuming that in this case C remains practically constant,[32] one obtains the following square relation between R_D and $\mathbf{D}$

$$\mathbf{D} \approx \text{constant} \times R_D^2 \qquad (5)$$

therefore

$$\Delta\mathbf{D}/\mathbf{D} \approx 2\Delta R_D/R_D \qquad (6)$$

Thus one expects that a given change in the refraction will correspond to twice as great a relative change in the dispersion. It will be seen in this and following sections that in general, in simple cases, this expectation is fulfilled.[33]

Table IV, based on direct experimental data given in Table I, shows that the square relation applies to the noble gases, the hydrogen halides and H_2O, H_2S, and H_2Se with an accuracy sufficient for our present purpose. The squares of the ratios of the molar refraction for any two of these substances belonging to the same noble gas type agree within about 4% on the average with the corresponding ratios of the molar dispersion, which is surprisingly good in view of the approximations used in arriving at (5).

(32) The dispersion of noble gases and of Li, Na and K halides can be represented with sufficient accuracy in the visible by a single term (equation 2). For those salts of this group for which the cations can be expected to contribute only a few tenths of a per. cent to the total dispersion (*e. g.*, NaBr), one can compare the values of C and ν_0^2 for a noble gas with those of the corresponding halide ion in the crystal; whereas in such cases the ν_0^2 values differ by a factor of nearly two, the differences between $C_{N.G.}$ and C_{X^-} are less than 10%, on the average. Closely connected with this are the results of K. F. Herzfeld and K. L. Wolff, *Ann. Physik*, **78**, 50 (1925), who concluded from multiple term dispersion formulas that the total transition probability (number of electrons in classical theory) for argon was practically the same as that for Cl^- in NaCl and KCl.

(33) The ratio of $\Delta R/R$ to $\Delta D/D$ differs considerably from two in relation (12) for the hydration effect of Li^+, in Fig. 3 for the values for KI and RbI and in Table X. In all these cases, apparent quantities are involved.

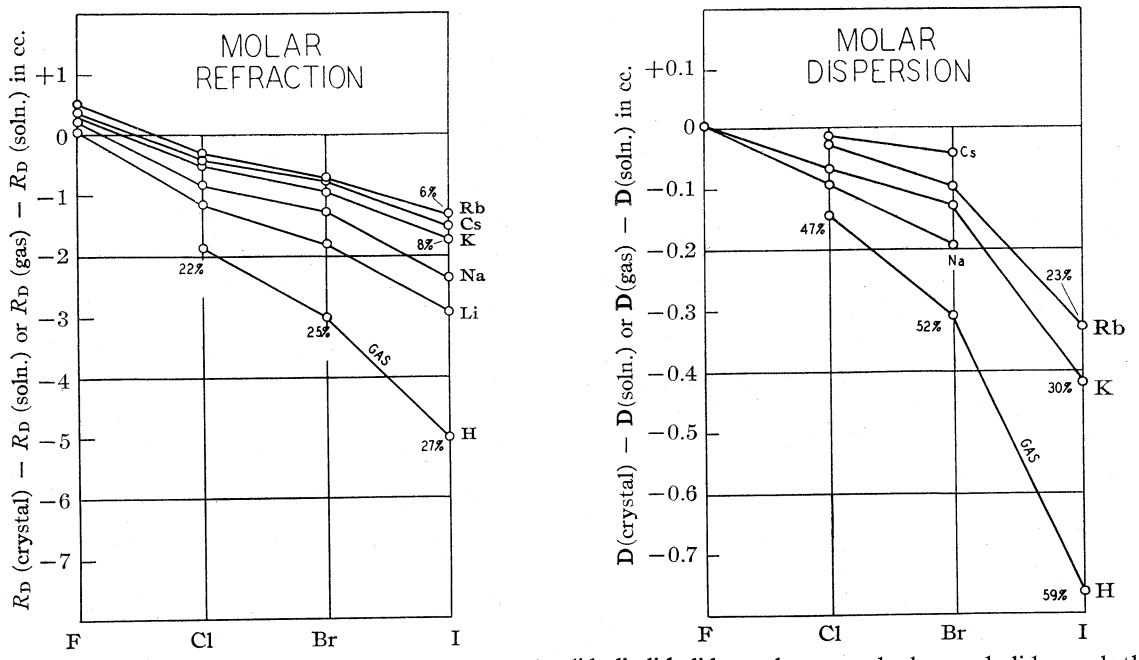


Fig. 3A.—Difference between the molar refraction of solid alkali halides and gaseous hydrogen halides and their apparent molar refraction in aqueous solution. Fig. 3B gives the corresponding differences for the molar dispersion **D**. The percentage deviations from additivity are given relative to the values of the aqueous electrolytes and are greater for dispersion than for refraction.

In (5) we have neglected the difference between R_D and R_∞, as well as the influence of a second frequency $(\nu_0)_2$. Such neglections will in general be the more justified, the smaller the values of R_D and $1/(\nu_0)_1$ are; therefore it is reasonable to apply the square relation (5) to ions having the same noble gas structure, providing their R_D and $1/(\nu_0)_1$ values are not larger than those of the substances used in verifying the relation (Table IV).[34]

TABLE IV

TEST OF THE SQUARE RELATION (5) BETWEEN MOLAR REFRACTION AND MOLAR DISPERSION

Ratios	For R_D	For R_D^2	For **D**
HCl/A	1.59	2.52	2.47
HBr/Kr	1.43	2.04	2.13
HI/Xe	1.315	1.73	1.78
H_2O/Ne	3.73	13.9	12.9
H_2S/A	2.28	5.20	5.00
H_2Se/Kr	1.875	3.52	3.69
H_2S/HCl	1.44	2.07	2.02
H_2Se/HBr	1.315	1.73	1.75

5. The Partition of the Molar Dispersion into Values for Individual Ions.—The above results, establishing an analogy between the behavior of the molar refraction and dispersion, justify the attempt to apply to the partition of dispersion the same principles which have been used in the case of refraction. For the latter, as mentioned in the introduction, it proved to be very helpful to introduce values for the refraction of free gaseous ions.

It is important to emphasize here that the molar refraction and dispersion of free gaseous ions are real physical quantities like those for a noble gas, and are connected by equation (1) with the electronic polarizability α of the free particles. In this respect the molar refraction and dispersion differ from the volume[35] or radii of free ions or atoms, which according to wave mechanics do not have an exact physical meaning.

For any property (X) of analogous ions, the value of which can be assumed to decrease monotonously with increasing forces between the nucleus and the electronic system, one can expect the following regularities to hold. They were in part stated in considering the relative size of noble gas ions,[36] and were extensively used for the derivation of ionic refractions (I and XXX).

(a) For ions possessing the same noble gas (N. G.) structure, the nuclear charge of which

(34) We assume that the agreement in Table IV is not due to an accidental cancelling of effects which might arise from the different symmetry of the particles involved.

(35) However, single ionic values of the apparent molar volume are defined quantities which for the case of infinitely dilute aqueous solutions have been approximately obtained. See, *e. g.*, K. Fajans and O. Johnson, THIS JOURNAL, **64**, 668 (1942).

(36) K. Fajans and K. F. Herzfeld, *Z. Physik*, **2**, 309 (1920).

increases in the following series from left to right, one has[37]

$$\cdots > X_{\text{ion}^{--}} > X_{\text{ion}^{-}} > X_{\text{N.G.}} > X_{\text{ion}^{+}} > X_{\text{ion}^{++}} > \cdots \quad (7)$$

(b) For a given noble gas type it should hold that

$$\cdots > \frac{X_{\text{ion}^{--}}}{X_{\text{ion}^{-}}} > \frac{X_{\text{ion}^{-}}}{X_{\text{N.G.}}} > \frac{X_{\text{N.G.}}}{X_{\text{ion}^{+}}} > \frac{X_{\text{ion}^{+}}}{X_{\text{ion}^{++}}} > \cdots \quad (8)$$

The inequalities (8) are based on the expectation that a given absolute difference in nuclear charge Z will cause the greater relative change in the property X, the smaller the magnitude of Z.

(c) For particles of a different noble gas type one can expect inequalities (9) to hold for the same reason given for (8); *e. g.*

$$\frac{X_{\text{F}^-}}{X_{\text{Ne}}} > \frac{X_{\text{Cl}^-}}{X_{\text{A}}} \quad \text{or} \quad \frac{X_{\text{Ne}}}{X_{\text{Na}^+}} > \frac{X_{\text{A}}}{X_{\text{K}^+}} \quad (9)$$

These regularities, in spite of being inequalities, were found (XXX) to provide a basis for the derivation of refraction values for free gaseous ions which is at least as reliable as other methods used for this purpose except for the case of helium type cations. The main difficulty in the derivation is caused by the fact that while the inequalities refer to free gaseous particles, the available experimental data extend only to noble gases and aqueous ions. However, for noble gas ions having strong electric fields it was possible to obtain an estimate of the differences $\Delta^{R}_{\text{hydr.}} = R_{\text{aq. ion}} - R_{\text{gas ion}}$ between the values of hydrated and gaseous ions (see Table VII, Sec. 6).

In order to obtain a set of values for the molar dispersion of individual ions, we proceeded in two ways which led to results agreeing within the limits of the uncertainties in both methods. One method is analogous to that applied previously (I) to the molar refraction. Besides the uncertainty connected with the hydration effect, the application of this method to the molar dispersion encounters an additional difficulty at present because of the low accuracy of the experimental values of **D** for the heavier alkali and halide ions.

The other method is based on an application of the square relation (5) between R_{D} and **D**. Assuming the values for the molar refraction of free gaseous ions to be known,[38] one can arrive directly at the values of molar dispersion of gaseous ions, using also the experimental values of R_{D} and **D** for the noble gases; comparing the results with the experimental information on aqueous ions one can further try to decide whether or not it is necessary to distinguish here between free gaseous and dissolved ions.

We shall present only the second method, which is based on a new principle and which has proved to be more straightforward than the first one. For reasons given in Section 4, it appears quite safe to use relation (5) in deriving molar dispersions for gaseous alkali and alkaline earth ions; very probably fluoride ion also obeys the square relation.[39] The results of the calculation are given in Table V, along with values for R_{D} and the ratios which correspond to the regularities expected from relations (8) and (9).

However, it is uncertain whether the application of the square relation to the larger halide ions can give exact enough results because their ν_0 values are considerably smaller than those of the noble gases, and they have large refractions. The results for these ions are therefore given in parentheses (see footnote *c*, Table V). For the doubly charged negative ions the same reservations apply, in addition to the restriction that here the values of both molar refraction and dispersion represent only extrapolated auxiliary quantities because these ions are not stable in the gaseous state.[40]

6. The Difference between the Molar Dispersion of Ions in the Free Gaseous State and in Aqueous Solution.—From the analogous behavior of refraction and dispersion, one would expect that the tightening of the electronic system of water molecules by cations would produce a negative hydration effect for molar dispersion, *i. e.*, $\Delta^{\mathbf{D}}_{\text{hydr.}} = (\mathbf{D}_{\text{aq. cation}} - \mathbf{D}_{\text{gas cation}}) < 0$ and that the absolute value of this effect should be greater, the greater the electric field of the cation (see XXX, p. 121). We can test this using the most accurately known values for $\mathbf{D}_{\text{g}}$ and $\mathbf{D}_{\text{aq. salt}}$: From $(\mathbf{D}_{\text{aq.}})_{\text{K}^+} - (\mathbf{D}_{\text{aq.}})_{\text{Na}^+} = 0.364 - 0.329 = 0.035 \pm .004$ (Table II, 1) and $(\mathbf{D}_{\text{g}})_{\text{K}^+} - (\mathbf{D}_{\text{g}})_{\text{Na}^+} = 0.0169$ (Table V) it follows that

$$(\Delta^{\mathbf{D}}_{\text{hydr.}})_{\text{Na}^+} = (\Delta^{\mathbf{D}}_{\text{hydr.}})_{\text{K}^+} - 0.018 \text{ cc./mole} \quad (10)$$

(37) Relation (7) was first applied to refraction by J. A. Wasastjerna [*Oeversikt av. Finska Soc. Foerdhandl.*, **LXIII A4**, 1 (1920–21); *Z. physik. Chem.*, **101**, 193 (1922)], to ionic radii by A. Landé, *Z. Physik*, **1**, 191 (1920).

(38) For reasons mentioned in XXX, p. 125 and in ref. (35) under 6c, the refractions given in XXX for gaseous ions can be expected to require some corrections. However, the results of the present paper give additional support to the belief that these refraction values cannot be far from the true ones, and that in any case they represent a consistent set.

(39) Although free fluoride ion can be expected to have an absorption band around 300 mμ (electron affinity ≈ 4 volts), which is closer to the visible than that of any of the substances used in verifying (5), the small value of its refraction ($R_{\text{F}^-} = 2.5$ cc. compared with $R_{\text{HI}} = 13.7$) makes it improbable that the second absorption band (ν_0)$_2$ is important in the visible (see Sec. 4).

(40) See, *e. g.*, O. K. Rice, "Electronic Structure and Chemical Binding," McGraw-Hill Book Company, 1940, p. 101.

TABLE V

MOLAR DISPERSION D[a] AND MOLAR REFRACTION R_D[b] OF GASEOUS IONS IN CC.

	$X^=$	$X^=/X^-$	X^-	$X^-/N.G.$	N.G.	$N.G./X^+$	X^+	X^+/X^{++}	X^{++}
					He		Li^+		Be^{++}
D					**0.00351**		**0.0001**		**0.0000**
R_D					.521		(.08)		
	$O^=$		F^-		Ne		Na^+		Mg^{++}
D	**(0.32)**	**(8.1)**	**0.039**	**6.0**	**0.0066**	**4.4**	**0.00149**	**3.3**	**0.00045**
R_D	6.95	*2.84*	2.44	*2.43*	1.004	*2.11*	.475	*1.82*	.26
	$S^=$		Cl^-		A		K^+		Ca^{++}
D	**(1.9)**	**(6.3)**	**(0.30)**[c]	**(4.7)**	**0.064**	**3.5**	**0.0184**	**2.6**	**0.0071**
R_D	22.7	*2.50*	9.065	*2.16*	4.203	*1.86*	2.255	*1.61*	1.40
	$Se^=$		Br^-		Kr		Rb^+		Sr^{++}
D	**(2.6)**	**(5.2)**	**(0.50)**[c]	**(3.9)**	**0.129**	**2.9**	**0.0447**	**2.2**	**0.0206**
R_D	28.8	*2.27*	12.66	*1.98*	6.397	*1.69*	3.79	*1.47*	2.58
	$Te^=$		I^-		Xe		Cs^+		Ba^{++}
D	**(4.6)**	**(4.6)**	**(1.01)**[c]	**(3.4)**	**0.298**	**2.5**	**0.117**	**1.9**	**0.061**
R_D	40.9	*2.13*	19.21	*1.84*	10.435	*1.60*	6.535	*1.38*	4.73

[a] The values of **D** were derived by using the square relation (5) between R_D and **D**, the above values of R_D and the experimental values of R_D and **D** for the noble gases. [b] The values of R_D are taken from XXX, Table (3), except for small changes in Xe and Kr, as given by Damkoehler (XL). [c] For reasons given in Section 6, we prefer to use (*e. g.* in Table VIII) the values of $\mathbf{D}_{aq.}$ = 0.346, 0.63 and 1.3 cc./mole (Table VI) for Cl^-, Br^- and I^-, respectively, as the provisional estimate of $\mathbf{D}_g$. for these ions.

One can see that (10) agrees with the above expectation.

Since there is not sufficient information for evaluating the smaller hydration effect of K^+, we shall neglect it as a first approximation, as was done in the case of refraction[41]; *i. e.*, we put

$$(\mathbf{D}_{aq.})_{K^+} = (\mathbf{D}_{g.})_{K^+} = 0.0184 \text{ cc./mole} \qquad (11)$$

The numerical value in (11) comes from Table V. Using the experimental sums and differences given in Table II for aqueous electrolytes, the values of $\mathbf{D}_{aq.}$ for all aqueous ions follow at once from relation (11). They are given in Table VI. By subtracting from the $\mathbf{D}_{aq.}$ values for aqueous ions the values of $\mathbf{D}_{g.}$ for those corresponding gaseous ions which in Table V are considered to be certain, one obtains the magnitude of the hydration effect $\Delta^{\mathbf{D}}_{hydr.}$ The values of $\Delta_{hydr.}$, given in Table VII, allow one to test whether or not the derivation in Section 5 leads to a consistent system.

TABLE VI

APPARENT EQUIVALENT DISPERSION OF IONS IN AQUEOUS SOLUTION AT 25° IN CC.[a]

Li^+	−0.038	$\frac{1}{2}Be^{++}$	−0.047	F^-	0.057
Na^+	−0.0166	$\frac{1}{2}Sr^{++}$	− .010	Cl^-	.346
K^+	**.0184**	$\frac{1}{2}Ba^{++}$	.005	Br^-	.63
Rb^+	.04	$\frac{1}{2}Zn^{++}$	.002	I^-	1.3
Cs^+	.07	$\frac{1}{2}Hg^{++}$	.14	OH^-	0.205
NH_4^+	.046	$\frac{1}{2}Pb^{++}$	.24	NO_3^-	.50
Ag^+	.141	$\frac{1}{3}Al^{+++}$	− .041	ClO_4^-	.229
Tl^+	.53	H^+	(− .05)	$\frac{1}{2}SO_4^=$	.1416

[a] Based on the experimental values of **D** for electrolytes at infinite dilution (Table II) and relation (11).

Assumption (11) leads to the conclusion that for alkali ions larger that K^+, the hydration effect should also be negligible, while for the hydrogen ion,[42] lithium ion and small cations of double or triple charge, the value of $\Delta^{\mathbf{D}}_{hydr.}$ should have a negative sign and its absolute value should be larger than that for Na^+.

Table VII not only agrees with the above conclusion,[43] but in addition it shows that qualitatively the gradation of $\Delta_{hydr.}$ is the same for the molar dispersion as for the molar refraction. In a quantitative respect one can only state that relative to the magnitude of R_D and **D** of one mole of water, the hydration effect is considerably greater for dispersion than for refraction. For example, one has for Li^+

$$\Delta^{\mathbf{D}}_{hydr.}/\mathbf{D}_{liq.H_2O} = -0.038/0.082 = -0.46$$

while

$$\Delta^{R}_{hydr.}/R_{liq.H_2O} = -0.33/3.72 = -0.09 \qquad (12)$$

It is of especial interest that for F^- a positive value of $\Delta^{\mathbf{D}}_{hydr.}$ is obtained, analogous to the

(41) For the evidence that such solution effects exist also for large ions, see XXI and ref. (35), section 6c.

(42) For the apparent molar dispersion of aqueous hydrogen ion one finds **D** = −0.05 ± 0.05. The large error is due to uncertainties in extrapolating values of $\mathbf{D}_{acid}$ to infinite dilution; therefore it is not warranted to place H^+ in Table VII. However, the plot of hydrogen halides in Fig. 3 is not appreciably affected by such an error.

(43) Concerning Rb^+ and Cs^+, see ref. 26.

TABLE VII

DIFFERENCES $\Delta_{hydr.}$ BETWEEN AQUEOUS AND FREE GASEOUS IONS FOR THE MOLAR REFRACTION R_D AND THE MOLAR DISPERSION **D** IN CC.

1. Refraction[a] [$(R_D)_{liq.H_2O}$ = 3.72 cc./mole]

	OH^-	F^-	Cs^+	Rb^+	K^+	Na^+	Li^+	Ba^{++}	Sr^{++}	Be^{++}	Al^{3+}
$\Delta^R_{hydr.}$	+0.34	+0.16	0.0	0.0	**0.0**	−0.27	−0.33	−0.36	−0.69	−2.12	−2.49
Ion/Na^+	−1.3	− .6				1	1.2	1.3	2.5	7.85	9.2

2. Dispersion.[b] [$D_{liq.H_2O}$ = 0.0825 cc./mole (XLVIII)]

	OH^-	F^-	Cs^+	Rb^+	K^+	Na^+	Li^+	Ba^{++}	Sr^{++}	Be^{++}	Al^{3+}
$\Delta^D_{hydr.}$	+0.056	+0.018	(−0.05 ± 0.03)	(0.0 ± 0.05)	**0.0**	−0.018	−0.038	−0.05	−0.04	−0.094	−0.12
Ion/Na^+	−3.1	−1.0				1	2.0	2.7	2.2	5.2	6.7

[a] The values of $\Delta^R_{hydr.}$ are taken from XXX, p. 121.

[b] The values of $\Delta^D_{hydr.}$ are based on Tables V (VIII for HO^-) and VI and the assumption (11); concerning Cs^+, see ref. (62.)

corresponding refractometric effect. The positive sign indicates a loosening of the electronic shells of the adjacent water molecules by the action of the field of the small fluoride anion (see the similar result for OH^- in Section 7.)

It would be premature to draw definite conclusions concerning the values of $\Delta^D_{hydr.}$ for the heavier halide ions. A comparison of values in Table V with those in Table VI indicates that the **D** derived from the square relation for gaseous Cl^-, Br^- and I^- is smaller than that for the aqueous ions by 0.05, 0.13 and 0.1 cc., respectively. However, because of the uncertainty in $\mathbf{D}_g$. for the large halide ions (see Section 5) and in $\mathbf{D}_{aq.}$ for Br^- and I^- (see Table II), the above values of the hydration effect are not reliable.

We shall, as was done for refraction, provisionally use the values of $\mathbf{D}_{aq.}$ in Table VI as being equal to those for the free gaseous Cl^-, Br^- and I^- ions. These values of **D** do not lead to contradictions with the regularities expected in the ratios (8) and (9) for gaseous ions; we have, *e. g.*

$$\underset{5.4}{Cl^-/A} > \underset{4.9}{Br^-/Kr} > \underset{4.3}{I^-/Xe}$$

7. The Change of Molar Dispersion by the Addition of Protons.—In Section 3 it was shown that the molar dispersion generally decreases when protons are transferred from the electronic shell of a hydride into the nucleus. Now, having the values of **D** for individual ions, we can discuss the effect of protons being brought from outside

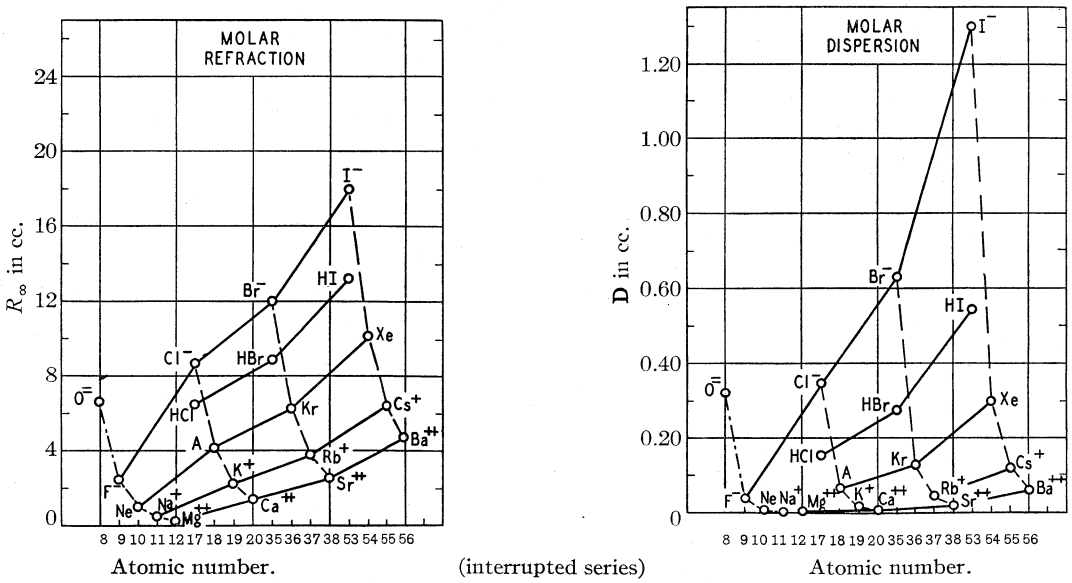


Fig. 4A.—Comparison of the molar refraction for infinite wave length: 1, of ions and atoms of a given noble gas type as a function of the nuclear charge (dashed lines); 2, of analogous ions, atoms, and molecules belonging to different periods (full lines); 3, of hydrogen halide molecules with the corresponding halide ions. Fig. 4B gives the same for the molar dispersion **D** ($\mathbf{D} = R_D - R_\infty$). In all cases the relative changes are larger for dispersion than for refraction.

TABLE VIII

THE CHANGE OF MOLAR DISPERSION BY THE ADDITION OF PROTONS

(I)	I^-	HSe^-	HS^-	Br^-	Cl^-	HO^-
$\mathbf{D}_I$	1.3	(1.14)	(0.75)	0.63	0.346	(0.149)
$\Delta\mathbf{D}$	0.76	(0.66)	(.43)	.36	.188	(.064)
$\mathbf{D}_{II}$	.54	.48	.320	.274	.158	.085
(II)	HI	H_2Se	H_2S	HBr	HCl	H_2O
$Q_I^D = (\mathbf{D}_I - \mathbf{D}_{II})/\mathbf{D}_I$	0.58	(0.58)	(0.57)	0.57	0.54	(0.43)
Q_I^D/Q_I^R	**2.03**	2.04	2.04	**2.05**	**2.04**	2.04

the electronic shell into either (1) the nucleus (*e. g.*, the process $Cl^- \rightarrow A$) or (2) into the electronic system (*e. g.*, $Cl^- \rightarrow HCl$).

The data for case (1) are contained in Table V and represented graphically in Fig. 4B which gives a plot of **D** for ions, atoms and molecules as a function of atomic number, and which is naturally analogous to the corresponding figure for refraction (Fig. 4A). We notice that the absolute change in the molar dispersion caused by the addition of one proton depends on the polarizability of the initial particle; *e. g.*, the decrease is 0.28 cc. (93% of $\mathbf{D}_{Cl^-}$) for the process $Cl^- \rightarrow A$, and 0.046 cc. (72% of $\mathbf{D}_A$) for $A \rightarrow K^+$. The percentage change is, as implied in the square relation, about twice as great for molar dispersion as for refraction.

For case (2) we have a chemical change according to the equation $H^+ + I = II$, in which I is the initial, II the final particle. These changes are simpler than other chemical processes in the respect that the electronic system of only one of the reacting particles is involved. The introduction of positive charge into the electronic system causes the electrons to be more tightly bound, *i. e.*, its polarizability becomes smaller. The observed diminution ΔR of the refraction R_I^D of a charged anion or neutral molecule (I) caused by the addition of protons was found (XXX)[43a] to obey a simple exponential relation

$$Q_I^R = \Delta R/R_I^D = 0.2859\ (1 - e^{-0.2848 R_I^D}) \quad (13)$$

The relative change of refraction Q_I^R increases with R_I^D and reaches the value 0.2847 for I^- ($R_I^D = 19.21$) which is nearly equal to the limiting value 0.2859 for $R_I = \infty$.

Table VIII, for which the unbracketed values are either known experimentally or obtained above (see footnote *c*, Table V) and for which the bracketed ones are derived below, shows that the change of molar dispersion by protons behaves qualitatively in an analogous way. The relative change $Q_I^D = (\mathbf{D}_I - \mathbf{D}_{II})/\mathbf{D}_I$ for dispersion increases from 0.54 for Cl^- to 0.57 for Br^- and 0.58 for I^-.[44] For all three halide ions the ratio Q_I^D/Q_I^R equals 2.04, showing again that the molar dispersion is about twice as sensitive as refraction. This relation can be made the basis for a derivation of ionic dispersions for gaseous HO^- HS^- and HSe^- from the known values of H_2O, H_2S and H_2Se. Assuming the ratio $Q_I^D/Q_I^R = 2.04$ to apply to these substances as well, and using the known values of Q_I^R (XXX, p. 134), one obtains Q_I^D given in Table VIII. Since $\mathbf{D}_{II}$ is known, we have the bracketed values of $\mathbf{D}_I$ in Table VIII at once.

The comparison of $(\mathbf{D}_{OH^-})_{g.} = 0.149$[45] with $(\mathbf{D}_{OH^-})_{aq.} = 0.205$ leads to a positive hydration effect $\Delta^D_{hydr.}$ which again fits qualitatively with the idea of a loosening of water molecules due to adjacent anions.

8. Changes in Molar Dispersion of Ions in Crystals and Complex Ions.—The decrease in molar dispersion discussed in Section 7 is caused by the tightening action of protons. This tightening of an electronic system also shows up in cases where the positively charged particle attached to it has an electronic system of its own. Thus for the alkali halides the tightening effect in dispersion is apparent from the regular increase in the absolute values of the negative differences $\mathbf{D}_{cryst.} - \mathbf{D}_{aq.\ ions}$ in Fig. 3[46]; *i. e.*, in the order of increasing polarizability of the anion (from Cl^- to I^-) and of increasing field of the cation (from Cs^+ to Li^+).[26]

In general one expects the tightening effect to be more or less compensated by the loosening action of negatively charged particles. This loosening effect shows up in the refraction of

(43a) See also K. Fajans and N. Bauer, *J. Chem. Phys.*, **10**, 410 (1942).

(44) The quantity $Q_{II}^D = \Delta D/D_{II}$ also shows a regular but more rapid gradation; *i. e.*, Q_{II}^D changes from 1.12 (Cl^-) to 1.41 (I^-). If we use the values of D_{X^-} derived from the square relation (5), the value of Q_I^D is approximately 0.46 for all three ions.

(45) Use of the square relation as an alternative method of calculation gives $(D_{OH^-})_{g.} = 0.148$.

(46) The regularities of Fig. 3 are not affected by comparing $D_{cryst.}$ with $D_{g.}$ instead of with $D_{aq.}$

fluorides of the heavier alkali ions (see Fig. 3). Of these salts, data on the dispersion are available only for potassium fluoride; here, as expected, the molar dispersion of the crystal ($\mathbf{D} = 0.080$) is larger than that of free gaseous ions ($\mathbf{D}_{g.\ ion} = 0.057$).

In the case of compounds of doubly charged noble gas ions (BeO to BaTe), the large deviations from additivity of the molar refraction[30] generally show the expected gradations.[47] An example of similar behavior for the molar dispersion is given by the differences in Table IX, obtained from the most reliable **D** values in Table III. The reason for the large differences between corresponding Δ values can be expressed in the simplest way by stating that the tightening effect is greatest in MgS, as expected.

TABLE IX

DEVIATIONS FROM ADDITIVITY FOR THE MOLAR DISPERSION OF COMPOUNDS HAVING DOUBLY CHARGED IONS

	D in cc.	Δ		D in cc.
CaS	0.71 ± 0.02	**0.54**	CaO	0.17 ± 0.02
Δ	**.33 ± .04**		Δ	**.08 ± .03**
MgS	.38 ± .02	**0.29**	MgO	.09 ± .01

The molar dispersion of oxide ion is the most reliable among the values calculated for doubly charged anions (see Section 5); it is of interest to compare this $\mathbf{D}_{O^-} = 0.32$ cc. with the values of the apparent molar dispersion which $O^=$ shows in compounds. One obtains $\mathbf{D}_{O^-\,app.}$, given in Table X, by subtracting the value of $\mathbf{D}_{g.}$ for the attached positive ion (Table V[48]) from the

TABLE X

THE APPARENT MOLAR DISPERSION OF THE OXYGEN OCTET IN CRYSTALS AND COMPLEX IONS, IN CC.

Attached cation	Ba^{++}	Sr^{++}	None	Ca^{++}	H^+	Mg^{++}	S^{6+}	Cl^{7+}
Apparent $\mathbf{D}_{O^-}$	0.70	0.37	0.32	0.16	0.149	0.09	0.070	0.057
Apparent R_{O^-}	7.91	6.81	6.95	6.03	4.76	4.24	3.68	3.31

corresponding value for the crystal (Table III) or complex ion $SO_4^=$, ClO_4^-, and OH^- (Tables VI and VIII). Concerning the corresponding data for refraction, see refs. (30) and XLIII and Table V. We note from Table X that again the dispersion of a given electronic system subjected to various force fields shows relatively larger changes than the corresponding ones previously found for refraction; *e. g.*, on going from the free ion to the oxygen octet in perchlorate, where $O^=$ is deformed by the field of Cl^{7+}, $\mathbf{D}_{O^-}$ changes by a factor of 5.6, R_{O^-} by a factor of 2.1.

Especially significant in Table X is the high value of $\mathbf{D}_{O^-\,app.}$ in BaO. It gives support to the former conclusion (VII) that the oxygen ion appreciably loosens the barium ion. This conclusion was based on the fact that also the apparent refraction of $O^=$ in BaO (7.91) is higher than the refraction obtained for free oxide ion (6.95) by extrapolation from the R values for other noble gas ions.

(47) K. Fajans, *Z. Krist.*, **66**, 325 (1928).

(48) It is apparent from extrapolating the values in Table V that R and **D** are negligibly small for S^{6+} and Cl^{7+}.

Summary

1. The difference $\mathbf{D} = R_D - R_\infty$ between the molar (Lorentz–Lorenz) refraction for the sodium D line and that extrapolated to infinite wave length from measurements in the visible is used as measure of the *molar dispersion.*

2. For isoelectronic substances, the dispersion of which can be represented by a single term formula in the visible, one is led to expect that **D** is approximately proportional to the square of R_D. It is shown that this *square relation* applies satisfactorily to noble gases (N. G.), hydrogen halides and H_2O, H_2S, H_2Se.

3. The molar dispersion $\mathbf{D}_{g.}$ for free gaseous ions of the noble gas type is obtained by applying the square relation to the corresponding values of molar refraction found previously and to the experimental data on $R_{N.G.}$ and $\mathbf{D}_{N.G.}$ A comparison of the gradations of $\mathbf{D}_{g.}$ with the gradations of the experimental molar dispersions for aqueous electrolytes leads to an estimate of the effect of hydration on the apparent ionic dispersion.

4. The molar dispersion proves to be a property which is even more sensitive to changes in the forces acting on the electronic systems of ions and molecules than is the molar refraction; in general the relative changes in **D** are about twice as great as the corresponding changes in R_D.

ANN ARBOR, MICHIGAN RECEIVED JUNE 27, 1942

[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, U. S. DEPARTMENT OF AGRICULTURE]

The Vapor Pressure of Phenothiazine[1]

BY O. A. NELSON AND L. E. SMITH

During recent years considerable experimental work has been done with phenothiazine for the purpose of establishing the value of this compound as an insecticide. It has been tested as a stomach poison against a great variety of insects,[2] but thus far the most extensive field tests have been aimed at the substitution of this compound for arsenicals for the control of the codling moth larva.

When freshly applied, phenothiazine is more toxic to this insect than lead arsenate at the same dosage. After a few days, however, the deposit loses much of its toxicity. This loss may be due to loss of deposit due to lack of adhesive properties or to decomposition in sunlight. Although the rate of vaporization of phenothiazine is very low, nevertheless it has been suggested that the loss in toxicity might be due to the evaporation of the smaller particles from the surfaces of the sprayed fruits or leaves. For this reason the vapor pressure and the rate of evaporation of this compound were determined.

Method.—It was evident that the vapor pressure of phenothiazine was much too low to be determined by the static method. An apparatus was designed, therefore, whereby the vapor pressure could be determined by the air-saturation method. The apparatus, a modification of the one used by Vanstone,[3] is shown in Fig. 1.

The saturator, about 14 inches long, was loosely packed with glass wool and powdered phenothiazine and suspended in a constant-temperature bath. Packing it in this manner reduced to a minimum the possibility of channeling and also provided an enormous surface, thus facilitating saturation of the air with the compound. The exit tube of the saturator was electrically heated to prevent condensation of the vapors before they reached the thin-walled condenser, cooled in an ice-salt mixture. The weight of the phenothiazine condensed was determined by a colorimetric method developed in the Division of Insecticide Investigations, which is based on the transformation of the compound into a red product by treatment with bromine. The limit of accuracy of this method was 1.0 microgram of phenothiazine, representing an error of less than 5% in most of the determinations. This method is essentially the same as the one described by Eddy and DeEds.[4] For the lower temperatures 11.8 liters of air was drawn through the aspirator, while for the higher temperatures only 2 liters was required. The rate of flow of the air through the apparatus was controlled by means of the capillary tip at the outlet tube from the aspirator.

In determinations of vapor pressure by the air-saturation method it is imperative that the air drawn through or over the sample be completely saturated with the compound under investigation. That the air was saturated with respect to the phenothiazine was evidenced by the observation that air could be drawn through the saturator at a rate twice that used in the vapor-pressure determination without lowering the results.

In order to verify the results obtained in the 14-inch saturator and only one condenser, a second series of vapor pressure determinations was made in which the saturator consisted of three, and later five, 10-inch glass tubes, filled as described above, and heated in an electrically controlled air furnace, and two condensers instead of one. Not a trace of phenothiazine was obtained in the second condenser, thus proving complete absorption in the former experiments. The results of this series are given in Table I, series 2.

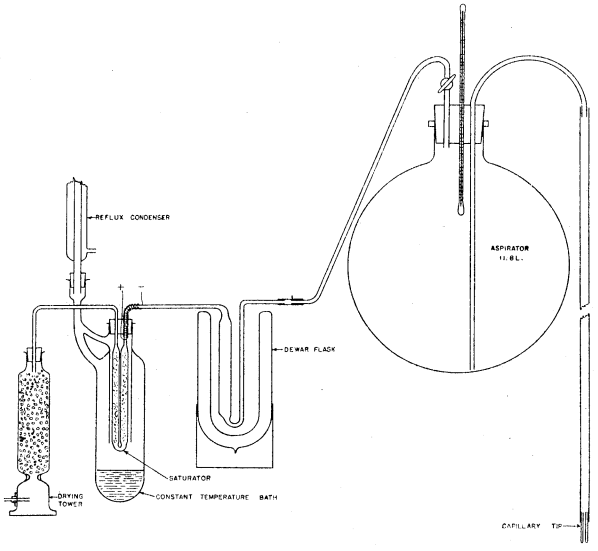


Fig. 1.

Experimental Results

After the weight of the compound vaporized in a known volume of air had been determined, the vapor pressure was readily calculated from Dalton's law of partial pressures. The expression used by Vanstone, correcting the volume of air for temperature and pressure, is

$$\text{V. P.} = \frac{wV_cTP\ 760}{273pV + 760wV_cT}$$

(1) Original manuscript received November 29, 1940. Not copyrighted.

(2) L. E. Smith, *U. S. Dept. Agr., Bur. Entomol. Plant Quarantine, Entomol. Tech. Cir.*, E-399 (1937) (mimeo.).

(3) Ernest Vanstone, *J. Chem. Soc.*, **97**, 429 (1910).

(4) C. W. Eddy and Floyd DeEds, *J. Food Research*, **2**, 2059 (1937).

wherein

V. P. = vapor pressure of phenothiazine, in mm.
w = weight of phenothiazine condensed, in grams
V_c = specific volume of phenothiazine = 22.41 liters/gram-mole = 0.1126 liter per gram
P = pressure of atmosphere, in mm.
p = pressure of air in aspirator, in mm.
V = volume of air aspirated, in liters
T = absolute temperature of air in aspirator

Table I gives the experimental data obtained in this investigation, together with the vapor pressures as calculated by means of the above equation.

TABLE I

EXPERIMENTAL DATA FOR VAPOR PRESSURE OF PHENOTHIAZINE

Temp., °C.	Replications, number	Vapor pressure, mm.	Standard error, mm.
	Series 1		
63	7	0.00008	0.00002
66	3	.00014	.00003
78	6	.00026	.00003
100.5	3	.0016	.0001
111	10	.0038	.0002
121.5	4	.0089	.0004
	Series 2		
78	4	0.0002	
90	1	.00064	
96.5	1	.0014	
99	3	.0018	
100	3	.0019	
110	2	.0037	
112	1	.0042	
121	2	.0085	

Over limited ranges of temperature and pressure the relation between these factors can be expressed by the equation $\log p = 9.265 - 4490.0/T(\text{abs.})$. By means of this equation the vapor pressures of phenothiazine were calculated at 10-degree intervals from 40 to 140°. These data are recorded in Table II.

TABLE II

CALCULATED VAPOR PRESSURES OF PHENOTHIAZINE

Temp., °C.	Vapor pressure, mm.	Temp., °C.	Vapor pressure, mm.
40	0.000008	100	0.0016
50	.000023	110	.0035
60	.000058	120	.0070
70	.00015	130	.013
80	.00032	140	.025
90	.00081		

Rate of Vaporization of Phenothiazine

The rate at which phenothiazine vaporized was determined in two series of experiments, in which glass plates were dusted with finely divided phenothiazine. In the first series two glass plates with areas totaling 384 sq. cm. were placed inside a 4-inch glass tube, which in turn was kept at 45° in a constant-temperature air thermostat. A gentle current of air was drawn over the dusted surfaces to carry off the phenothiazine vapors. The runs were continued for two to four days. An absorption bulb filled with ethyl alcohol and kept at ice–salt temperature was inserted in the air line for three to six hours, and the weight of phenothiazine was determined by the colorimetric method. To determine whether all the phenothiazine was absorbed, a second absorption bulb was inserted in the line, and air was drawn through for four hours. No phenothiazine was found in the second bulb.

In the second series of experiments, the finely divided phenothiazine was dusted on 45 by 50 mm. cover glasses, which were then placed at an angle of about 45° in echelon arrangement on a wire rack in the air thermostat at 45°. A moderate current of air was drawn over the dusted surfaces for ninety-six hours. The loss in weight of phenothiazine was determined by direct weighing of the cover glasses, before and after evaporation, on a micro balance sensitive to 0.002 mg.

Table III gives a summary of the results obtained in these experiments.

TABLE III

RATE OF VAPORIZATION OF PHENOTHIAZINE

Series	Replications	Rate of evaporation μg./sq. cm./hr.	Probable error of the mean μg./sq. cm./hr.
1	11	0.019	0.002
2	8	.027	.0027
Average		.023	.0013

The average particle size of the sample used in these experiments, as determined by the air-permeation method,[5] was 3 microns diameter.

The method used in determining the rate of vaporization was designed to yield results comparable to those obtained under field conditions, where the insecticide is sprayed or dusted on the surfaces of fruits and leaves. The weight of phenothiazine per unit area of glass surface in these experiments was about five times the amount applied to fruits or foliage, and because of this difference in density of phenothiazine particles there might possibly be a slight difference in rate of evaporation. The difference is believed to be small, however, and the rates recorded here are considered good estimates of the rate of loss of this compound due to vaporization in actual use.

The original weight of phenothiazine on the glass plates was approximately 200 micrograms per square centimeter. As the average rate of loss amounted to only 0.023 microgram per square centimeter per hour, the loss over a period

(5) E. L. Gooden and C. M. Smith, *Ind. Eng. Chem., Anal. Ed.*, **12**, 479 (1940).

of one hundred hours would be slightly more than 1%.

Summary

The vapor pressure of phenothiazine within the temperature range of 63–121° and the rate of evaporation of the finely powdered compound at 45° have been determined.

The results obtained show that the loss in toxicity of phenothiazine when used for the control of insect pests is not due to evaporation.

BELTSVILLE, MARYLAND RECEIVED AUGUST 6, 1942

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

Tracer Studies with Radioactive Hydrogen. Some Experiments on Photosynthesis and Chlorophyll

BY T. H. NORRIS, S. RUBEN AND M. B. ALLEN

Since nothing is known regarding the role of chlorophyll in green plant photosynthesis, there has been, and still is, considerable speculation on the subject. The many theories that have been proposed may be divided into two classifications: (1) chlorophyll participates as a reducing agent (hydrogen donor), (2) chlorophyll merely acts as a sensitizer (as certain dyes function on photographic plates, for example). The first category is by far the larger and we may cite a few of the more interesting proposals found in this group.

Dixon and Ball[1] have suggested that chlorophylls *a* and *b* are involved in a reversible oxidation–reduction cycle in which chlorophyll *a* (GH_2) is oxidized to *b* (GO).

$$GH_2 + CO_2 + \text{light} \longrightarrow GO + 1/n(H_2CO)n \quad (1)$$

and *b* in turn is reduced to *a* as follows[2]:

$$GO + H_2O + \text{light} \longrightarrow GH_2 + O_2 \quad (2)$$

The discovery that the chlorophylls contain a readily oxidizable group led Conant[3] and coworkers to propose that the pigment might act as a two electron reducing agent.

$$12GH_2 + 6CO_2 \xrightarrow{\text{enzyme}} 12G + C_6H_{12}O_6 + 6H_2O \quad (3)$$

in a dark reaction,[3] chlorophyll being regenerated by a photochemical process.[4]

$$12G + 12H_2O + \text{light} \longrightarrow 12GH_2 + 6O_2 \quad (4)$$

Stoll[4] and Willstätter[5] independently consider chlorophyll to function as a hydrogen donor in a photochemical reaction producing monodehydrochlorophyll (GH). This free radical is supposed to revert to the original dye via another photochemical process.

$$GH + H_2O + h\nu \longrightarrow GH_2 + OH \quad (5)$$

Franck[6,7] has a somewhat similar point of view, but has formulated the chlorophyll regeneration as

$$GH + R'OH + h\nu \longrightarrow GH_2 + R'O \quad (6)$$

where R'OH is different from water.

It occurred to us that using radioactive hydrogen[8] H^3, as a tracer it might be possible to learn whether or not chlorophyll is participating in photosynthesis as a donor of hydrogen. If photosynthesis is allowed to proceed for a sufficiently long time in water containing HTO[9] chlorophyll containing T should be formed[10] if the idea underlying equations 2, 4, 5, 6 is correct.

Experimental

Eleven cc. of the unicellular green alga *Chlorella pyrenoidosa* was suspended in 220 cc. of 0.05 *M* potassium bicarbonate solution containing HTO and strongly illuminated for three hours. During this period 2.5×10^{-3} mole of oxygen was evolved and a simple calculation shows that if the donor scheme is correct each chlorophyll should have been oxidized and reduced at least 100 times.[10a] The algae were centrifuged and the chlorophyll removed by exhaustive extraction with 95% acetone. All operations from the end of the illumination to the final burning of the chlorophyll were performed in strict darkness. In order to facilitate operations in the dark, the volumes of all solutions and vessels were carefully predetermined. To remove a lower layer from a separatory funnel, an evacuated

(1) Dixon and Ball, *Sci. Proc. Roy. Dublin Soc.*, **16**, 435 (1922).

(2) For an attempt at an experimental check on this proposal *cf.* Ruben, Frenkel and Kamen, *J. Phys. Chem.*, **46**, 710 (1942).

(3) Conant, Dietz and Kamerling, *Science*, **73**, 268 (1931).

(4) Stoll, *Naturw.*, **20**, 955 (1932); **24**, 53 (1936).

(5) Willstätter *ibid.* **21** 252 (1933)

(6) Franck and Herzfeld, *J. Phys. Chem.*, **45**, 978 (1941).

(7) Franck and Gaffron, "Advances in Enzymology," I, Interscience Publishers, Inc., New York, N. Y., 1941, p. 215.

(8) Alvarez and Cornog, *Phys. Rev.*, **56**, 613 (1939).

(9) We use the symbol T for H^3 (*cf.* Libby and Barter, *J. Chem. Phys.*, **10**, 184 (1942)).

(10) The possibility of an isotope separation will be discussed below.

(10a) Since the quantum yield is 0.1–0.08 (*cf.* Manning, Stauffer, Duggar and Daniels, THIS JOURNAL, **60**, 266 (1938), and Emerson and Lewis, *Am. J. Bot.*, **28**, 789 (1941)).

vessel of known volume was attached to the bottom. The chlorophyll was transferred by extraction to pentane and this solution washed twice with 80% acetone. The pentane layer was thoroughly washed with water. Under such conditions chlorophyll will usually precipitate, but the solution was too dilute in the present case for this to occur to an appreciable extent. The solvent was distilled off *in vacuo* at room temperature and the chlorophyll[11] carefully dried under high vacuum for several days. It was then burned in a stream of dry oxygen to carbon dioxide and water, the gases being passed over heated cupric oxide and the water collected in a cold trap. This water was converted quantitatively to magnesium oxide and hydrogen with excess fresh magnesium turnings at ~625°.[12] The conversion was carried out in a large test-tube filled with turnings, connected to the vacuum system through a rubber stopper sealed with de Khotinsky cement. The water was frozen in the bottom of the tube by immersion in liquid air. After evacuation the upper section was heated to ~625° electrically and the water then distilled up through the turnings, one distillation usually being sufficient for complete reaction. The evolved hydrogen was dried by passage through a liquid air trap and introduced directly into a Geiger counter containing 1.5 cm. of ethanol vapor and its radioactivity measured.[13] By using a new test-tube and stopper for each conversion the difficulty of decontamination was greatly reduced. The counter and the vacuum line were rid of adsorbed radiohydrogen by repeated flushing with ethanol vapor. The results of three separate experiments are summarized in Table I.

TABLE I

FORMATION OF RADIOACTIVE CHLOROPHYLL DURING CHLORELLA PHOTOSYNTHESIS IN HTO

Expt.	Algae,[b] cc.	Conditions	O_2 evolved (millimoles)	Radioactivity (counts/min.) Found experimentally	Radioactivity (counts/min.) Theoretical[a] for complete exchange
1	11.0[c]	175 min. in light	2.0	< 80	2200
2	3.1[d]	185 min. in light	0.5	< 65	5260
3	5.5[e]	180 min. in dark	...	<100	9350

[a] Calculated on the assumption that each chlorophyll molecule in the algae has one hydrogen atom capable of undergoing photodissociation and moreover that each cycle involves the same C—H bond. [b] 1 cc. of algae contains 2×10^{-5} mole of chlorophyll. [c] Suspended in 220 cc. of 0.05 *M* $KHCO_3$ containing 2.0×10^7 c./min./mole H_2O. [d] Suspended in 55 cc. of 0.05 *M* $KHCO_3$ containing 1.7×10^8 c./min./mole H_2O. [e] Suspended in 50 cc. of 0.05 *M* $KHCO_3$ containing 1.7×10^8 c./min./mole H_2O.

It is apparent from Table I that no evidence for a photochemical exchange between chlorophyll and H^+ (*e. g.*, H_2O, —OH, —NH_2, —COOH) was obtained. Before concluding that chlorophyll does not act as a hydrogen donor in photosynthesis we must consider two possible objections: (1) loss of H^3 from chlorophyll by thermal exchange during the extraction process; (2) an isotope effect—*i. e.*, H^3 is not an ideal tracer for hydrogen of mass 1.

The possibility that chlorophyll contains labile hydrogen which can undergo photochemical or thermal exchange with water, etc., was therefore investigated. Pure chlorophyll was prepared from fresh spinach leaves following the procedure of Mackinney.[14] After drying in high vacuum for several weeks, the final product was analyzed spectrophotometrically[15] and found to be 97 ± 1% pure while the *a*/*b* ratio was 1.77. A weighed portion (40 mg.) of this chlorophyll was dissolved in 8 cc. of absolute ethanol and then 2 cc. of water (HDO) containing HTO and DTO was added.[16] This solution was shaken in the light for thirty minutes and the solvent distilled off *in vacuo* at room temperature. An attempt was made to free the chlorophyll of adsorbed or trapped solvent by maintaining a high vacuum (10^{-6} mm.) over it for several days, after which the chlorophyll and its glass container (crushed) were introduced into a combustion tube and burned in a stream of dry air. In order to obtain sufficient hydrogen for several entirely independent radioactivity determinations, a weighed portion of anhydrous glucose (Merck reagent grade) was added to the chlorophyll just prior to combustion. The resulting water was converted to hydrogen and counted. The results of this and similar experiments are summarized in Table II.

TABLE II

SEARCH FOR EXCHANGEABLE HYDROGEN IN CHLOROPHYLL

Expt.	Chlorophyll, g.	Specific activity of hydroxyl hydrogen in solvent (80% EtOH) counts/min./g. atom H	Experimental conditions	Tritium content of chlorophyll Exptl.	Tritium content of chlorophyll Theoretical[a]
1	0.040	2.78×10^8	30 min. light	187 ±30	3820
2	.095	0.53×10^8	60 min. light[b]	51 ±20	2430
3	.034	2.78×10^8	30 min. light[c]	100 ±25	3240

[a] Calculated on the assumption that each chlorophyll molecule has one exchangeable hydrogen atom. In experiments (1) and (3) 30.8% of the total H_2 generated was introduced in the Geiger counter; in (2) 43.4% of the H_2 was counted. [b] O_2 excluded at all times during experiment. After removing active solvent (25 cc.) the chlorophyll was dissolved in 10 cc. of 95% ethanol (inactive) which after ~five minutes was distilled off *in vacuo* at room temperature. This operation was repeated twice, the intention being the removal of firmly adsorbed or trapped radio-active solvent. [c] Washed once with 10 cc. of inactive 95% ethanol.

Since the small amount of radiohydrogen found in Experiments 1–3 was approximately 10^{-6} of the T used in each experiment, it was of interest to determine if exchange with the glass occurred. To this end Experiment (1) was repeated except that the chlorophyll was omitted. The hydrogen obtained in this experiment gave 30 ± 10 counts/minute in the Geiger counter.

(11) This probably contained small amounts of yellow pigments, etc., *cf.* Mackinney, *J. Biol. Chem.*, **132**, 91 (1940).

(12) In order to avoid any isotope separation it is essential that this conversion be quantitative. This method was found to be more rapid than the reaction with hot zinc.

(13) For a brief discussion of counting radiohydrogen see Allen and Ruben, THIS JOURNAL, **64**, 948 (1942).

(14) Mackinney, *J. Biol. Chem.*, **132**, 91 (1940).

(15) We are indebted to Dr. S. Aronoff for this analysis.

(16) Radio-water of this composition was obtained by condensation of the exhaust gases from the acceleration chamber of the 60" Berkeley cyclotron.

Discussion

It would appear from Tables I and II that $< 5\%$ of the chlorophyll has exchanged one hydrogen. However, due to the possibility of an appreciable isotope separation, the low values shown in Tables I and II do not exclude the possible existence of a cycle (Equations (7) and (8)) in which a photoactivated chlorophyll (G^*H_2) acts as a donor of

$$h\nu + GH_2 + A \longrightarrow G^*H_2 + A \longrightarrow GH + HA \quad (7)$$

hydrogen to some unknown substance (A)[17] and the chlorophyll free radical (GH) formed in this process is reduced to native chlorophyll (GH_2) by a thermal reaction such as (8).

$$GH + ROH \longrightarrow GH_2 + RO \quad (8)$$

Process (8) very likely has a lower activation energy than the analogous reaction (9) involving an oxygen–tritium bond.

$$GH + ROT \longrightarrow GHT + RO \quad (9)$$

The difference in energies of activation could be of the order of 2 kcal. and consequently the specific reaction rate for (8) would be ~20 times greater than that of (9).

It might be of interest to mention some simple reactions involving hydrogen and deuterium in which the differences in activation energies have been obtained by kinetic studies. Rollefson[18] found a difference of 1630 calories in the energies of activation for the following

$$Cl + H_2 \longrightarrow HCl + H \quad (10)$$
$$Cl + D_2 \longrightarrow DCl + D \quad (11)$$

Farkas and Farkas[19] studied

$$Cl + H_2 \longrightarrow HCl + H \quad (12)$$
$$Cl + HD \longrightarrow DCl + H \quad (13)$$

and found the difference to be 600 calories.

In the photochemical reaction (7) the absorption of a light quantum would raise the photoactivated chlorophyll to an energy level well over the top of the energy barrier and therefore the specific reaction velocities for (7) and (14) would be the same and no isotope separation would occur.

$$h\nu + GHT + A \longrightarrow GH^*T + A \longrightarrow GH + TA \quad (14)$$

This seems to be a reasonable assumption since the quantum yield of photosynthesis is essentially the same[20] for wave lengths of light from 4500 to 6900 Å.

On the other hand, if (7) and (14) were thermal or if the photoactivated compound dropped to a lower energy level (by fluorescence or by a tautomeric change such as suggested by Franck and Livingston[21] such that the energy content was within say 1 kcal. of the activation energy of (7), the isotope separation would result in which GHT would tend to accumulate over GH_2. Moreover, if (8) and (9) were photochemical no isotope separation would occur.

It should be noted that Trelease and coworkers[22,23,24] have found the rate of photosynthesis in pure deuterium oxide (heavy water) to be 0.41 the rate in water. They have also shown that the thermal reactions and not the photochemical processes are slowed by the deuterium. If a reaction such as (8) is the rate determining step the difference in activation energies of (15) and (8)

$$GH + ROD \longrightarrow GHD + RO \quad (15)$$

is ~600 calories. Assuming the difference in energies of activation is due primarily[25] to the difference in zero point energies, one calculates that the difference in activation energies in rupturing a carbon–tritium and a carbon–hydrogen bond is ~25% greater than the corresponding difference between a carbon–deuterium and a carbon–hydrogen bond. However, it is possible that photosynthesis involves several thermal reactions in which isotope separations may occur. Therefore, in the tritium experiments where there is competition between ROH and ROT the isotope separation may be greater or less than one would expect from a simple consideration of the rate in pure deuterium oxide.

If the experiments described in this communication were repeated using 100% D_2O and the chlorophyll analyzed for deuterium content, all uncertainties due to isotopic effects would be completely eliminated and an unequivocal conclusion regarding the role of chlorophyll in photosynthesis could be reached. We hope to do this experiment in the near future.

It is evident that the results obtained in this research cannot be considered as definite evidence for or against the hydrogen donor hypothesis, but we may reasonably conclude that *either no isotope separation accompanies (7) and does take place in*

(17) Equation (7) is essentially similar to the formulation by Franck and Gaffron

$$GH_2\text{-}CO_2 \text{ complex} + h\nu \longrightarrow GH + \text{intermediate.}$$

(18) Rollefson, *J. Chem. Phys.*, **2**, 144 (1934).
(19) Farkas and Farkas, *Naturw.*, **22**, 218 (1934).
(20) Emerson and Lewis, *J. Gen. Phys.*, **25**, 579 (1942).
(21) Franck and Livingston, *J. Chem. Phys.*, **9**, 184 (1941).
(22) Pratt, Craig and Trelease, *Science*, **85**, 271 (1937).
(23) Craig and Trelease, *Am. J. Botany*, **24**, 232 (1937).
(24) Pratt and Trelease, *ibid.*, **25**, 133 (1938).
(25) *Cf.* "Light and Heavy Hydrogen," by A. Farkas, Cambridge University Press, 1935.

(8) or else the hypothesis that chlorophyll acts as a donor of hydrogen in photosynthesis should be abandoned.

Acknowledgments.—We wish to thank Professors G. K. Rollefson and J. Franck for many helpful suggestions and discussions. We are indebted to Professor E. O. Lawrence and members of the Radiation Laboratory, particularly Dr. M. D. Kamen, for the tritium samples.

Summary

1. The formation of chlorophyll containing T could not be detected during photosynthesis of *Chlorella pyrenoidosa* in HTO + H_2O.

2. No (<5%) thermal exchange was observed between purified chlorophyll and 80% ethanol containing HTO.

3. The implications of these results for the theory that chlorophyll acts as a hydrogen donor in photosynthesis are discussed.

4. It is pointed out that repetition of the experiments herein described using 100% D_2O would avoid the question of isotope separation and make possible an unequivocal conclusion regarding the role of chlorophyll.

BERKELEY, CALIFORNIA RECEIVED SEPTEMBER 14, 1942

NOTES

Characteristics of β-[2,5-Dimethoxyphenyl]-β-hydroxyisopropylamine Hydrochloride

BY RICHARD BALTZLY AND JOHANNES S. BUCK

This compound was reported recently[1]; subsequent investigation makes it evident that the substance to which that formula was attributed is actually β-[2,5-dimethoxyphenyl]-β-oxoisopropylamine hydrochloride. This could have been anticipated[2] but was not at the time. The error arose partly from the difficulty of interpreting small absorptions of hydrogen when using a catalyst (palladized charcoal) that itself binds relatively large amounts of hydrogen and partly from adverse conditions over which the analyst had no control.

The substance previously obtained (m. p. 176° dec.) when dissolved in water and reduced with hydrogen and platinum-black absorbed 1 mole of hydrogen. A new hydrochloride was isolated melting at 215°.

Anal. Calcd. for $C_{11}H_{18}O_3N$: C, 53.31; H, 7.33. Found: C, 53.43; H, 7.53.

When the corresponding base was acetylated with acetic anhydride a diacetyl derivative was formed melting at 120° and crystallizing from ethyl acetate–hexane in parallelogrammatic plates.

Anal. Calcd. for $C_{15}H_{21}O_5N$: C, 60.98; H, 7.17. Calcd. for $C_{13}H_{17}O_4N$: C, 62.12; H, 6.83. Found: C, 61.09; H, 7.30.

THE BURROUGHS WELLCOME & CO. U. S. A.
EXPERIMENTAL RESEARCH LABORATORIES
TUCKAHOE, NEW YORK RECEIVED OCTOBER 24, 1942

(1) Baltzly and Buck, THIS JOURNAL, **62**, 164 (1940).
(2) *Cf.* Hartung, *ibid.*, **53**, 4149 (1931).

Identification of *o*- and *p*-Sulfobenzoic Acids[1] as their S-Benzylthiuronium Salts

BY E. CAMPAIGNE[2] AND C. M. SUTER[3]

The structure of the alkylated benzenesulfonic acids may be partially clarified by oxidation to the sulfobenzoic acids. The identity of the *o*-, *m*- and *p*-sulfobenzoic acids may be determined by conversion to the acid chlorides and to the amides.[4] This involves separation and drying of the salts of the sulfobenzoic acids, and the somewhat tedious conversion to the chlorides with a phosphorus halide. The use of S-benzylthiuronium chloride as an analytical reagent for sulfonic acids[5] has recently been reported. Since the benzylthiuronium derivatives are prepared in water solutions, the use of this reagent should give a quick and easy method for the identification of the oxidation products of alkylbenzenesulfonic acids and related compounds.

The S-benzylthiuronium salts of *o*- and *p*-sulfobenzoic acid were obtained in good yield from water solutions of the acid sodium or ammonium salts, but the derivative of the *m*-sulfobenzoic acid was found to be quite soluble in water, and could not be isolated conveniently. The *o*-sulfo-

(1) This investigation was supported by a grant from the Abbott Fund of Northwestern University.
(2) Present Address: University of Texas, Medical Branch, Galveston, Texas.
(3) Present Address: Winthrop Chemical Company, Inc., Rensselaer, N. Y.
(4) Beilstein's "Handbuch," 4th ed., Vol. XI, p. 369.
(5) Chambers and Watt, *J. Org. Chem.*, **6**, 376 (1941).

benzoic acid gave an immediate precipitate from hot dilute acid. This salt was extremely insoluble, and analysis showed it to be the di-(S-benzylthiuronium) *o*-sulfobenzoate. The *p*-sulfobenzoic acid gave a derivative which was more soluble, crystallizing slowly from cold dilute acid. Analysis shows this to be the acid salt, S-benzylthiuronium hydrogen *p*-sulfobenzoate. The difference in solubilities of these three salts gives a convenient method of identification of the three acids. A solution of the free acid, or a solution of a salt of the acid which has been acidified with a few drops of concentrated hydrochloric acid, is heated to boiling and the calculated quantity of a 10% solution of S-benzylthiuronium chloride is added. An immediate precipitate indicates *o*-sulfobenzoic acid. A precipitate which crystallizes slowly on cooling indicates *p*-sulfobenzoic acid, and if no precipitate, or an oil, is obtained, the acid is *m*-sulfobenzoic acid.

Experimental

***p*-Sulfobenzoic Acid.**—Two grams of *p*-toluenesulfonic acid was oxidized with 5 g. of potassium permanganate in basic solution. The precipitated manganese dioxide was filtered off, and hydrochloric acid was added until the solution became acidic. The addition of barium chloride caused an immediate precipitate of white flakes of the barium salt of *p*-sulfobenzoic acid, which was soluble in base and reprecipitated by acid. One gram of this salt was digested in 30 ml. of hot water with excess sodium sulfate and 1 ml. of concentrated hydrochloric acid. The precipitate of barium sulfate was removed, and 10 ml. of 10% S-benzylthiuronium chloride was added. The clear solution, on cooling, gave flat plates of S-benzylthiuronium hydrogen *p*-sulfobenzoate which were recrystallized with difficulty from ethyl alcohol, m. p. 212.6–214.4° (cor.).

Anal. Calcd. for $C_{15}H_{16}N_2O_5S_2$: N, 7.61; Found: N, 7.80.

***m*-Sulfobenzoic Acid.**—This acid was prepared in the usual manner by sulfonating benzoic acid in 30% fuming sulfuric acid and salting out the acid sodium salt. One gram of this salt was dissolved in 20 ml. of distilled water containing 1 ml. of concentrated hydrochloric acid and 10 ml. of 10% S-benzylthiuronium chloride was added. No precipitate formed on cooling. At freezing temperatures an emulsion formed which redissolved as it warmed to room temperature. No further attempt was made to isolate this salt.

***o*-Sulfobenzoic Acid.**—The acid ammonium salt of this acid was prepared from saccharin according to the method of Clarke and Dreger.[6] One gram of the crude salt was dissolved in 30 ml. of hot water, 1 ml. of concentrated hydrochloric acid and 10 ml. of 10% S-benzylthiuronium chloride were added. An immediate precipitate was formed in the hot solution. After cooling, the di-(S-benzylthiuronium) *o*-sulfobenzoate was recrystallized from 70% alcohol as fine white needles, m. p. 205.5–206.5° (cor.). When mixed with the derivative from *p*-sulfobenzoic acid the melting point was 194–196°.

Anal. Calcd. for $C_{23}H_{26}N_4O_5S_3$: N, 10.25. Found: N, 10.35.

(6) Clarke and Dreger, "Organic Syntheses," Coll. Vol. I, p. 13.

CHEMICAL LABORATORY
NORTHWESTERN UNIVERSITY
EVANSTON, ILLINOIS RECEIVED SEPTEMBER 11, 1942

The Formation of Insoluble Sulfur in the Presence of Gases Other than Sulfur Dioxide

BY EDWARD A. FEHNEL

The work of Smith and Holmes[1] and, more recently, of Das and Ghosh[2] would indicate that the plasticity and insolubility of certain forms of sulfur are dependent upon the presence of at least a trace of sulfur dioxide. The former investigators considered the presence of this compound an essential condition for the formation of plastic sulfur; the latter believe that all insoluble forms of the element owe their distinctive property to the presence of an insulating film of sulfur dioxide about the minute crystallites. On the other hand, suggestions have been made by various investigators, notably Deines[3] and Meyer,[4] that possibly other foreign substances might also be capable of causing the formation of insoluble forms of sulfur.

In order to decide between these two conflicting points of view, an improved quenching method was devised in this Laboratory for the preparation of insoluble, plastic sulfur in a closed system which permitted contact with any desired gas while eliminating all possibility of contact with air. Under these conditions the formation of traces of sulfur dioxide by aerial contact is avoided, and it becomes possible to ascribe the various effects to their true causes.

It was found that while air and sulfur dioxide gave the expected results, yielding clear, amber, plastic masses analyzing about 36% insoluble sulfur after 6 days, and while nitrogen and ammonia gave opaque, yellow, brittle masses analyzing less than 4% insoluble sulfur, both hydrogen chloride and hydrogen sulfide were capable of producing clear, amber, plastic masses analyzing 36% and 8% insoluble sulfur, respectively. The plasticity of these latter forms was, it is true, rela-

(1) Smith and Holmes, *Z. physik. Chem.*, **42**, 469 (1903); THIS JOURNAL, **27**, 979 (1905).
(2) Das and Ghosh, *Indian J. Phys.*, **13**, 91 (1939).
(3) Deines, *Z. anorg. allgem. Chem.*, **213**, 183 (1933).
(4) Meyer, *Trans. Faraday Soc*, **32**, 148 (1936)

tively short-lived, lasting about twenty minutes in the case of the HCl-produced material and only two minutes in the case of the H_2S-produced material. Nevertheless, the plastic state was observed to exist, and in contrast to the immediate solidification of the material formed in the presence of the inert gases nitrogen and ammonia, its life in this state was quite appreciable. The corresponding increases in the proportion of insoluble sulfur present in the hardened samples is also indicative of the ability of hydrogen chloride and hydrogen sulfide to act similarly to sulfur dioxide in the formation of the plastic and insoluble modifications.

Thus, theories postulating the indispensability of sulfur dioxide in the formation of plastic sulfur or for the maintenance of insolubility in the hardened mass appear, on the basis of these facts, to be untenable. The suggestions by Deines and by Meyer that foreign substances other than sulfur dioxide might be effective in causing similar results are upheld by the experimental evidence.

DEPARTMENT OF CHEMISTRY
LEHIGH UNIVERSITY
BETHLEHEM, PENNSYLVANIA RECEIVED AUGUST 6, 1942

Preparation of Germanium Tetrachloride, $GeCl_4$

BY LAURENCE S. FOSTER, J. W. DRENAN AND A. F. WILLISTON

When germanium dioxide, GeO_2, is boiled with hydrochloric acid, germanium tetrachloride, $GeCl_4$, volatilizes if the concentration of hydrogen chloride approaches 6 *N*.[1] It has been observed in this Laboratory and elsewhere, however, that if the concentration of hydrogen chloride is too high, germanium tetrachloride vapor is carried uncondensed through a water cooled condenser.[2] The loss of germanium is readily explained. When the acid concentration is high, germanium tetrachloride is not hydrolyzed and, in addition, is not very soluble in such acid solutions. Its vapor pressure, furthermore, is quite high at the temperature of the cooling water in the condenser. When 6 *N* hydrochloric acid, approximately the constant boiling mixture, is used, both the acid and the germanium tetrachloride are completely condensed; when mixtures with higher concentrations of hydrogen chloride are boiled, however, gaseous hydrogen chloride passes through the condenser and carries considerable germanium tetrachloride along with it.

Aitkenhead and Middleton[2b] took advantage of this phenomenon in the analysis of minerals for small amounts of germanium; germanium tetrachloride was distilled in a stream of hydrogen chloride gas, thus removing the germanium completely from the rest of the dissolved sample. The gases which escaped from the top of a reflux condenser were absorbed in a small volume of water and the germanium content readily determined.

At very low temperatures (−72°) no complexes form between germanium tetrachloride and hydrogen chloride[3] so that it is possible to separate the two by judicious cooling. It has been found that if the vapors which emerge from the top of a reflux condenser, after being dried, are cooled in a "dry-ice"–isopropyl alcohol mixture, the hydrogen chloride (b. p. −85°) escapes uncondensed and the germanium tetrachloride freezes out as a pure white solid (m. p. −49.5°). The method has the added advantage that the germanium dioxide is more readily dissolved in the boiling flask when the concentration of hydrogen chloride is kept high.

Procedure.—Germanium oxide is suspended in 6 *N* hydrochloric acid and the suspension is boiled gently under a reflux condenser. Hydrogen chloride is passed into the flask at a rapid rate at first so that some of it escapes slowly through a sulfuric acid trap at the end of the train. Later, when the absorption in the boiling flask nears completion, the rate of flow is reduced. As the gases pass through the reflux condenser, condensed germanium tetrachloride and constant boiling hydrochloric acid return to the flask, but the gases escaping through the condenser carry a high percentage of germanium tetrachloride and gradually all of it is volatilized. The gas mixture, having been cooled to the dew point of the germanium tetrachloride at the temperature of the cooling water, will be unsaturated at room temperature and will not deposit liquid germanium tetrachloride in the calcium chloride tower used to remove residual moisture. When passed through the tube cooled by means of dry-ice, however, the germanium tetrachloride is completely removed and entrains very little hydrogen chloride. An all glass apparatus is preferable, but no difficluties are encountered if rubber connections are used. By this procedure 5 to 10 g. of GeO_2 may be converted to the tetrachloride within an hour. Residual hydrogen chloride may be removed by allowing the product to stand over sodium carbonate, filtering and distilling in dry apparatus.[1b]

CONTRIBUTION FROM THE
JESSE METCALF CHEMICAL LABORATORY
OF BROWN UNIVERSITY
PROVIDENCE, R. I. RECEIVED OCTOBER 2, 1942

(1) (a) Dennis and Johnson, THIS JOURNAL, **45**, 1380 (1923); (b) Tabern, Orndorff and Dennis, *ibid.*, **47**, 2040 (1925); (c) Pugh and Thomas, *J. Chem. Soc.*, 1052 (1926).

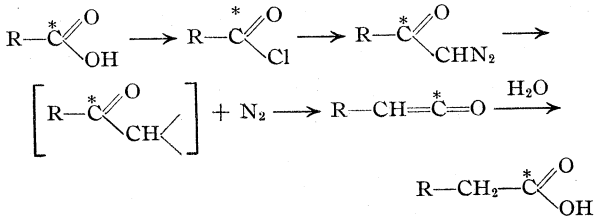
(2) (a) H. Lundin, *Trans. Am. Electrochem. Soc.*, **63**, 149 (1933); (b) W. C. Aitkenhead and A. R. Middleton, *Ind. Eng. Chem., Anal. Ed.*, **10**, 633 (1938).

(3) R. Schwarz and H. Giese, *Ber.*, **63**, 2429 (1930).

The Mechanism of the Arndt-Eistert Reaction[1]

BY CLAYTON HUGGETT, RICHARD T. ARNOLD AND T. IVAN TAYLOR

The conversion of an acid to its next higher homolog by the Arndt–Eistert procedure is of considerable value to organic chemists. The most reasonable mechanism[2] for the reaction proposes the formation and decomposition of a ketene.



This mechanism readily explains the type of products formed under varying experimental conditions, and the analogy to the Curtius and Hofmann rearrangements has been recognized.[3]

From the above equation it is seen that the carbonyl carbon atom of the starting acid becomes the carbonyl carbon atom in the final product; the newly introduced carbon atom then occupies the alpha position.

We have found substantial evidence to support this formulation of the mechanism by using C^{13} isotopes as tracer elements. Heavy benzoic acid prepared by the carbonation of ordinary phenylmagnesium bromide with carbon dioxide[4] containing a high per cent. of C^{13} was converted to phenylacetic acid by the method of Arndt and Eistert. The heavy isotope was found in the carbonyl group of the phenylacetic acid as shown by decarboxylation with copper chromite and quinoline.

The carbon dioxide from the heavy benzoic acid contained 2.51 per cent. C^{13} and that from the phenylacetic acid measured 2.53 per cent. C^{13}. Within experimental error these values are identical and support the ketene mechanism.[2]

Of necessity this work has been discontinued but will be renewed when conditions permit.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MINNESOTA
MINNEAPOLIS, MINNESOTA RECEIVED OCTOBER 19, 1942

(1) For an excellent discussion see Bachmann and Struve, "Organic Reactions," Vol. I, J. Wiley and Sons, Inc., New York, N. Y., 1942, p. 38.

(2) Eistert, *Ber.*, **68**, 208 (1935).

(3) Lane, Willenz, Weissberger and Wallis, *J. Org. Chem.*, **5**, 276 (1940).

(4) We are indebted to Dr. A. O. Nier for the heavy methane from which this was formed.

The Ionization Constant of Morpholine in Water[1]

BY ALVIN R. INGRAM[2] AND W. F. LUDER

In connection with an investigation of the conductivity of morpholine solutions, it seemed desirable to know the strength of morpholine as a base. Accordingly, the ionization constant of morpholine in water was measured by the conductivity method.

Since great accuracy was not required, no special precautions were taken in the preparation of conductivity water. This, together with the low conductance of morpholine solutions, resulted in solvent corrections of several per cent. at the most dilute concentrations. Another source of error entered into the determination of Λ_0. In order to find Λ_0 it was necessary to measure the conductance of morpholinium chloride. The slight hydrolysis of this salt was not taken into account in the extrapolation for its Λ_0.

However, analysis of the results indicates that the value for the ionization constant of morpholine in water at 25° is 2.44×10^{-6} within the limits of error to which most ionization constants in the literature are given.

Experimental

Materials, Apparatus, and Procedure.—The bridge[3] and procedure[4] have been described previously. The temperature of the oil thermostat was kept at 25 ± 0.01° by an electronic relay. The water used was ordinary distilled water once redistilled and usually had a specific conductance of about 1×10^{-6} mho. Morpholine was dried over barium oxide and aluminum oxide, then fractionated three times off aluminum oxide, the constant boiling portion being used for runs. The best conductance for morpholine treated in this way was 6×10^{-10} mho. Morpholinium chloride (m. p. 177°) was prepared by passing dry hydrogen chloride over the surface of purified morpholine, washing the product with redistilled petroleum ether and diethyl ether, and pumping in a vacuum desiccator over phosphorus pentoxide.

Results.—Values of Λ are given in Tables I and II. Plots of $1/\Lambda$ against $c\Lambda$ for morpho-

(1) Abstracted from a portion of a thesis submitted by Alvin R. Ingram to the faculty of Northeastern University in partial fulfillment of the requirements for the M. S. degree, June, 1942.

(2) Present address: General Chemical Defense Corporation, Point Pleasant, West Virginia.

(3) W. F. Luder, THIS JOURNAL, **62**, 89 (1940).

(4) D. J. Mead, R. M. Fuoss and C. A. Kraus, *Trans. Faraday Soc.*, **32** 594 (1936).

TABLE I

MORPHOLINE IN WATER

$C \times 10^3$	Λ	$C \times 10^3$	Λ
8.45	4.11	10.15	3.811
5.60	4.98	33.80	2.182
2.559	7.40	16.03	3.172
1.221	10.04	7.34	4.63
191.6	0.849	3.560	5.98
108.6	1.164	2.133	8.14
68.9	1.477	1.063	11.02
27.65	2.342		

TABLE II

MORPHOLINIUM CHLORIDE IN WATER

$C \times 10^3$	Λ	$C \times 10^3$	Λ
56.25	98.6	0.861	111.8
22.49	103.7	48.1	99.6
8.47	108.2	22.02	104.1
4.56	109.9	6.55	108.0
2.341	111.0		

line and Λ against $\sqrt{c}$ for morpholinium chloride indicate, by their deviations from the expected curves,[5] that the values of Λ for the most dilute points have been somewhat over-corrected for solvent conductance. The extrapolation to Λ_0 for morpholinium chloride takes this into account, but may be a few per cent. in error because of hydrolysis. This determination seems to be the source of greatest error. However, it seems unlikely that it can be more than two or three per cent. Assuming it to be 3% the error in K would be slightly less, about 2.8%. The value of Λ_0 was taken as 115.

Using this value and 261.5[6] for NaOH and 126.4[7] for NaCl, Λ_0 for morpholinium hydroxide is 250. Plotting the straight line form of the Arrhenius conductance ratio equation for the ionization constant, $1/\Lambda = c\Lambda/K\Lambda_0^2 + 1/\Lambda_0$, the graphically determined slope $1/K\Lambda_0^2$ gives a value of 2.44×10^{-6} for K.

(5) The ionization constant of morpholine is low enough so that in view of the two sources of error previously mentioned, it was considered unnecessary to use the more accurate forms of the $1/\Lambda - c\Lambda$ plot proposed by Fuoss (THIS JOURNAL, **57**, 488 (1935)) and Shedlovsky (*J. Franklin Inst.*, **225**, 739 (1938)).

(6) H. Jeffery and A. I. Vogel, *Phil. Mag.*, **15**, 395 (1933).

(7) D. A. MacInnes, T. Shedlovsky and L. G. Longsworth, THIS JOURNAL, **54**, 2758 (1932).

HAYDEN MEMORIAL LABORATORIES
NORTHEASTERN UNIVERSITY
BOSTON, MASSACHUSETTS RECEIVED OCTOBER 24, 1942

Action of Macerans Enzyme on a Component of Corn Starch

BY RALPH W. KERR

The origin of the Schardinger dextrins, when starch is treated in the presence of *B. Macerans* or the enzyme prepared from this bacillus[1] has been a matter of speculation for many years. In another paper[2] the writer sought to show that, in procedures which might ordinarily be used to convert corn starch with this enzyme, the yield of Schardinger dextrins, precipitable with trichloroethylene, arose almost entirely from a degradation of the most permanently dispersed fraction of the starch, which latter amounts to approximately 55% of the total starch. It was concluded that these dextrins were probably formed by synthesis from the more simple configurations in this product.

We are now able to elaborate on these conclusions. In another communication[3] we discussed the isolation of an amylose in yields of 5 to 6% of starch, by crystallizing the product from a warm water extract of corn starch with butanol. The amylose quickly changes to an insoluble form, however, in concentrations over 1 g. per 100 cc. in water solution. In this condition it might be expected to be rather inert in the presence of starch splitting enzymes. It may, however, be held in a relatively stable solution at *p*H 6.0 at lesser concentrations, *e. g.*, 0.30 g. per 100 cc.

A conversion of such a solution of the amylose was attempted adding 40 cc. of a *Macerans* enzyme preparation of 0.3 unit activity[2] to 2 l. of water containing 6 g. of the amylose in its soluble form. The conversion was made at *p*H 6.0 and 45° for forty-eight hours. The liquors were then concentrated by vacuum distillation to 400 cc. at 45° and allowed to stand at this temperature for another twenty-four hours at *p*H 6.0. Practically no insolubles were in evidence. The liquors were concentrated to 130 cc., a small amount of floc filtered off and 130 cc. of trichloroethylene added. The mixture was allowed to stand for forty-eight hours at room temperature, with intermittent stirring, and then for forty-eight hours in the refrigerator. The dextrins were filtered off, washed with ice water, then with methanol, dried and weighed: 4.2 g. of mixed dextrins, precipitable with trichloroethylene resulted, a yield of 70%. Further quantities precipitated when the mother liquors were concentrated.

Inasmuch as the crystalline amylose gives a conversion limit[3,4] of 93% maltose with β-amylase

(1) E. B. Tilden and C. S. Hudson, THIS JOURNAL, **61**, 2900 (1939).

(2) R. W. Kerr, "On the Significance of the Degradation of Starch by Macerans Enzyme," presented at the 102nd meeting of the American Chemical Society, September, 1941.

(3) R. W. Kerr and G. M. Severson, "The Isolation of an Amylose in Crystalline Form," in press.

(4) R. W. Kerr, O. R. Trubell and G. M. Severson, *Cereal Chemistry*, **19**, 64 (1942).

and hence is essentially linear in configuration, and inasmuch as β-amylase produces no reducing sugars whatsoever from the Schardinger dextrins,[2] it would seem evident that the *Macerans* enzyme was able to synthesize the cyclo amyloses from linear arrangements of glucopyranose units.

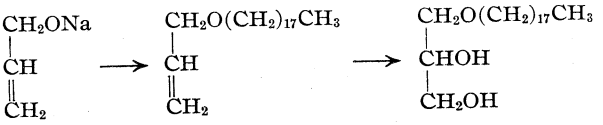
An explanation as to why the enzyme normally produces no greater yield of dextrins from whole corn starch might be that the more linear chains, which are probably coils in water solution, become enmeshed or oriented, thus blocking the approach of the enzyme to the individual molecules and possibly inhibiting the closing of the cycle to form the dextrin; whereas the linear configurations in our highly branched fraction,[3] which are principally the side branches in this case, are held more or less rigidly into space, thus greatly reducing the number that become enmeshed, one with the other. This condition would favor the production of large yields of the Schardinger dextrins from this latter component according to this viewpoint, and would, incidentally, account for the greater colloidal stability of solutions of this constituent, which we have called, provisionally, the more alcohol-soluble fraction.

CORN PRODUCTS REFINING CO.
ARGO, ILLINOIS RECEIVED FEBRUARY 2, 1942

Batyl Alcohol[1]

BY N. KORNBLUM[2] AND HARRY N. HOLMES

An earlier communication from this Laboratory described the isolation and identification of batyl alcohol $CH_2OH\text{-}CHOH\text{-}CH_2O(CH_2)_{17}\text{-}CH_3$, from the non-saponifiable fraction of yellow bone marrow.[3] Preliminary tests carried out by Dr. Roy Kracke of Emory University with a crystalline product obtained by us from yellow bone marrow indicated that batyl alcohol might be of value in the treatment of agranulocytosis. In order to permit of an extended program of physiological testing, a substantial quantity of pure batyl alcohol was needed. The synthesis employed here is that of Davies, Heilbron and Owens,[4] modified to give better yields of pure products.



Substitution of octadecyl iodide for the chloride (used by Davies, *et al.*) and a reaction temperature of 60–65° instead of reflux conditions resulted in a significant increase in the yield of pure allyl octadecyl ether. This is a consequence of the fact that the lower operating temperature minimizes the conversion of allyl alcohol to high boiling products which contaminate the desired allyl octadecyl ether. This auto-condensation of allyl alcohol containing sodium allyl oxide, which apparently has not been hitherto reported, proceeds in the presence or absence of oxygen and gives a complex series of unsaturated neutral and acidic compounds.

Conversion of the allyl ether to the glycerol derivative was best effected by the improved hydroxylation procedure of Scanlan and Swern,[5] except that it was found necessary to heat the reaction mixture in batches of the size employed here.

Experimental

Octadecyl Iodide.—This substance was prepared by the procedure of Bleyberg and Ulrich.[6] The product was purified by distillation *in vacuo;* b. p. 194–197° (2 min.); yield 70–75%. Upon recrystallization from acetone white plates melting at 33–34° were obtained.

Allyl *n*-Octadecyl Ether.—To a solution of 31 g. of sodium in 450 g. of allyl alcohol was added 150 g. of *n*-octadecyl iodide. The mixture was maintained at 60–65° for twenty hours and when cold was diluted with water and, *without* being acidified, extracted with ether. After washing the extracts with water the major portion of the solvent was distilled, approximately 25 ml. of benzene added, and the residual ethyl ether, benzene and entrained moisture then removed by distillation. A final bath temperature of about 160° was required. The yellow oil which remained was fractionally distilled *in vacuo* through a Widmer column. After an appreciable forerun which separated into two layers, there was obtained 85–96 g. (70–79%) of a colorless liquid, b. p. 150–152° (2 mm.); m. p. 28.5–29° (thermometer in melt); $n^{32}D$ 1.4441. Recrystallization from ethanol did not alter the refractive index. Davies, Heilbron and Owens[4] reported m. p. 27.5–28.5°.

Octadecyl Glyceryl Ether (Batyl Alcohol).—A mixture of 41.7 g. of 30% hydrogen peroxide solution and 500 ml. of glacial acetic acid was heated at 80–85° for one hour, at which point 49.5 g. of allyl *n*-octadecyl ether dissolved in 420 ml. of glacial acetic acid was added and the resulting

(1) Presented in part before the division of Biological Chemistry of the American Chemical Society, St. Louis meeting, April, 1941. At this same meeting Erich Baer and H. O. L. Fischer announced an alternate synthesis of batyl alcohol and subsequently published the details in *J. Biol. Chem.*, **140**, 397 (1941).

(2) Present address: Converse Memorial Laboratory, Harvard University, Cambridge, Mass.

(3) Holmes, Corbet, Geiger, Kornblum and Alexander, THIS JOURNAL, **63**, 2607 (1941).

(4) Davies, Heilbron and Owens, *J. Chem. Soc.*, 2542 (1930).

(5) Scanlan and Swern, THIS JOURNAL, **62**, 2305 (1940).

(6) Bleyberg and Ulrich, *Ber.*, **64**, 2510 (1931).

solution maintained at 70–80° for 20–22 hours. When cold, the mixture was rendered alkaline with dilute ammonium hydroxide, extracted with ether and the ether distilled off. The residue obtained upon removal of the ethyl ether was treated at 60° for seven hours with a solution containing 220 g. of potassium hydroxide, 660 ml. of water and 2500 ml. of ethanol. The solution was then concentrated to approximatley 750 ml. at 40° under reduced pressure. The resulting mixture was extracted with ether, the extracts washed with water and the ether removed. The product was purified by two recrystallizations from ethanol; white crystals, which sinter at 69° and melt 70–71° (cor.); yield 30–37 g. (55–67%). Hydroxylation of 50 g. of allyl *n*-octadecyl ether according to the procedure described by Davies, Heilbron and Owens[4] gave only 19 g. (34%) of pure glyceryl ether.

Allyl Alcohol and Sodium Allyl Oxide.—A solution of sodium (45 g.) in allyl alcohol (700 cc., Eastman Kodak Co. white label quality) was protected by a soda-lime guard tube while it was refluxed gently for forty-eight hours. The turbid mixture was cooled, diluted with water and extracted thoroughly with ether. The aqueous alkaline solution was then acidified with sirupy phosphoric acid and again extracted with ether. In this way the product was separated into a neutral (A) and an acidic (B) fraction. The ether solutions were washed with water, dried and distilled at 2 mm. From (A) was obtained 66 g. of material boiling at 63–140° with $n^{25}D$ ranging from 1.4696 to 1.5148. (B) gave 90 g. of material boiling at 73–155° with $n^{25}D$ ranging from 1.4673 to 1.5021. In each instance the first portion of the distillate was colorless and very fluid; with rising boiling point the distillate gradually becomes light yellow and quite viscous. Both (A) and (B) were insoluble in water, but soluble in ethanol, and both gave negative fuchsin tests. Both absorbed hydrogen over Adams catalyst and gave positive tests for unsaturation with bromine in carbon tetrachloride. (A) reacted with sodium, evolving a gas.

This experiment was repeated several times with substantially the same results. In one run allyl alcohol which had been dried over Drierite was employed and the reaction carried out in an atmosphere of nitrogen with results essentially the same as those described above. Conversion of allyl alcohol to high boiling products under these conditions has apparently not been reported previously.

The neutral and acidic fractions were not investigated further.

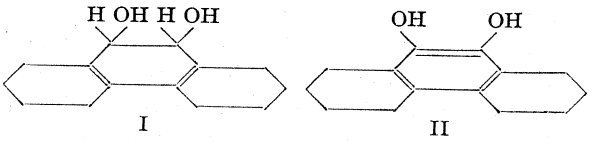
OBERLIN COLLEGE
OBERLIN, OHIO

RECEIVED SEPTEMBER 30, 1942

The Structure of Skita's "Decahydro-9,10-dihydroxyphenanthrene"

BY PHILIP LEVINE[1]

In a previous article,[2] reference was made to the preparation of a compound identical with that described by Skita[3] as decahydro-9,10-dihydroxyphenanthrene (I). Further investigation of this substance has now shown that the meso positions have not been hydrogenated and that the compound in question is *s*-octahydro-9,10-dihydroxyphenanthrene (II).



I II

The reasons for questioning the structure proposed by Skita were the resistance of the compound to hydrogenation over Raney nickel at 120°, the failure to undergo dehydration to *s*-octahydro-9-phenanthrol, and the readiness with which the compound is oxidized by the atmosphere. Also Skita's only evidence for the glycol structure (I) was the analytical data for the compound itself and for its diacetate. A comparison of Skita's figures with the calculated values for (II) and its derivative shows that the analytical data do not suffice to distinguish between (I) and (II).

Oxidation of the compound to the octahydroquinone requires only one equivalent of lead tetraacetate. Assuming Skita's formula, one might expect either normal cleavage to the dialdehyde or the consumption of *two* equivalents of lead tetraacetate for oxidation to the quinone.

The question was unequivocally settled in favor of the hydroquinone structure (II) by reductive acetylation of the quinone obtained by oxidizing the compound. The diacetate thus obtained was identical in appearance and melting point with the diacetate from the original compound and no depression of the melting point was observed on mixing the two samples. The method used for the reductive acetylation of the quinone was that which normally converts a quinone into the diacetate of the corresponding hydroquinone without effecting any further reduction.

Experimental[4]

Lead Tetraacetate Oxidation of Octahydrophenanthrenehydroquinone.—To 0.7 g. of the hydroquinone in 15 cc. of benzene was added in small portions 1.4 g. (one equivalent) of lead tetraacetate. The solution became deep red. Additional lead tetraacetate was unreacted as shown by tests with starch–iodide paper. A small amount of glycerol was added to remove excess oxidizing agent. The benzene solution was washed twice with water, dried over magnesium sulfate, and evaporated almost to dryness. The brilliant red crystals, melting at 139–141°, were evi-

(1) Present address, The Squibb Institute for Medical Research, New Brunswick, New Jersey.

(2) Linstead and Levine, THIS JOURNAL, **64**, 2022 (1942).

(3) Skita, *Ber.*, **58**, 2685 (1925).

(4) All melting points are corrected.

dently identical with the quinone obtained by Skita, m. p. 142°. Needles melting at 142–144° were obtained by crystallization from methanol.

Silver Oxide Oxidation of Octahydrophenanthrenehydroquinone.—A mixture of 0.42 g. of hydroquinone (m. p. 133–137°), 1 g. of silver oxide, and 1 g. of magnesium sulfate in absolute ether was shaken for one-half hour and filtered. The quinone proved to be soluble with difficulty in ether and was therefore extracted from the solids with benzene. Most of the benzene was evaporated and the product (0.338 g., m. p. about 137°) precipitated from the remaining solvent with hexane. Red needles melting at 142° were obtained by crystallization from acetone, which proved to be the best solvent for the purpose.

Reductive Acetylation of Octahydrophenanthraquinone.—Two drops of triethylamine was added to 0.1 g. of quinone with 0.1 g. of zinc dust in 2 cc. of acetic anhydride. The mixture was allowed to stand for ten minutes, heated to boiling, filtered, and the residue washed with hot acetic acid. Water was added to the boiling filtrate and washings to the cloud point. On cooling, the solution deposited 0.134 g. of white needles melting at 162–163°.

Acetylation of the Hydroquinone.—Addition of a drop of triethylamine to some of the hydroquinone (m. p. 135–137°) with a pinch of zinc dust in acetic anhydride caused slight warming. The mixture was allowed to stand a few hours and boiled for five minutes. The mixture was worked up in the same way as the product from the reductive acetylation of the quinone. The white needles melted at 161.5–163°. The mixed m. p. with the diacetate from the quinone was 162–163°.

CONVERSE MEMORIAL LABORATORY
HARVARD UNIVERSITY
CAMBRIDGE, MASSACHUSETTS
RECEIVED SEPTEMBER 24, 1942

[CONTRIBUTION FROM THE COMMITTEE ON MEASUREMENT OF GEOLOGIC TIME, DIVISION OF GEOLOGY AND GEOGRAPHY, NATIONAL RESEARCH COUNCIL]

Atomic Weight of Lead from a Second Sample of Pitchblende, Great Bear Lake, N. W. T., Canada

BY JOHN PUTNAM MARBLE

In a continuation of the geochemical studies on the pitchblende ores of Great Bear Lake, the atomic weight of the lead in a second sample has been determined. This sample, from the 800-foot section of the No. 2 vein, Eldorado mine, Labine Point, Great Bear Lake, N. W. T., Canada, was received from H. S. Spence, Esq., of the Canada Department of Mines and Resources, for whose coöperation we are deeply grateful. The material is of the pitchblende-silica type ore, came from depth (below 100 feet), and carried no visible alteration products. Microscopic studies show a very small amount of galena, estimated at a fraction of one per cent.

The lead–uranium ratio uncorrected for "common lead," with an autoradiograph showing little evidence of alteration[1] and a complete analysis[2] have been previously published. While the results of this present work are admittedly incomplete, it was thought worth while to put them on record, as they are in virtual agreement with those of the first sample[3] and the carrying out of further atomic weight determinations, or preferably of the determination of the isotope ratios of this sample, have necessarily had to be deferred. Since the pitchblende is virtually thorium-free, the atomic weight indicates the approximate correction to be made for "common lead," which cannot be done for thorium-rich minerals.

The preparation of the material for analysis, the extraction and purification of the lead, and the method of analysis were essentially the same as in the case of the first sample of Great Bear Lake lead.[3] The work was done in the T. Jefferson Coolidge Memorial Laboratory of Chemistry at Harvard University, by kind permission of Dr. Gregory P. Baxter, for whose interest and assistance we are deeply grateful. The results of the analysis are as follows

Vac. wt. $PbCl_2$	1.56541 g.
Vac. wt. Ag	1.21935 g.
Wt. Ag added in solution	0.00010 g.
Vac. wt. $Ag \simeq PbCl_2$	1.21945 g.
Ratio $PbCl_2/2Ag$	1.28370
Atomic weight Pb	206.057

(Ag = 107.880; Cl = 35.457)

This value agrees so closely with that of the work on the earlier sample (Pb = 206.054), that we may conclude that the lead in the Great Bear Lake pitchblende ore shows no appreciable variation in isotopic composition in different parts of the deposit, and also that a correction of about 4 per cent. should be applied to the "uncorrected" lead–uranium ratio of the second analyzed sample, as was done for the first. Further work may confirm these conclusions.

(1) J. P. Marble, *Am. Mineralogist*, **22**, 564 (1937).
(2) J. P. Marble, *ibid.*, **24**, 272 (1939).
(3) J. P. Marble, THIS JOURNAL, **56**, 854 (1934).

U. S. NATIONAL MUSEUM
WASHINGTON, D. C.
RECEIVED OCTOBER 7, 1942

Saponins and Sapogenins. XX. Some Color Reactions of Triterpenoid Sapogenins

BY C. R. NOLLER, R. A. SMITH, G. H. HARRIS AND J. W. WALKER

While attempting to prepare the acid chlorides of some triterpenoid acids by means of thionyl

chloride, it was noted that one of two commercial preparations of thionyl chloride caused the formation of highly colored solutions, for example burgundy red with echinocystic acid and a brilliant blue with hederagenin, while the other lot gave only colorless, yellow or red solutions. When the first lot of thionyl chloride was purified by the usual procedure over quinoline and linseed oil, it no longer gave the brilliant colors. Fractional distillation using a packed column gave no appreciable separation of the impurity. Accordingly a systematic qualitative analysis was made of the impure sample. This indicated a considerable amount of tin to be present, some iron and a trace of phosphorus. Quantitative analysis showed amounts equivalent to 0.007% stannic chloride, 0.004% ferric chloride and less than 0.001% phosphorus. When a solution of 0.01% of anhydrous stannic chloride and 0.005% of sublimed ferric chloride in purified thionyl chloride was allowed to react with various triterpenoids, the colors produced by the impure thionyl chloride were practically duplicated. Differences may be attributed to traces of phosphoric acid in the commercial sample.

Pure stannic chloride dissolved in pure thionyl chloride produced characteristic colors but stannic chloride dissolved in benzene, petroleum ether, ethyl ether, carbon tetrachloride, chloroform or cyclohexane was without effect. Ferric chloride, antimony trichloride, antimony pentachloride, phosphoric acid, or phosphorus oxychloride which has been exposed to moisture, and concentrated sulfuric acid in thionyl chloride produced colors but purified phosphorus oxychloride, phosphorus trichloride, phosphorus pentachloride, silicon tetrachloride, chlorine, sulfur dioxide and hydrogen chloride, when dissolved in thionyl chloride, do not give a color-producing reagent.

The colors produced vary with the reagent and with the compound used. Sometimes a sequence of colors is produced, which may be so rapid at first that the solution must be observed continuously in order to note them. Usually the color changes are complete after an hour although sometimes they are not complete after twenty-four hours. In the case of the hydroxy acids, the intense colors are produced only if at least one free hydroxyl group is present; if all the hydroxyl groups are esterified the intensity of the colors is greatly decreased. Esterification of the carboxyl group is without effect. In the case of the α- and β-amyrins, which lack a carboxyl group, the intensity of the colors is little changed by esterification. Differences between isomeric compounds, for example echinocystic acid and hederagenin, or α-amyrin and β-amyrin, may be sufficiently great to distinguish readily between them.

Little can be said concerning the cause of the colors. The inorganic compounds producing the color all may be considered as electron accepting reagents but we see no reason why stannic chloride should be effective only in thionyl chloride solution and not in other anhydrous solvents. The colored compounds might be looked upon as halochromic salts but the intensity and brilliance of the colors, particularly the blues and purples with stannic chloride, would seem to call for a chromophoric group with greater possibilities of resonance than are afforded by a single unconjugated carbon–carbon double bond, a carboxyl group and two hydroxyl groups.[1]

The color changes produced on treating 0.02 g. each of a wide variety of triterpenoids and their derivatives with 0.5 cc. of 0.01% anhydrous stannic chloride in pure thionyl chloride in a small test-tube which was kept stoppered during observation, may be summarized as follows:

Hederagenin, light pink → violet → light blue → deep orange after one hour.

Hederagenin methyl ester, pink → purple → violet → deep yellow after eight hours.

Hederagenin diacetate, light yellow → yellow after eight hours.

Echinocystic acid, pink → purple → blue → light red → very deep red after twenty-four hours.

Methyl echinocystate, red → blue-green → purple → very deep red after one hour.

Echinocystic acid diacetate, colorless → light violet → light orange after twenty-four hours.

Methyl echinocystate diacetate, colorless → light violet → deep yellow after twenty-four hours.

Echinocystic acid monoacetate (by esterification), pink → violet → deep blue → red after two hours.

Echinocystic acid monoacetate (by hydrolysis), violet → deep green → very deep red after twenty minutes.

Isonorechinocystenedione, yellow → orange → red after twenty-four hours.

Ursolic acid, light pink → deep red → light red → very deep red after eight hours.

Oleanolic acid, light pink → very deep red after one hour.

Methyl oleanolate, light pink → very deep red after one hour.

Methyl oleanolate acetate, light yellow → light violet → deep yellow after twenty-four hours.

Betulin, colorless → light pink → light violet → dark muddy green after one hour.

(1) One of the referees states, "There is no question but that we are dealing here with some very complex adsorption reactions."

α-Amyrin, orange → very deep red → very deep purple after twenty-four hours.
β-Amyrin, purple → very deep red after five minutes.
α-Amyrin benzoate, light pink → deep red after one hour.
β-Amyrin benzoate, light yellow → red → deep yellow → orange after twenty-four hours.
α-Amyrone, colorless → yellow → orange after twenty-four hours.
β-Amyrone, colorless → light blue → purple → deep red after eight hours.

The color changes of a limited group of triterpenoids with (A) pure thionyl chloride, (B) 0.01% anhydrous ferric chloride in thionyl chloride, (C) 0.01% antimony trichloride in thionyl chloride, (D) 0.01% antimony pentachloride in thionyl chloride, (E) 10% phosphorus oxychloride + 0.5% water in thionyl chloride, (F) 0.01% stannic chloride + 0.005% ferric chloride in thionyl chloride and (G) commercial thionyl chloride may be summarized as follows:

Hederagenin, (A) colorless → light amber (B) orange → red → green → amber (C) orange → violet → blue → green → red → brown (D) yellow → red → green → yellow → orange (E) blue → green → orange → red (F) violet → purple → blue → green → amber (G) red → blue → green → amber.
Echinocystic acid, (A) colorless → pink → red (B) orange → red → violet → red (C) pink → violet → blue-green → red (D) pink → violet → blue → violet → red (E) violet → blue-green → violet → red (F) red → purple → blue-green → red (G) violet → blue → blue-green → red.
Oleanolic acid, (A) pink → violet → red (B) violet → purple → red (C) violet → red (D) violet → blue → red (E) pink → red (F) violet → red (G) violet → purple → red.
Ursolic acid, (A) yellow → orange → red (B) violet → purple → red (C) violet → red (D) yellow → orange → red (E) orange → red (F) red (G) violet → blue → purple → red.
α-Amyrin, (A) pink → purple → red (B) orange → red (C) yellow → orange → red (D) yellow → red (E) colorless → yellow → orange → red (F) yellow → red (G) red.
β-Amyrin (A) colorless → pink → violet → red (C) purple → blue → red (D) red → blue → purple → red (E) blue → opaque.
Betulin, (A) colorless → yellow → green (F) yellow → red → purple → green (G) yellow → red → purple → green.

STANFORD UNIVERSITY
STANFORD UNIV., CALIF.
RECEIVED JUNE 15, 1942

Peroxides in Isopropanol

BY C. ERNST REDEMANN

While it is a widely known fact that ethyl ether, isopropyl ether, and dioxane readily form peroxides when stored in contact with air or oxygen, there seems to be no mention of the formation of peroxides in isopropanol when stored under similar conditions.

A sample of 99.5% isopropanol, which had been stored for many months in strong daylight in a clear glass bottle only about one-third filled, was observed to have a strong unpleasant odor. Since this odor greatly resembled the odor of isopropyl ether when it is badly contaminated with peroxides, the isopropanol was investigated for the presence of peroxides. The following tests for peroxides were strongly positive: (1) immediate liberation of iodine from acidified potassium iodide solution, (2) the formation of blue peroxychromic acid, soluble in ether, from chromic acid solutions, (3) the production of chemiluminescence from 3-amino-phthalhydrazide catalyzed by hemoglobin,[1] (4) precipitation of Prussian blue from a solution containing ferric chloride and potassium ferricyanide,[2] (5) reduction of black nickelic oxide to pale green nickelous hydroxide,[3] (6) decolorization of lead sulfide.[4]

Quantitative iodometric determinations were made of the peroxide content of all samples of isopropanol available in this Laboratory with the results shown in the table.

Sample	Peroxide, mole/l.	Conditions of storage
1	0.36	Clear glass bottle, 1/3 full, strong light
2	.13	Clear glass bottle, 2/3 full, strong light
3	.04	Clear glass bottle, 5/6 full, strong light
4	.05	Clear glass bottle, 5/6 full, strong light
5	.003	Tin can, nearly full, dark
6	.007	Redistilled, stored about four years, largely in the dark

This reaction appears, in part, to be a photochemical process. The following brief experiment was designed to indicate the comparatively rapid rate of formation of peroxide in strong light. Twenty-five ml. of isopropanol was placed in a 500-ml. Pyrex glass flask fitted with a capillary tube to equalize external and internal pressure. The flask was left on the roof in full daylight for two days. Initial peroxide content 0.003 mole/l.; after two days 0.026 mole/l.

These data are presented to call the attention of experimenters to the need for making sure that isopropanol is peroxide free when working with easily oxidizable material. Likewise, some care should be exercised when evaporating old isopropanol solutions to dryness as an explosion

(1) Schales, *Ber.*, **72**, 167 (1939).
(2) Schönbein, *J. prakt. Chem.*, [1] **79**, 67 (1859).
(3) Feigl and Fränkel, *Mikrochemie*, **12**, 304 (1932/1933).
(4) Kempf, *Z. anal. Chem.*, **89**, 88 (1933).

might occur, although no actual experience of the latter kind is known.

770 S. Arroyo Parkway
Pasadena, California Received August 14, 1942

Tracer Studies with Radioactive Carbon. The Exchange between Acetic Anhydride and Sodium Acetate

By S. Ruben, M. B. Allen and P. Nahinsky

In connection with some tracer studies in these Laboratories it was desired to develop a rapid method for the synthesis from labelled carbon dioxide of an unsaturated acid containing C* only in the carboxyl group. The Perkin synthesis, in which the unsaturated acid is formed by reaction of an aldehyde with an acid anhydride in the presence of a salt (Equation (1)), seemed well suited to our needs.

$$2R_1CHO + R_2CH_2C(=O)-O-C(=O)-CH_2R_2 \xrightarrow{R_2CH_2COONa} 2R_1C(H)=C(R_2)-COOH + H_2O \quad (1)$$

Since we wished to obtain the unsaturated acid with the highest possible specific radioactivity, it was desirable to measure the rate of exchange between the salt and the anhydride. Michael[1] and more recently Breslow and Hauser[2] have shown that within several hours at 100° the exchange reaction between sodium acetate and butyric anhydride has come to equilibrium. We have found that the exchange between acetic anhydride and labelled sodium acetate *at room temperature* is surprisingly rapid.

Experimental

Labelled sodium acetate was prepared by shaking 10^{-3} mole of C^*O_2[3] with 5 cc. of 1 *M* CH_3MgI in ether at room temperature for ~ten minutes. After hydrolysis with dilute sulfuric acid the ether was removed by evaporation. Excess solid silver sulfate was added to precipitate silver iodide and the acetic acid distilled off *in vacuo*. The yield was ~95% based upon carbon dioxide. The acetic acid distillate was carefully neutralized with sodium hydroxide solution and evaporated to dryness. A small amount of dilute acetic acid was added and the solution again evaporated to dryness to free the sodium acetate from traces of base. This preparation was thoroughly dried at 100° *in vacuo* until a vacuum of better than 10^{-5} mm. of mercury could be maintained over the solid without pumping.

The dry labelled sodium acetate was shaken with acetic anhydride[4] for twenty minutes at room temperature and the anhydride distilled off at room temperature *in vacuo*. The anhydride was converted into sodium acetate and counted as such.[5] The results of this and a similar experiment employing C^{14} are summarized in Table I.

Table I

Exchange between NaAc* and $(Ac)_2O$ at Room Temperature

Expt.	Equivalents of NaAc	Equivalents of Ac_2O	Time of exchange, min.	Per cent. of random distribution of Ac*
1	$2\cdot10^{-3}$	$95\cdot10^{-3}$	20	55
2	$1\cdot10^{-3}$	$4.8\cdot10^{-3}$	30	62

In view of the fact that sodium acetate is very insoluble in acetic anhydride it was surprising to find such rapid exchange at room temperature in this two-phase system.

A similar result was obtained with sodium butyrate and acetic anhydride. 4.7 grams of carefully dried sodium butyrate[6] was shaken with 17.6 cc. of acetic anhydride for ~forty minutes at room temperature, after which the anhydride was distilled off at room temperature *in vacuo*.

When the distillate was fractionally distilled it was found that 4.6 cc. had a boiling point above that of acetic anhydride. The acetic and butyric acid content of the high boiling fraction was determined by means of a Duclaux distillation. This fraction consisted of 72% butyric and 28% acetic acid. Thus 18.7% of the acid equivalent in the total anhydride fraction is butyric acid. For random distribution of butyrate between the sodium salt and the anhydride one would expect 10.3% for the above experiment. The marked tendency of butyrate to concentrate in the anhydride at room temperature is in keeping with the results of Michael[1] and Breslow and Hauser.[2]

(1) Michael, *J. prakt. Chem.*, **60**, 364 (1899).

(2) Breslow and Hauser, This Journal, **61**, 786 (1939).

(3) $C^{11}O_2$ was employed in the first experiment and $C^{14}O_2$ in the second.

(4) Distilled from phosphorus pentoxide into a glass receiver which had been thoroughly baked at 200° for several days. The fraction boiling between 138–139° was used.

(5) A description of the production and measurement of C^{11} and C^{14} may be found elsewhere: Ruben, Kamen and Hassid, This Journal, **62**, 3443 (1940); Ruben and Kamen, *Phys. Rev.*, **59**, 349 (1941).

(6) Previously evaporated to dryness in the presence of excess butyric acid and then kept at 100° in high vacuum (10^{-5} mm.) for several hours.

Department of Chemistry
University of California
Berkeley, California Received September 8, 1942

Preparation of β-(2-Methyl-6-oxo-1-cyclohexen-1-yl)-propionic Acid

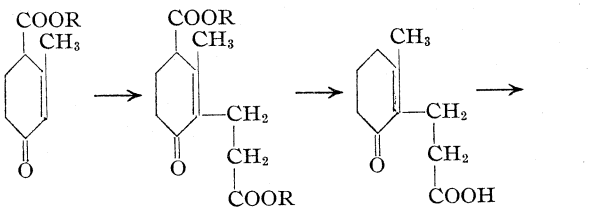
By Erwin Schwenk and Edith Bloch

Unsaturated cyclic ketoesters of the type of 3-carbomethoxy-2-methyl-6-oxo-1-cyclohexene (I) contain the same atomic grouping as α,β-dialkylglutaconic acids and like the latter can be alkylated with alkyl halides and sodium ethoxide,[1] but apparently only simple alkyl halides have been studied.[2]

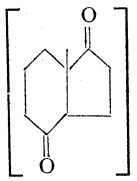
(1) Richter-Taylor, "The Chemistry of the Carbon Compounds," 3rd English ed., Vol. II, p. 139.

(2) See, for instance, Koetz, *et al.*, *Ann.*, **400**, 83 (1913); E. Bergmann and A. Weizmann, *J. Org. Chem.*, **4**, 266 (1939).

We were interested in the introduction of a side-chain bearing a carboxyl group into the ester I because the propionic acid III finally obtainable as indicated should be useful in the synthesis of cyclic diketones with an angular methyl group of the type IV. So far we have not been able to effect the ring closure.



I II III



IV

Experimental

3-Carbomethoxy-2-methyl-6-oxo-1-cyclohexene (I, R = CH_3).—This substance was obtained by a modification of the procedure described for the corresponding ethyl ester (Hagemann ester), I, R = C_2H_5.[3]

Nine hundred and twenty grams (8 moles) of freshly distilled methyl acetoacetate and 35 cc. of piperidine were warmed to 60°. One hundred and twenty grams (4 moles) of trioxymethylene was added in small portions under stirring while keeping the temperature at 60–80°. The mixture was cooled to room temperature, 200 g. of anhydrous sodium sulfate was added and the flask left standing in the refrigerator overnight. The product was filtered from the sodium sulfate and the residue washed well with ether. The combined filtrate and washings were washed in a separatory funnel with small portions of water, 10% hydrochloric acid and again with water. The ether solution was dried over sodium sulfate, the solvent removed and the residue of crude 1,3-dicarbomethoxy-2-methyl-6-oxo-1-cyclohexene was saponified partially by refluxing for two hours in an oil-bath with a solution of 96 g. of sodium (4 moles) in 2.5 liters of absolute alcohol. After standing overnight the alcohol was removed *in vacuo*, the residue taken up in 500 cc. of ice-water and acidified under cooling with 25% sulfuric acid. The resulting oil was taken up in ether, the ether solution washed with water, dried over anhydrous sodium sulfate and the ether evaporated. The residue was distilled *in vacuo*, b. p. 135° (2 mm.), yield, 240 g. (37%). A considerable low boiling fraction was obtained (b. p. 70° (2 mm.)) consisting chiefly of 2-methyl-6-oxo-1-cyclohexene.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.3; H, 7.2. Found: C, 64.7; H, 7.2.

The semicarbazone was prepared as usual, m. p. 168–170°.

(3) Hagemann, *Ber.*, **26**, 879 (1893); Rabe and Rahm, *Ann.*, **332**, 13 (1904); *Ber.*, **38**, 969 (1905).

Anal. Calcd. for $C_{10}H_{15}O_3N_3$: N, 18.7. Found: N 18.7.

Methyl β-(3-Carbomethoxy-2-methyl-6-oxo-1-cyclohexen-1-yl)-propionate (II, R = CH_3).—Twenty-three grams of sodium was dissolved in 500 cc. of absolute methyl alcohol (dried over magnesium methylate) and 168 g. of 3-carbomethoxy-2-methyl-6-oxo-1-cyclohexene was added, followed by 168 g. of methyl-β-bromopropionate. The mixture was refluxed for one hour; the alcohol removed *in vacuo*, the residue taken up in ether, washed, dried over sodium sulfate and the solvent evaporated. The ether residue was distilled in vacuum. Thirty-two grams of low boiling material was obtained, consisting mostly of unchanged starting material. The main fraction boiled at 170–180° (1 mm.), yield, 170 g. (83% considering recovered starting material).

Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61.4; H, 7.1. Found: C, 61.5; H, 7.4.

The semicarbazone was prepared by refluxing 1 g. of the ester with 1 g. of semicarbazide hydrochloride and 1 g. of sodium acetate; recrystallized from dilute alcohol, it melted at 145–148°.

Anal. Calcd. for $C_{14}H_{21}N_3O_5$: N, 13.5. Found: N, 13.9.

Ethyl β-(3-Carbethoxy-2-methyl-6-oxo-1-cyclohexen-1-yl)-propionate.—This ester was prepared from Hagemann's ester and ethyl-β-bromopropionate as described above; b. p. 184–186° (2 mm.), yield, 70%. No satisfactory analysis could be obtained from this material but the 2,4-dinitrophenylhydrazone obtained as usual crystallized from ethanol in orange-red prisms, m. p. 120–122°.

Anal. Calcd. for $C_{21}H_{26}O_8N_4$: N, 12.0. Found: N, 12.1.

β-(2-Methyl-6-oxo-1-cyclohexen-1-yl)-propionic Acid.—One hundred grams of II (R = CH_3) was refluxed for six hours with 200 cc. of hydriodic acid (42%). After cooling the mixture was carefully made alkaline by adding it to excess concentrated sodium carbonate solution under cooling and stirring. All neutral material was removed by repeated extraction with ether and the dark brown solution was acidified again. The acid was taken up in ether and the ether solution washed with dilute sodium thiosulfate solution and with water. After drying over anhydrous sodium sulfate the ether was evaporated and the residue was distilled *in vacuo* at about 1 mm.; yield, 40 g. The distillate crystallized on standing. Recrystallization from ligroin (b. p. 70–90°) yields the acid in long feather-shaped crystals; m. p. 79–81°. The same acid was obtained from II (R = C_2H_5).

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.9; H, 7.7. Found: C, 65.6; H, 7.7.

RESEARCH DIVISION
SCHERING CORPORATION
BLOOMFIELD, NEW JERSEY RECEIVED SEPTEMBER 4, 1942

A New Modification of Willgerodt's Reaction

BY ERWIN SCHWENK AND EDITH BLOCH

It was first shown by Willgerodt[1] that treatment of aryl methyl ketones with yellow am-

(1) Willgerodt, *Ber.*, **20**, 2467 (1887); **21**, 535 (1888).

monium sulfide yields the amides of arylacetic acids which by saponification with aqueous alkali give arylacetic acids. The method would probably find more use if it were not necessary to heat the reagents in a closed vessel to 150°. This disadvantage of the method has not been eliminated by recent modifications.[2,3,4,5]

We have tried to avoid the use of an autoclave by replacing the ammonium sulfide with higher boiling amines and sulfur. Morpholine[6] now made technically in very pure form and at a cheap price has been found to be most suitable. The process differs from the reaction as described by Willgerodt in that first the morpholides of

$$ArCOCH_3 \longrightarrow ArCH_2CSC_4H_8ON$$

the arylthioacetic acids are formed. The reason for this course of the reaction is probably the absence of water in the reaction mixture similar to Kindler and Tsauping Li's procedure[5], who also obtained derivatives of the arylthioacetic acids. The morpholides of the arylthioacetic acids often can be isolated in crystalline form. If that is not possible because of the oily consistency of these morpholides, even the crude oily morpholides may be submitted to a saponification with either aqueous or alcoholic alkali, which will afford the arylacetic acids after acidification of the alkaline solution.

The reaction apparently is applicable to all aryl methyl ketones in which the aryl part of the molecule is either unsubstituted or substituted by a stable group like the alkoxy group or halogen. To substances containing nitro-, amino-, hydroxy- or acetoxy- groups, the reaction seems not to be applicable in this form.

As an example, we describe the preparation of the as yet not known *o*-benzyloxyphenylacetic acid with our new method. In general, it may be said that the aryl thioacetmorpholides crystallize easily. In cases where they remained oily, we have taken the crude material and submitted it, without purification, to the saponification step. Some of the morpholides are quite difficult to saponify; we have not made an investigation of this part of the method and believe that study of the saponification in special cases may improve the final yield considerably.

Yields, melting points (not corrected) and analyses of some arylthioacetmorpholides of known arylacetic acids which we have prepared are given in the table.

TABLE I

Aryl methyl ketone Aryl-	Morpholide of arylthioacetic acid Yield, %	M. p., °C.	Arylacetic acid Yield, %	Melting point, °C. Found	Literature
Phenyl-	92[a]	79–80	75	76–77	76, 78
o-Methoxyphenyl-		oily	55	120–122	120.5, 123, 124
m-Methoxyphenyl-	85[b]	82–84	65	66–67	67
p-Bromophenyl-		oily	10	112–113	114–115
2,5-Dimethoxyphenyl-		oily	28	123–124[d]	124.5
2-Naphthyl-	87[c]	108–109	..	140–142	137.5–139, 142
2-Phenanthryl		oily	41	179–183	181–183

[a] Calcd. for $C_{12}H_{15}NOS$: N, 6.3; S, 14.5. Found: N, 5.9; S, 14.7. [b] Calcd. for $C_{13}H_{17}NO_2S$: N, 5.6; S, 12.7. Found: N, 6.0; S, 12.5. [c] Calcd. for $C_{16}H_{17}NOS$: N, 5.0; S, 11.6. Found: N, 5.2; S, 12.0. [d] Mixed m. p. with a sample prepared from natural homogentisic acid (for which we have to thank Dr. M. Volterra, Mt. Sinai Hospital, New York City) by methylation with dimethyl sulfate and sodium hydroxide showed no depression.

Experimental

Preparation of *o*-Benzyloxyacetophenone.—Ten grams of *o*-hydroxyacetophenone, 12.5 g. of benzyl chloride and 75 cc. of 15% sodium hydroxide were refluxed for two hours. The reaction mixture was extracted, with ether, the ether extract washed and dried and distilled *in vacuo;* yield 12.5 g.; b. p. 182–184° at 11 mm. There was some unreacted material recovered from the alkaline solution.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.7; H, 6.3. Found: C, 79.8; H, 6.5.

2,4-Dinitrophenylhydrazone m. p. 207–209°. *Anal.* Calcd. for $C_{21}H_{18}O_5N_4$: N, 13.8. Found: N, 14.1.

Semicarbazone m. p. 175–177°. *Anal.* Calcd. for $C_{16}H_{17}O_2N_3$: N, 14.9. Found: N, 14.6.

Preparation of *o*-Benzyloxyphenylthioacetmorpholide.—11.3 grams of *o*-benzyloxyacetophenone, 4.5 g. of morpholine, and 1.6 g. of sulfur were refluxed for eight hours and then poured into ice. The morpholide was extracted with ether. The oily residue crystallized partially after standing for a day. It was several times recrystallized from dilute methanol; yield, 12 g.; m. p. 117, 118–119°. *Anal.* Calcd. for $C_{19}H_{21}O_2SN$: N, 4.3; S, 9.7. Found: N, 4.5; S, 9.5.

Preparation of *o*-Benzyloxyphenylacetic Acid.—Nine grams of *o*-benzyloxyphenylthioacetmorpholide was refluxed with 100 cc. of 10% potassium hydroxide for twelve hours. The alkaline solution was acidified, extracted with ether, and the extracts washed, dried and evaporated. The ether residue was recrystallized from benzene–petrol ether; yield 4.1 g.; m. p. 97–99°. *Anal.* Calcd. for $C_{20}H_{22}O_6$: C, 74.7; H, 5.8. Found: C, 74.7; H, 6.4.

SCHERING CORPORATION
RESEARCH DIVISION
BLOOMFIELD, NEW JERSEY

RECEIVED SEPTEMBER 25, 1942

(2) Mosettig and van de Kamp, THIS JOURNAL, **55**, 3442 (1933).
(3) Fieser and Kilmer, *ibid.*, **62**, 1354 (1940).
(4) Bachmann and Carmack, *ibid.*, **63**, 2494 (1941).
(5) Kindler and Tsauping Li, *Ber.*, **74**, 321 (1941).
(6) Piperidine was also used in some experiments.

Change in Potential of Silver–Silver Chloride Electrodes with Time

By Edgar Reynolds Smith and John Keenan Taylor

An aging effect with freshly prepared silver–silver chloride electrodes was first noted by MacInnes and Parker,[1] who found it to be always in the same direction. This effect was investigated by Smith and Taylor,[2] who attributed its origin to concentration-polarization and made tests, the results of which harmonized with this explanation. When silver electrodes are coated electrolytically with silver chloride, the solution within the pores of the silver chloride becomes more dilute than the surrounding solution and these electrodes, freshly prepared, therefore, act as cathodes toward electrodes previously aged in the solution, since the latter have had the electrolyte within their pores replenished. Because the aging behavior is always in the same direction and, for relatively thick coatings of silver chloride, amounts at least to several tenths of a millivolt, it appears to be an effect different from the fluctuating bias of a few hundredths of a millivolt frequently observed after the electrodes have apparently come to equilibrium. If sufficient time is allowed, the freshly prepared electrodes attain the same average potential as the aged electrodes. The time required for this equilibrium to be attained depends on several factors, among which are the amount of silver chloride deposited per unit area, *i. e.*, the thickness of the layer through which the diffusion must occur, and the current density at which the layer is formed. The smaller the current density of silver chloride formation, the nearer is the concentration within the pores of the layer kept to equilibrium with the surrounding solution and consequently the smaller is the aging effect.

In some recent work, Hornibrook, Janz and Gordon[3] made experiments, the results of which they consider to contradict the conclusions of Smith and Taylor. Their results, however, instead of being contradictory to these conclusions are in agreement with what is to be expected for thin films of silver chloride formed at low current densities. It should be emphasized that no dispute as to the facts is involved and no criticism of the validity of the technique and results of the excellent work of Hornibrook, Janz and Gordon is intended.

From the dimensions of the electrodes and the time and current used for coating with silver chloride, it appears that the thickness of the coatings and the magnitude of the current density used by Smith and Taylor were, respectively, about 13.4 and 5.6 times as large as those used by Hornibrook, Janz and Gordon. The latter point out that concentration differences tend to disappear with exp $(-\pi^2 kt/x^2)$, where k is the diffusion constant, t the time, and x the distance from the plane where the concentration is constant. The time required for the exponential to fall to a given value increases as the square of the distance, x, which can be taken as the thickness of the layer of silver chloride. Hornibrook, Janz and Gordon found no indication of aging after twenty-five minutes in one experiment and after forty minutes in another. If the time of aging with their relatively thin layer was of the order of ten minutes, it would escape detection, while with a layer 13 times as thick, about twenty-eight hours would elapse before the aging was over, and the effect would be readily found.

Present conditions of work make it unjustifiable for us to spend the time required to show experimentally how the aging period of freshly prepared silver–silver chloride electrodes varies from a negligible time for a very small thickness of silver chloride deposited at a low current density to an appreciable time for a thicker layer deposited at a higher current density. Our previous work, however, has shown the latter, and the results of Hornibrook, Janz and Gordon not only show the former, but are what would reasonably be expected on the basis of our explanation of the aging effect.

Because of the various factors, such as film thickness, current density, temperature, concentration and agitation of the solution, which affect the time of aging, different investigators using different conditions of preparation of their silver–silver chloride electrodes will find marked differences in the magnitude and duration of the aging effect. In any case, however, it is important to recognize the possibility of the occurrence of the effect and to make sure it has been eliminated from the results of the final measurements.

(1) D. A. MacInnes and K. Parker, This Journal, **37**, 1445 (1915).

(2) E. R. Smith and J. K. Taylor, *J. Research Natl. Bur. Standards*, **20**, 837 (1939).

(3) W. J. Hornibrook, G. J. Janz and A. R. Gordon, This Journal, **64**, 514 (1942).

Washington, D. C. Received September 10, 1942

The Alkylation of Linseed Oil

BY JUDSON G. SMULL AND JOHN S. SAYLOR

The structures of linoleic and linolenic acids which are present in linseed oil, have been indicated as having the $=CHCH_2CH=$ grouping.[1,2,3] It occurred to the authors that the CH_2— portion of the grouping might be active enough to show the reactions of active methylene groups, as shown by such compounds as cyclopentadiene, malonic ester and others.

The first evidence of reaction which it is desired to report at this time is a reaction analogous to that of malonic ester. For this purpose an alkali-refined neutral linseed oil was converted to the mixed methyl esters directly by alcohol interchange. An excess of absolute methanol, containing hydrogen chloride was added to dry linseed oil and refluxed until the reaction was complete. The mixed methyl esters after purification were distilled at 200° under 6 mm. pressure.

Approximately 0.1 mole of these mixed methyl esters was treated with 0.1 mole of sodium ethoxide dissolved in excess absolute ethanol, and refluxed at 60° for about ten minutes. To the cooled mixture in the flask, 0.13 mole of ethyl iodide was added gradually, with thorough shaking. This reaction mixture after heating at 90° on the water-bath for forty minutes, was allowed to stand overnight. The excess ethanol and ethyl iodide were distilled and the remaining solution filtered. The filtrate was dissolved in ether, washed with brine, then water, and dried. After removal of the ether, the major portion distilled at 205° and 14 mm. pressure, as a very pale, highly mobile liquid. This procedure was followed closely on two other runs. All of the samples were kept under nitrogen to prevent oxidation. The analytical data are given in the tabulation.

		Iodine No. (Wijs) Determined	Theoretical[a]	Refractive index
Linseed oil		192.0	...	1.4811
Mixed methyl esters		186.0	...	1.4632
Alkylated esters				
Samples	A	170.9	167.0	1.4616
	B	178.1		1.4619
	C	183.1		1.4613
	Av.	177.4		1.4616

[a] The theoretical iodine number was calculated on the assumption that linseed oil contains 60% linoleic acid, with one active CH_2— group and 25% linolenic acid, with two active CH_2— groups.

(1) Erdmann, Bedford and Raspe, *Ber.*, **42**, 1334 (1909).
(2) Goldsobet, *Chem. Ztg.*, **30**, 825 (1906).
(3) Hilditch and Vidyarthi, *Proc. Roy. Soc.* (London), **A122**, 563 (1929).

With an average of 1.1 active CH_2— groups, condensation with 1.1 ethyl groups should be expected, forming an ethylated methyl ester of the mixed acids. The fair agreement of the determined iodine number with the calculated value (an approximation) is evidence of reaction. The lower values for refractive index are also evidence of reaction. Furthermore, it was believed that if alkylation had occurred, the alkylated esters should give a negative fulvene reaction whereas unalkylated ester should be positive. This actually was the case. Again, confirmation of the fulvene test was obtained by oxidation tests, where a dark red color was produced in the original methyl ester but no appreciable darkening in the alkylated methyl ester. The oxidation presumes the formation of a —CO— group, according to Scheiber.[4] The oxidized portion should in turn condense with unoxidized oil to give the fulvene color reaction.

This study is being continued on pure methyl linoleate and pure methyl linolenate.

(4) J. Scheiber, *Farbe u. Lack.*, 477 (1929); 585 (1929).

LEHIGH UNIVERSITY
BETHLEHEM, PA.

RECEIVED SEPTEMBER 3, 1942

The Oxidation of Amino Acids by Hydrogen Peroxide in Formic Acid

BY GERRIT TOENNIES AND RICHARD P. HOMILLER

It has been shown[1] that the action of hydrogen peroxide on casein dissolved in formic acid causes a selective oxidation of its tryptophan, methionine and (partly) cystine units. As regards the effect of other acid oxidizing agents on the natural amino acids Williams and Woods[2] stated that of 16 samples tested only cystine, tyrosine and tryptophan were oxidized by iodic acid (at 100°), and Nicolet and Shinn[3] showed that periodic acid selectively attacks tryptophan, methionine and cystine, as well as the α-hydroxy amino acids. Since, however, according to the same authors the latter type of compound seemed to be protected against the oxidation by acylation or by peptide formation through the amino group, and since our own observations[1] on the action of performic acid (the product of interaction of hydrogen peroxide and formic acid), which showed

(1) Toennies, *J. Biol. Chem.*, **145**, 667 (1942).
(2) Williams and Woods, THIS JOURNAL, **59**, 1408 (1937).
(3) Nicolet and Shinn, *ibid.*, **51**, 1615 (1929).

TABLE I

OXIDATION OF FORMIC ACID SOLUTIONS OF AMINO ACIDS BY HYDROGEN PEROXIDE

Initial concentration of the amino acids, 0.20 *M*, except for cystine (0.10 *M*); of H_2O_2, 0.83 *M*. Temperature 26 ± 1°. The figures in the table are rounded to the nearest 0.05, in accordance with the approximate precision of the measurements. The prefix *l*- is used to indicate the "natural" enantiomorph of the amino acids.

Compound[a]	Oxygen consumed, atoms per molecule after 1 hr.	after 2 hrs.	Compound[a]	Oxygen consumed, atoms per molecule after 1 hr.	after 2 hrs.
l-Isoleucine	0.05	0.00	*dl*-Aspartic acid	0.15	0.40
d-Isoleucine	.05	.00	*l*-Histidine[b]	.15	.40
l-Leucine	.05	.00	*dl*-Threonine	.20	.40
dl-Phenylalanine	.05	.00	*dl*-Threonine	.20	.50
l-Tyrosine	.00	.10	*dl*-Threonine	.25	.70
dl-Alanine	.10	.25	*l*-Arginine	.20	.50
dl-Serine	.35	.65	*l*-Hydroxyproline	.20	.55
dl-Serine	.15	.25	*l*-Lysine[c]	.30	.70
d-Serine	.40	.80	*l*-Glutamic acid	.30	.75
l-Proline	.10	.35	*dl*-Methionine	2.05	2.05
Glycine	.10	.40	*dl*-Cystine	5.25	5.00
dl-Valine	.10	.40	*l*-Tryptophan	3.05	3.00

[a] Where more than one compound of the same designation is listed, products of different origin were used. [b] Solution prepared from the monohydrochloride with the aid of silver acetate. [c] Solution prepared from the dihydrochloride with the aid of silver acetate.

α-hydroxy amino acid units to be resistant, had been obtained on unhydrolyzed protein, it became of interest to examine the action of performic acid on the free amino acids.

In order to obtain insight into the interaction of hydrogen peroxide and formic acid,[4] 1 cc. of 30% hydrogen peroxide was diluted to 10 cc. with 88% formic acid, and one-half-cc. samples of the resulting solution were titrated both for active peracid and for the sum of peracid and hydrogen peroxide. The iodometric method employed was that previously used by one of us[5] for the determination of permonosulfuric acid and hydrogen peroxide. The results (Fig. 1) show that under the stated conditions the concentration of performic acid approaches its maximum after one hour and changes little during the next hour.

The action of the per-compounds on the amino acids was examined as follows. 2 mM. of the compound was dissolved in 88% formic acid, 1 cc. of 30% hydrogen peroxide was added and the volume was completed with the formic acid to 10 cc. A similar blank solution, without amino acid, was prepared at the same time. One-half-cc. samples of each solution were pipetted at intervals, during a total period of approximately two hours, into 20 cc. of a solution containing 5 mM. potassium iodide, 0.1 mM. $(NH_4)_2MoO_4$ and 5 mg. of starch, and the liberated iodide was at once titrated with 0.024 *N* thiosulfate solution. The blank solutions showed an approximately linear loss of 4 ± 1% per hour while in the presence of the majority of the amino acids the resulting curves were similar except that in most cases they fell somewhat more rapidly. Only in the case of methionine, tryptophan and cystine were curves similar to C (Fig. 1) obtained, showing consumption of 2, 3 and 5 atoms of oxygen, respectively, per molecule. Most of the amino acids were used as purchased; some had been prepared or purified by us. All had been analytically identified. The results are summarized by the data of Table I. The arrangement is in the approximate order of increasing susceptibility to oxidation as revealed by these experiments.

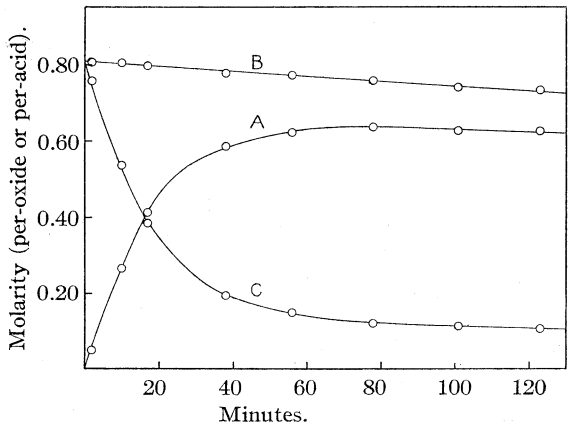


Fig. 1.—The behavior of hydrogen peroxide in formic acid: 1 cc. of superoxol dissolved to 10 cc. with 88% HCOOH; temperature 26.5°. Curve A represents peracid (HCOOOH), curve B the sum of peracid and hydrogen peroxide, and curve C (obtained by calculation from A and B) hydrogen peroxide (*cf.* text for analytical procedures).

From the results obtained on the first 4 or 5 compounds listed one might conclude that the typical structural elements of amino acids are quite stable toward the oxidizing agent used. The further data show, however, that depending on the structure and, perhaps, on the presence of impurities, some amino acids are slowly attacked. Three amino acids stand definitely apart, in that they show a rapid, stoichiometrically well-defined reaction. The data indicate that within one hour (when the majority of the amino acids consume one-third atom of oxygen or less) methionine is oxidized to the sulfone[6] level, while during the same time the oxygen consumption of cystine corresponds to the requirements for conversion to cysteic acid.

(4) d'Ans and Kneip, *Ber.*, **48**, 1136 (1915).

(5) Toennies, THIS JOURNAL, **59**, 552 (1937).

(6) Toennies and Kolb, *J. Biol. Chem.*, **140**, 131 (1941).

The apparently stoichiometric oxidation of tryptophan by 3 atoms of oxygen leaves room for different interpretations which cannot be evaluated without further work. In addition to the behavior of these three compounds it seems worth noting that in contrast to their behavior with periodic acid, the hydroxy amino acids are not distinguished by a special reactivity toward performic acid.

THE LANKENAU HOSPITAL
RESEARCH INSTITUTE
PHILADELPHIA, PENNSYLVANIA

RECEIVED SEPTEMBER 18, 1942

Density and Refractive Index of Cumene

BY JAMES E. TROYAN

In a recent investigation of alkyl benzenes at this Laboratory, the variation with temperature of density and refractive index of cumene (isopropyl benzene) was determined. Previous data on these properties had been found in the literature, but the inconsistency in published values led to the new measurements reported in this article.

The plots of densities and of refractive indices against temperatures defined curves which were fitted to the general equation, d^t_4 or $n^t_D = a + bt + ct^2$, by the method of least squares. The following expressions were obtained

$$\text{Density} - d^t_4 = 0.8777 - 0.73 \times 10^{-3}t - 2.8 \times 10^{-6}t^2$$
$$\text{R. I.} - n^t_D = 1.5017 - 0.54 \times 10^{-3}t + 0.46 \times 10^{-6}t^2$$

Densities were determined by means of pycnometer weighings between 6.1° and 37.8°. The close agreement between experimental data and the calculated curve is shown in Fig. 1. The

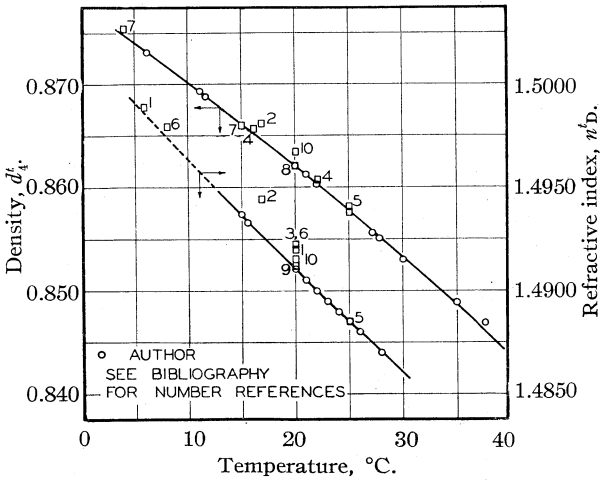


Fig. 1.

average deviation of individual points from this curve is ±0.0001 or about 0.01%. Refractive indices were measured with an Abbé refractometer at temperatures ranging from 15–28°. Experimental points, which are likewise plotted in Fig. 1, show an average deviation of only 0.002% from values indicated by the curve of the R. I. equation given above. Density and R. I. data reported by other investigators are included for comparison with the author's results.

Best grade Eastman Kodak Company cumene was used in these measurements without any further purification. This was considered acceptable since the density and refractive index of the middle cut of a redistillation (b. p. 152–153°) were not significantly different from those of the original material, which had the following properties: b. p. 151–153°, f. p. −95.2°, d^{20}_4 0.8620, $n^{20}D$ 1.4911. By comparison, best values in the literature are: b. p. 152.5°, f. p. −96.2°, d^{20}_4 0.8620, $n^{20}D$ 1.4912–1.4920.

Although the author's data may be limited somewhat in accuracy by the purity of the cumene used, it is assumed that the equations offered here are sufficiently reliable for general use in industry.

(1) K. Auwers and H. Kolligs, *Ber.*, **55B**, 21 (1922).
(2) K. Auwers, *Ann.*, **419**, 107 (1919).
(3) V. N. Ipatieff, B. B. Corson and Herman Pines, THIS JOURNAL, **58**, 919 (1936).
(4) H. Landolt and H. Jahn, *Z. physik. Chem.*, **10**, 303 (1892).
(5) J. F. McKenna and F. J. Sowa, THIS JOURNAL, **59**, 470 (1937).
(6) W. Perkin, *J. Chem. Soc.*, **77**, 275 (1900).
(7) W. Perkin, *ibid.*, **69**, 1194 (1896).
(8) T. W. Richards and J. W. Shipley, THIS JOURNAL, **38**, 996 (1916).
(9) J. Smittenberg, H. Hoog and R. A. Henkes, *ibid.*, **60**, 17 (1938).
(10) J. D. White and F. W. Rose, *J. Research Natl. Bur. Standards*, **21**, 164 (1938).

GULF RESEARCH AND DEVELOPMENT CO.
P. O. DRAWER 2038
PITTSBURGH, PA.

RECEIVED JULY 24, 1942

NEW COMPOUNDS

4-Nitrodiphenyl Ether-4′-Sulfonyl Chloride and -4′-Sulfonamide

p-Nitrodiphenyl ether was sulfonated by heating and stirring with concentrated sulfuric acid until test portions were completely soluble in water. The sodium salt was isolated, dried and converted to the sulfonyl chloride with phosphorus pentachloride. The light cream-colored sulfonyl chloride was recrystallized from isopropyl ether: m. p. 84–85° (cor.). It was analyzed by refluxing a weighed portion in 50% ethanol for three hours, evaporating to dryness repeatedly on the steam-bath to remove hydrogen chloride, and titrating the residual sulfonic acid with standard alkali.[1]

Anal. Calcd. for $C_{12}H_8O_5NSCl$: equiv. wt., 314. Found: equiv. wt., 322.

(1) *Cf.* Davis and Davies, *J. Chem. Soc.*, **123**, 2976 (1923).

To prove the structure of this compound, diphenyl ether was converted to diphenyl ether-4-sulfonyl chloride by the directions of Suter.[2] This compound was nitrated by dissolving 1 g. of it in 5 ml. of glacial acetic acid, adding 4 ml. of concentrated nitric acid, and then adding portionwise 2 ml. of concentrated sulfuric acid while keeping the temperature at about 60–70°. After the reaction mixture had stood several hours it was poured into water and the oily nitro compound was seeded to cause crystallization. Recrystallization from ethyl ether gave a product, m. p. 85.5–86.5°, indicated by melting point and mixture melting point to be identical with that made by sulfonating *p*-nitrodiphenyl ether.

The sulfonamide was obtained from either sulfonyl chloride as very light yellow crystals from dilute ethanol, m. p. 130–131°. Before Kjeldahl digestion the sample was allowed to stand with cold sulfuric acid and zinc dust.[3]

Anal. Calcd. for $C_{12}H_{10}O_5N_2S$: N, 9.5. Found: N, 9.4.

Since this work indicates that 4-nitrodiphenyl ether sulfonates mainly in the 4′-position, as might be expected, the 4-nitrodiphenyl-ether-*x*-sulfonic acid of Jones and Cook[4] may now be concluded to have been the 4′-sulfonic acid.

N,N-Di-*n*-butylhydroxylamine and its Oxalate

This hydroxylamine was made by substantially Wieland's procedure.[5] A 5% solution of nitrogen dioxide in anhydrous ether was prepared and cautiously dropped into a well-stirred solution of *n*-butylmagnesium bromide in ether. As soon as starch–iodide paper indicated the presence of excess nitrogen dioxide, the mixture was let stand for two hours and then decomposed with a little water. The N,N-di-*n*-butylhydroxylamine was extracted with ether and precipitated therefrom by adding a solution of oxalic acid in ether. The oxalate, recrystallized from methanol, melted at 144.0–144.5°.

Anal. Calcd. for $C_{10}H_{21}O_5N$: N, 5.94; equiv. wt. (dibasic acid), 118. Found: N (Kjeldahl), 5.95; equiv. wt., 118.

(2) Suter, THIS JOURNAL, **53**, 1112 (1931).
(3) Weizmann, Yofe and Kirzon, *Z. physiol. Chem.*, **192**, 70 (1930).
(4) Jones and Cook, THIS JOURNAL, **38**, 1534 (1916).
(5) Wieland, *Ber.*, **36**, 2315 (1903).

The free N,N-di-*n*-butylhydroxylamine was obtained by warming the oxalate with concentrated alkali solution, chilling, and isolating the product by filtration. After recrystallization from aqueous ethanol it melted at 52.5–53.0°. It was very soluble in all organic solvents tested, but only slightly soluble in water, giving a neutral solution; its weakness as a base is indicated also by the fact that the acid in the oxalate may be titrated as if free. When warmed with solutions of silver, cupric or auric salts, it exhibits the expected reducing power.

Anal. Calcd. for $C_8H_{19}ON$: N, 9.66. Found: N, 9.59.

DEPARTMENT OF CHEMISTRY V. H. DERMER
OKLAHOMA AGRICULTURAL AND MECHANICAL COLLEGE
STILLWATER, OKLAHOMA O. C. DERMER

RECEIVED AUGUST 17, 1942

4-Toluenesulfonates of the Nitro-4-phenylphenols

2,6-Dinitro-4-phenylphenyl 4-Toluenesulfonate.—This compound was prepared by the treatment of 2,6-dinitro-4-phenylphenol in pyridine solution with tosyl chloride. The crude, faintly yellow product was obtained in quantitative yield and, after crystallization from propanol, from which 88% was recovered as colorless prisms, it melted at 186–187°.

Anal. Calcd. for $C_{19}H_{14}O_7N_2S$: S, 7.73. Found: S, 7.69.

2,6-Dinitro-4-(4-nitrophenyl)-phenyl 4-Toluenesulfonate.—For the preparation of this compound it was necessary to dissolve the 2,6-dinitro-4-(4-nitrophenyl)-phenol and the tosyl chloride in warm 1,4-dioxane and then to add the pyridine. The crude product was obtained in quantitative yield, and after crystallization from methanol the recovery was 80%. The crystals so obtained were faintly yellow prisms, but after drying at 130° and 15 mm. the color disappeared; m. p. 219–220°.

Anal. Calcd. for $C_{19}H_{13}O_9N_3S$: S, 6.97. Found: S, 6.85.

DEPARTMENT OF CHEMISTRY STEWART E. HAZLET
STATE COLLEGE OF WASHINGTON DALE A. STAUFFER
PULLMAN, WASHINGTON HARRIS O. VAN ORDEN

RECEIVED OCTOBER 13, 1942

COMMUNICATIONS TO THE EDITOR

THE TOXIC PRINCIPLES OF POISON IVY

Sir:

We have investigated the active principles of poison ivy and find that the toxic oil is a complex of at least three active components and several innocuous concomitants.

Hill and his co-workers[1] isolated a toxic yellow oil from poison ivy with the stated boiling point of 210° (0.5 mm.), and presented evidence to prove that it was identical with urushiol, the boiling point of which was quoted as 210° (0.4–0.6 mm.). From this toxic oil they prepared a series of derivatives, identical when crystallizable with those prepared from urushiol, but no yields were reported.

"Urushiol" is a name first applied by Majima[2] to an extract of Japan lac which boiled over a range of 210–222° ((0.4–0.6 mm.), and, upon redistillation, from 195° to "above 210°." It was shown to consist of four components[3] the structures of which were partially elucidated.

Since it is known that plants of the *Anacardiaceae* family, to which both poison ivy and Japan lac belong, elaborate a number of vesicant mono- and dihydric alkyl phenols with fifteen and seventeen carbon side chains, the derivatives prepared by Hill only prove the presence of a compound or compounds with a 3-pentadecacatechol skeleton in the distillate. This is a property it possesses in common with urushiol.

Essentially we followed Hill's method of isolation; our concentrate boiled over a range, the major portion distilling at 185–250° (2 microns) with considerable resinification. Redistillation in a Hickman molecular still yielded three fractions at bath temperatures up to 125°, 165° and 170°, the principal superficial difference being one of color. The products, although containing innocuous concomitants, were all toxic, 0.5 gamma of oil per sq. cm. of hypersensitive skin being sufficient to elicit a strong characteristic poison ivy reaction.

Chromatographed under nitrogen on barium carbonate–Hyflo Super Cel (Johns Mansville Sales Corporation), fraction 1 was separated into an unsaturated acid (or acids, hydrogenation yielding a solid, m. p. 66–67°, depressed by palmitic but not stearic acid; C, 75.4; H, 12.5; amide m. p. 105–106°, depressed by palmitamide but not stearamide; therefore stearic acid[4]) and a phenolic oil, log ϵ 265 mμ = 3.02, log ϵ 273 mμ = 3.09 in absolute ethanol. In twenty-four hours absorption decreased to log ϵ 265 mμ = 2.72 and the ferric chloride test became negative in the original concentration, 6 mgm./100 cc. This suggests that the presence of drying oils in the vesicant-bearing sap accounts at least in part for the extraordinary stability of the toxic principles in their natural environment.

Chromatographed on alumina (Alorco) deactivated with 90% ethanol, fraction 1 yielded *six* bands, from the top: orange, four colorless with bright blue-white fluorescence under ultraviolet light, and yellow. One fluorescent band, eluted with 90% ethanol, was phenolic and autooxidized with extreme rapidity. The other fluorescent bands could not be removed without major destruction, but were shown to be highly toxic, while the remaining fractions were not. We conclude that at least three toxic components are present, and are engaged in improving this technique and elucidating the structures of the toxic compounds. The exigencies of the day have required this short report at this time.

(1) Hill, Mattacotti and Graham, THIS JOURNAL, **56**, 2736 (1934).
(2) Majima, *Ber.*, **42**, 1418 (1909).
(3) Majima, *et al.*, *ibid.*, **55B**, 172 (1922).

(4) We are indebted to Dr. Arthur T. Ness for the microchemical analyses.

SECTION OF DERMATOSES INVESTIGATIONS
DIVISION OF INDUSTRIAL HYGIENE
NATIONAL INSTITUTE OF HEALTH HOWARD S. MASON
BETHESDA, MARYLAND LOUIS SCHWARTZ

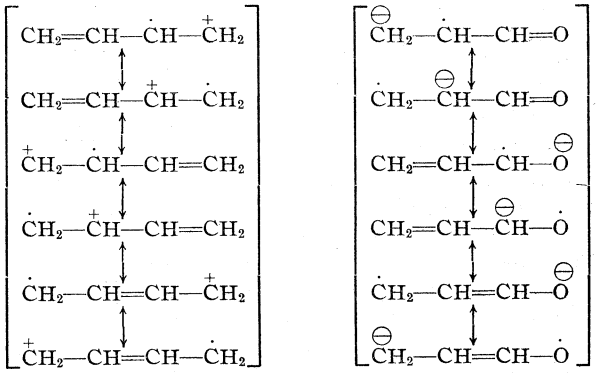
RECEIVED OCTOBER 21, 1942

THE MECHANISM OF THE DIELS-ALDER REACTION

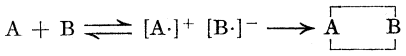
Sir:

It is noteworthy that in the usual case the Diels–Alder reaction involves, on the one hand, a substance, *e. g.*, a diene, of relatively low ionization potential and, on the other, a molecule of high electron affinity, *e. g.*, an α,β-unsaturated carbonyl compound. We may therefore expect an electron-transfer from the diene to the dienophile with the formation of an ion-pair intermediate of the type recently postulated in general for molecu-

lar compound formation by Weiss.[1] Both components, after the electron exchange, will be hybridized, *viz.*, in the simplest case, the reaction between butadiene and acrolein,



We thus arrive at a mechanistic picture in which collision results in electron transfer followed by formation of a dipolar aggregate, held together



by ionic forces (and possibly further by interparticular overlapping of the orbitals of the nonbonded electrons in each half; in this event, the link could be described as an *intermolecular semipolar bond*,[2] *cf.* $[A^+]:[B^-]$). Stereochemically, the aggregate would consist of two parallel charged (usually flat) surfaces, oriented in such wise as to take maximum advantage of electrostatic attractive forces. The first step is probably in most cases rapid and reversible, the rate-controlling process being the usually (but not always) substantially irreversible rearrangement of the ion-pair complex to the product [A B *above*].

This picture is in complete conformity with the large body of observed phenomena attendant upon the reaction. There may be cited: (i) transient color formation, (ii) steric course of the reaction, (iii) effect of substituents of divers electrical character on the ease of reaction both of the diene and the dienophile, (iv) observed molecular compound formation preceding reaction in certain cases, (v) the occasional abnormal course of the reaction (notably in the case of heterocyclic nitrogen bases, and ketenes), (vi) solvent effects.

The procession of the reaction by the above course further indicates the possibility of catalysis by donor or acceptor molecules which cannot themselves participate in the diene-addition reaction. Preliminary experiments designed to test this possibility give some qualitative indication that dimethylaniline and 1,3,5-trinitrobenzene exert such an accelerating effect.

The situation will be considered in detail in a forthcoming publication.

CONVERSE MEMORIAL LABORATORY
HARVARD UNIVERSITY
CAMBRIDGE, MASSACHUSETTS R. B. WOODWARD

RECEIVED NOVEMBER 12, 1942

(1) Weiss, *J. Chem. Soc.*, 245 (1942).

(2) (Note added in proof, November 25, 1942.) This concept is a logical extension (or modification) of the theory of molecular complex formation which is not implied in Weiss' paper.[1] I intend to develop these ideas further; meanwhile, I note that Dr. L. C. Bateman (*Chemistry and Industry*, **61**, 453 (1942), received November 23) has independently proposed a similar picture during a discussion at the Chemical Society (London) on October 15, 1942. On this side these ideas were first embodied in Dr. J. J. Leavitt's Dissertation, "Some Properties and Reactions of Unsaturated γ-Lactones," Harvard University, September 1, 1942.

NEW BOOKS

Elementary Physical Chemistry. By MERLE RANDALL, Professor of Chemistry in the University of California, and LEONA ESTHER YOUNG, Professor of Chemistry in Mills College. Randall and Sons, 2512 Etna St., Berkeley, California, 1942. (Photolith reproduction.) xiv + 455 pp. Illustrated. 15.5 × 23.5 cm. Price, $4.50.

Physical Chemistry. By FRANK THOMSON GUCKER, JR., Associate Professor of Chemistry, Northwestern University, and WILLIAM BUELL MELDRUM, Professor of Chemistry, Haverford College. American Book Company, 88 Lexington Avenue, New York, N. Y., 1942. xii + 683 pp. 262 figs. 14.5 × 22.5 cm. Price, $4.00.

As physical chemistry has advanced beyond its historic preoccupation with aqueous solutions of electrolytes, an adequate grasp of its subject matter has become increasingly difficult to obtain in a single year-course. An "introductory" course in the third, or even second, year of college is a frequent answer to this problem as well as to the needs of students majoring in other sciences or preparing for medicine. Such a course, covering one or two semesters, is the province of the two text-books with which we are concerned. They both deal mainly with "classical" principles; both stress experimental facts and the deductive approach, with a minimum of mathematics and thermodynamics. Parallel or previous study of the calculus would be desirable but not essential. In both cases the problems of beginning students have been kept clearly in mind; extensive use of illustrations, graphs, exercises and applications should go far to stimulate interest and

assure comprehension. Both books can be recommended as sound, carefully written and well made contributions to the teaching of *introductory* physical chemistry.

The Randall and Young book has several unique features. It introduces the physico-chemical method of treatment by analyzing a familiar process—vaporization of a liquid. Gradually, and quite naturally, *concepts* are developed, *e. g.*, boiling point, vapor pressure, equilibrium, heat content, temperature scale, escaping tendency, partial pressure, activity, activity quotient, cycles. Soon important relations begin to appear as experimental facts, such as the Clausius–Clapeyron equation, Trouton's rule, and Raoult's law. The first third of the book is devoted to this kind of analysis of phenomena encountered in analytical or organic laboratory. The remainder of the book develops the basic principles in a more quantitative and fairly systematic manner. The emphasis is strongly on equilibrium, and particularly heterogeneous equilibrium, including distillation, freezing point, solubility and distribution. There are brief sections on flow of fluids and reaction rates, but almost no mention of atomic, molecular or crystal structure, isotopes, colloids, surface phenomena or photochemistry. Though much briefer than most such texts, it is notable for the extensive use of figures (279). Many of these excellently illustrate principles by graphs of experimental data (with copious references); others show laboratory or industrial apparatus. All figures are supplied with explanatory paragraphs which of themselves give a good descriptive picture of physico-chemical behavior. Another important feature are the 690 exercises distributed in small groups at appropriate points throughout the text. They are original and stimulating, and often serve to extend the textual discussions or to apply them to other fields.

The Gucker and Meldrum book is more conventional in plan. After brief discussions of fundamental chemical theory, atomic structure and valence, it takes up in order the states of aggregation (123 pp.), thermochemistry (27 pp.), solutions (55 pp.), kinetics (19 pp.), equilibrium with particular reference to solutions of electrolytes (about 200 pp.), colloids and surface phenomena (78 pp.), phase equilibrium (31 pp.), and thermodynamics (34 pp.). Structure and its relation to properties, reaction mechanisms, and quantitative aspects of hetereogeneous equilibrium receive only minor attention. The book owes much to "Introduction to Theoretical Chemistry" by the same authors, but covers much more of the "classical" ground and at a somewhat more advanced level. The development is largely empirical, with little aid from thermodynamics or calculus, although such aids are available in the final chapter if use can be made of them there. There is strong emphasis throughout on the application of chemical principles in biological phenomena. There is contained an unusual amount of well-selected experimental data (262 figures, 124 tables). The numerous figures showing how well, or sometimes how badly, theories accord with actual facts are particularly commendable. An adequate number (258) of problems and review questions is provided; several of a given type are usually included, but there is fair variety and range of difficulty. Each chapter closes with a carefully prepared reading list of books and review articles, frequently with specific page references and helpful comments on scope and character.

ARTHUR F. BENTON

The Electron Microscope. By E. F. BURTON, Head of the Department of Physics, University of Toronto, and W. H. KOHL, Development Engineer, Rogers Radio Tubes Limited, Toronto. Reinhold Publishing Corporation, 330 West 42nd Street, New York, N. Y., 1942. 233 pp. Illustrated. 15.5 × 23.5 cm. Price, $3.85.

Great things are expected of the electron microscope as a tool of the investigator in pure and applied research. Like all things not well understood, it has sometimes been the subject of over-enthusiastic expectations. On the other hand, a lack of comprehension of the instrument operates to delay the useful applications to which it may be put.

In this volume, the authors by simple steps lead the reader gradually to a comprehension of the nature of vision and the elements of optical science, through a brief course in electronics and its branch called electron optics, the basis of taking magnified pictures without light.

This is a book for the thoughtful reader, not a picture book. Copiously illustrated, however, with homely diagrams, adequate although executed with non-professional draftsmanship, and with half-tone reproductions of photo and electron micrographs, it presents a physicist's explanation of the theory and operation of this modern instrument in a manner easily comprehended by scientists in fields other than that of electronics. For the lay reader who enjoys a certain amount of homework the thoughtful study of this volume will present much that is authentically and interestingly informing in various fields of life of today and of tomorrow.

JOHN W. M. BUNKER

Introduction to Semimicro Qualitative Chemical Analysis. By LOUIS J. CURTMAN, Professor of Chemistry, The City College, The College of the City of New York. The Macmillan Company, 60 Fifth Avenue, New York, N. Y., 1942. x + 377 pp. 38 figs. 14.5 × 22 cm. Price, $2.75.

This book is a follow-up of the author's earlier "Qualitative Chemical Analysis," based on experimental testing of modifications of macro methods to semi-micro scale, and containing some relatively new procedures, also. The first 130 pages (Part I) are a discussion of the usual background topics of modern qualitative analysis, ranging from coördination theory and acid–base theory, through solutions, equilibrium, ionization, solubility product, and oxidation–reduction, to buffer solutions, hydrolysis and colloids. Part II (75 pp.) takes up the reactions of the metal ions, followed by a much shorter section on the anions, with copious equations. Part III (16 pp.) deals with calculations, and includes many simple weight relation and normality problems. Part IV on laboratory work (87 pp.) devotes several pages to general advice, directions and warnings on semi-micro work, followed by orientation and practice tests on various metal ions. Then come the systematic procedures for the metal ions, followed by tests

on anions. Part V gives the systematic detection of the anions, preparation of the solution for metal analysis, the phosphate separation. The 30-page Appendix gives recording notes for data, desk equipment lists, reagent lists, and specifications for stock solutions, with a long table of solubilities.

The background section seems to be well written and adequate, while the sections on the characteristics of the various ions give a variety of tests on each ion. The cation analysis scheme has a few departures from the usual procedures: the separation of the copper and tin subgroups using potassium hydroxide; an extra step for complete separation of arsenate ion in strongly acid solution; ammonium sulfide precipitation of the iron–nickel family with immediate separation of manganese with nitric acid and potassium chlorate; partial precipitation of magnesium with the calcium group. The anion analysis is worked out in some detail. The typography, design and mechanical execution are good; a few small details which might have been improved are the lack of style consistency in the literature citation footnotes, the use of unattractive full capital abbreviations (such as E. M. F. instead of e. m. f.), a few old-fashioned spellings (sulphur, in particular), and the hyphenation of such words as silver-ion (as nouns).

ALLEN D. BLISS

Introduction to the Microtechnique of Inorganic Analysis. By A. A. BENEDETTI-PICHLER, Dr. Techn. Sc., Assistant Professor of Chemistry, Queens College, Flushing, N. Y. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1942. vii + 302 pp. 84 figs. 15.5 × 23.5 cm. Price, $3.50.

In the 1920's Dr. Benedetti-Pichler came to New York from Austria, where he had been a student of the chief founder of inorganic microchemistry, Friedrich Émich, and inaugurated one of the first, if not the first, systematic course in that subject at an American university. At that time microchemistry was very young indeed, and untried; now it has matured and its standing in the science is secure, and it has a place in most educational curricula that emphasize analysis and manipulative technique; moreover, there is nowadays scarcely an industrial laboratory of any pretensions that does not have some facilities for microchemical work. Dr. Benedetti-Pichler deserves much of the credit for these developments.

The book under review "is intended as an introduction to the microtechnique of chemical experimentation." Briefly summarized, it purports to do two things: describe, in the manner of a laboratory manual, certain of the basic manipulative and observational techniques that have been developed for or adapted to microchemistry, in order to facilitate operations on a reduced scale; and illustrate the application of these techniques to qualitative and quantitative inorganic analysis. Thus this volume, which is presented as a college textbook, is divided into three parts: I, Apparatus for General Use; II, Qualitative Analysis, A, Confirmatory Tests, B, Microtechnique of Qualitative Analysis; III, Quantitative Analysis, A, Gravimetric Determinations, B, Titrimetric Determinations; followed by a bibliography and the usual appendices.

The present book replaces an earlier work, "Introduction to the Microtechnique of Inorganic Qualitative Analysis," by Professor Benedetti-Pichler and Dr. W. F. Spikes. Readers familiar with the older book will be interested in a comparison of its subject matter with that of the new one. The three parts in the older were: I, The Microscope; II, Qualitative Analysis (Apparatus and Technique); III, Microqualitative Scheme. Thus the most important addition in the volume under review is the inclusion of microquantitative analysis; some may feel that the most important omission is the systematic scheme for microqualitative analysis. Many writers make a rather vague distinction between "micro-" and "semimicro-" procedures. The present volume carries this a step further and describes typical "centigram, milligram and microgram procedures." The reviewer believes that this is a useful pedagogical device.

The reviewer believes that the book will serve very satisfactorily for the purposes intended. But he cannot refrain from deploring the lack in this book, as in most other texts on microchemistry, of any material that will qualify the student to apply microtechniques in a practical way when he sets up as a microchemist in an industrial or a research laboratory. Deplorable especially is the lack of emphasis on the fact, so palpably real to supervisors of microlaboratories in industry, that more often than not the selection, isolation and preparation of the sample for microanalytical attack requires at least as much effort and skill as the actual microanalysis. The reviewer does not quarrel with what is in this book: clearly the student must learn all of this before he is even competent to microanalyze pure substances; but it is contended that the book would have had a great deal more value in orienting the student of microchemistry into the "world of things as they are," if another fifty pages, giving some applications of microtechniques to practical problems, had been added. There is no dearth of these, as the author is well aware. Doubtless the author would reply that his book is not a compendium but an introduction, and that he deliberately chose to cover only those aspects of the subject that he did cover, leaving to others the industrial applications. That is a valid reply, which the reviewer would have to accept; but he still deplores the fact that the "others" have not arisen, and he hopes for their early emergence.

Minor criticisms are the absence of an author index, and of a presentation of the increasingly versatile and important electrographic technique.

BEVERLY L. CLARKE

Physical Chemistry for Students of Biochemistry and Medicine. By EDWARD STAUNTON WEST, Ph.D., Professor of Biochemistry in the University of Oregon Medical School. The Macmillan Company, 60 Fifth Avenue, New York, N. Y., 1942. xiv + 368 pp. 24 figs. 16 × 24 cm. Price, $5.75.

The jacket informs us: "The primary aim of this book is to present the selected phases of physical chemistry recognized as basic to an understanding of biological phenomena." In doing so, the author has treated the following topics: the structure of matter, including atomic structure; valence, including in his discussion electro-

valence, covalence, coördinate valence, and the hydrogen bond; the gas laws; theories of solutions, including solubility, osmotic pressure, electrolytic dissociation, diffusion, and the mass law; acids and bases, including buffer solutions; the determination of *p*H by various methods; the colloidal state and membrane phenomena including surface phenomena, size of colloidal particles, adsorption and the Donnan equilibrium; oxidation and reduction, including reference to the theory of oxidation-reduction potentials and the mechanisms of biological oxidations; and finally, the velocity of reactions.

These topics have, on the whole, been chosen with discrimination and have generally been treated in the light of contemporaneous theory. Omission of any reference to the theory of Debye and Hückel is surprising to this reviewer, as is the bare statement that: "Neutralization of toxins by antitoxins seems to proceed according to the laws of adsorption." Whereas the very elementary treatment presupposes only a low level of preparation in mathematics, physics, and chemistry, the insertion of numerous simple problems, and pertinent questions should help the reader to coördinate his knowledge on an elementary, quantitative plane. The more inquisitive reader is referred to more extended summaries, but rarely to original definitive literature. The relations of physical chemical principles to biology are well illustrated and stressed.

In these days when inadequate preparation is likely to become more general, this book can be used profitably by both premedical and medical students.

RONALD M. FERRY

Organic Reactions. Volume I. ROGER ADAMS, Editor-in-Chief, WERNER E. BACHMANN, LOUIS F. FIESER, JOHN R. JOHNSON and H. R. SNYDER. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1942. vii + 391 pp. 15.5 × 23.5 cm. Price, $4.00.

Organic chemists will welcome this first volume of the series with more than ordinary enthusiasm, for it is a landmark in the literature of organic chemistry. The series is a new departure, and will make available extremely valuable information in a readily applicable form. Perhaps the nearest approaches to the present series are the still useful but quite out-of-date special parts of Houben–Weyl and Lassar–Cohn on general organic reactions such as condensation, nitration, etc.

Primarily, the work is concerned with the scope and limitations of important laboratory reactions. "The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method." The textual material, tables and extensive bibliographies provide a coverage that is as nearly complete as one might wish.

The twelve chapters have been written by authors who have had particular experience with the reactions or processes described: (1) "The Reformatsky Reaction" (Ralph L. Shriner); (2) "The Arndt–Eistert Synthesis" (W. E. Bachmann and W. S. Struve); (3) "Chloromethylation of Aromatic Compounds" (Reynold C. Fuson and C. H. McKeever); (4) "The Amination of Heterocyclic Bases by Alkali Amides" (Marlin T. Leffler); (5) "The Bucherer Reaction" (Nathan L. Drake); (6) "The Elbs Reaction" (Louis F. Fieser); (7) "The Clemmensen Reduction" (Elmore L. Martin); (8) "The Perkin Reaction and Related Reactions" (John R. Johnson); (9) "The Acetoacetic Ester Condensation and Certain Related Reactions" (Charles R. Hauser and Boyd E. Hudson, Jr.); (10) "The Mannich Reaction" (F. F. Blicke); (11) "The Fries Reaction" (A. H. Blatt); and (12) "The Jacobsen Reaction" (Lee Irvin Smith).

Some of the chapters have many more formulas in the tables than others. A strictly uniform pattern of presentation may not be the best procedure for a work of this kind, but a more extensive use of formulas instead of names in some of the chapters would be preferred by students and others.

It is interesting to note the occasional cases where "name" reactions bear the name not of the original discoverer, but of one who subsequently explored the broad aspects of the reaction.

The series, separate volumes of which will appear periodically, will form something more than a mere adjunct to laboratory procedures. It is the sort of work that not only stands alone, but that will prove an invaluable supplement to every text or reference work in organic chemistry. With the appearance in recent years of a wide variety of excellent books on organic chemistry, the content of some seminar and special topics courses may be revised to place added emphasis on immediately current articles instead of extensive surveys which are increasingly available.

Although this work appears in war times, the general idea was conceived several years ago and in this respect is unlike "Organic Syntheses," the origin of which is directly traceable to meeting the needs for research chemicals in the last war. The editors and authors are to be complimented and thanked for a splendid work which must have made unusual demands on them in these strenuous times.

HENRY GILMAN

Chemical Refining of Petroleum, the Action of Various Refining Agents and Chemicals on Petroleum and its Products. By VLADIMIR A. KALICHEVSKY, Research and Development Laboratories, Socony-Vacuum Oil Co., Inc., and BERT ALLEN STAGNER, Ph.D., Consulting and Research Chemist. Revised edition. Reinhold Publishing Corporation, 330 West 42nd St., New York, N. Y., 1942. 550 pp. Illustrated. 23.5 × 15 cm. Price, $7.50.

The rapid advances which have been made in the refining art during the past decade have made necessary revision of this well-known book which was first published in 1933. Much of the book was rewritten (apparently in 1940) and the material rearranged with improved results. The subjects covered include the composition of petroleum; treatment with sulfuric acid; sulfuric acid sludge and hydrogen sulfide; recovery and manufacture of sulfuric acid; treatment with alkaline reagents; sweetening operations; refining by adsorption; refining with solvents; deterioration and anti-detonants; inhibitors of atmospheric oxidation; gums and cracked petroleum products;

and deterioration of lubricating and similar oils. A very useful supplementary list of U. S. patents on petroleum refining is presented, patents issued up to January, 1940, being listed. The glossary of terms which occupied some 23 pages in the first edition is now omitted; definitions of such terms as aldol, alkyl, amine, anthracene, bauxite, benzoyl, etc., are certainly superfluous in an A. C. S. Monograph.

The authors have written a very readable treatise. The style and makeup are excellent; subheadings are used liberally. The chemical reactions which occur in the various refining processes are discussed briefly but perhaps adequately for the purpose of the book.

Although the book will appeal chiefly to the refiner and to the petroleum technologist, it can be read with profit by chemists who are interested in the application of chemical procedures to the refining of petroleum.

V. N. IPATIEFF

Organic Syntheses. An Annual Publication of Satisfactory Methods for the Preparation of Organic Chemicals. Vol. 22. LEE IRVIN SMITH, Editor-in-Chief, HOMER ADKINS, C. F. H. ALLEN, W. E. BACHMANN, NATHAN L. DRAKE, R. L. SHRINER, H. R. SNYDER, and A. H. BLATT, Secretary. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1942. 114 pp. 15.5 × 23.5 cm. Price, $1.75.

The addition of this new book to the series of publications in the field of synthetic chemistry entitled "Organic Syntheses," must be considered as filling a useful service. We have now available for reference twenty-two volumes of this practical organic text. The organic preparations recorded have been selected, approved and checked by a competent editorial board experienced in the modern technique of synthetic organic chemistry, and the new volume should prove to be just as helpful as any of the editions already published.

In this volume are described satisfactory methods for the laboratory preparation of thirty-four different organic compounds representative of the aliphatic, aromatic and heterocyclic series. Several of these will prove of immediate service as key substances in new research programs.

The very complete literature references are extremely useful for workers interested in the different fields represented by the preparations recorded. The practical nature of the work should prove very helpful to those workers who do not have access to good library facilities and the literature of chemistry. A subject index for volumes 20–22 is printed in this volume.

TREAT B. JOHNSON

Technical Report Writing. By FRED H. RHODES, Professor of Chemical Engineering, Cornell University. McGraw-Hill Book Company, Inc., New York, N. Y., 1941. vii + 125 pp. 8 figs. including one of conventional symbols. 15.5 × 23.5 cm. Price, $1.50.

The author, struck, as many others have been, "by the appalling lack of ability of students and graduates to write effective reports," and having concluded that they are unlikely to learn in courses in English how to construct and write a good report, decided that it was up to him to train his students in technical writing by requiring that the reports in his courses be written in good English and subjected "to the same careful criticism that is exercised in the editing of articles for publication in the better technical journals." As there was no satisfactory textbook covering this precise field, he proceeded to write one, and has succeeded admirably in what he set out to do. In a series of brief chapters he outlines the importance of effective presentation, written or oral, of the results of an investigation, particularly where this presentation is to reach the less strictly technical members of an organization, and discusses the characteristics and proper organization of a good technical report, with pertinent remarks on many details of style and usage to which the writer of a report should, but usually does not, pay attention. In these pages I saw no statement with which I do not fully concur, nor any significant omission; and noted only a single error which might puzzle the reader, namely, that on page 99 in the columns headed "deviation" the numbers are the square of the deviation. The last few chapters, occupying more than half of the book, deal briefly with some of the simpler methods of analyzing, correlating, and depicting experimental data; references are given to other books which treat these matters more fully. If ways can be found to induce students—and not only students, but graduates—to absorb, and make use of, the teachings of this book, there should be fewer complaints of poor organization of reports and articles and of sloppy writing which makes it more difficult for the reader to grasp what the writer is trying to convey.

JOHN JOHNSTON

A Shorter Course in Organic Chemistry. By J. C. COLBERT, Associate Professor of Chemistry in the State University of Oklahoma. Second Edition. D. Appleton–Century Company, Inc., 35 West 32nd Street, New York, N. Y., 1942. xvii + 355 pp. 15 × 23 cm. Price, $3.75.

Introductory Organic Chemistry. By E. WERTHEIM, Professor of Organic Chemistry in the University of Arkansas. The Blakiston Company, 1012 Walnut Street, Philadelphia. Penna., 1942. vii + 482 pp. 82 figs. 15.5 × 23.5 cm. Price, $3.00.

These two books are intended for students who are in related sciences of biology, medicine, home economics, etc. Both aim to give a student a well grounded appreciation of the graphic formula and of the structural theory of organic chemistry. The means by which each attains this end are, however, widely different and represent two views on the method of instruction. The book by Colbert begins with a chapter on the theoretical basis of organic chemistry which includes such topics as the Bohr atom, the coördinate and covalent bond, the valence of carbon, resonance, isomerism (structural, dynamic, optical and geometrical), classification as aliphatic, aromatic, and heterocyclic, and the importance of analysis and physical constants of organic compounds. After this introduction there is (part one) a sequence of fourteen chapters (246 pages) on aliphatic compounds, in which hydrocarbons, halogen alkyls, alcohols, acids, the lipids (fats, phosphatides, waxes and

sterols), amino acids and proteins and other topics are described. In part two, there are five chapters (68 pages) which describe aromatic compounds, monosubstituted benzene derivatives and heterocyclic compounds. The aim of the author is to develop the fundamental theory slowly but thoroughly in about the first third of the book and then give the remainder as a rapid survey. The book contains many excellent charts, directions for study and numerous questions. A short appendix gives the methods of calculating yields and the formulas of compounds.

The opening chapter of the text by Wertheim emphasizes the special fields covered in organic chemistry, the elements present in organic compounds, the industrial value of organic products such as leather, oils, chemicals, resins, etc.; the sources of organic compounds, the general methods by which the chemist analyzes them, the skeleton structure, the carbon atom and structural isomerism. After this introduction there follows a series of twenty chapters on hydrocarbons, halogen derivatives, alcohols, etc., in which the chemistry of functional groups and aromatic compounds are discussed. This material is divided into about 227 pages on aliphatic and 92 pages on aromatic and heterocyclic compounds. The concluding four chapters are, respectively, on digestion and absorption of foods, metabolism, nutrition and foods. Throughout the work the author has chosen to omit technicalities while stressing points of fundamental importance. The commercial and social aspects of organic chemistry are emphasized. Numerous illustrations of such subjects as the processing of soap, uses of cellophane and synthetic resins, synthetic rubber, animals showing the effect of diet deficiency, and respiratory apparatus are included. The photographs of molecular models are especially good. A generous supply of study questions is included with each chapter. The forty pages of appendix contain a glossary of terms in chemistry, biology and medicine, a discussion on the removal of stains, a list of reference books and analytical data on foods.

This review does not argue the merits of the two methods of instruction. The opening chapter of each text probably presents a pretty good picture of the principle which each author proposes to use with students who desire only a short course in organic chemistry. A conscientious student who will study either text and solve the problems can undoubtedly acquire a good knowledge of the subject.

AVERY A. MORTON

Equilibrium and Kinetics of Gas Reactions. An Introduction to the Quantum-Statistical Treatment of Chemical Processes. By ROBERT N. PEASE. Princeton University Press, Princeton, New Jersey, 1942. ix + 236 pp. Illustrated. 15.5 × 23.5 cm. Price, $3.75.

This is a textbook designed for first year graduate students. The first part, about one-third of the book, is a review of the fundamental thermodynamics of equilibrium in gaseous systems. Nearly half of this part is devoted to the formulation of thermodynamic quantities in terms of partition functions and illustrations of their use. Only sufficient theory is developed as is needed in the numerous practical applications.

The rest of the book treats the rate and mechanism of gas reactions. This part begins with a brief description of the theory of the absolute rate of reactions. Chapters on reactions of simple order, quasi-unimolecular, chain, and oxidation reactions follow. The book closes with a brief account of surface-catalyzed reactions.

It is unfortunate that there are few gas reactions even moderately free of complications, as much might be learned from them. The reluctance of chemical reactions to proceed in a straightforward way is in itself remarkable, and the result is that the theory of reaction rates is far ahead of experimental confirmation. Indeed, it is almost true that the reactions which are least understood are those which have been studied most. While the reviewer does not agree with all of the conclusions of the author, the evidence for and against particular mechanisms is presented fairly. Such help in interpreting the mechanism of complex reactions as can be given by the theory of absolute reaction rates is freely used. The complicated behavior of oxidation reactions is particularly well presented.

Typographical errors are few and unimportant. The book emphasizes a common viewpoint of equilibrium and the approach to equilibrium in gas reactions, and the author is to be congratulated on his clear and readable survey of a complicated and fascinating field of study.

DARRELL V. SICKMAN

Introductory College Chemistry. By HORACE C. DEMING, Professor of Chemistry, and B. CLIFFORD HENDRICKS, Professor of Chemistry, University of Nebraska. Second edition, completely revised. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1942. xii + 521 pp. 176 figs. 15.5 × 23.5 cm. Price, $3.00.

This revision of Deming's popular and widely used "Introductory College Chemistry" should be of interest to anyone teaching a group who are either less advanced or do not need a detailed and comprehensive course in general chemistry. In the preparation of this revision the original text has been largely rewritten. A few changes in order of presentation have been made and new questions and exercises have been added. However, in this rewriting there has been no loss of clarity or logical presentation. The practical aspects of chemistry are stressed, but not to the exclusion of fundamental principles.

The order of treatment is the fairly standard: Introduction—Oxygen—Water—Atomic Structure—Hydrogen—Acids—Bases—Salts—Non-metals—Metals—Organic Chemistry. Although the order may not appeal to some teachers, the authors seem to have maintained excellent continuity.

All in all, the book would seem to be worthy of the careful consideration of anyone interested in a well-written, up-to-date, and readable, but less comprehensive textbook.

C. H. SORUM

Du Pont—One Hundred and Forty Years. By WILLIAM S. DUTTON. Charles Scribner's Sons, New York, N. Y., 1942. x + 396 pp. 16.5 × 23.5 cm. Price, $3.00.

This book presents the story of a chemical enterprise through which from remote beginnings in colonial days runs

unbroken for seven score years the red thread of a family name and a spirit which as the years went by became a cherished tradition to be passed on from generation to generation. It is to a notable degree a biography of an institution. The outstanding figure of the earlier chapters is Eleuthère Irénée du Pont, one of two sons of Pierre Samuel du Pont de Nemours, who had been elevated to the nobility because of distinguished services to his country, and his work in connection with the Peace of Paris between the United States and England. At the country estate of his father he met many notable visitors, among them Benjamin Franklin, Lafayette, Talleyrand, and Lavoisier. The latter became interested in the boy of fourteen and two years later gave him a position in the gunpowder factory of which Lavoisier was chief. After four years there he became first assistant to Lavoisier in his laboratory. Then followed the French Revolution, the reign of terror, the migration of the du Pont family to America, and the erection of the little gunpowder factory on the Brandywine near Wilmington in 1802 based on the training given by Lavoisier and financed by French and American capital.

The close connection of ammunition and explosives with the pioneering development of the West, and the wars, of the last century gives historical interest to the large section of the book which covers that period in which nitroglycerine and dynamite and nitrocellulose and smokeless powder gave a new trend to the explosive industry. With the present century there began an era of expansion which in its broader outlines reflects the progress of the chemical industry in America over the past forty years. The reader finds here much which appeals to his imagination. In no field of human endeavor more than in chemistry is the spirit of the pioneers more clearly reflected, and adventure and discovery and individual initiative and resourcefulness become the keys to accomplishment. The concluding chapters dealing with the development of a broad program of research, dyestuffs, cellulose products, plastics, synthetic rubber, nylon, high pressure reactions, and the management and policies of the Company, although presented in popular vein, are informative and interesting. The book is written in excellent literary style, and bears evidence of a painstaking effort on the part of the author to write with authority and accuracy, without sending his bucket too often to the well of sentimentality.

ROBERT E. SWAIN

Practical Physical Chemistry. By ALEXANDER FINDLAY, Professor of Chemistry, University of Aberdeen. Seventh edition, revised and enlarged. Longmans, Green and Co., 55 Fifth Avenue, New York, N. Y., 1942. x + 335 pp. 124 figs. 14 × 22 cm. Price, $3.00.

The most recent edition of this well-known book embodies few innovations. Six new experiments and a number of alternative applications of the previously used experimental methods have been added.

The book has sixteen sections; the first three of which are general in nature—Calculation of Results and Errors, Determination of Weight and Volume and Thermostats. The first two of these present very satisfactory discussions of the material covered. Chapter III on Thermostats is a useful compendium of temperature control mechanisms. The discussion of circulation of the bath fluid—an extremely important factor in constant temperature control—is rather inadequately treated.

The thirteen chapters following cover convenient groupings of experiments. The chapter headings, showing the range of topics, are: Density of Gases and Vapours, Density and Vapour Pressure of Liquids, Viscosity and Surface Tension, Optical Measurements, Osmotic Properties of Solutions, Distribution of a Substance between Two Non-Miscible Solvents, Conductivity of Electrolytes, Transport Numbers, Measurements of Electromotive Force, Velocity of Chemical Reaction in Homogeneous Systems, Thermochemistry, Heterogeneous Equilibria, and Colloids. Each chapter includes a short discussion of the underlying principles, then a rather complete description of the apparatus used and the technique of measurement, and finally several alternative experiments illustrating each method. Under each heading the more important types of apparatus are described and experiments suitable to each are suggested.

A good feature of this manual is the unusually large number (approximately 90) of experiments included in this edition. This gives the user wide latitude in the selection of exercises adapted to his needs.

The use of the concept of activity and the application of the Debye–Hückel theory to conductance experiments are evidences of the author's modernity in viewpoint. This edition includes experiments on absorption spectra, the glass and antimony electrodes for *p*H measurements, and the tungsten electrode for redox reactions. The author explains that he has been "reluctantly compelled to omit" certain subjects such as unimolecular films, dielectric constants, colorimetry, and photochemical reactions.

The book is well written and should be found thoroughly satisfactory by most users. It is to be hoped that the publishers will make new cuts for the next edition, some of the cuts in this edition being so old that they detract considerably from the appearance of the book.

ELIJAH SWIFT, JR.

Experimental Physical Chemistry. By W. G. PALMER, M.A., Sc.D., D.Sc., Fellow of St. John's College, Cambridge, University Lecturer in Chemistry in the University of Cambridge. The Macmillan Company, 60 Fifth Avenue, New York, N. Y., 1942 (Cambridge: at the University Press). xi + 321 pp. 89 figs. 13.5 × 21.5 cm. Price, $2.75.

Some seventy-five experiments divided into eight sections comprise the contents of this new volume. Most of the experiments are the result of the author's experience over a number of years in the Physical Chemistry Laboratory at the University of Cambridge. As a result, the directions given are rather detailed and allow for the mistakes in technique and understanding which the average student might be expected to make. The author includes sufficient theoretical material in each section so that reference to other texts is usually not necessary, though references for further reading are suggested. Carefully worked out sample calculations are included with each experiment.

An unusual section in this book is the chapter on Crystallization and Properties of Crystals. Several experiments are given, illustrating supersaturation, influence of foreign substances on crystal habit, isomorphism and isodimorphism, alternative systems being suggested in each case.

The author has confined the experiments to those requiring apparatus "simple enough to be assembled or constructed by the students themselves from ordinary laboratory equipment." While many of the fundamental principles taken up in the elementary course in Physical Chemistry are illustrated by such equipment, the limitation imposed cuts out a large group of experiments which not only demonstrate alternate methods, but also offer invaluable experience to the student. Experiments using more costly equipment should not be scorned—thus, most students find the Abbé refractometer an easily handled piece of equipment giving them excellent results as an analytical tool when working with minimum boiling mixtures. The use of the polarimeter, refractometer, spectrometer, bomb calorimeter, oil film balance, tensiometer, etc., show the student more refined methods of measurement which do not offer too great difficulties in manipulation and which produce results satisfactory in every sense.

The author is apparently unaware of the work of Grinnell Jones and collaborators on conductance measurements and on the redetermination of the conductance standards (see p. 187). It is also surprising to find no mention of the parachor in this book.

In spite of the poor binding and paper, which are to be expected in these times, the type is clean and very legible and the cuts clear and well drawn. Laboratories without the more expensive facilities mentioned above will find that the directions for assembling equipment given in this text will enable them to carry out a very satisfactory program of experiments covering the fundamental principles of physical chemistry.

ELIJAH SWIFT, JR.

General Chemistry. By HARRY N. HOLMES, Professor of Chemistry in Oberlin College. Fourth edition. The Macmillan Company, 60 Fifth Avenue, New York, N. Y., 1941. viii + 720 pp. 198 figs. 16 × 24 cm. Price, $3.75.

The fourth edition of General Chemistry by Harry N. Holmes has not lost any of the values that made the text so teachable in the first edition.

The arrangement of the non-metals is just the same as in the previous editions but there is a decided improvement in the arrangement of the metals. These are studied according to the metallurgy of various groups. They are then taken up again according to their position in the Periodic system. This seems to be a decided improvement over the usual method of presenting the metals.

The historical method of presenting chemistry has been fairly well preserved although enough of the modern concept of the atom has been given in the first few chapters to permit the use of the modern theories if one desires.

The exercises at the end of each chapter as well as the references are very well done. The chapter outline and the review suggestions in the early part of the book should be quite a help to the conscientious student.

The application of chemistry to industry and to ordinary living has been brought up to date and should help to create an interest in the science of chemistry.

It is a text that should be examined in order to be appreciated.

JOHN B. ZINN

BOOKS RECEIVED

October 10, 1942–November 10, 1942

FREDERICK J. BATES AND ASSOCIATES. "Polarimetry, Saccharimetry and the Sugars." Circular of the National Bureau of Standards C440 (May 1, 1942). 810 pp. For sale by the Superintendent of Documents, Washington, D. C. $2.00.

HARRY C. BIDDLE. "Chemistry in Health and Disease." Second edition. F. A. Davis Company, 1914 Cherry Street, Philadelphia, Pa. 718 pp. $3.50.

J. AUSTIN BURROWS, PAUL ARTHUR, AND OTTO M. SMITH. "Semimicro Laboratory Exercises in General Chemistry." The Macmillan Company, 60 Fifth Avenue, New York, N. Y. 331 pp. $2.50.

NICHOLAS D. CHERONIS. "Semimicro and Macro Organic Chemistry. A Laboratory Manual." Thomas Y. Crowell Company, 432 Fourth Avenue, New York, N. Y. 388 pp. $2.75.

EDWARD F. DEGERING. "The Quadri-Service Manual of Organic Chemistry." Houghton Mifflin Company, 2 Park Street, Boston, Mass. 221 pp. $2.50.

ED. F. DEGERING, CARL BORDENCA AND B. H. GWYNN, *et al.* "An Outline of Organic Nitrogen Compounds." Planographed by John S. Swift Co., Inc., Third and Vine Streets, Cincinnati, Ohio. 381 pp. $6.00.

ED. F. DEGERING AND NINETY-SIX ASSISTANT EDITORS. "An Outline of Organic Chemistry." Fourth edition. Barnes and Noble, Inc., Fifth Avenue at 18th Street, New York, N. Y. 386 pp. $1.25.

ED. F. DEGERING AND ONE HUNDRED ELEVEN COLLABORATORS. "The Work Book of Fundamental Organic Chemistry." Barnes and Noble, Inc., Fifth Avenue at 18th Street, New York, N. Y. 256 pp. $1.25.

ALFRED BENJAMIN GARRETT, LAURENCE LARKIN QUILL AND FRANK HENRY VERHOEK. "Introductory Chemistry for the Laboratory." Ginn and Company, Statler Building, Boston, Mass. 239 pp. $1.60.

AMÉ PICTET. "Souvenirs et Travaux d'un Chimiste." Éditions de la Baconnière, Boudry (Neuchâtel), Switzerland. 228 pp. 9.—fr. suisses (l'exemplaire); 20.—fr. suisses (luxe).

ROGER J. WILLIAMS. "A Textbook of Biochemistry." Second edition. D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N. Y. 533 pp. $4.00.

HERMAN FREDERICK WILLKIE AND PAUL JOHN KOLACHOV. "Food for Thought." Indiana Farm Bureau, Inc., Indianapolis, Indiana. 209 pp. $2.00.

Additions and Corrections

NOTICE TO READERS.—For the convenience of those who wish to cut out the corrections and attach them to the margins of the articles corrected, they have been printed upon one side of the page only.

1936, Vol. 58

Paul J. Flory. Molecular Size Distribution in Linear Condensation Polymers.

Page 1879. In the third sentence of the second paragraph of note (13) for $1 - x$ read $x - 1$.

Page 1882. In equations (16) and (17) the symbols on the left side should be, respectively, Π'_x (even) and Π''_x (even). On the right side of (18) for N' read N'_0.

Page 1883. At the end of the third line after equation (24) read Π''_x for Π''. In the right-hand members of (25) and (26) read N'_0 for N'. Equation (27) should read

$$\Pi_x(odd\text{–A}) = \frac{xN_x(odd\text{–A})}{1/2(N'_0 + N''_0)} = xp^{x-1}r^{x/2}\frac{(1-p)^2r^{1/2}}{1+r} \qquad (27)$$

The right side of equation (28) should read

$$xr^{x/2}(1-r)^2r^{-1/2}/(1+r)$$

Page 1884. In the sentence preceding equation (32) for the word "equivalents" read "non-equivalents."

—PAUL J. FLORY.

1938, Vol. 60

Frank C. Whitmore, R. E. Meyer, G. W. Pedlow, Jr., and A. H. Popkin. The Reducing Action of Primary Grignard Reagents with Trimethylacetyl Chloride.

Page 2788. The title should read "The Reducing Action of Primary and Secondary Grignard Reagents with Trimethylacetyl Chloride." An investigation of the reaction of isopropylmagnesium bromide with trimethylacetyl chloride is included in this study.—FRANK C. WHITMORE.

1939, Vol. 61

William O. Baker and Charles P. Smyth. The Vitrification and Crystallization of Organic Molecules and the Dielectric Behavior of *i*-Butyl and *i*-Amyl Bromides.

Page 2069. The values of $\epsilon''_{max.}$, calcd., in Table II, are incorrect because of arithmetical error. The values at the given frequencies should be:

f, kc.	$\epsilon''_{max.}$, calcd.	$\epsilon''_{max.}$, obsd.
	i-Butyl Bromide	
50	7.5	5.3
5	7.6	5.6
0.5	7.8	5.9
	i-Amyl Bromide	
50	5.0	3.8
5	5.2	4.5
0.5	5.5	5.0

—W. O. BAKER.

Roger Adams, E. F. Rogers and F. J. Sprules. Structure of Monocrotaline. II. Monocrotic Acid Obtained by Alkaline Hydrolysis of the Alkaloid.

Page 2819. Throughout this paper read "α,β-dimethyl-Δ^{β}-angelicalactone" for "α,β,γ-trimethylangelicalactone." —ROGER ADAMS.

Roger Adams, E. F. Rogers and R. S. Long. The Structure of Monocrotaline. III. Monocrotalic Acid.

Page 2822. Throughout this paper read "α,β-dimethyl-Δ^{β}-angelicalactone" for "α,β,γ-trimethylangelicalactone." —ROGER ADAMS.

1940, Vol. 62

S. Winstein and R. E. Wood. Dielectric Constants of some Pairs of Diastereomers.

Page 550. Onsager's equation should read

$$\mu^2 = \frac{(n^2+2\epsilon)(\epsilon-n^2)}{\epsilon(n^2+2)^2}\cdot\frac{M}{D}\left(\frac{9kT}{4\pi N}\right)$$

—S. WINSTEIN.

Roger Adams and R. S. Long. Structure of Monocrotaline. IV. Monocrotalic Acid.

Page 2289. Throughout this paper for "α,β,γ-trimethylangelicalactone" read "α,β-dimethyl-Δ^{β}-angelicalactone."—ROGER ADAMS.

Ernst Bergmann and Eliahu Bograchov. Some Reactions of Pyrene.

Page 3016. "In a recent paper [THIS JOURNAL, **63**, 2494 (1941)] Bachmann and Carmack describe methyl β-3-pyrenylpropionate with m. p. 95.5–96.5°. Its melting point was given by us erroneously as 81°. We actually had observed 94° and 180° in the corresponding free acid (Bachmann and Carmack, 178–179°), as described in the thesis of E. Bograchov (Jerusalem, 1941, p. 23).—ERNST BERGMANN."

1941, Vol. 63

Jerome R. Vinograd and James W. McBain. Diffusion of Electrolytes and of the Ions in their Mixtures.

Page 2011. Column 1, lines 34–55, for "gram equivalents" read "gram molecules."—J. W. MCBAIN.

Roger Adams and H. W. Stewart. Restricted Rotation in Arylamines. II. Preparation and Resolution of N-Succinyl-N-ethyl-3-bromomesidine and 5-Alkoxy-4-N-succinyl-4-amino-1,3-dimethylbenzenes.

Page 2860. Col. 1, line 1 of last paragraph, for "(1 mole)" read "(0.1 mole)," and same below for diethyl sulfate and sodium nitrate.

T. Q. Chou and T. T. Chu. The Preparation and Properties of Peimine and Peiminine.

Page 2936. Col. 1, line 5, for "wereas signed" read "were assigned."

George Wash, Billie Shive and H. L. Lochte. Normal and Abnormal Alkylation of 2-Methylcyclopentyl Methyl Ketone.

Page 2975. In the title, for "Methyl" read "Phenyl."—H. L. LOCHTE.

W. D. Larson and W. J. Tomsicek. The Activity Coefficients of the Undissociated Part of Weak Acids. II. Oxalic Acid.

Page 3330. Equation (4) should read

$$E^0 = E + 0.02957 \log_{10} K_1 K_2 C \left(1 - \frac{-K_1 + \sqrt{K_1^2 + 4K_1 c}}{2c}\right)$$

—W. D. LARSON.

1942, VOL. 64

W. R. Forsythe and W. F. Giauque. The Entropies of Nitric Acid and its Mono- and Tri-hydrates. Their Heat Capacities from 15 to 300°K. The Heats of Dilution at 298.1°K. The Internal Rotation and Free Energy of Nitric Acid Gas. The Partial Pressures over its Aqueous Solutions.

Pages 60 and 61. The authors call attention to the following arithmetical errors:

$$^1/_2N_2 + {}^3/_2O_2 + {}^1/_2H_2 = HNO_3 \quad (1)$$

$\Delta F^0_{298.1}$ should be −19030 cal. instead of −11,539 cal.

$$^1/_2N_2 + {}^3/_2O_2 + {}^1/_2H_2 = HNO_3 \quad (g)$$

$\Delta F^0_{298.1}$ should be −17948 cal. instead of −10.457

$$^1/_2N_2 + {}^3/_2O_2 + {}^1/_2H_2 = HNO_3 \quad (a = 1)$$

$\Delta F_{298.1}$ should be −26345 cal. instead of −18854 cal.

The above errors are repeated in the summary.

Also in the summary

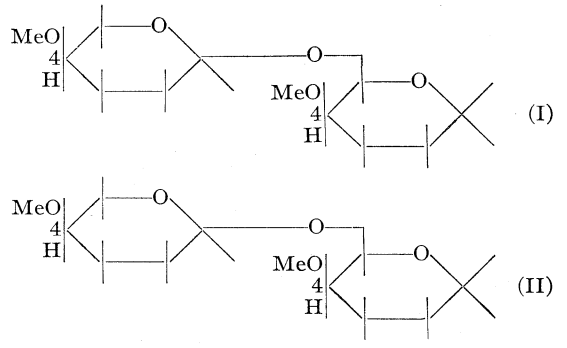
$$^1/_2N_2 + {}^3/_2O_2 + {}^1/_2H_2 = HNO_3 \quad (g)$$

$\Delta H_{298.1}$ should be −31994 cal. instead of −3199 cal.

—W. R. FORSYTHE and W. F. GIAUQUE.

E. V. White. The Constitution of Arabo-galactan. II. The Isolation of Heptamethyl- and Octamethyl-6-galactosidogalactose through Partial Hydrolysis of Methylated Arabo-galactan.

Page 303. The author writes "Formulas 1 and 2 representing octamethyl-6-*d*-galactosidogalactose and heptamethyl-6-*d*-galactosidogalactose are incorrect in the relative positions of the methoxyl and hydrogen groups at position 4 in all the monosaccaride units, which should be reversed as indicated



Page 304. In col. 1 of the Experimental, line 30, in the formula, for "Hg" read "H_8."—E. V. WHITE.

Emmett R. Barnum and Cliff S. Hamilton. 5-Amino- and 1-Aminobenzo(f)-quinolines and Derivatives.

Page 542. Col. 2, lines 11 and 20, for "*p*-dimethylaminobenzaldehyde" read "*p*-diethylaminobenzaldehyde."—C. S. HAMILTON.

H. J. Lucas and Clark W. Gould, Jr. Brucine as a Reagent for Partially Resolving Bromoalkanes; the Configurations of Some Diastereomeric Dibromoalkanes.

Page 602. In footnote (7) for "(+1.0016)" read "(0.0016)," for "compound" read "compared" and in the citation, for "1471" read "147."

N. Howell Furman and Clark E. Bricker. A Polarographic Study of *o*-Phthalic Acid and Phthalates.

Page 665. In the legend for Fig. 6, the last four lines should read "Curve a at *p*H 4.02; curve b at *p*H 3.94; curve c at *p*H 3.75; curve d at *p*H 3.57; curve e at *p*H 3.48; curve f at *p*H 3.25; curve g at *p*H 3.06; curve h at *p*H 2.60; polarogram was made with capillary no. 3."—N. H. FURMAN.

S. C. Schumann, J. G. Aston and Malcolm Sagenkahn. The Heat Capacity and Entropy, Heats of Fusion and Vaporization and the Vapor Pressures of Isopentane.

Page 1041. The authors write "In Table IV the molal heat of vaporization of isopentane at 298.16°K. calculated from Eq. (1) and the modified Berthelot equation at 298.16°K. with T_c = 461°K. and P_c = 32.9 atm. is 5965 calories (Berthelot correction = 239 calories), instead of the value given."

Page 1043. "In Table VII the free energy of neopentane was accidentally computed using the free rota-

tional entropy. Using the correct value for this quantity [Aston and Messerly, THIS JOURNAL, **58**, 2354 (1936)] Table VII should then be:

FREE ENERGY OF FORMATION OF THE PENTANES AT 298.16°K.

	ΔF_{298}, calories	% in equilibrium mixture	% if no neopentane
Neopentane	-3289 ± 320	48.7	...
Isopentane	-3243 ± 300	48.3	93.7
n-Pentane	-1647 ± 270	3.0	6.3

These changes do not affect the rest of the paper, since no other numerical values or conclusions were derived from the erroneous values.—S. C. SCHUMANN, J. G. ASTON AND M. L. SAGENKAHN.

Joseph R. Stevens, Ralph H. Beutel and Earl Chamberlin. 3,4-Substituted Pyridines. I. Synthesis of 3-Vinyl-4-methylpyridine.

Page 1093. The absorption spectrum in Fig. 1 is for Compound VI instead of V, and in Fig. 2 for Compound VII instead of VI.—R. T. MAJOR.

H. A. Laitinen. The Potential of the Ytterbic-Ytterbous Ion Electrode.

Page 1135. Col. 2, line 13, for "−1.69 volts" read "−1.169 volts."—H. A. LAITINEN.

Arthur C. Cope and Evelyn M. Hancock. Synthesis of 2-Alkylaminoethanols from Ethanolamine.

Pages 1504 (Table I) and 1505 (line 7 of the Experimental Part), for "2,2,6-" read "3,3,5-trimethylcyclohexyl" and "3,3,5-trimethylcyclohexanone."—ARTHUR C. COPE.

James W. McBain and A. M. Soldate. The Solubility of Propylene Vapor in Water as Affected by Typical Detergents.

Page 1556. Heading of Table I, for "10^{-5}" read "10^{-7}." O'Connor (ref. 1) obtained 3.8, 3.8, 3.7 and 3.5 × 10^{-7} g. of propylene per gram of water per millimeter pressure. —J. W. MCBAIN.

Bradford P. Geyer with George McP. Smith. Preparation and Properties of Some Peri-hydroxyquinone Inner Complexes.

Page 1649. In col. 2, line 2, for "chloroform" read "chlorobenzene."—B. P. GEYER and G. MCP. SMITH.

A. Polgár and L. Zechmeister. Isomerization of β-Carotene. Isolation of a Stereoisomer with Increased Adsorption Affinity.

Page 1858. Line 23, omit the word "no."—L. ZECHMEISTER.

W. D. Kumler and George M. Fohlen. The Dipole Moment and Structure of Urea and Thiourea.

Page 1945. In Table II for "*unsym*-Diphenylure" read "*unsym*-Diphenylurea."

Page 1946. Both formulas at the end of col. 1 should have a single bond between carbon and oxygen.

Page 1947. In the middle of col. 2, the last structure of thiourea should have the charge removed over the nitrogen that is singly bonded to carbon.—W. D. KUMLER.

R. P. Linstead and W. E. Doering. The Stereochemistry of Catalytic Hydrogenation. II. The Preparation of the Six Inactive Perhydrodiphenic Acids.

Page 1993. In Col. 2, first line of the diagram, for "Diphenyl" read "Dimethyl."—R. P. LINSTEAD.

Page 1994. In formula II, there should be a third black dot in the blank "hole" in the formula.

R. P. Linstead and W. E. Doering. The Stereochemistry of Catalytic Hydrogenation. III. Optically Active Perhydrodiphenic Acids. A Proof of the Configuration of the Backbone.

Page 2004. Col. 1, in the second formula there should be another black dot in the space in the right-hand ring.

R. P. Linstead and Selby B. Davis. The Stereochemistry of Catalytic Hydrogenation. IV. Hexahydrodiphenic Acids.

Page 2007. In formula II a black dot is missing in the right-hand ring of formula II.

R. P. Linstead, Richard R. Whetstone and Philip Levine. The Stereochemistry of Catalytic Hydrogenation. VI. The Hydrogenation of 9-Phenanthrol and Related Substances and the Identification of Three of the Possible Stereoisomeric Forms of the Perhydrophenanthrene Ring.

Page 2017. Col. 1 in, the second line above the table, insert the word "table" between "The" and "below." Also, in Col. 2, in the table under "Alcohols," the first compound should be "*sym*-octahydro-9-phenanthrol."—R. P. LINSTEAD.

M. L. Wolfrom and P. W. Morgan. O-Pentaacetyl-*d*-gluconates of Polyhydric Alcohols and Cellulose.

Page 2026. Column 1, lines 9 and 16, for "*dextro*-sorbitol" read "*levo*-sorbitol," as the ordinary form is meant.

Page 2027. In Table I the fifth entry should read *levo* instead of *dextro*, and the same change should be made in line 11 of col. 1.

Page 2028. In the first line of paragraph 2 of the Summary read *levo* for *dextro*.—M. L. WOLFROM.

Alfred Saffer and T. W. Davis. Products from the Wurtz Reaction and the Mechanism of their Formation.

Page 2039. The apparatus diagram which should have been included in the experimental section was inadvertently omitted, and is printed herewith.

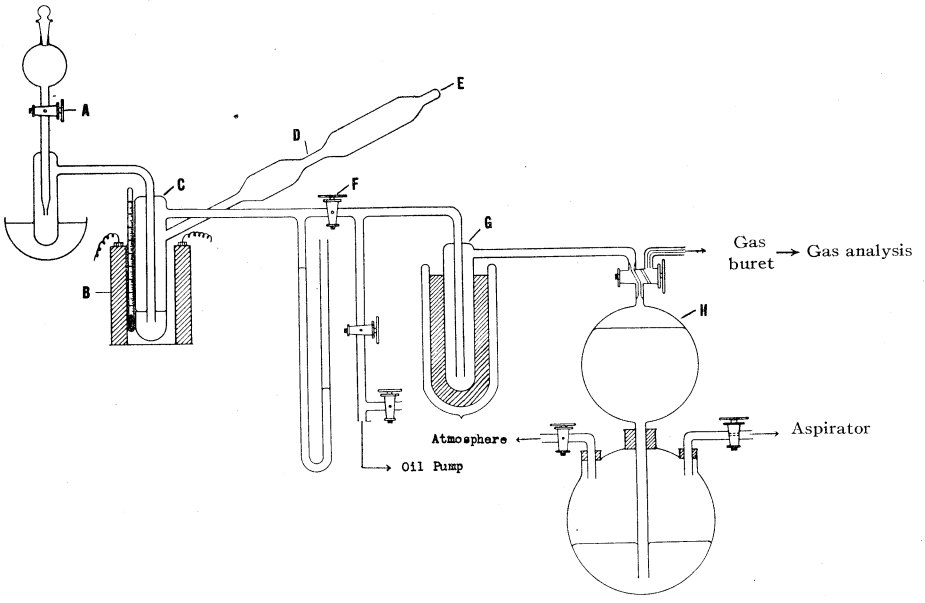


Fig. 1.—Apparatus for the Wurtz reaction.

—ALFRED SAFFER AND T. W. DAVIS

Avery A. Morton, John B. Davidson, T. R. P. Gibb, Jr., Ernest L. Little, E. F. Clarke and A. G. Green. Condensations by Sodium. XXV. Reactions of Amylsodium with Naphthalene, Acenaphthene and Decalin.

Page 2250. In the title, the last two names should be E. W. Clarke and A. J. Green.—AVERY A. MORTON.

Roger Adams and J. E. Mahan. Basicity Studies of Tertiary Vinyl Amines.

Page 2590. In column 2, lines 5 and 4 from bottom read "compare 1 with 7, 2 with 8, 4 with 9, and 6 with 14."

Page 2591. Table VI, line 7 for "11.99" read "11.11."—ROGER ADAMS.

Author Index to Volume LXIV, 1942

ABERNETHY, J. L. See Savoy, C. M. S.
ABRAMOVITCH, B. See Hauser, C. R.
ABRAMOVITCH, B., AND HAUSER, C. R. Condensations (XVII) acylation of anions of certain alkyl esters with Ph esters—new method for prepn. of Et propionylacetate and certain related β-keto esters, 2271; acylation of acetonitrile with Et *n*-butyrate and the alcoholysis of the resulting ketonitrile to Et *n*-butyrylacetate 2720
ADAMS, E. Q. Reviews of "Higher Chem. Calcns." (Mee), 1012; "Introduction to Theory of Relativity" (Bergmann) 2517
ADAMS, H. E. See Stout, J. W.
ADAMS, J. T. See Hauser, C. R.
ADAMS, M. See Tilden, E. B.
ADAMS, R. Org. Reacns. Vol. I (book review) 3062
ADAMS, R., AND ALBERT, A. A. Restricted rotation in aryl amines (III) prepn. and resolution of N-succinyl-1-methylamino-2-methylnaphthalene and N-succinyl-1-methylamino-4-chloro-2-methylnaphthalene 1475
ADAMS, R., BINDER, L. O., AND MCGREW, F. C. Restricted rotation in aryl olefins (V) β-bromo-β-(2-alkoxynaphthyl)-α-alkylacrylic acids 1791
ADAMS, R., CARMACK, M., AND MAHAN, J. E. Structure of monocrotaline (VII) structure of retronecine and related bases 2593
ADAMS, R., CARMACK, M., AND ROGERS, E. F. Alkaloid of *Crotalaria grantiana* (I) grantianine 571
ADAMS, R., AND GROSS, W. J. Restricted rotation in aryl olefins (IV) prepn. and resolution of β-chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-α-methylacrylic and the corresponding acrylic acid. 1786
ADAMS, R., AND HAMLIN, K. E., JR. Structure of monocrotaline (VIII) proof of primary and secondary hydroxyl groups in retronecine 2597
ADAMS, R., HAMLIN, K. E., JR., JELINEK, C. F., AND PHILLIPS, R. F. Structure of riddelliine, the alkaloid in *Senecio Riddellii* (I) 2760
ADAMS, R., LOEWE, S., SMITH, C. M., AND MCPHEE, W. D. Tetrahydrocannabinol homologs and analogs with marihuana activity (XIII) 694
ADAMS, R., LOEWE, S., THEOBALD, C. W., AND SMITH, C. M. Tetrahydrocannabinol analogs with Marihuana activity (XV) 2653
ADAMS, R., AND LONG, R. S. Structure of monocrotaline (IV) (corrn.) 3067
ADAMS, R., AND MAHAN, J. E. Basicity studies of *l*-vinyl amines, 2588, (corrn.) 3073
ADAMS, R., MILLER, M. W., MCGREW, F. C., AND ANDERSON, A. W. Restricted rotation in aryl olefins (VI) substituted β-(2,7-dimethoxy-1-naphthyl)-α-methylacrylic acids 1795
ADAMS, R., ROGERS, E. F., AND LONG, R. S. Structure of monocrotaline (III) (corrn.) 3067
ADAMS, R., ROGERS, E. F., AND SPRULES, F. J. Structure of monocrotaline (II) (corrn.) 3067
ADAMS, R., SMITH, C. M., AND LOEWE, S. Optically active synthetic tetrahydrocannabinols; *d*- and *l*-1-hydroxy-3-*n*-amyl-6,9,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrans (XIV) 2087
ADAMS, R., AND STEWART, H. W. Restricted rotation in arylamines (II) prepn. and resolution of N-succinyl-N-Et-3-bromomesidine and 5-alkoxy-4-N-succinyl-4-amino-1,3-dimethylbenzenes (corrn.). 3069
ADKINS, H., AND WHITMAN, G. M. Hydrogenation of β-iminonitriles 150
ADAMS, R. M. See Brown, H. C.
ADDINALL, C. R. Review of "The Chemistry of Org. Medicinal Products" (Jenkins, Hartung) 1012
ALBERT, A. A. See Adams, R.
ALEXANDER, L. See Klug, H. P.
ALFREY, T., BARTOVICS, A., AND MARK, H. Effect of temp. and solvent type on intrinsic viscosity of high polymer solns 1557
ALLEN, C. F. H., AND BELL, A. Action of Grignard reagents on certain pentacenequinones, 6,13-diphenylpentacene 1253
ALLEN, C. F. H., AND GATES, J. W., JR. Action of alkaline reagents on the bimol. product formed by the action of acidic dehydrating agents on anhydracetonebenzil, 2120; structure of the bimol. product formed by the action of acidic dehydrating agents on anhydracetonebenzil, 2123; structures of certain highly arylated indenones and their behavior with Br_2, 2127; behavior of certain carbonyl bridge compds. with alkaline H_2O_2 2439
ALLEN, C. F. H., AND PINGERT, F. P. Chemistry of *o*-terphenyl (*o*-diphenylbenzene) (I) the general reactivity, basal structure and rearrangements of the hydrocarbon, 1365; (II) derivs. prepared from the hydrocarbon 2639
ALLEN, C. F. H., AND VAN ALLAN, J. Carbonyl bridge compds 1260
ALLEN, M. B. See Norris, T. H.; Ruben, S.
ALLEN, M. B., AND RUBEN, S. Tracer studies with radioactive C and H—synthesis and oxidation of fumaric acid 948
ALLEN, T. W. See Gucker, F. T., Jr.
ALLES, G. A., ICKE, R. N., AND FEIGEN, G. A. Some analogs of synthetic tetrahydrocannabinol 2031
ALTIMIER, D. F. Sp. gr. of $Na_2Cr_2O_7$ solns 175
AMIS, E. S. See Padgitt, F. L.
AMIS, E. S., CHOPPIN, A. R., AND PADGITT, F. L. Temp. and compn. coeffs. of the d., refractive index, and viscosity of MeOH–dioxane system ... 1207
ANDERSON, A. W. See Adams, R.
ANDERSON, C. M., AND GILBERT, E. C. Apparent energy of the N–N bond as calcd. from heats of combustion 2369
ANDERSON, G. W. See Winnek, P. S.
ANDERSON, G. W., FAITH, H. E., MARSON, H. W., WINNEK, P. S., AND ROBLIN, R. O., JR. Studies in chemotherapy (VI) sulfanilamido heterocycles .. 2902
ANDERSON, H. H. Cyanates and thiocyanates of Pb, As and Sb 1757
ANDERSON, H. V., AND HAZLEHURST, T. H. Qual. Analysis (book review) 1491
ANDERSON, H. W., AND ROLLEFSON, G. K. Production of radicals by illumination of diacetyl with λ 4358 Å 717
ANDERSON, L. C., AND MACNAUGHTON, N. W. Mechanism of catalytic reduction of some carbonyl compds 1456
ANDERSON, R. C. See Lemons, J. F.
ANDREEN, J. H. See Snyder, H. R.
ANDREWS, D. H. See Ziegler, W. T.
ANDREWS, J. T. See Scott, A. W.
ANTHES, H. I. See McElvain, S. M.
ARCHER, S. See Burwell, R. L., Jr.
ARDIS, A. E. See Buck, J. S.; Ferry, C. W.
ARDIS, A. E., BUCK, J. S., AND BALTZLY, R. Some N-aralkyl barbituric acids 2514
ARMBRUSTER, M. H. Adsorption of gases at low temp. and pressure on smooth Ag 2545
ARNOLD, R. T. See Huggett, C.
ARNOLD, R. T., AND BORDWELL, F. Studies in the veratrole and methylenedioxybenzene series 2983
ARNOLD, R. T., BORTNICK, N., AND MCMULLEN, E. Base-catalyzed cleavage of methylenedioxy rings .. 1410
ARNOLD, R. T., AND LIGGETT, R. W. Mechanism

of the reacn. between hindered carbonyl compds. and the Grignard reagent (II) 2875
ARNOLD, R. T., AND MCCOOL, J. C. Orientation studies in coumaran series 1315
ARNOLD, R. T., MCCOOL, J., AND SCHULTZ, E. Thermal rearrangement of *m*-acetamidophenyl allyl ether 1023
ARNOLD, R. T., AND MORAN, J. Studies in the coumaran series 2986
ARNOW, L. E. See Opsahl, J. C.
ASTLE, M. J. See Bachman, G. B.
ASTON, J. G. See Schumann, S. C.
ASTON, J. G., CLARKE, J. T., BURGESS, K. A., AND GREENBURG, R. B. New acid synthesis (II) effect of hindrance—Me *t*-Bu and MeEtPr acetic acids .. 300
ASTON, J. G., NEWKIRK, J. D., DORSKY, J., AND JENKINS, D. M. Mechanism of haloform reacn.—prepn. of mixed haloforms 1413
ASTON, J. G., AND SCHUMANN, S. C. Heat capacity and vapor pressure hysteresis in liquid isopentane—isomers due to hindered rotation 1034
AUDRIETH, L. F. See Marvel, C. S.; Schirmer, F. B., Jr.; Steinman, R.
AUDRIETH, L. F., SCOTT, L. D., AND HILL, O. F. Catalytic effect of electrolytes on solvolytic reacns. 2498
AUDRIETH, L. F., AND TOY, A. D. F. Aquo ammono phosphoric acids (II) prepn. of N-substituted derivs. of Ph esters of amido- and diamidophosphoric acids, 1337; (III) N-substituted derivs. of phosphoryl and thiophosphoryl triamide as H bonding agents 1553
AUSTIN, F. L. See Smith, L. I.
AYLING, H. S. See Robinson, R. A.
AYRES, E. B., AND HAUSER, C. R. Rearrangement of 1,1,3,3,5,5-hexamethylcyclohexatriol-2,4,6 to hexamethylbenzene 2461
AYRES, G. B. See Tobie, W. C.

BACHMAN, G. B., AND ASTLE, M. J. Dropping Hg electrode in AcOH (I) discontinuous current–voltage curves, 1303; (II) electrocapillary curves and the theory of maxima 2177
BACHMAN, G. B., AND GOEBEL, C. G. Prepn. and isolation of 4-Me-1,3-pentadiene 787
BACHMANN, W. E., KUSHNER, S., AND STEVENSON, A. C. Total synthesis of a stereoisomer of the sex hormone estrone 974
BACHMANN, W. E., AND NESS, A. B. Synthesis of an isomer of estrone containing a phenolic B ring .. 536
BACHMANN, W. E., AND THOMAS, D. G. Synthesis of an analog of the sex hormones 94
BACHMANN, W. E., AND WILDS, A. L. γ-Phenoxypropyl *p*-anisyl ketone 186
BADGER, W. L., AND BAKER, E. M. Inorg. Chem. Technology (book review) 1237
BAER, E. Oxidative cleavage of cyclic α-keto alcs. by means of $PbAc_4$ (II) 1416
BAHNER, C. T., AND HAMILTON, D. N,N′-Piperazinium bis-(2-Me-5-isopropylbenzenesulfonate) .. 1741
BAILEY, A. Hydrolytic derivs. of lignin volatile compds. 22
BAILEY, J. R. See Shive, B.
BAILEY, W. A., JR. See Corwin, A. H.
BAIN, J. P. Resin acids from pine tar 871
BAIR, R. K., AND SUTER, C. M. Identification of alcs. and alkyl H sulfates with S-benzylthiuronium chloride 1978
BAKER, B. R., AND CARLSON, G. H. Water-soluble compds. with antihemorrhagic activity 2657
BAKER, B. R., DAVIES, T. H., MCELROY, L., AND CARLSON, G. H. Antihemorrhagic activity of sulfonated derivs. of 2-Me-naphthalene 1096
BAKER, E. M. See Badger, W. L.
BAKER, E. M., AND GILBERT, E. C. Kinetics of transformation of hydrazine cyanate into semicarbazide 2777
BAKER, R. H. See Lipscomb, W. N.
BAKER, W. O. See Yager, W. A.
BAKER, W. O., AND FULLER, C. S. Macromol. disorder in linear polyamides—relation of structure to phys. properties of copolyamides 2399
BAKER, W. O., FULLER, C. S., AND PAPE, N. R. Effects of heat, solvents and H-bonding agents on crystallinity of cellulose esters 776
BAKER, W. O., AND SMYTH, C. P. Vitrification and crystallization of org. mols. and the dielec. behavior of *i*-Bu and *i*-amyl bromides (corrn.) 3067
BAKER, W. O., AND YAGER, W. A. Relation of dielec. properties to structure of crystalline polymers (II) linear polyamides 2171
BALL, C. D. See King, L. C.
BALLARD, E., AND JOHNSON, T. B. Synthesis of derivs. of pyrimidine-5-carboxylic acid 794
BALTZLY, R. See Ardis, A.; Buck, J. S.; Ide, W. S.
BALTZLY, R., AND BUCK, J. S. Characteristics of β-(2,5 - dimethoxyphenyl) - β - hydroxyisopropylamine hydrochloride 3040
BALTZLY, R., BUCK, J. S., AND IDE, W. S. N,N-Dimethylethylenediamine and some derivs. 2232
BALTZLY, R., FERRY, C. W., AND BUCK, J. S. Some new quaternary salts 2231
BALTZLY, R., IDE, W. S., AND BUCK, J. S. Some diamino peptides, 2231; chaulmoogryl quaternary salts 2514
BANCROFT, W. D., AND HUBARD, S. S. New method for detg. dineric distribution 347
BARKER, R. M. Diffusion in and through Solids (book review) 1013
BARNES, M. D., AND LAMER, V. K. Kinetics and equil. of carbinol formation of phenolphthalein ... 2312
BARNES, R. P., AND COCHRANE, C. C. Properties of *o*-methoxybenzoylmesitoylmethane 2262
BARNES, R. P., AND LUCAS, W. M. Effect of methoxyl toward stabilizing enediols, 2258; prepn. and properties of an enediol—α-*o*-methoxyphenyl-β-mesitoylacetylene glycol 2260
BARNUM, E. R., AND HAMILTON, C. S. 5-Amino- and 1-aminobenzo(f)quinolines and derives., 540, (corrn.) 3069
BARROWS, R. S., AND LINDWALL, H. G. Condensation reacns. of isoquinaldehyde 2430
BARTELL, F. E. See Kraemer, E. O.
BARTELL, F. E., AND CARDWELL, P. H. Reproducible contact angles on reproducible metal surfaces (I) contact angles of H_2O against Hg and Au, 494; (II) interfacial contact angles between water and org. liquids on surfaces of Ag and Au, 1530; (III) contact angles of satd. aq. solns. of different org. liquids on Ag and Au 1641
BARTLETT, P. D. Review of "The Theory of Org. Chemistry" (Branch, Calvin) 474
BARTLETT, P. D., AND JONES, J. E. Tri-*o*-tolylmethane 1837
BARTLETT, P. D., AND ROSEN, L. J. An acetylenic analog of neopentyl bromide; evidence that the hindrance to displacement reacns. in neopentyl halides is steric in nature 543
BARTLETT, P. D., RYAN, M. J., AND COHEN, S. G. Triptycene (9,10-*o*-benzenoanthracene) 2649
BARTOVICS, A. See Alfrey, T.
BARUSCH, M. R. See Lieberman, S.
BATES, R. G. Thermodynamics of bi-univalent electrolytes (VII) activity coeffs. of $PbBr_2$ from 5 to 40°. 1136
BAUER, E. E. See Cornog, J.
BAUER, N., AND FAJANS, K. Molar dispersion and refraction of free and bonded ions 3023
BAUER, S. H., AND BEACH, J. Y. Structures of methylenecyclobutane and hexamethylethane 1142
BAUER, S. H., AND HASTINGS, J. M. Structures of $B(CH_3)_2F$ and BCH_3F_2 2687
BAXT, V. J. See Saylor, J. H.
BAXTER, J. G., AND ROBESON, C. D. Crystalline aliphatic esters of vitamin A, 2407; crystalline vitamin A 2411
BEACH, J. Y. See Bauer, S. H.

BEAR, R. S. Long X-ray diffraction spacings of collagen, 727; significance of the "V" X-ray diffraction patterns of starches..... 1388

BEATTIE, J. A., INGERSOLL, H. G., AND STOCKMAYER, W. H. Vapor pressures and crit. consts. of isobutene, 546; compressibility of and an eq. of state for gaseous isobutene..... 548

BELL, A. See Allen, C. F. H.

BELL, P. H. See English, J. P.

BELL, P. H., AND ROBLIN, R. O., JR. Studies in chemotherapy (VII) theory of the relation of structure to activity of sulfanilamide type compds. 2905

BEMBRY, T. H., AND POWELL, G. Synthesis of phenolic glycosides..... 2419

BENEDETTI-PICHLER, A. A. Introduction to Microtechnique of Inorg. Analysis (book review)..... 3061

BENSON, S. W., AND KISTIAKOWSKY, G. B. Photochem. decompn. of cyclic ketones..... 80

BENTON, A. F. Reviews of "Elementary Phys. Chemistry" (Randall, Young), and "Phys. Chemistry" (Gucker, Meldrum)..... 3059

BENTON F. L., AND DILLON, T. E. Cleavage of ethers with BBr_3 (I) some common ethers..... 1128

BERGER, L. See Preisler, P. W.

BERGMANN, E., AND BOGRACHOV, E. Some reacns. of pyrene (corrn.)..... 3067

BERGMANN, F. 9-Vinylphenanthrenes (III) α-(9-phenanthryl)-stilbene, 69; mechanism of "aromatizing" diene reacns. in nitrobenzene..... 176

BERGMANN, F., ESCHINAZI, H. E., AND SCHAPIRO, D. Polyphenylnaphthalenes (I) 1,2-diphenylnaphthalene..... 557

BERGMANN, F., SCHAPIRO, D., AND ESCHINAZI, H. E. Polyphenylnaphthalenes (II) 1,2,3-triphenylnaphthalene..... 559

BERGMANN, M. See Stein, W. H.

BERGMANN, P. G. Introduction to the Theory of Relativity (book review)..... 2517

BERGMANN, W., AND KIND, C. A. Location of double bond in clionasterol..... 473

BERGSTROM, F. W. See McCrosky, C. R.

BERGSTROM, F. W., AND BUEHLER, J. S. Direct diazotization of nitrobenzene..... 19

BERKMAN, S., MORRELL, J., AND EGLOFF, G. Catalysis, Inorg. and Org. (book review)..... 474

BERLIN, A. S. See Skinner, G. S.

BERLINER, E. Mechanism of cyclization reacns... 2894

BERRY, K. L., AND STURTEVANT, J. M. Fluorochlorobromomethane..... 1599

BERRY, M. A. See Stonehill, H. I.

BEST, R. J. See Morton, A. A.

BEUTEL, R. H. See Stevens, J. R.

BEYER, K. H. Color reacn. of sympathomimetic amines with diazonium compds..... 1318

BIEGNER, J. E. See Schwob, C.

BIGELEISEN, J. See Lewis, G. N.; Redlich, O.

BILLMAN, J. H., RADIKE, A., AND MUNDY, B. W. Alkylation of amines (I)..... 2977

BILLMEIER, R. A. See Dermer, O. C.

BINDER, L. O. See Adams, R.

BINGHAM, E. C., AND ROEPKE, R. R. Rheology of the blood (II) effect of fibrinogen on the fluidity of blood plasma..... 1204

BJORKSTEN, J., AND CHAMPION, W. J. Mechanical influence on tanning..... 868

BLACET, F. E., AND HELDMAN, J. D. Photolysis of aliphatic aldehydes (X) acetaldehyde and I mixts. 889

BLACET, F. E., AND LOEFFLER, D. E. Photolysis of aliphatic aldehydes (XI) acetaldehyde and I mixts. 893

BLAEDEL, W. J., OGG, R. A., JR., AND LEIGHTON, P. A. Attempt to detect free hydroxyl as an intermediate in photochem. reacns., 2499; photoöxidation of MeI..... 2500

BLANCHARD, K. C. See Shepherd, R. G.

BLATT, A. H. See Gilman, H.

BLENKHORN, C. W. See Grummitt, O.

BLICKE, F. F., AND BURCKHALTER, J. H. Prepn. of β-keto amines by Mannich reacn., 451; α-thienylaminoalkanes..... 477

BLICKE, F. F., AND JENNER, E. L. Esters of pyridinecarboxylic acids as local anesthetics..... 1721

BLICKE, F. F., AND MAXWELL, C. E. Synthetic mydriatics (I), 428; (II)..... 431

BLISS, A. D. Reviews of "Quant. Analysis" (Kanning), 1012; "Qual. Analysis" (Anderson, Hazlehurst), 1491; "Org. Anal. Reagents" (Yoe, Sarver), 2518; "Introduction to Semimicro Qual. Chem. Analysis" (Curtman)..... 3060

BLOCH, E. See Schwenk, E.

BLOCK, L. P. See Whitmore, F. C.

BLOCK, P., JR., AND POWELL, G. Synthesis of 3',5'-diiodothyronine..... 1070

BOBTELSKY, M., AND GLASNER, A. Rate of reduction of V_2O_5 in concd. acid solns.—reduction of V_2O_5 by arsenious acid, oxalic acid, formaldehyde and EtOH..... 1462

BOBTELSKY, M., AND SIMCHEN, A. E. Anomalies in conductivity measurements in presence of H_2O_2, 454; catalysts for peroxide decompn..... 2592

BODART, J. See Luyckx, A.

BOGERT, M. T. See Levitz, M.; Masters, E. J.

BOGRACHOV, E. See Bergmann, E.

BOHLMAN, E. G., AND WILLARD, J. E. Reacns. of Br with CCl_4 and tetrachloroethylene following neutron capture and isomeric nuclear transition.. 1342

BOLSER, C. E. Review of "An Introduction to Org. Chemistry" (Williams)..... 728

BOND, P. A. Review of "Principles of General Chemistry" (Brinkley)..... 474

BOOTH, H. S., AND MARTIN, D. R. Systems with BF_3..... 2198

BORDENCA, C. See Degering, E. F.

BORDWELL, F. See Arnold, R. T.

BORTNICK, N. See Arnold, R. T.

BOST, R. W., AND SCHULTZE, H. C. S studies (XVIII) sulfonium derivs. of *p*-phenylphenacyl bromide..... 1165

BOTTORFF, E. M. See Fuson, R. C.

BOUGHTON, W. A. Review of "Chem. Dictionary" (Campbell)..... 2519

BOYD, G. E. See Harkins, W. D.; Hoffman, E. J.

BOYD, G. E., AND COPELAND, L. E. Surface tensions, densities and parachors of the aliphatic nitroparaffins..... 2540

BOYD, G. E., AND HARKINS, W. D. Energy of immersion of crystalline powders in water and org. liquids (I)..... 1190

BOYD, G. E., AND LIVINGSTON, H. K. Adsorption and energy changes at crystalline solid surfaces.. 2383

BOYD, G. R., JR. See Yoe, J. H.

BRADSHER, C. K. Cyclization of β-styrylacetaldehyde..... 1007

BRANCH, G. E. K., AND CALVIN, M. Theory of Org. Chemistry (book review)..... 474

BRANT, J. H. Phys. consts. of Me isopropenyl ketone..... 2224

BRATTON, A. C. See Shepherd, R. G.

BRAY, R. H. Ionic competition in base-exchange reacns..... 954

BREDIG, M. A. Crystal structure of Ca cyanamide. 1730

BREWER, L. See Pressman, D.

BREWSTER, C. M., AND WATTERS, G. G. Some derivs. of 2-propionyl-1-naphthol..... 2578

BRICKER, C. E. See Furman, N. H.

BRIDGMAN, P. W. The Nature of Thermodynamics (book review)..... 2524

BRIDGMAN, W. B. Some phys. chem. characteristics of glycogen..... 2349

BRIGHAM, H. R. See Sheppard, S. E.

BRIGHT, R. D. See McElvain, S. M.

BRINKLEY, S. R. Principles of General Chemistry (book review)..... 474

BRINKLEY, S. R., JR. See Owen, B. B.

BROCKWAY, C. E. See Washburn, E. R.

BRODE, W. R. See Raasch, M. S.

BRODE, W. R., AND RAASCH, M. S. Optically active vasopressor amines..... 1449
BROOKER, L. G. S., KEYES, G. H., AND WILLIAMS, W. W. Color and constitution (V) absorption of unsym. cyanines—resonance as a basis for a classification of dyes..... 199
BROOKS, B. T. Review of "The Technology of Natural Resins" (Mantell, Kopf, Curtis, Rogers). 1491
BROWN, A. E. See Wolfrom, M. L.
BROWN, D. H. See Pressman, D.
BROWN, D. J. Review of "Electrochemistry and Electrochem. Analysis" (Sand)..... 2728
BROWN, H. C. See Davidson, N.; Kharasch, M. S.
BROWN, H. C., AND ADAMS, R. M. Studies in stereochemistry (II) steric strains as a factor in the relative stability of some etherates of BF_3.. 2557
BROWN, H. C., AND GROOT, C. Convenient procedure for prepn. of DCl, 2223; studies in stereochemistry (III) prepn. of *d*-1-deutero-2-methylbutane and the study of its optical rotation..... 2563
BROWN, H. C., SCHLESINGER, H. I., AND CARDON, S. Z. Studies in stereochemistry (I) steric strains as a factor in the relative stability of some coordination compds. of B..... 325
BROWN, H. T., AND FRAZER, J. C. W. Mixed heteropoly acid catalysts for vapor phase air oxidation of naphthalene..... 2917
BROWN, R. A. See Trimble, H. M.
BROWN, R. L. See Wolfrom, M. L.
BROWNE, C. A., AND ZERBAN, F. W. Phys. and Chem. Methods of Sugar Analysis (book review). 1014
BRÜLL, W. See Li, N. C. C.
BRUNAUER, S. See Love, K. S.
BRUNAUER, S., LOVE, K. S., AND KEENAN, R. G. Adsorption of N and mechanism of NH_3 decompn. over Fe catalysts..... 751
BRUNDAGE, D. See Halford, J. O.
BRUNINGS, K. J. See Corwin, A. H.
BRUNINGS, K. J., AND CORWIN, A. H. Steric influences on aromaticity of dipyrrylmethenes—synthesis and study of properties of a di-N-methyldipyrrylmethene..... 593
BRUNSON, A. M. See White, J. W., Jr.
BRUSON, H. A. Chemistry of acrylonitrile (I) cyanoethylation of active methylene groups..... 2457
BRUSON, H. A., AND RIENER, T. W. Chemistry of acrylonitriles (II) reacns. with ketones..... 2850
BUCHMAN, E. R. See Sargent, H.
BUCHMAN, E. R., REIMS, A. O., AND SCHLATTER, M. J. Cyclobutane derivs. (III) *cis*-1,3-cyclobutanedicarboxylic acid..... 2703
BUCHMAN, E. R., REIMS, A. O., SKEI, T., AND SCHLATTER, M. J. Cyclobutane derivs. (I) degradation of *cis*- and *trans*-1,2-cyclobutanedicarboxylic acids to the corresponding diamines..... 2696
BUCHMAN, E. R., SCHLATTER, M. J., AND REIMS, A. O. Cyclobutane derivs. (II) thermal decompn. of *trans*-1,2-cyclobutane-*bis*-(trimethylammonium) hydroxide..... 2701
BUCHMANN, F. J., AND HAMILTON, C. S. Syntheses in quinoline series (IV) 2,4-disubstituted quinoline derivs..... 1357
BUCK, J. S. See Ardis, A.; Baltzly, R.; Ferry, C. W.; Ide, W. S.
BUCK, J. S., AND ARDIS, A. E. 2-Me-1,4-naphthoquinone derivs..... 725
BUCK, J. S., AND BALTZLY, R. Esters of *s*-hydroxyaralkylalkylamines..... 2263
BUCK, J. S., BALTZLY, R., AND FERRY, C. W. Some mono- and disubstituted guanidines..... 2231
BUCK, J. S., IDE, W. S., AND BALTZLY, R. Some unsym. disubstituted ureas, 2233; some N-substituted barbituric acids..... 2233
BUCKLES, R. E. See Winstein, S.
BUEHLER, J. S. See Bergstrom, F. W.
BUNKER, J. W. M. Review of "The Electron Microscope" (Burton, Kohl)..... 3060
BUNNETT, J. F. See Scott, A. F.
BURCHFIELD, P. E. Vapor pressures of indene, styrene and dicyclopentadiene..... 2501
BURCKHALTER, J. H. See Blicke, F. F.
BURGER, A. See Krahler, S. E.
BURGESS, K. A. See Aston, J. G.; Eastes, J. W.
BURK, D. Review of "Mechanisms of Biol. Oxidations" (Green)..... 1236
BURKE, S. S. See Crowell, W. R.
BURKETT, H. See McElvain, S. M.
BURNHAM, H. D., AND PEASE, R. N. Studies in gaseous hydrogenation and polymerization reacns. 1404
BURR, G. O. See Kass, J. P.
BURTON, E. F., AND KOHL, W. H. Electron Microscope (book review)..... 3060
BURWELL, R. L., JR. Action of HF, H_2SO_4 and H_3PO_4 on optically active 2-butanol..... 1025
BURWELL, R. L., JR., AND ARCHER, S. Alkylation of benzene in presence of acid catalysts..... 1032
BUTZ, L. W. Dehydration of 1,5-hexadiene-3-ol to 1,3,5-hexatriene and 1,3-cyclohexadiene..... 1978
BUTZ, L. W., AND JOSHEL, L. M. Synthesis of condensed ring compds. (VIII) further application of the dienyne double addn. reacn..... 1311
BYERLY, W. See Morris, H.
BYERLY, W., AND SELWOOD, P. W. Magnetic susceptibilities of *cis*- and *trans*-decalin..... 717
BYERS, D. J. See Fuson, R. C.
BYWATER, W. G. See Cheney, L. C.

CALDWELL, W. T., AND KORNFELD, E. C. Substituted 2-sulfonamido-5-aminopyridines..... 1695
CALINGAERT, G., SOROOS, H., AND HNIZDA, V. Oxidation of triethylbismuth..... 392
CALINGAERT, G., SOROOS, H., AND SHAPIRO, H. Disproportionation of R_6Pb_2 compds..... 462
CALVIN, M. See Branch, G. E. K.; Segesser, J. R.; Sherwood, D. W.
CALVIN, M., AND SEGESSER, J. R. Prepn. of tri-*m*-nitrophenyl orthoformate..... 186
CAMPAIGNE, E., AND SUTER, C. M. Identification of *o*- and *p*-sulfobenzoic acids as their S-benzylthiuronium salts..... 3040
CAMPBELL, A. N. Systems: $LiNO_3$–NH_4NO_3 and $LiNO_3$–NH_4NO_3–H_2O..... 2680
CAMPBELL, A. N., AND EPSTEIN, S. D. of Se..... 2679
CAMPBELL, A. W. See Kanning, E. W.
CAMPBELL, D. H. See Pauling, L.
CAMPBELL, F. H. Chem. Dictionary (book review). 2519
CAMPBELL, J. A. See Gardner, J. H.
CAMPBELL, W. P., AND SOFFER, M. D. Structure of cadinene..... 417
CAMPBELL, W. P., SOFFER, M. D., AND STEADMAN, T. R. Some observations on oxidation and detn. of mol. wt. of polynuclear aromatic compds..... 425
CAMPBELL, W. P., AND TODD, D. Structure and configuration of resin acids—podocarpic acid and ferruginol..... 928
CANNON, G. W. See Snyder, H. R.
CANNON, R. K. The Amphoteric Properties of Proteins (book review)..... 2237
CARDON, S. Z. See Brown, H. C.
CARDWELL, P. H. See Bartell, F. E.
CARLIN, R. B. See Smith, L. I.
CARLSON, G. H. See Baker, B. R.
CARMACK, M. See Adams, R.
CARPENTER, D. C., AND LOVELACE, F. E. Reacn. of formaldehyde with l(−)-asparagine..... 2899
CARSON, K. J. See Schwob, C.
CARTER, H. E., AND NEY, L. F. Synthesis of α-bromo-β-methoxy-*n*-butyric acid..... 1223
CASE, E. N. See Grummitt, O.
CASE, F. H. Further nitration of certain dinitrobiphenyls, 2225; nitration of certain halobiphenyls (I) nitro derivs. of 4-bromobiphenyl..... 1848
CASON, J Branched-chain fatty acids (I) synthesis of 17-Me-octadecanoic acid..... 1106
CASS, W. E. 2-Phenyloxazole and ortho-substituted

derivs., 785; see Craig, J. J.; Keilin, B.; Rosenbaum, J. J.
CASSIDY, H. G. Review of "Chromatographic Adsorption Analysis" (Strain) ... 1013
CASTRO, A. J. See Noller, C. R.
CHADWICK, D. H. See Iddles, H. A.
CHAKRAVORTY, P. N., AND LEVIN, R. H. Studies on cholesteryl oxides ... 2317
CHAKRAVORTY, P. N., AND WESNER, M. M. On the chem. behavior of cafesterol ... 2235
CHALMERS, B., AND QUARRELL, A. G. Phys. Examn. of Metals. Vol. II. Elec. Methods (book review). 2519
CHAMBERLIN, E. See Stevens, J. R.
CHAMPION, W. J. See Bjorksten, J.
CHANG, F. C. See Fieser, L. F.; Lieberman, S.
CHANLEY, J. See Grigsby, W. E.
CHAPIN, E. C. See Price, C. C.
CHAPPELL, D. See English, J. P.
CHAUDHURI, T. C. New synthesis of phthalaldehydes ... 315
CHELDELIN, V. H., AND WILLIAMS, R. J. Adsorption of org. compds. (I) adsorption of ampholytes on an activated charcoal ... 1513
CHENEY, L. C., AND BYWATER, W. G. 4-Morpholinealkyl esters and amides possessing antispasmodic activity ... 970
CHI, Y.-F., AND TSHIN, S.-Y. Thiazole research: synthesis of 2-phthalimido-Me-4-N-diethylamino-Me-thiazole ... 90
CHILD, E. Tools of the Chemist—Their Ancestry and American Evolution (book review) ... 1982
CHILD, R., AND NATHANAEL, W. R. N. Seed fat of *Litsea longifolia* Bth. & Hk ... 1079
CHOLNOKY, L. See Zechmeister, L.
CHOPPIN, A. R. See Amis, E. S.
CHOU, T. Q., AND CHU, T. T. Prepn. and properties of peimine and peiminine (corrn.) ... 3069
CHRISTENSEN, B. E. See Dimick, K. P.
CHU, T. T. See Chou, T. Q.
CLAPP, J. W. See Iddles, H. A.
CLAPP, R. C. See Fieser, L. F.
CLARK, E. P. Quassin (IV) a minor constituent of Jamaica quassia wood ... 2883
CLARK, G. L., AND KERN, S. F. Studies of Pb oxides (VI) effect of grinding on the X-ray diffraction patterns of mixts. containing Pb oxides ... 1637
CLARKE, B. L. Review of "Introduction to the Microtechnique of Inorg. Analysis" (Benedetti-Pichler) ... 3061
CLARKE, D. G. See Whitmore, F. C.
CLARKE, E. F. See Morton, A. A.
CLARKE, J. T. See Aston, J. G.
CLARKE, R. L. See McElvain, S. M.
CLARKE, R. P. See Conner, W. P.
CLAYTON, W. R., AND REID, E. E. Some esters of thiodiglycol ... 908
CLEGG, W. J. See Owen, K.
CLEVELAND, F. F. See Murray, M. J.; Saunders, R. H.
CLOWES, G. H. A. See Davis, W. W.
COCHRANE, C. C. See Barnes, R. P.
COGHLAN, C. A. See Skinner, G. S.
COHEN, B. Catalytic decompn. of H_2O_2 by basic BeI_2 hydrosols ... 1340
COHEN, H. See McElvain, S. M.
COHEN, S. G. See Bartlett, P. D.
COLBERT, J. C. A Shorter Course in Org. Chemistry (book review) ... 3063
COLEMAN, G. H., FARNHAM, A. G., AND MILLER, A. Azoyl derivs. of sugars and sepn. by chromatographic adsorption ... 1501
COLLINS, B. T. See De Vries, T.
CONN, J. B., KISTIAKOWSKY, G. B., ROBERTS, R. M., AND SMITH, E. A. Heats of org. reacns. (XIII) heats of hydrolysis of some acid anhydrides ... 1747
CONNER, W. P., CLARKE, R. P., AND SMYTH, C. P. Dielec. investigation of polypeptides (I) dielec. increments of amino acid polypeptides ... 1379
CONNER, W. P., AND SMYTH, C. P. Dielec. investigation of polypeptides (II) dispersion of simple amino acid polypeptides ... 1870
CONNOR, R. See Fuson, R. C.
COOK, E. L. See Weiser, H. B.
COOK, K. H. See Cook, W. A.
COOK, W. A., AND COOK, K. H. Halogenation of *m*-diphenylbenzene (II) the monoiodo deriv ... 2485
COPE, A. C., AND HANCOCK, E. M. Synthesis of 2-alkylaminoethanols from ethanolamine, 1503, (corrn.) ... 3071
COPELAND, L. E. See Boyd, G. E.
COPELAND, L. E., AND HARKINS, W. D. Pressure–area–temp. and energy relations of monolayers of octadecanenitrile ... 1600
CORNER, J. O. See Marvel, C. S.
CORNOG, J., AND BAUER, E. E. ICl (IV) system KCl–ICl ... 2620
CORWIN, A. H. See Brunings, K. J.; Quattlebaum, W. M., Jr.
CORWIN, A. H., BAILEY, W. A., JR., AND VIOHL, P. Structural investigations on a substituted dipyrrylmethane—an unusual melting point–symmetry relationship ... 1267
CORWIN, A. H., AND BRUNINGS, K. J. Rearrangements of pyrrole rings in oxidation of dipyrrylmethanes ... 2106
CORWIN, A. H., AND ELLINGSON, R. C. Detn. of the bridge structure of dipyrrylmethanes—new method for estimation of active H ... 2098
CORYELL, C. D. See McMillan, W. G., Jr.
COSBY, J. N. See Whitmore, F. C.
COTTLE, D. L. See Magrane, J. K., Jr.
COX, E. H. Prepn. of *p*-aminobenzenesulfonyl urea. 2225
CRAIG, J. J., AND CASS, W. E. Derivs. of aminoisoquinolines ... 783
CRAMER, R. See Jacobs, T. L.
CRAWFORD, H. M. 1,2-Diphenyl-3,4-dihydronaphthalene ... 727
CRAWFORD, H. M., SAEGER, M. E., AND WARNEKE, F. E. Reacn. of *n*-BuMgBr with some aromatic ketones ... 2862
CRETCHER, L. H. See Tipson, R. S.
CROMWELL, N. H. See Lauer, W. M.
CROMWELL, N. H., WILES, Q. T., AND SCHROEDER, O. C. Amino ketones (I) synthesis of amino alcs. and 1,3-diamino compds. from β-amino ketones. . 2432
CROOKS, H. M., JR. See Marker, R. E.
CROSSLEY, F. S. See Miller, E.
CROUCH, W. W. See Lochte, H. L.
CROWELL, W. R., MERTES, R. W., AND BURKE, S. S. Electromotive force of HgBr electrode ... 3021
CRUSE, K. See Ulich, H.
CUDD, H. H., AND FELSING, W. A. Activity coeffs. of Rb and Cs sulfates in aq. soln. at 25° ... 550
CURRAN, B. C. Elec. moments of some org. mercuric halides in dioxane, 830; see Lane, T. J.; McCusker, P. A.
CURTIS, J. L. See Mantell, C. L.
CURTMAN, L. J. Introduction to Semimicro Qual. Chem. Analysis (book review) ... 3060

DARBY, W. J., LEWIS, H. B., AND TOTTER, J. R. Prepn. of 4(5)-hydroxymethylimidazole ... 463
DARKEN, L. S., AND MEIER, H. F. Conductances of aq. solns. of hydroxides of Li, Na and K at 25°. 621
DAUDT, W. H. See Fieser, L. F.
DAVIDSON, A. W., LANNING, W. C., AND ZELLER, M. M. Plumbic acetate–anhyd. AcOH solns. . . . 1523
DAVIDSON, J. B. See Morton, A. A.
DAVIDSON, N., AND BROWN, H. C. Polymerization of some derivs. of trimethylaluminum, 316; prepn. and properties of dimethylphosphine ... 718
DAVIES, T. H. See Baker, B. R.
DAVIS, A. L., AND GARDNER, W. H. Nature and constitution of shellac (XVI) prepn. of 8,9,15-trihydroxypentadecylamine from aleuritic acid by the Naegeli–Curtius series of reacns ... 1902

DAVIS, C. O. See Johnston, H. L.
DAVIS, S. B. See Linstead, R. P.
DAVIS, T. L. Review of "Liebig and after Liebig." 2237
DAVIS, T. W. See Saffer, A.
DAVIS, W., JR., AND NOYES, W. A., JR. Photochem. studies (XXXV) photochem. decompn. of *n*-Bu Me ketone..... 2676
DAVIS, W. W., KRAHL, M. E., AND CLOWES, G. H. A. Soly. of carcinogenic and related hydrocarbons in water..... 108
DAVIS, W. W., AND PARKE, T. V., JR. Nephelometric method for detn. of solubilities of extremely low order..... 101
DAWSON, C. R. See Miller, W. H.; Steinman, H. G.
DAY, A. R. See Green, H.; Stein, C. W. C.
DEGERING, E. F. See Gwynn, B. H.; Sprang, C. A.
DEGERING, E. F., BORDENCA, C., AND GWYNN, B. H. An Outline of Org. N Compds. (book review).... 2729
DEGRAFF, R. A. See Long, E. A.
DE LANGHE, J. See Deulofeu, V.
DEMING, H. G., AND HENDRICKS, B. C. Introductory College Chemistry (book review)..... 3064
DEMING, P. See Washburn, E. R.
DENO, N. C. See Price, C. C.
DERMER, O. C. See Dermer, V. H.
DERMER, O. C., AND BILLMEIER, R. A. Comparison of metallic chlorides as catalysts for Friedel–Crafts ketone synthesis (II)..... 464
DERMER, V. H., AND DERMER, O. C. 4-Nitrodiphenyl ether-4′-sulfonyl Chloride and -4′-sulfonamide..... 3056
DEULOFEU, V., AND DE LANGHE, J. Studies on Argentine plants (III) alkaloids from *Lycopodium saururus*..... 968
DEULOFEU, V., LABRIOLA, R., AND DE LANGHE, J. Studies on Argentine plants (V) identification and characterization of some alkaloids in *Fagara coco* (Gill) Engl..... 2326
DE VRIES, T. See Montgomery, J. B.
DE VRIES, T., AND COLLINS, B. T. Heat capacity of org. vapors (III) nitromethane..... 1224
DILLON, T. E. See Benton, F. L.
DILLS, W. L., AND NELSON, J. M. Isolation of a Cu bearing protein from cow's milk..... 1616
DIMICK, K. P., AND CHRISTENSEN, B. E. New fructosan isolated from *Yucca mohavensis*, Sarg. 2501
DINGLE, H. Special Theory of Relativity (book review)..... 189
DOAK, G. O., EAGLE, H., AND STEINMAN, H. G. Arsine oxides of naphthalene and biphenyl..... 1064
DOERING, W. E. See Linstead, R. P.
DOESCHER, R. N. See Osborne, D. W.
DORINSON, A., MCCORKLE, M. R., AND RALSTON, A. W. Refractive indices and ds. of normal satd. fatty acids in the liquid state..... 2739
DORSKY, J. See Aston, J. G.
DOUGHERTY, G. See McDuffie, H. F., Jr.; Westlake, H. E., Jr.
DOWNING, M. L. See Hockett, R. C.
DRENAN, J. W. See Foster, L. S.
DUFF, V. B. See Henze, H. R.
DUGAN, L., JR., AND HAENDLER, H. M. Benzylidene aminomorpholine compds..... 2502
DUNKER, M. F. W. See Riegel, B.
DUNKERLEY, F. J. See Seltz, H.
DURHAM, D. A. See Price, C. C.
DUTTON, W. S. Du Pont—One Hundred and Forty Years (book review)..... 3064
DYAS, H. E., AND HILL, D. G. Mutarotation of glucose in H_2O–MeOH mixts..... 236
DYER, W. S. See Lauer, W. M.

EAGLE, H. See Doak, G. O.
EAKIN, R. E. See Pennington, D.
EANES, R. D. See Kilpatrick, M.
EASTES, J. W., AND BURGESS, W. M. Study of products obtained by reducing action of metals upon salts in liquid NH_3 solns. (VII) reduction of complex Ni cyanide: mono-valent Ni, 1187; (VIII) reduction of complex cyanides..... 2715
EBERLY, K. See Kharasch, M. S.
ECK, J. C., AND HOLLINGSWORTH, E. W. Prepn. of $\Delta^{6,8(14)}$-, $\Delta^{7,9,11}$-, $\Delta^{7,14}$- and $\Delta^{8,14}$-cholestadienes. 140
ECKERT, C. F. See Klotz, I. M.
EDENS, C. O. See Johnson, T. B.
EDSALL, J. T. Review of "Practical Methods in Biochemistry" (Koch)..... 189
EDWARDS, A. E., AND ROSEVEARE, W. E. The 2nd virial coeffs. of gaseous mixts..... 2816
EDWARDS, W. R., JR., AND REEVES, L. H. Furfuryl formate..... 1583
EGLOFF, G. See Berkman, S.
EKELEY, J. B. See Fisher, H. J.; Waugh, R. C.
ELLINGSON, R. C. See Corwin, A. H.
ENGELDER, C. J. Review of "Tools of the Chemist—Their Ancestry and American Evolution" (Child)..... 1982
ENGLE, C. J. See Trimble, H. M.
ENGLISH, J. P. See Roblin, R. O.
ENGLISH, J. P., CHAPPELL, D., BELL, P. H., AND ROBLIN, R. O., JR. Substituted sulfonamides... 2516
EPSTEIN, S. See Campbell, A. N.
ERICKSON, A. E. See Weijlard, J.
ERICKSON, J. L. E. See Stevens, P. G.
ESCHINAZI, H. E. See Bergmann, F.
ESSEX, H. See McGuinness, M. J., Jr.
EVANS, H. M. See Li, C. H.
EVANS, R. J. See Stross, F. H.
EVANS, W. L. See MacDonald, N. S.
EVANS, W. V., AND PEARSON, R. Ionic nature of the Grignard reagent..... 2865
EWART, R. H. See Roe, C. P.
EWING, W. W., GLICK, C. F., AND RASMUSSEN, H. E. Vapor pressure–temp. relations and heats of soln. and diln. of the binary system $Mn(NO_3)_2$–H_2O. 1445
EWING, W. W., AND RASMUSSEN, H. E. Temp.–compn. relations of the binary system $Mn(NO_3)_2$–H_2O..... 1443

FAITH, H. E. See Anderson, G. W.; Winnek, P. S.
FAJANS, K. See Bauer, N.
FAJANS, K., AND JOHNSON, O. Apparent volumes of individual ions in aq. soln..... 668
FALLON, W. A. See Hurd, C. B.
FAN, S. See Suen, T.-J.
FANG, H. See Li, N. C. C.
FANKUCHEN, I. Some X-ray diffraction measurements on biotin, 1742; X-ray and optic measurements on β-lactoglobulin..... 2504
FANTA, P. E. See Price, C. C.
FARKAS, A., AND FARKAS, L. Mechanism of catalytic conversion of para-H on Ni, Pt and Pd..... 1594
FARKAS, L. See Farkas, A.
FARNHAM, A. G. See Coleman, G. H.
FARQUHAR, J. P. See Sargent, H.
FEENEY, R. E., AND STRONG, F. M. Growth stimulating substances for *Lactobacillus casei*..... 881
FEIGEN, G. A. See Alles, G. A.
FEHNEL, E. A. Formation of insol. S in presence of gases other than SO_2..... 3041
FELSING, W. A. See Cudd, H. H.; Jones, J. H.; Patterson, A.; Phillips, B. A.
FELSING, W. A., AND WATSON, G. M. Compressibility of liquid *n*-octane..... 1822
FERNELIUS, W. C. See Greenlee, K. W.
FERRY, C. W. See Baltzly, R.; Buck, J. S.
FERRY, C. W., ARDIS, A. E., AND BUCK, J. S. Some quaternary salts from β-dimethylamino-β′-cymoxydiethyl ether..... 2232
FERRY, J. D. Mechanical properties of substances of high mol. wt. (II) rigidities of the system polystyrene–xylene and their dependence on temp. and frequency, 1323; (III) viscosities of system polystyrene–xylene..... 1330
FERRY, R. M. Review of "Phys. Chemistry for Students of Biochemistry and Medicine" (West).. 3061

FIELDNER, A. C. Review of "War Gases. Their Identification and Decontamination" (Jacobs)... 2519
FIESER, L. F., AND CHANG, F. C. Alkylation of α-naphthoquinones with esters of tetravalent Pb... 2043
FIESER, L. F., CLAPP, R. C., AND DAUDT, W. H. Methylation of aromatic nitro compds. with $PbAc_4$. 2052
FIESER, L. F., AND HEYMANN, H. Reacn. of Grignard reagents with acyloxyanthrones..... 376
FIESER, L. F., AND JONES, J. E. N-Methylformanilide synthesis of aldehydes..... 1666
FIESER, L. F., AND NEWTON, L. W. Reacns. of perinaphthane derivs..... 917
FIESER, L. F., AND NOVELLO, F. C. Synthesis of 4,10-ace-1,2-benzanthracene utilizing Δ^4-tetrahydrophthalic anhydride..... 802
FIESER, L. F., AND OXFORD, A. E. Alkylation of para quinones with acyl peroxides..... 2060
FINDLAY, A. Practical Phys. Chemistry (book review)..... 3065
FISHER, H. J., EKELEY, J. B., AND RONZIO, A. R. The glyoxalines (I) some hydantoins resulting from reacn. between phenylglyoxal and urea and substituted ureas..... 1434
FISCHER, H. O. L. See Sowden, J. C.
FLANNAGAN, G. N. See Spencer, H. M.
FLORY, P. J. Statistics of intramol. aldol condensations in unsatd. ketone polymers, 177; random reorganization of mol. wt. distribution in linear condensation polymers, 2205; mol. size distribution in linear condensation polymers, (corrn.) 3067; review of "Diffusion in and through Solids" (Barker)..... 1013
FOHLEN, G. M. See Kumler, W. D.
FOLKERS, K., KONIUSZY, F., AND SHAVEL, J., JR. Erythrina alkaloids (XIII) studies on constitution of erythraline, erythramine and erythratine.. 2146
FOLKERS, K., AND SHAVEL, J., JR. Erythrina alkaloids (XII) chromatographic analyses of erysodine, erysovine and "erysocine" and technique for preparative isolation..... 1892
FONDA, G. R. Review of "Fluorescent Chem. and their Applications" (de Ment)..... 1983
FONTANA, B. J. H exchange of aromatic amines with D_2O and T_2O..... 2503
FOOTE, G. L. See Huntress, E. H.
FORMAN, E. O. See Henze, H. R.
FORSTER, W. S. See Whitmore, F. C.
FORSYTHE, W. R., AND GIAUQUE, W. F. Entropies of HNO_3 and its mono- and tri-hydrates—their heat capacities from 15 to 300 °K.—heats of diln. at 298.1 °K.—internal rotation and free energy of HNO_3 gas—partial pressures over its aq. solns., 48, (corrn.)..... 3069
FOSTER, J. F. See Levine, M.
FOSTER, L. S., DRENAN, J. W., AND WILLISTON, A. F. Prepn. of $GeCl_4$..... 3042
FOSTER, R. E. See Fuson, R. C.
FOWLER, R. D. See Koskoski, W.
FRAENKEL-CONRAT, H. See Li, C. H.
FRANK, R. L. See Marvel, C. S.
FRANK, R. L., HOLLEY, R. W., AND WIKHOLM, D. M. 3,2′-Nicotyrine—insecticidal properties of certain azo derivs..... 2835
FRANKEL, M., AND KATCHALSKI, E. Polycondensation of α-amino acid esters (I) polycondensation of glycine esters, 2264; (II) polycondensation of alanine Et ester..... 2268
FRAZER, J. C. W. Review of "Catalysis Inorg. and Org." (Berkman, Morrell, Egloff), 474; see Brown, H. T.
FREDERICKSEN, J. M. See Pierce, J. S.
FREIFELDER, M. See Raiziss, G. W.
FRENCH, D., AND RUNDLE, R. E. Mol. wts. of the Schardinger α- and β-dextrins..... 1651
FRENCH, H. E., AND GALLAGHER, D. M. Action of alkali on cyclohexenecarbonals..... 1497
FRENCH, H. S., MAGEE, M. Z., AND SHEFFIELD, E. Configuration of org. coördination compds. of Ni, with especial reference to bis-formylcamphorethylenediamine-Ni..... 1924
FRENCH, S. J. Torch and Crucible (book review).. 729
FRIESEN, E. See Kreider, L. C.
FROSCH, C. J. See Fuller, C. S.
FROST, W. S. Bis(amino acid) derivs. (I) diglycine halogen acid addn. products..... 1286
FRY, E. M., WILSON, E. J., JR., AND HUDSON, C. S. Novel type of Cannizzaro reacn..... 872
FU, S.-C., AND SAH, P. P. T. Synthesis of 4,4′-dicyanostilbene..... 1482
FUGUITT, R. E., STALLCUP, W. D., AND HAWKINS, J. E. Phys. properties of terpenes (I) system α- and β-pinene..... 2978
FULLER, C. S. See Baker, W. O.
FULLER, C. S., FROSCH, C. J., AND PAPE, N. R. Chain structure of linear polyesters—trimethylene glycol series..... 154
FUOSS, R. M. See Mead, D. J.
FURMAN, N. H. Review of "Polarography. Polarographic Analysis and Voltammetry. Amperometric Titrations" (Kolthoff, Lingane)..... 2728
FURMAN, N. H., AND BRICKER, C. E. Polarographic study of *o*-phthalic acid and phthalates 660, (corrn.)..... 3069
FURRY, W. H. Review of "The Special Theory of Relativity" (Dingle)..... 189
FUSON, R. C., BOTTORFF, E. M., FOSTER, R. E., AND SPECK, S. B. Para acylation of polyalkylbenzophenones by aryl 2,4,6-trialkylbenzoates..... 2573
FUSON, R. C., BOTTOROFF, E. M., AND SPECK, S. B. Reacn. of Grignard reagent with esters of highly hindered acids..... 1450
FUSON, R. C., BYERS, D. J., AND RACHLIN, A. I. Enediols (XI) vinylogs of ethylene and acetylene glycols..... 2891
FUSON, R. C., BYERS, D. J., RACHLIN, A. I., AND SOUTHWICK, P. L. Vinyl alcs. (IV) oxidative cleavage..... 2886
FUSON, R. C., CONNOR, R., PRICE, C. C., AND SNYDER, H. R. A Brief Course in Org. Chemistry (book review)..... 189
FUSON, R. C., HORNING, E. C., WARD, M. L., ROWLAND, S. P., AND MARSH, J. L. Bimol. reduction of hindered aldehydes..... 30
FUSON, R. C., LINDSEY, R. V., JR., AND WELLDON, P. B. Vinyl alcs. (V) isomeric bromo-1,2-dimesityl-1-propen-1-ols..... 2888
FUSON, R. C., AND RACHLIN, A. I. Reductive cleavage of dioxolones by the Grignard reagent..... 1567
FUSON, R. C., AND SCOTT, S. L. Enediols (X) an amino stilbenediol..... 2152
FUSON, R. C., AND SPECK, S. B. ortho Alkylation and arylation of mesityl aryl ketones..... 2446
FYTELSON, M., AND JOHNSON, T. B. Action of ketene on 5,5-dibromoxyhydrouracil..... 306

GALE, R. H., AND LYNCH, C. C. Potentiometric titration of dibasic acids in dioxane–water mixts. 1153
GALLAGHER, D. M. See French, H. E.
GARDNER, J. H., AND CAMPBELL, J. A. Notes on chemistry of the aloins—formation of formaldehyde and furfural..... 1378
GARDNER, T. S., AND PURVES, C. B. Distribution of acetyl groups in a tech. acetone-soluble cellulose acetate..... 1539
GARDNER, W. H. See Davis, A. L.
GARNER, C. S. See Hughes, R. H.
GARRETT, A. B., AND LEMLEY, J. Soly. relations of HgO in aq. solns. of HCl..... 2380
GATES, J. W., JR. See Allen, C. F. H.
GATES, M. D., AND MISANI, F. Condensation of β-cyclogeraniol with leucoisonaphthazarin..... 1979
GEBHART, A. I. See Whitmore, W. F.
GEISSMAN, T. A. Anthochlor pigments (III) pigments of *Cosmos sulphureus*..... 1704
GELBACH, R. W., AND KING, G. B. Secondary ionization and activity coeffs. of selenic acid..... 1054

GELBACH, R. W., AND LOUDERBACK H. M. Partial molal volumes of $NiSO_4$ solns. 2379
GEORGE, R. S. See Whitmore, F. C.
GERTLER, S. I., AND HALLER, H. L. N-Substituted piperonylamides 1741
GERTNER, S. See Lichtenstein, N.
GEYER, B. P. Synthesis of 2-(2'-methoxybenzoyl)-benzoic acid 2226
GEYER, B. P., AND SMITH, G. McP. Prepn. and properties of some peri-hydroxyquinone inner complexes, 1649, (corrn.) 3071
GIAUQUE, W. F. Review of "Thermochem. Calcns." (Wenner), 1237; see Forsythe, W. R.
GIBB, T. R. P., JR. See Morton, A. A.
GILBERT, E. C. See Anderson, C. M.; Baker, E. M.; Williams, G. E.
GILMAN, H. Review of "Org. Reacns." Vol. I (Adams) 3062
GILMAN, H., AND BLATT, A. H. Org. Syntheses. Coll. Vol. I (book review) 1492
GILMAN, H., and Stuckwisch, C. G. Diazotization of an aminoaryllead compd 1007
GLADDING, J. V. K. See Huntress, E. H.
GLASNER, A. See Bobtelsky, M.
GLASS, D. B. See Weissberger, A.
GLASSTONE, S. See Taylor, H. S.
GLICK, C. F. See Ewing, W. W.
GLICK, D. Specificity studies on enzymes hydrolyzing esters of substituted amino and N heterocyclic alcs. 564
GLICK, F. See Riebsomer, J. L.
GOEBEL, C. G. See Bachman, G. B.
GOLD, M. H. See Riegel, B.
GOLL, M. See Tauber, H.
GOLUMBIC, C. Antioxidants and autoxidation of fats (XIV) isolation of new antioxidants from vegetable fats 2337
GORDON, A. R. Temp. coeff. of the conductance of KCl solns., 2517; see Hornibrook, W. J.
GORDY, W. See Pauling, L.
GORDY, W., AND PAULING, L. Mol. structure of Me isocyanide 2952
GORMAN, M., AND LEIGHTON, P. A. Soly. of SnO in $HClO_4$ 719
GOTTFRIED, S. P. See Natelson, S.
GOULD, C. W., JR. See Lucas, H. J.
GOULD, R. K., AND VOSBURGH, W. C. Complex ions (III) study of some complex ions in soln. by means of the spectrophotometer 1630
GRAHAM, C. L. See Washburn, E. R.
GRAHAME, D. C., AND WHITNEY, R. B. Thermodynamic theory of electrocapillarity 1548
GRANICK, S. See Michaelis, L.
GREEN, A. G. See Morton, A. A.
GREEN, D. E. Mechanisms of Biol. Oxidations (book review) 1236
GREEN, H., AND DAY, A. R. Tautomeric character of the imidazole ring 1167
GREENBURG, R. B. See Aston, J. G.
GREENLEE, K. W., AND FERNELIUS, W. C. Hydrogenation of disubstituted acetylenes 2505
GREISEN, E. C. See Hand, D. B.
GRIFFIN, C. W. Sorption of CO by metals—temp. variation expts. 2610
GRIGSBY, W. E., HIND, J., CHANLEY, J., AND WESTHEIMER, F. H. Malonic ester synthesis and Walden inversion 2606
GRINNELL, S. W., AND KOENIG, F. O. Detn. of transference nos. of KI from e. m. f. of iodide–I gravity cells 682
GROOT, C. See Brown, H. C.
GROSS, P. M. See Saylor, J. H.
GROSS, S. T. See Schirmer, F. B., Jr.
GROSS, W. J. See Adams, R.
GROSSE, A. V. See Pines, H.
GROSSE, A. V., AND LINN, C. B. Addn. of HF to the triple bond 2289
GROSSER, F. See Shriner, R. L.
GRUMMITT, O. Oxidation of *n*-BuB oxide 1811
GRUMMITT, O., AND CASE, E. N. Study of action of an Al–$AlCl_3$ catalyst in Friedel–Crafts reacns.—benzoylation 878
GRUMMITT, O., KLOPPER, R. S., AND BLENKHORN, C. W. Reacns. with tetraphenylcyclopentadienone—condensation with cyclic 1,3-diene systems. 604
GUCKER, F. T., JR., AND ALLEN, T. W. Ds. and sp. heats of aq. solns. of *dl*-α-alanine, β-alanine and lactamide 191
GUCKER, F. T., JR., AND MELDRUM, W. B. Phys. Chemistry (book review) 3059
GULLEDGE, H. C. See Russell, A.
GWYNN, B. H. See Degering, E. F.
GWYNN, B. H., AND DEGERING, E. F. Condensation products of ketene with ketones 2216

HADEN, W. W. See Pierce, J. S.
HAENDLER, H. M. Cu(II) and Ni(II) complex ions of diethylenetriamine, 686; see Dugan, L., Jr.; Worth, H. J.
HAENSEL, V. See Ipatieff, V. N.
HAKAN, B. L. See Morton, A. A.
HALFORD, J. O., AND BRUNDAGE, D. Vapor phase esterification equil. 36
HALL, C. E., JAKUS, M. A., AND SCHMITT, F. O. Electron microscope observations of collagen 1234
HALL, W. T. Textbook of Quant. Analysis (book review) 190
HALLER, H. L. See Gertler, S. I.; LaForge, F. B.; Schechter, M. S.
HALVERSTADT, I. F. See Kumler, W. D.
HALVERSTADT, I. F., AND KUMLER, W. D. Dipole moments of cyclohexanol and cyclohexanone in dioxane, 1982; solvent polarization error and its elimination in calculating dipole moments 2988
HAMBURGER, G. See McCullough, J. D.
HAMILTON, C. S. See Barnum, E. R.; Buchmann, F. J.; Holcomb, W. F.
HAMILTON, D. See Bahner, C. T.
HAMLIN, K. E., JR. See Adams, R.
HAMMETT, L. P. See Lucas, G. R.
HAMMOND, R. P. See McCoy, H. N.
HANCOCK, E. M. See Cope, A. C.
HAND, D. B., AND GREISEN, E. C. Oxidation and reduction of vitamin C 358
HANN, R. M. See Haskins, W. T.; Maclay, W. D.; Ness, A. T.; Wolfe, J. K.
HANN, R. M., HASKINS, W. T., AND HUDSON, C. S. Structure of dimethylene dulcitol (1,3:4,6-dimethylene-dulcitol), 986; structure of di-*o*-nitrobenzylidene-dulcitol (1,3:4,6-di-*o*-nitrobenzylidene-dulcitol) 1614
HANN, R. M., AND HUDSON, C. S. An anhydro deriv. of D-mannosan $< 1,5 > \beta < 1,6 >$ (presumably 3,4-anhydro-D-talosan $< 1,5 > \beta < 1,6 >$), 925; studies on D-galactosan $< 1,5 > \beta < 1,6 >$.. 2435
HANSON, J. E. See Jacobs, T. L.
HAPPOLDT, W. B., JR. See Russell, A.
HARKINS, W. D. See Boyd, G. E.; Copeland, L. E.
HARKINS, W. D., AND BOYD, G. E. Binding energy between a crystalline solid and a liquid: the energy of adhesion and emersion—energy of emersion of crystalline powders (II) 1195
HARMAN, D., STEWART, T. D., AND RUBEN, S. Tracer studies with radioactive H—synthesis of labelled MeI, 2293; study of the Menschutkin reacn. using radioactive H as tracer 2294
HARRIS, G. C. Oxidation product of $\Delta^{9,10}$-octalin.. 720
HARRIS, G. H. See Noller, C. R.
HART, R. T. See Iddles, H. A.
HART, W. F. See Niederl, J. B.
HARTUNG, W. H. See Jenkins, G. L.; Ruddy, A. W.
HASKINS, W. T. See Hann, R. M.
HASKINS, W. T., HANN, R. M., AND HUDSON, C. S. Structure of dibenzylidene dulcitol (1,3:4,6-dibenzylidene-dulcitol), 132; a new dibenzylidene dulcitol (2,3,4,5-dibenzylidene-dulcitol), 136; a

second 2,3,4,5-dibenzylidene-dulcitol, 137; syntheses of cellobiose, 1289; syntheses of lactose and its epimer, 1490; syntheses of epi-lactose and lactose..... 1852
HASSELSTROM, T., AND TODD, D. Investigations in the 1-Me-phenanthrene series (III) synthesis of 3-acetyl-1-Me-phenanthrene..... 1225
HASTINGS, J. M. See Bauer, S. H.
HASTINGS, T. J., JR. See Young, R. C.
HAUGAARD, G., AND ROBERTS, R. M. Heats of org. reacns. (XIV) digestion of β-lactoglobulin by pepsin..... 2664
HAUSER, C. R. See Abramovitch, B.; Ayres, E. B.; Skell, P.
HAUSER, C. R., ABRAMOVITCH, B., AND ADAMS, J. T. Condensations (XVIII) acylation of anions of certain esters with Et carbonate..... 2714
HAUSER, C. R., AND ADAMS, J. T. Introduction of *t*-Bu group into Et acetoacetate by means of BF_3. 728
HAWK, C. O. See Storch, H. H.
HAWKINS, J. E. See Fuguitt, R. E.; Stallcup, W. D.
HAWKINS, W. L. See Levi, I.
HAYNES, W. The Stone that Burns (book review). 2521
HAYS, J. T. See Niemann, C.
HAZLEHURST, T. H. See Anderson, H. V.
HAZLET, S. E., HENSLEY, L. C., AND JASS, H. Bromination of 4-PhPh chloroacetate..... 2449
HAZLET, S. E., AND MORROW, R. W. Compd. formation between the isomeric phenylphenols and pyridine..... 2625
HAZLET, S. E., STAUFFER, D. A., AND VAN ORDEN, H. O. 4-Toluenesulfonates of the nitro-4-phenylphenols..... 3057
HAZLET, S. E., AND VAN ORDEN, H. O. Nitration of 4-PhPh benzoate..... 2505
HEARON, W. M. See Huntress, E. H.
HELDMAN, J. D. See Blacet, F. E.
HELMHOLZ, L., AND LEVINE, R. Detn. of parameters in K dihydrogen arsenate and Ag arsenate... 354
HENDRICKS, B. C. See Deming, H. G.
HENICK, A. S. See Ungnade, H. E.
HENNE, A. L., AND TURK, A. Conjugated diolefins by double bond displacement..... 826
HENNE, A. L., AND WHALEY, A. M. Prepn. and directed chlorination of 1,1,1-trifluoropropane.... 1157
HENNION, G. F., AND MCLEESE, S. F. DEC. Friedel–Crafts acylations of some sterically hindered alkylbenzenes..... 2421
HENNION, G. F., AND MURRAY, W. S. Catalytic addn. reacns. of acetylenic alcs..... 1220
HENNION, G. F., AND PIERONEK, V. R. Some BF_3 catalyzed alkylations of halobenzenes..... 2751
HENSLEY, L. C. See Hazlet, S. E.
HENZE, H. R. See Jones, R. V.; Lesesne, S. D.; McCown, W. H.; Schenck, L. M.; Wallace, W. P.
HENZE, H. R., DUFF, V. B., MATTHEWS, W. H., JR., MELTON, J. W., AND FORMAN, E. O. Keto ethers (IX) propoxymethyl alkyl (or Ph) ketones..... 1222
HENZE, H. R., AND HUMPHREYS, D. D. Prepn. of mixed, *s*-aliphatic amines, RR′NH, 2878; 5,5-dimethylhydantoins containing a —NRR′ substituent (II)..... 2881
HENZE, H. R., AND MCKEE, R. L. Hydantoins containing a tetrahydropyranyl substituent..... 1672
HENZE, H. R., AND SPEER, R. J. Identification of carbonyl compds. through conversion into hydantoins..... 522
HESS, H. V. See Winstein, S.
HEYMANN, H. See Fieser, L. F.
HIBBERT, H. See Levi, I.
HICKEY, J. W. See Wilson, W. K.
HICKS, E. M., HICKS, M. H., AND SAMPEY, J. R. Water effects on photochem. bromination of acetophenone..... 887
HICKS, M. H. See Hicks, E. M.
HILDEBRAND, J. H. See Young, F. E.
HILL, D. G. See Dyas, H. E.
HILL, O. F. See Audrieth, L. F.
HILL, T. L. Rate eq. for consecutive reacns..... 465
HIMEL, C. M. See Marvel, C. S.
HIND, J. See Grigsby, W. E.
HINDIN, H. See Kraemer, C. B.
HIPPLE, J. A., JR. See Stevenson, D. P.
HIRSCHY, H. W., AND RUOFF, P. M. Polarographic detn. of citrinin..... 1490
HIXON, R. M. See Levine, M.
HNIZDA, V. See Calingaert, G.
HOARD, J. L. See Vincent, W. B.; Williams, M. B.
HOARD, J. L., AND WILLIAMS, M. B. Structures of complex fluorides—ammonium hexafluosilicate–ammonium fluoride, $(NH_4)_2SiF_6 \cdot NH_4F$..... 633
HOBDAY, R. W. See Hurd, C. B.
HOBSTETTER, J. N. Review of "The Phys. Examn. of Metals. Vol. II. Elec. Methods" (Chalmers, Quarrell)..... 2519
HOCKETT, R. C., AND DOWNING, M. L. Rates of reacn. of diacetone glucose, diacetone galactose and diacetone sorbose with *p*-toluenesulfonyl chloride in pyridine soln..... 2463
HOERR, C. W. See Ralston, A. W.
HOERR, C. W., AND RALSTON, A. W. Studies on high mol. wt. aliphatic amines and their salts (IX) behavior of various salts of dodecylamine in water, EtOH and benzene..... 2824
HOFFMAN, E. J. See Ralston, A. W.
HOFFMAN, E. J., BOYD, G. E., AND RALSTON, A. W. Studies on high mol. wt. aliphatic amines and their salts (V) sol. and insol. films of the amine hydrochlorides, 498; (VIII) sol. and insol. films of the amine acetates (A) surface tension of aq. solns. of dodecylamine acetate..... 2067
HOFMANN, K. See du Vigneaud, V.
HOGNESS, T. R., AND JOHNSON, W. C. Ionic Equil. as Applied to Qual. Analysis (book review)..... 1492
HOLCOMB, W. F., AND HAMILTON, C. S. Derivs. of 4-amino-6-methoxyquinaldine..... 1309
HOLLEY, R. W. See Frank, R. L.
HOLLINGSWORTH, E. W. See Eck, J. C.
HOLMES, H. N. General Chemistry (book review), 3066; review of "Principles and Practice of Chromatography" (Zechmeister, Cholnoky), 2729; see Kornblum, N.
HOMEYER, A. H. See Wallingford, V. H.
HOMEYER, A. H., AND WALLINGFORD, V. H. Study of diethyl 1,4-dihydroxy-2,3-naphthalate..... 798
HOMILLER, R. P. See Toennies, G.
HORECZY, J. See Shive, B.
HORNIBROOK, W. J., JANZ, G. J., AND GORDON, A. R. Thermodynamics of aq. solns. of KCl at temps. from 15–45° from e. m. f. measurements on cells with transference..... 513
HORNING, E. C. See Fuson, R. C.
HOWARD, H. C. See Weiler, J. F.
HOWE, J. P. See Kieffer, W. F.
HOWELL, W. J., JR. See Spitzer, R.
HUBACHER, M. H. Carvacrolphthalein..... 2538
HUBARD, S. S. See Bancroft, W. D.
HUBBARD, W. N. See Rowley, H. H.
HUBER, C. F. See Price, C. C.
HUDSON, C. S. See Fry, E. M.; Hann, R. M.; Haskins, W. T.; McClenahan, W. S.; Maclay, W. D.; Montgomery, E. M.; Ness, A. T.; Richtmyer, N. K.; Schoch, T. J.; Tilden, E. B.; Wolfe, J. K.
HUFFMAN, M. N. Derivs. of estrone containing O at position 16..... 2235
HUGGETT, C., ARNOLD, R. T., AND TAYLOR, T. I. Mechanism of the Arndt–Eistert reacn..... 3043
HUGGINS, K. A., AND YOKLEY, O. E. Studies on substituted diphenylbutadienes (I) addn. of Br to 1-*p*-bromophenyl-4-Ph-1,3-butadiene..... 1160
HUGGINS, M. L. Theory of solns. of high polymers, 1712; viscosity of dil. solns. of long-chain mols. (IV) dependence on concn..... 2716
HUGHES, D. W. See Padgitt, F. L.

HUGHES, E. W., AND MOORE, W. J. Crystal structure of β-glycylglycine..... 2236
HUGHES, R. H., AND GARNER, C. S. Formal oxidation–reduction potentials of thallous–thallic salts in aq. HCl solns.—formation of chlorothallate complex ions..... 1644
HULL, D. E. See Seelig, H.
HUMPHREYS, D. D. See Henze, H. R.
HUNTRESS, E. H., AND FOOTE, G. L. Identification of org. compds. (VI) prepn. of *p*-nitrobenzylpyridinium salts of aromatic sulfonic acids..... 1017
HUNTRESS, E. H., AND GLADDING, J. V. K. Synthesis of aminobenzoyleneureas and of dihydroxyquinoxalines isomeric with "luminol"..... 2644
HUNTRESS, E. H., AND HEARON, W. M. Synthesis of 5-aminocoumarone-2,3-dicarboxylic acid cyclohydrazide—a heterocyclic analog of 4-aminophthalhydrazide..... 86
HUNTRESS, E. H., PFISTER, K., 3RD, AND PFISTER, K. H. T. Fluorenones and diphenic acids (IX) establishment of authentic 1-bromo- and 4-bromofluorenones..... 2845
HURD, C. B., FALLON, W. A., AND HOBDAY, R. W. Studies on the hydrogel of zirconia (I) time of set. 110
HURD, C. D., AND WINBERG, H. E. Behavior of pyrogallol trimethyl ether and 3,4,5-trimethoxybenzonitrile toward Grignard reagents..... 2085
HURDIS, E. C., AND SMYTH, C. P. Dipole moments in the vapor state and resonance effects in some substituted benzenes, 2212; Dipole moment, induction and resonance in nitroethane and some chloronitroparaffins..... 2829
HUSTON, R. C., AND KAYE, I. A. Condensation of some *s*-aliphatic alcs. with benzene in presence of $AlCl_3$..... 1576
HUSTON, R. C., AND MELOY, C. R. Condensation of Me dipropyl carbinols with phenol in presence of $AlCl_3$..... 2655

ICKE, R. N. See Alles, G. A.
IDDLES, H. A., CHADWICK, D. H., CLAPP, J. W., AND HART, R. T. Formation and rearrangement of diphenylmethyl ether of *o*-cresol..... 2154
IDE, W. S. See Baltzly, R.; Buck, J. S.
IDE, W. S., BALTZLY, R., AND BUCK, J. S. Some quaternary salts containing aryloxyethyl and aryloxypropyl groups..... 2234
IKAWA, M. See Pauling, L.
IKEDA, C. See Pauling, L.
INGERSOLL, H. G. See Beattie, J. A.
INGRAM, A. R., AND LUDER, W. F. Some reacns. of morpholine, 2506; ionization const. of morpholine in water..... 3043
IPATIEFF, V. N. Review of "Chem. Refining of Petroleum" (Kalichevsky, Stagner), 3062; see Pines, H.
IPATIEFF, V. N., AND HAENSEL, V. Hydrogenation of alkyl Ph ketones in presence of Cu–alumina catalysts..... 520
IRREVERRE, F., AND SULLIVAN, M. X. N,N′-Diacetylsulfanilyl- and N,N′-disulfanilyl-*l*-cystine, 1488; certain naphthylidene sulfanilamide derivs.. 2230

JACKSON, E. L. A new type of sulfanilamide deriv. of D-glucose—sulfanilyl-2-amino-α-D-glucose and certain derivs..... 1371
JACOBS, M. B. War Gases. Their Identification and Decontamination (book review)..... 2519
JACOBS, T. L. Review of "A Brief Course in Org. Chemistry" (Fuson, Connor, Price, Snyder)..... 189
JACOBS, T. L., CRAMER, R., AND HANSON, J. E. Acetylenic ethers (II) ethoxy- and butoxy-acetylene..... 223
JACOBS, T. L., AND WHITCHER, W. J. Acetylenic ethers (III) halogen derivs. of phenoxyacetylene.. 2635
JAKUS, M. A. See Hall, C. E.
JAMES, T. H. Effect of catalysis upon oxidation products of hydroxylamine..... 731
JANZ, G. J. See Hornibrook, W. J.
JASPER, J. J., AND ROSENSTEIN, L. Effect of temp. on surface tension and d. of some halogen substituted acetic acids..... 2078
JASS, H. See Hazlet, S. E.
JELINEK, C. F. See Adams, R.
JENKINS, D. M. See Aston, J. G.
JENKINS, G. L., AND HARTUNG, W. H. Chemistry of Org. Medicinal Products (book review)..... 1012
JENNER, E. L. See Blicke, F. F.
JOHNSON, O. See Fajans, K.
JOHNSON, T. B. Reviews of "An Outline of Org. N Compds." (Degering, Bordenca, Gwynn), 2729; "Org. Syntheses" (Smith), 3063; see Ballard, E.; Fytelson, M.
JOHNSON, T. B., AND EDENS, C. O. Complex formations between I_2 and μ-mercaptodihydroglyoxalines..... 2706
JOHNSON, W. C. See Hogness, T. R.
JOHNSTON, H. L., AND DAVIS, C. O. Chem. sepn. of isotopes of H by addn. of metals and compds. of metals to water, acids and bases (I) relative efficiencies of sp. reacns.—effects of certain factors other than temp..... 2613
JOHNSTON, J. Review of "Tech. Report Writing" (Rhodes)..... 3063
JOHNSTONE, H. F., WEINGARTNER, H. C., AND WINSCHE, W. E. System $FeCl_3$–NaCl..... 241
JONES, D. M. See Wallingford, V. H.
JONES, E. M. See Marker, R. E.
JONES, G. Reviews of "Chem. Engineers' Handbook" (Perry), 190; "Industrial Instruments for Measurement and Control" (Rhodes), 728; "American Cotton Handbook" (Merrill, Macormac, Mauersberger), 1014; "Inorg. Chem. Technology" (Badger, Baker), 1237; "Thorpe's Dictionary of Applied Chemistry" (Thorpe, Whiteley). 2237
JONES, G., AND RAY, W. A. Surface tension of solns. of electrolytes as a function of the concn. (IV) $MgSO_4$..... 2744
JONES, G. D. See McElvain, S. M.; Marvel, C. S.
JONES, J. E. See Bartlett, P. D.; Fieser, L. F.
JONES, J. H., SPUHLER, F. J., AND FELSING, W. A. Detn. of activity coeffs. of methylamine hydrochlorides from f. p. data..... 965
JONES, R. V., AND HENZE, H. R. Synthesis from rhodanine-oxindoles of keto and mercapto derivs. of cinchoninic acid..... 1669
JOSHEL, L. M. See Butz, L. W.
JOSHEL, L. M., AND PALKIN, S. Oxidation of β-pinene with SeO_2..... 1008

KADESCH, R. G. Substituted amides of 2,4,6-trimethylbenzoic acid..... 726
KAHAN, G. J. See Kolthoff, I. M.
KAHLER, F. H. See Transue, L. F.
KALICHEVSKY, V. A., AND STAGNER, B. A. Chem. Refining of Petroleum (book review)..... 3062
KAMEN, M. D. See Nahinsky, P.; Ruben, S.
KANE, S. S. See Kharasch, M. S.
KANNING, E. W. Quant. Analysis (book review)... 1012
KANNING, E. W., AND CAMPBELL, A. W. Standard potential of the Ag–AgBr electrode in anhyd. MeOH at 25°..... 517
KASS, J. P., NICHOLS, J., AND BURR, G. O. Certain derivs. of the octadecenoic acids (I) the *p*-phenylphenacyl esters (II) S-benzylthiuronium salts.... 1061
KASS, J. P., AND RADLOVE, S. B. Diastereoisomerism of the 9,10,12-trihydroxystearic acids and the geometric configurations of ricinoleic and ricinelaidic acids..... 2253
KATCHALSKI, E. See Frankel, M.
KAUZMANN, W. Effect of temp. on validity of Hudson's rules of isorotation..... 1626
KAVANAGH, K. E. Catalytic hydrogenation of cystine..... 2721
KAYE, I. A. See Huston, R. C.; Sobel, A. E.
KEENAN, G. L. See Welsh, L. H.

KEENAN, R. G. See Brunauer, S.
KEEVIL, N. B. Vapor pressures of aq. solns. at high temps. 841
KEILIN, B., AND CASS, W. E. Deamination of 5-amino-8-nitroisoquinoline. 2442
KELL, R. W. See Price, C. C.
KELLEY, K. K. See Moore, G. E.
KELSEY, E. B. Review of "Ionic Equil. as Applied to Qual. Analysis" (Hogness, Johnson). 1492
KENYON, W. O. See Reynolds, D. D.; Unruh, C. C.; Yackel, E. C.
KERN, S. F. See Clark, G. L.
KERR, R. W. Action of *macerans* enzyme on a component of corn starch. 3044
KERTESZ, D. J. See Northey, E. H.
KERTESZ, Z. I. Note on invertase activity in identical mixts. in the liquid and frozen state. 2577
KEYES, G. H. See Brooker, L. G. S.
KHARASCH, M. S. See Oesper, P. F.
KHARASCH, M. S., AND BROWN, H. C. Carboxylation (I) photochem. and peroxide-catalyzed reacns. of oxalyl chloride with paraffin hydrocarbons. 329
KHARASCH, M. S., EBERLY, K., AND KLEIMAN, M. Carboxylation (IV) direct introduction of the chloroformyl (—COCl) group into alicyclic and aliphatic acid chlorides. 2975
KHARASCH, M. S., KANE, S. S., AND BROWN, H. C. Carboxylation (II) reacn. of oxalyl chloride with unsatd. hydrocarbons, 333; (III) the peroxide-catalyzed reacn. of oxalyl chloride with the side-chains of aralkyl hydrocarbons—a preliminary study of the relative reactivity of free radicals. 1621
KHARASCH, M. S., AND SAYLES, D. C. Factors detg. the course and mechanism of Grignard reacns. (V) effect of metallic halides on the reacn. of Grignard reagents with benzalacetophenone and with benzophenone. 2972
KIEFFER, W. F., AND HOWE, J. P. Photochemistry of isobutene (I). 1
KIEHL, S. J. See Lanford, O. E.; Rohrer, C. S.
KIENLE, R. H., AND SAYWARD, J. M. Solubilities of orthoanilamide, metanilamide and sulfanilamide. 2464
KILMER, G. W. See Whitmore, F. C.
KILPATRICK, M. See Krieger, K. A.
KILPATRICK, M., AND EANES, R. D. Relative acid strengths of formic, acetic and propionic acids in alcs. and dioxane–H_2O mixts. 2065
KIND, C. A. See Bergmann, W.
KING, A. J. X-Ray study of Ca–Sr alloy series. 1226
KING, G. B. See Gelbach, R. W.
KING, L. C., AND BALL, C. D. Sterols of alfalfa seed oil (II) isolation of β-spinasterol and δ-spinasterol. 2488
KINNEY, C. R., AND KOLBEZEN, M. J. Org. B–N compds. (II) reacn. of BCl_3 with *p*-toluidine. 1584
KIPERASH, M., AND PARKS, G. S. Some heat capacity data for gaseous 2,2,4-trimethylpentane. 179
KISTIAKOWSKY, G. B. See Benson, S. W.; Conn, J. B.
KISTIAKOWSKY, G. B., AND TICHENOR, R. L. Use of D as tracer in the Claisen rearrangement. 2302
KISTLER, S. S. See Kraemer, E. O.
KLEENE, R. D. *p*-Cyclohexylphenyl-phenylsulfone. 1489
KLEIMAN, M. See Kharasch, M. S.
KLOPPER, R. S. See Grummitt, O.
KLOTZ, I. M., AND ECKERT, C. F. Apparent molal vols. of aq. solns. of H_2SO_4 at 25°. 1878
KLUG, H. P., AND ALEXANDER, L. Crystal-chem. studies of alums (IV) coeffs. of linear thermal expansion. 1819
KNELL, M. See Price, C. C.
KNIGHT, C. A. Basic amino acids in strains of tobacco mosaic virus. 2734
KNOWLES, C. M., AND WATT, G. W. Reacns. between *sym*-diphenyltriazene and Hg(II) salts. 935
KOBE, K. A., AND STEWART, P. B. System Ca$(NO_3)_2$–Sr$(NO_3)_2$–H_2O at 25 and 60°. 1301
KOCH, F. C. Practical Methods in Biochemistry (book review). 189
KOENIG, F. O. See Grinnell, S. W.
KOHL, W. H. See Burton, E. F.
KOHN, E. J. See Wolfrom, M. L.
KOLBEZEN, M. J. See Kinney, C. R.
KOLTHOFF, I. M. See Orlemann, E. F.; Smith, L. I.; Zlotowski, I.
KOLTHOFF, I. M., AND KAHAN, G. J. Attachment and detachment of dropping Hg under various conditions. 2553
KOLTHOFF, I. M., AND LAITINEN, H. A. *p*H and Electro Titrations (book review). 1016
KOLTHOFF, I. M., AND LINGANE, J. J. Polarography. Polarographic Analysis and Voltammetry. Amperometric Titrations (book review). 2728
KOLTHOFF, I. M., AND STENGER, V. A. Volumetric Analysis (book review). 2730
KONIUSZY, F. See Folkers, K.
KOPF, C. W. See Mantell, C. L.
KORNBLAU, S. See Natelson, S.
KORNBLUM, N., AND HOLMES, H. N. Batyl alc. 3045
KORNFELD, E. C. See Caldwell, W. T.
KOSKOSKI, W., AND FOWLER, R. D. Radio halogen exchanges in P halides. 850
KOSOLAPOFF, G. M. An improved method of prepn. of *bis*-arylphosphonic acids. 2982
KRAEMER, E. O., BARTELL, F. E., AND KISTLER, S. S. Advances in Colloid Science (book review). 2521
KRAHL, M. E. Review of "A Symposium on Respiratory Enzymes," 2520; see Davis, W W.
KRAHLER, S. E., AND BURGER, A. Nitration of lepidine and 2-chlorolepidine. 2417
KRAYBILL, H. R. See Mitchell, J. H., Jr.
KREBS, E. See Price, C. C.
KREIDER, H. R., AND MENOTTI, A. R. Dimorphism of amylcaine hydrochloride. 1227
KREIDER, L. C., AND FRIESEN, E. Rotational relationships of alkyl glucosides. 1482
KREMER, C. B. Purification of $ThCl_4 \cdot 8H_2O$. 1009
KREMER, C. B., AND MELTSNER, M. Intermediates of pentryl analogs—chloronitroanilino alkanols. 1285
KREMER, C. B., MELTSNER, M., AND HINDIN, H. Action of monoethanolamine on Et bromomalonate. 1010
KREMER, C. B., AND WALDMAN, E. Alkanolamines (XI) monoalkylamino alcs. and their esters. 1089
KRIEGER, K. A., AND KILPATRICK, M. Conductance of KIO_3 at 25° and mobility of IO_3^-. 7
KRINBILL, C. A. See Marshall, C. E.
KUBICO, M. A. See Riegel, B.
KUMLER, W. D. Dissocn. const., dipole moment and structure of α-nitrotetronic acid, 1948; dipole moment of *ms*-tetraphenylporphine, 2993; see Halverstadt, I. F.
KUMLER, W. D., AND FOHLEN, G. M. Dipole moment and structure of urea and thiourea, 1944, (corrn.). 3071
KUMLER, W. D., AND HALVERSTADT, I. F. Dipole moments of some bile acids. 1941
KUNDIGER, D. See McElvain, S. M.
KUSHNER, S. See Bachmann, W. E.

LABRIOLA, R. See Deulofeu, V.
LAFORGE, F. B., HALLER, H. L., AND SULLIVAN, W. N. Presence of an insecticidal principle in the bark of southern prickly ash. 187
LAITINEN, H. A. Potential of the ytterbic–ytterbous ion electrode, 1133, (corrn.) 3071; see Kolthoff, I. M.; Wawzonek, S.
LAITINEN, H. A., AND WAWZONEK, S. Reduction of unsatd. hydrocarbons at dropping Hg electrode (I) Ph substituted olefins and acetylenes. 1765
LAMB, A. B. Reviews of "Torch and Crucible" (French), 729; "Solubilities of Org. Compds." (Seidell), 1014; "Four Treatises of Theophrastus von Hohenheim Called 'Paracelsus'" (Sigerist), 1237; "The Stone that Burns" (Haynes), 2521; "Advances in Colloid Science" (Kraemer, Bartell, Kistler). 2521

LAMBERT, F. See Riebsomer, J. L.
LAMER, V. K. See Barnes, M. D.
LANE, T. J., MCCUSKER, P. A., AND CURRAN, B. C. Elec. moments of inorg. halides in dioxane (II) chlorides of B, Al, Fe, Si, Ge and Sn..... 2076
LANFORD, O. E. See Rohrer, C. S.
LANFORD, O. E., AND KIEHL, S. J. Reacn. of ferric ion with orthophosphate in acid soln. with thiocyanate as an indicator for ferric ions..... 291
LANGLEY, W. D., AND NOONAN, T. R. Soly. of the flavianates of certain org. bases in H_2O, EtOH and *n*-BuOH at 3 and 30°..... 2507
LANNING, W. C. See Davidson, A. W.
LARSON, W. D., AND TOMSICEK, W. J. Activity coeffs. of the undissociated part of weak acids (II) oxalic acid (corrn.)..... 3069
LAUER, W. M. Review of "Micromethods of Quant. Org. Analysis" (Niederl, Niederl)..... 2729
LAUER, W. M., AND CROMWELL, N. H. Action of benzoyl chloride on Et β-diethylaminocrotonate.. 612
LAUER, W. M., AND DYER, W. S. Oxidation of benzophenone oxime..... 1453
LAUFER, S. See Tauber, H.
LEDINGHAM, A. E. See Manske, R. H. F.
LEGAULT, R. R., AND LEWIS, D. C. Studies on O absorption induced by ether linkages—rates of O absorption by dioxolane and methyldioxolane.... 1354
LEHNINGER, A. L. 1-Carbamyl-5-Me-pyrazole-3-carboxylic acid..... 2507
LEHNINGER, A. L., AND WITZEMANN, E. J. Prepn. and reacns. of acetopyruvic acid (α,γ-diketo-*n*-valeric acid)..... 874
LEHRMAN, L. Nature of fatty acids associated with starch—adsorption of palmitic acid by potato and defatted corn and rice starches..... 2144
LEIFER, E., AND UREY, H. C. Kinetics of gaseous reacns. by means of mass spectrometer—thermal decompn. of dimethyl ether and acetaldehyde.... 994
LEIGHTON, P. A. See Blaedel, W. J.; Gorman, M.; Noyes, W. A., Jr.
LEMLEY, J. See Garrett, A. B.
LEMONS, J. F., WILLIAMSON, P. M., ANDERSON, R. C., AND WATT, G. W. Influence of electrolytes on ammonolysis by liquid NH_3..... 467
LEOPOLD, R. S. See Williams, J. W.
LEROSEN, A. L. A method for standardization of chromatographic analysis, 1905; see Zechmeister, L.
LEROSEN, A. L., AND ZECHMEISTER, L. Prolycopene. 1075
LESESNE, S. D., AND HENZE, H. R. Utilization of alkoxy ketones in synthesis of quinoline by the Pfitzinger reacn. (II)..... 1897
LESLIE, J. D. See Seyer, W. F.
LESTER, C. T. See Whitmore, F. C.
LEVI, I., HAWKINS, W. L., AND HIBBERT, H. Studies on reacns. relating to carbohydrates and polysaccharides (LXV) an improved technique for fractionation of partially methylated glucosides, 1957; (LXVI) structure of the dextran synthesized by action of *Leuconostoc mesenteroides* on sucrose..... 1959
LEVIN, R. H. See Chakravorty, P. N.
LEVINE, J. See Wollner, H. J.
LEVINE, M., FOSTER, J. F., AND HIXON, R. M. Structure of the dextrins isolated from corn sirup. 2331
LEVINE, P. Structure of Skita's "decahydro-9,10-dihydroxyphenanthrene," 3046; see Linstead, R. P.
LEVINE, R. See Helmholz, L.
LEVITZ, M., AND BOGERT, M. T. Studies in dehydrogenation (II) spirocyclopentane-1,1′-tetralin. 1719
LEWIS, C. E. See Whitmore, F. C.
LEWIS, D. C. See Legault, R. R.
LEWIS G. L. See Oesper, P. F.
LEWIS, G. N., AND BIGELEISEN, J. Initial step in action of acids on tetraarylhydrazines..... 2808
LEWIS, G. N., AND LIPKIN, D. Reversible photochem. processes in rigid media: dissocn. of org. mols. into radicals and ions..... 2801
LEWIS, G. N., MAGEL, T. T., AND LIPKIN, D. Isomers of crystal violet ion—their absorption and re-emission of light..... 1774
LEWIS, H. B. See Darby, W. J.
LEWIS, R. N. See Niemann, C.
LI, C. H. Kinetics and mechanism of 2,6-diiodotyrosine formation..... 1147
LI, C. H., AND FRAENKEL-CONRAT, H. Electrophoresis of crotoxin..... 1586
LI, C. H., SIMPSON, M. E., AND EVANS, H. M. Physchem. characteristics of the interstitial cell stimulating hormone from sheep pituitary glands..... 367
LI, N. C. C., AND BRÜLL, W. Conductivity studies (IV) the limiting ionic mobilities of several univalent ions at temps. between 15 and 45°..... 1635
LI, N. C. C., AND FANG, H. Conductivity studies (III) the limiting equivalent conductances of KCl in H_2O at temps. between 15 and 40°..... 1544
LICHTENSTEIN, N., AND GERTNER, S. Prepn. of γ-alkylamides of glutamic acid..... 1021
LIEBERMAN, S., CHANG, F. C., BARUSCH, M. R., AND NOLLER, C. R. Saponins and sapogenins (XX) bethogenin and trillogenin, new sapogenins from *Trillium erectum*..... 2581
LIEBHAFSKY, H. A. Reacns. involving O, amalgams and H_2O_2, 852; see Winslow, E. H.
LIGGETT, R. W. See Arnold, R. T.
LILEK, E. F. See Schultz, M. L.
LINDSEY, R. V., JR. See Fuson, R. C.
LINDWALL, H. G. See Barrows, R. S.; Reeves, R. F.
LINGANE, J. J. Polarographic investigation of Re compds. (I) reduction of perrhenate ion at dropping Hg electrode, 1001; (II) oxidation of −1 Rhenium at the dropping electrode and the potential of the Re^{+2}–Re^{-1} couple, 2182; review of "The Polarographic Method of Analysis" (Müller), 1983; "A Course of Instruction in the Qual. Chem. Analysis of Inorg. Substances" (Noyes, Swift), 2522; see Kolthoff, I. M.
LINN, C. B. See Grosse, A. V.
LINSTEAD, R. P. Review of "Org. Syntheses," Coll. Vol. I (Gilman, Blatt)..... 1492
LINSTEAD, R. P., AND DAVIS, S. B. Stereochemistry of catalytic hydrogenation (IV) hexahydrodiphenic acids, 2006, (corrn.)..... 3071
LINSTEAD, R. P., DAVIS, S. B., AND WHETSTONE, R. R. Stereochemistry of catalytic hydrogenation (V) assignment of *cis*- and *trans*-configurations..... 2009
LINSTEAD, R. P., AND DOERING, W. E. Stereochemistry of catalytic hydrogenation (II) prepn. of the 6 inactive perhydrodiphenic acids, 1991; (III) optically active perhydrodiphenic acids—a proof of the configuration of the backbone, 2003, (corrn.)..... 3071
LINSTEAD, R. P., DOERING, W. E., DAVIS, S. B., LEVINE, P., AND WHETSTONE, R. R. Stereochemistry of catalytic hydrogenation (I) stereochemistry of the hydrogenation of aromatic rings. 1985
LINSTEAD, R. P., AND LEVINE, P. Stereochemistry of catalytic hydrogenation (VII) complete hydrogenation of phenanthraquinone..... 2022
LINSTEAD, R. P., WHETSTONE, R. R., AND LEVINE, P. Stereochemistry of catalytic hydrogenation (VI) hydrogenation of 9-phenanthrol and related substances and identification of 3 of the possible stereoisomeric forms of the perhydrophenanthrene ring, 2014, (corrn.)..... 3071
LIPKIN, D. See Lewis, G. N.; Weissman, S. I.
LIPSCOMB, W. N., AND BAKER, R. H. Identification of alcs. in aq. soln..... 179
LITTLE, E. L. See Morton, A. A.
LIVINGSTON, H. K. See Boyd, G. E.
LOCHTE, H. L. See Shive, B.; Wash, G.
LOCHTE, H. L., CROUCH, W. W., AND THOMAS, E. D. N compds. in petroleum distillates (XXIV) isola-

tion and identification of a $C_{11}H_{17}N$ base Calif. petroleum 2753
LOEFFLER, D. E. See Blacet, F. E.
LOEWE, S. See Adams, R.; Wollner, H. J.
LONG, E. A., AND DEGRAFF, R. A. Energy states of solids: evidence from thermal data for existence of low electronic energy levels in Eu ion—heat capacity of Eu sulfate octahydrate from 60 to 300 °K. 1346
LONG, E. A., AND TOETTCHER, F. C. Phase transitions (I) heat capacity of Ni nitrate hexammoniate from 54 to 300 °K.—transition at 243 °K. 629
LONG, F. A., AND NUTTING, G. C. Relative surface tension of KCl solns. by a differential bubble pressure method 2476
LONG, R. S. See Adams, R.
LOTHROP, W. C. 1,8-Dimethyl and 2,7-dimethoxybiphenylene 1698
LOUDERBACK, H. M. See Gelbach, R. W.
LOVE, K. S. See Brunauer, S.
LOVE, K. S., AND BRUNAUER, S. Effect of alkali promoter concn. on decompn. of NH_3 over double promoted Fe catalysts 745
LOVELACE, F. E. See Carpenter, D. C.
LUCAS, G. R., AND HAMMETT, L. P. Rate and mechanism in reacns. of *t*-Bu nitrate, and of benzyl nitrate with water and hydroxyl ion, 1928; hydration of isobutene in dil. HNO_3 1938
LUCAS, H. J. See Pressman, D.
LUCAS, H. J., AND GOULD, C. W., JR. Brucine as a reagent for partially resolving bromoalkanes; configurations of some diastereomeric dibromoalkanes, 601, (corrn.) 3069
LUCAS, W. M. See Barnes, R. P.
LUCK, J. M., AND SMITH, J. H. C. Annual Review of Biochemistry. Vol. XI (book review) 2522
LUDER, W. F. See Ingram, A. R.
LUSTIG, H. See Neuberg, C.
LUTZ, R. E., AND MCGINN, C. E. Halogen compds. derived from 4-Me-2,5-diphenylfuran, 2583; conversion of unsatd. 1,4-diketones into furans and hydroxyfuranones 2585
LUTZ, R. E., AND TERRY, D. H. Acylation of 1,4-dimesityl-1,2,4-butanetrione enol, 1375; prepn. and alkylation of 1,4-dimesityl-3-Me-1,2,4-butanetrione enol, 2423; stereoisomeric bromo 1,4-dimesityl unsatd. 1,4-diketones 2426
LUYCKX, A., BODART, J., AND RENS, G. Photoactivation of adsorption of H on ThO_2 1731
LYNCH, C. C. See Gale, R. H.

MCBAIN, J. W. See Vinograd, J. R.
MCBAIN, J. W., AND SOLDATE, A. M. Soly. of propylene vapor on H_2O as affected by typical detergents, 1556, (corrn.) 3071
MCCLELLAN, D. S. See Schirmer, F. B., Jr.
MCCLENAHAN, W. S., TILDEN, E. B., AND HUDSON, C. S. Study of products obtained from starch by action of the amylase of *Bacillus macerans* 2139
MCCOMAS, W. H., JR., AND RIEMAN, W., III. Soly. of Ca oxalate monohydrate in pure water and various neutral salt solns. at 25°, 2946; effect of *p*H on soly. of Ca oxalate 2948
MCCOOL, J. C. See Arnold, R. T.
MCCORKLE, M. R. See Dorinson, A.
MCCOWN, W. H., AND HENZE, H. R. Alkaline hydrolysis of fluorenone-spirohydantoin 689
MCCOY, H. N., AND HAMMOND, R. P. Sepn. of Yb from accompanying rare earths by means of its amalgam 1009
MCCROSKY, C. R., BERGSTROM, F. W., AND WAITKINS, G. On the structure of HCN 722
MCCULLOUGH, J. D. Spectrophotometric detn. of dissocn. consts. of diphenylselenium dibromide and diphenylselenium diiodide 2672
MCCULLOUGH, J. D., AND HAMBURGER, G. Crystal structure of diphenylselenium dichloride 508
MCCUSKER, P. A. See Lane, T. J.
MCCUSKER, P. A., AND CURRAN, B. C. Elec. moments of inorg. halides in dioxane (I) P, As and Sb trihalides 614
MACDONALD, N. S., AND EVANS, W. L. Synthesis of 5-D-glucosido-D-arabinose 2731
MCDUFFIE, H. F., JR., AND DOUGHERTY, G. Effect of structure on reactivity: nuclear substitution of benzene derivs 297
MCELROY, L. See Baker, B. R.
MCELVAIN, S. M., ANTHES, H. I., AND SHAPIRO, S. H. Ketene acetals (XI) pyrolysis of ketene acetals and orthoesters 2525
MCELVAIN, S. M., AND BURKETT, H. α-Alkoxyvinyl- and α-alkoxyethylbarbituric acids 1831
MCELVAIN, S. M., CLARKE, R. L., AND JONES, G. D. Ketene acetals (X) elimination of HBr from the acetals of α-bromoaldehydes–isopropyl- and *n*-propylketene diethylacetal 1966
MCELVAIN, S. M., AND COHEN, H. Ketene acetals (VIII) reacn. of ketene diethylacetal with α,β-unsatd. carbonyl compds. 260
MCELVAIN, S. M., AND KUNDIGER, D. Ketene acetals (VII) reacn. of ketene diethylacetal with various halogen compds. and acids 254
MCELVAIN, S. M., AND NELSON, J. W. Prepn. of orthoesters 1825
MCELVAIN, S. M., AND WALTERS, P. M. Ketene acetals (IX) ketene dialkylacetals, 1059; prepn. and properties of certain polyethoxyethanes and their bromo derivs. 1963
MCELVAIN, S. M., WALTERS, P. M., AND BRIGHT, R. D. Constituents of the volatile oil of catnip (II) the neutral components—nepetalic anhydride. 1828
MCGINN, C. E. See Lutz, R. E.
MCGREW, F. C. See Adams, R.
MCGUINNESS, M. J., JR., AND ESSEX, H. Effect of strong elec. fields on radiochem. decompn. of gaseous NH_3 1908
MACK, E., JR. Reviews of "Kurzes Lehrbuch der physik. Chemie" (Ulich, Cruse), 475; "Phys. Chemistry, An Introduction" (Moelwyn-Hughes), 730; "A Treatise on Phys. Chemistry" Vol. I "Atomistics and Thermodynamics" (Taylor, Glasstone) 1743
MACK, J. H. See Wilson, W. K.
MCKEE, R. L. See Henze, H. R.
MACKINNEY, G., AND SUGIHARA, J. M. Riboflavin estimation in fruits and vegetables 1980
MACLAY, W. D., HANN, R. M., AND HUDSON, C. S. Some studies of L-glucoheptulose 1606
MCLEESE, S. F. DEC. See Hennion, G. F.
MCMEEKIN, T. L., AND WARNER, R. C. Hydration of β-lactoglobulin crystals 2393
MACMILLAN, A. See Seeger, D. R.
MCMILLAN, W. G., JR., ROBERTS, J. D., AND CORYELL, C. D. Thermodynamic consts. of the dithionite (hydrosulfite) ion 398
MCMULLEN, E. See Arnold, R. T.
MACNAUGHTON, N. W. See Anderson, L. C.
MCNEELY, W. H. See Zechmeister, L.
MACORMAC, A. R. See Merrill, G. R.
MCPHEE, W. D. See Adams, R.
MACPHILLAMY, H. B. On the structure of fucosterol. 1732
MAGEE, M. Z. See French, H. S.
MAGEL, T. T. See Lewis, G. N.
MAGRANE, J. K., JR., AND COTTLE, D. L. Reacn. of epichlorohydrin with Grignard reagent 484
MAHAN, J. See Wolfrom, M. L.
MAHAN, J. E. See Adams, R.
MAHAN, R. I. See Shive, B.
MAHONEY, J. F., AND PURVES, C. B. New methods for investigating distribution of ethoxyl groups in a technical ethylcellulose, 9; relationship between method of prepn., distribution of substituents and soly. in water or alkali of Me and Et ethers of cellulose 15
MALKIEL, S., AND MASON, J. P. 1,1,1-Trichloro-2-

hydroxy-3-nitroalkanes and their reduction products..... 2515
MALLATT, R. C. See Tarbell, D. S.
MANNING, W. M. See Strain, H. H.
MANSKE, R. H. F., MARION, L., AND LEDINGHAM, A. E. Alkaloids of papaveraceous plants (XXXIV) *Hunnemannia fumariaefolia* Sweet and the constitution of a new alkaloid, hunnemanine.. 1659
MANTELL, C. L., KOPF, C. W., CURTIS, J. L., AND ROGERS, E. M. The Technology of Natural Resins (book review)..... 1491
MARBLE, J. P. At. wt. of Pb from a 2nd sample of pitchblende, Great Bear Lake, N. W. T., Canada. 3047
MARCY, H. O., 3rd, AND WYMAN, J., JR. Dielec. studies on muscle hemoglobin..... 638
MARGNETTI, C. See Thompson, A. F., Jr.
MARION, L. See Manske, R. H. F.
MARK, H. See Alfrey, T.
MARK, H., AND RAFF, R. High Polymeric Reacns., their Theory and Practice (book review)..... 1015
MARKER, R. E., AND CROOKS, H. M., JR. Sterols (CXLIV) some 16-alkyl-pregnenolones and progesterones..... 1280
MARKER, R. E., CROOKS, H. M., JR., JONES, E. M., AND SHABICA, A. C. Sterols (CXLIII) conversion of 5-pregnen-3(β)-ol-20-one to dehydro-isoandrosterone..... 1276
MARKER, R. E., CROOKS, H. M., JR., JONES, E. M., AND WITTBECKER, E. L. Sterols (CXXX) 3,6-diketo sterols and their reduction products..... 219
MARKER, R. E., CROOKS, H. M., JR., AND WAGNER, R. B. Sterols (CXVII) 17-bromopregnan-3(β)-ol-20-one, 210; (CXXVIII) 17,21-dibromopregnan-3(β)-ol-20-one and its conversion to pregnanol-3(β),21-diol-20-one, 213; (CXXXVIII) conversion of pregnan-3(β)-ol-20-one into *etio*-cholan-3(β)-ol-17-one..... 817
MARKER, R. E., CROOKS, H. M., JR., WAGNER, R. B., SHABICA, A. C., JONES, E. M., AND WITTBECKER, E. L. Sterols (CXL) 17-bromo-*allo*-pregnanone-20 and 17,21-dibromo-*allo*-pregnanone-20..... 822
MARKER, R. E., CROOKS, H. M., JR., WAGNER, R. B., AND WITTBECKER, E. L. Sterols (CLI) rearrangement of 17,21-dibromo-*allo*-pregnan-3(β)-ol-20-one acetate..... 2089
MARKER, R. E., JONES, E. M., AND WITTBECKER, E. L. Sterols (CXXXII) sapogenins (LIV) action of H_2O_2 on the pseudosapogenin acetates and on the pregnenolones..... 468
MARKER, R. E., AND SHABICA, A. C. Sterols (CXXV) sapogenins (LI) structure of the dibasic acid obtained by permanganate oxidation of anhydrosarsasapogenoic acid, 147; (CXXVI) sapogenins (LII) structure of the side chain of sarsasapogenin—identification of the acid obtained by haloform reacn. on the dibasic acid from the $KMnO_4$ oxidation of anhydrosarsasapogenoic acid, 180; (CXXXV) sapogenins (LVI) sarsasapogenoic acid, 721; (CXXXVII) sapogenins (LVIII) oxidation products of sarsasapogenin: keto-sarsasapogenin..... 813
MARKER, R. E., SHABICA, A. C., JONES, E. M., Crooks, H. M., Jr., AND WITTBECKER, E. L. Sterols (CXLI) 3(α),11,12-trihydroxycholanic acid. 1228
MARKER, R. E., AND TURNER, D. L. Sterols (CXXXIII) sapogenins (LV) 20-Me-pregnanetriol and related compds..... 481
MARKER, R. E., TURNER, D. L., OAKWOOD, T. S., ROHRMANN, E., AND ULSHAFER, P. R. Sterols (CXXXIV) some observations on the structure of ouabain..... 720
MARKER, R. E., TURNER, D. L., AND ULSHAFER, P. R. Sterols (CXLVIII) sapogenins (LXII) structure of the side chain in the dihydropseudosapogenins, 1655; (LXIII) position of hydroxyl groups in digitogenin..... 1843
MARKER, R. E., TURNER, D. L., AND WITTBECKER, E. L. Sterols (CXXXI) sapogenins (LIII) configuration of the hydroxyl groups in chlorogenin, 221; (LVII) structure of side-chain of chlorogenin..... 809
MARKER, R. E., AND WAGNER, R. B. Sterols (CXXIX) rearrangement of 17-bromopregnan-3(β)-ol-20-one, 216; (CXLII) 17-Me-pregnan-3(β)-ol-20-one and related compds., 1273; (CXLIX) hypoiodite oxidation of pregnanolones and pregnenolones..... 1842
MARKER, R. E., Wagner, R. B., AND ULSHAFER, P. R. Sterols (CXLVI) sapogenins (LX) some new sources of diosgenin, 1283; (LXI) bio-reduction of steroids..... 1653
MARKER, R. E., WAGNER, R. B., AND WITTBECKER, E. L. Sterols (CLII) rearrangement of 16,17-dibromopregnan-3(β)-ol-20-one..... 2093
MARKER, R. E., WITTBECKER, E. L., WAGNER, R. B., AND TURNER, D. L. Sterols (CXXXIX) sapogenins (LIX) bio-reduction of 4-dehydrotigogenone.. 818
MARKER, R. E., WITTLE, E. L., JONES, E. M., AND CROOKS, H. M., JR. Sterols (CXLV) 21-benzal-5-pregnen-3(β)-ol-20-one and allied compds..... 1282
MARON, S. H., AND TURNBULL, D. Thermodynamic properties of N at high pressures as analytic functions of temp. and pressures, 44; eq. of state for gases at high pressures involving only crit. consts.. 2195
MARSH, J. L. See Fuson, R. C.
MARSHALL, C. E., AND KRINBILL, C. A. Electrochem. properties of mineral membranes (V) beidellite membranes and detn. of Na..... 1814
MARSON, H. W. See Anderson, G. W.; Winnek, P. S.
MARTIN, D. R. See Booth, H. S.
MARVEL, C. S., AUDRIETH, L. F., AND SHARKEY, W. H. Non-peroxide catalysts for reacn. between SO_2 and olefins..... 1229
MARVEL, C. S., AND FRANK, R. L. Copolymerization of alkyl acrylates and alkyl maleates—some kinetic studies on copolymerization..... 1675
MARVEL, C. S., AND HIMEL, C. M. Dissocn. of hexaarylethanes (XIV) ethanes derived from mixts. of triaryl halides..... 2227
MARVEL, C. S., JONES, G. D., MASTIN, T. W., AND SCHERTZ, G. L. Structure of copolymers of vinyl chloride and vinyl acetate..... 2356
MARVEL, C. S., RIDDLE, E. H., AND CORNER, J. O. Structure of vinyl polymers (XII) polymer of Me isopropenyl ketone..... 92
MARVEL, C. S., SHACKLETON, J. W., HIMEL, C. M., AND WHITSON, J. Dissocn. of hexaarylethanes (XII) effect of naphthyl and biphenyl groups..... 1824
MASON, J. P. See Malkiel, S.
MASON, C. M. See Wilson, W. K.
MASON, H. S., AND SCHWARTZ, L. Toxic principles of poison ivy..... 3058
MASTERS, E. J., AND BOGERT, M. T. Researches on thiazoles (XXV) some new thiazolidinopyrimidines of barbituric acid type, 2709; (XXVI) some acyl derivs. of 2-aminothiazole..... 2712
MASTERSON, J. P. See Vernon, A. A.
MASTIN, T. W. See Marvel, C. S.
MATCHETT, J. R. See Wollner, H. J.
MATTHEWS, W. H., JR. See Henze, H. R.
MAUERSBERGER, H. R. See Merrill, G. R.
MAXWELL, C. E. See Blicke, F. F.
MEAD, D. J., AND FUOSS, R. M. Viscosities of solns. of polyvinyl chloride, 277; elec. properties of solids (XIII) polymethyl acrylate, polymethyl methacrylate, polymethyl-α-chloracrylate and polychloroethyl methacrylate..... 2389
MEAD, D. J., TICHENOR, R. L., AND FUOSS, R. M. Elec. properties of solids (XII) plasticized polyvinyl chloride..... 283
MEE, A. J. Higher Chem. Calcns. (book review)... 1012
MEIER, H. F. See Darken, L. S.
MELDRUM, W. B. See Gucker, F. T., Jr.
MELLOR, D. P. See Mills, J. E.
MELOY, C. R. See Huston, R. C.
MELTON, J. W. See Henze, H. R.

MELTSNER, M. See Kremer, C. B.
MELVILLE, D. B. See du Vigneaud, V.
MENOTTI, A. R. See Kreider, H. R.
DE MENT, J. Fluorescent Chem. and their Applications (book review)..... 1983
MERRILL, G. R., MACORMAC, A. R., AND MAUERSBERGER, H. R. American Cotton Handbook (book review)..... 1014
MERTES, R. W. See Crowell, W. R.
METCALF, E. A. See Wolfrom, M. L.
MEYER, R. E. See Whitmore, F. C.
MICHAELIS, L., AND GRANICK, S. Extension of the acidity scale..... 1861
MICHELL, J. H., AND PURVES, C. B. Probable structure of a crystalline substance derived from starches oxidized with periodate, 585; reacn. between peroxidate oxidized starch and MeOH containing HCl..... 589
VON MIKUSCH, J. D. Solid 10,12-octadecadienoic acid-1—a new conjugated linoleic acid melting at 57°..... 1580
MILLER, A. See Coleman, G. H.
MILLER, C. S. See Moore, M. L.
MILLER, E., CROSSLEY, F. S., AND MOORE, M. L. Synthesis of *p*-hydroxyphenyl amyl sulfide..... 2322
MILLER, E. E. See Roebuck, J. R.
MILLER, F. A. Prepn. of several D derivs. of pyrrole..... 1543
MILLER, H. C. See Smith, L. I.
MILLER, J. G. Measurement of dielec. consts. by the comparison method—dielec. const. of CCl_4 from 15 to 40°..... 117
MILLER, M. W. See Adams, R.
MILLER, W. H., AND DAWSON, C. R. Factors influencing the cresolase activity of tyrosinase—effect of gelatin and *p*-cresol concn..... 2344
MILLIGAN, W. O. See Weiser, H. B.
MILLS, J. E., AND MELLOR, D. P. Absorption spectra of para- and diamagnetic Ni complexes... 181
MISANI, F. See Gates, M. D.
MITCHELL, J. H., JR., AND KRAYBILL, H. R. Formation of conjugated material during bleaching of vegetable oils..... 988
MOELLER, T. Contribution to chemistry of In (V) hydrolysis consts. for In tribromide and triiodide solns., 953; basic In salicylates..... 2234
MOELWYN-HUGHES, E. A. Phys. Chemistry, an Introduction (book review)..... 730
MOFFETT, S. M. See Wolfrom, M. L.
MONTGOMERY, E. M., AND HUDSON, C. S. Crystalline modifications of D-manno-D-gala-heptose, and prepn. of some of its derivs..... 247
MONTGOMERY, E. M., RICHTMYER, N. K., AND HUDSON, C. S. Prepn. and rearrangement of phenylglycosides, 690; D-mannosan<1,5>β<1,6> from β-Ph-D-mannoside..... 1483
MONTGOMERY, J. B., AND DE VRIES, T. Heat capacity of org. vapors (III) comparison of flow calorimeters, 2372; (IV) benzene, fluorobenzene, toluene, cyclohexane, methylcyclohexane and cyclohexane. 2375
MOORE, D. H. Effect of urea on electrophoretic patterns of serum proteins..... 1090
MOORE, G. E. See Southard, J. C.
MOORE, G. E., AND KELLEY, K. K. Sp. heats at low temps. of anhydr. sulfates of Fe, Mg, Mn and K.. 2949
MOORE, M. L. See Miller, E.
MOORE, M. L., AND MILLER, C. S. Dicarboxylic acid derivs. of sulfonamides..... 1572
MOORE, S. See Stein, W. H.
MOORE, T. E., AND WATT, G. W. Reacns. of Co(III), Co(II), and Fe(II) oxides in liquid NH_3... 2772
MOORE, W. J. See Hughes, E. W.
MORAN, J. See Arnold, R. T.
MORGAN, P. W. See Wolfrom, M. L.
MORRELL, J. See Berkman, S.
MORRIS, H., BYERLY, W., AND SELWOOD, P. W. Tri-*o*-tolyltin and the instability of org.-metallic free radicals..... 1727
MORROW, R. W. See Hazlet, S. E.
MORTON, A. A. Reviews of "A Shorter Course in Org. Chemistry" (Colbert), and "Introductory Org. Chemistry" (Wertheim)..... 3063
MORTON, A. A., DAVIDSON, J. B., AND BEST, R. J. Condensations by Na (XXI) *n*-octyl- and *n*-decylsodium..... 2239
MORTON, A. A., DAVIDSON, J. B., GIBB, T. R. P., JR., LITTLE, E. L., CLARKE, E. F., AND GREEN, A. G. Condensations by Na (XXV) reacns. of amylsodium with naphthalene, acenaphthene and decalin, 2250, (corrn.)..... 3073
MORTON, A. A., DAVIDSON, J. B., AND HAKAN, B. L. Condensations by Na (XXIII) general theory of the Wurtz reacn. (II) second phase..... 2242
MORTON, A. A., DAVIDSON, J. B., AND NEWEY, H. A. Condensations by Na (XXII) general theory of the Wurtz reacn.—initial step..... 2240
MORTON, A. A., AND NEWEY, H. A. Condensations by Na (XXIV) pyrolysis of amylsodium..... 2247
MOWAT, J. H. See Stevens, P. G.
MÜLLER, O. H. Polarographic Method of Analysis (book review)..... 1983
MUNDY, B. W. See Billman, J. H.
MURPHY, M. T. See Rice, F. O.
MURRAY, M. J. See Saunders, R. H.
MURRAY, M. J., CLEVELAND, F. F., AND SAUNDERS, R. H. Raman spectra of some aromatic carbonyl and nitro compds..... 1181
MURRAY, W. S. See Hennion, G. F.
MURRELL, T. A. See Roebuck, J. R.
MYERS, R. R. See Smith, H. A.

NAHINSKY, P. See Ruben, S.
NAHINSKY, P., RICE, C. N., RUBEN, S., AND KAMEN, M. D. Tracer studies with radioactive C—synthesis and oxidation of several 3 C acids..... 2299
NATELSON, S., AND GOTTFRIED, S. P. Synthesis of derivs. of diphenylethane related to materials occurring naturally (IV) stilbene-2-acetic acid.... 2962
NATELSON, S., GOTTFRIED, S. P., AND KORNBLAU, S. 3,7-Dimethyloctene-2..... 1484
NATHANAEL, W. R. N. See Child, R.
NELSON, J. M. Review of "Die Fermente und ihre Wirkungen" (Oppenheimer), 1014; see Dills, W. L.
NELSON, J. W. See McElvain, S. M.
NELSON, O. A. See Smith, L. E.
NELSON, O. A., AND SMITH, L. E. F. ps. of binary mixts. of diphenylamine and other org. compds., 1057; vapor pressure of phenothiazine..... 3035
NESS, A. B. See Bachmann, W. E.
NESS, A. T., HANN, R. M., AND HUDSON, C. S. Structure of diacetone-L-fucitol (2,3,4,5-di-isopropylidene-L-fucitol)..... 982
NESSE, G. J. See Ricci, J. E.
NEUBERG, C., AND LUSTIG, H. Prepn. of *d*-fructose-1,6-diphosphate by means of baker's yeasts..... 2722
NEWEY, H. A. See Morton, A. A.
NEWKIRK, J. D. See Aston, J. G.
NEWMAN, M. S. Enolization in the Reformatsky reacn., 2131; mechanism for formation of anthraquinone from *o*-benzoylbenzoic acid..... 2324
NEWSOME, P. T. See Sheppard, S. E.
NEWTON, L. W. See Fieser, L. F.
NEY, L. F. See Carter, H. E.
NICHOLS, A. R., JR., AND WALTON, J. H. Autoxidation of $Mn(OH)_2$..... 1866
NICHOLS, J. See Kass, J. P.
NICHOLSON, D. G. Adsorption of simple and complex Co ions on TiO_2..... 2820
NIEDERL, J. B., AND HART, W. F. Phenylmercaptothiazolines..... 2487
NIEDERL, J. B., AND NIEDERL, V. Micromethods of Quant. Org. Analysis (book review)..... 2729
NIEDERL, J. B., AND ZIERING, A. Unsym. cyanostilbenes, 885; *sym.* cyanostilbenes..... 2486
NIEDERL, V. See Niederl, J. B.
NIELSEN, L. E. See Redlich, O.

NIEMANN, C., AND HAYS, J. T. Relation between structure and histamine-like activity..... 2288
NIEMANN, C., LEWIS, R. N., AND HAYS, J. T. Synthesis of 3 isomeric *dl*-β-pyridylalanines..... 1678
NIGHTINGALE, D., RADFORD, H. D., AND SHANHOLTZER, O. G. Orientation effects in alkylation of *m*-xylene by various procedures and reagents.. 1662
NOLLER, C. R. See Lieberman, S.
NOLLER, C. R., AND CASTRO, A. J. Composition of alkylmagnesium chloride solns. in Et ether..... 2509
NOLLER, C. R., SMITH, R. A., HARRIS, G. H., AND WALKER, J. W. Saponins and sapogenins (XX) some color reacns. of triterpenoid sapogenins..... 3047
NOONAN, T. R. See Langley, W. D.
NORD, F. F., AND WERKMAN, C. H. Advances in Enzymology and Related Subjects (book review). 1744
NORRIS, T. H., RUBEN, S., AND ALLEN, M. B. Tracer studies with radioactive H—some expts. on photosynthesis and chlorophyll..... 3037
NORTHEY, E. H., PIERCE, A. E., AND KERTESZ, D. J. Sulfanilamide derivs. (VIII) sulfanilylamidines... 2763
NOVELLO, F. C. See Fieser, L. F.
NOYES, A. A., AND SWIFT, E. H. A Course of Instruction in the Qual. Chem. Analysis of Inorg. Substances (book review)..... 2522
NOYES, W. A., JR. See Davis, W., Jr.
NOYES, W. A., JR., AND LEIGHTON, P. A. Photochemistry of Gases (book review)..... 476
NOZAKI, K. Catalytic interchange of groups in aliphatic amines (I)..... 2920
NOZAKI, K., AND OGG, R. A., JR. Halogen addn. to ethylene derivs. (I) Br addns. in presence of bromide ions, 697; (II) mechanism of the halide ion catalyzed addn. reacn., 704; (III) Br and I addn. in glacial AcOH..... 709
NUTTING, G. C. See Long, F. A.

OAKWOOD, T. S. See Marker, R. E.
O'BRIEN, S. J. Partial pressure of HCl from its solns. in β,β′-dichloroethyl ether and in anisole and the calcn. of the heat and entropy of soln..... 951
OESPER, P. F. See Turkevich, J.
OESPER, P. F., LEWIS, G. L., AND SMYTH, C. P. Dipole moment and resonance in heterocyclic mols. containing N and S..... 1130
OESPER, P. F., AND SMYTH, C. P. Dipole moments and structures of 5 org.-metallic halides, 173; dipole moments and structures of diketene and of certain acid anhydrides and related O and S compds..... 768
OESPER, P. F., SMYTH, C. P., AND KHARASCH, M. S. Reduction of dipole moment by steric hindrance in di-*t*-butylhydroquinone and its dimethyl ether.... 937
OGG, R. A., JR. See Blaedel, W. J.; Nozaki, K.
OLMER, F. G. See Thomas, L. B.
ONCLEY, J. L. Review of "The Amphoteric Properties of Proteins" (Cannon, *et al.*)..... 2237
O'NEILL, W. E. See Storch, H. H.
ONETO, J. F. See Way, E. L.
ONSAGER, L. Review of "Dielectrics" Vol. XL, N. Y. Acad. Sci..... 1238
OPIE, J. W. See Smith, L. I.
OPPENHEIMER, C. Die Fermente und ihre Wirkungen (book review)..... 1014
OPSAHL, J. C., AND ARNOW, L. E. Optical configuration of glutamic acid isolated from casein hydrolyzates by 6 procedures..... 2035
ORLEMANN, E. F., AND KOLTHOFF, I. M. Anomalous electroreduction of water at dropping Hg electrode in relatively concd. salt solns., 833; reduction of iodate and bromate in acid medium at the dropping Hg electrode, 1044; reduction of iodate and bromate at the dropping Hg electrode in neutral and basic media and the effects of salts on the current–voltage curves..... 1970
OSBORNE, D. W. See Russell, H., Jr.
OSBORNE, D. W., DOESCHER, R. N., AND YOST, D. M. Heat capacity, heats of fusion and vaporization, vapor pressure and entropy of dimethyl sulfide.... 169
OWEN, B. B., AND BRINKLEY, S. R., JR. Elimination of liquid junction potentials (IV) conditions of extrapolation..... 2071
OWEN, K., QUAYLE, O. R., AND CLEGG, W. J. Study of org. parachors (V) constitutive variations of the parachors of a series of normal ketones..... 1294
OWEN, L. N., AND SIMONSEN, J. L. Barbaloin..... 2516
OXFORD, A. E. See Fieser, L. F.

PACSU, E. Review of "Phys. and Chem. Methods of Sugar Analysis" (Browne, Zerban)..... 1014
PADGITT, F. L. See Amis, E. S.
PADGITT, F. L., AMIS, E. S., AND HUGHES, D. W. B. p.–compn. data of MeOH–dioxane system..... 1231
PALKIN, S. See Joshel, L. M.
PALMER, W. G. Exptl. Phys. Chemistry (book review)..... 3065
PAPADAKIS, P. E. Absorption spectra and X-ray examn. of isomeric glucononitriles..... 1950
PAPE, N. R. See Baker, W. O.; Fuller, C. S.
PARKE, T. V., JR. See Davis, W. W.
PARKS, G. S. See Kiperash, M.
PATTERSON, A., AND FELSING, W. A. Molal electrode potential of the Ag–AgCl electrode in EtOH–H_2O mixts., 1478; ionization consts. of propionic acid in MeOH and EtOH–H_2O mixts. from 0–40°..... 1480
PATTERSON, J. W. Ultraviolet absorption spectra of coronene..... 1485
PAULING, L. See Gordy, W.; Pressman, D.
PAULING, L., GORDY, W., AND SAYLOR, J. H. Electron diffraction investigation of propargyl chloride, bromide and iodide..... 1753
PAULING, L., PRESSMAN, D., CAMPBELL, D. H., AND IKEDA, C. Serological properties of simple substances (II) effects of changed conditions and of added haptens on pptn. reacns. of polyhaptenic simple substances..... 3003
PAULING, L., PRESSMAN, D., CAMPBELL, D. H., IKEDA, C., AND IKAWA, M. Serological properties of simple substances (I) pptn. reacns. between antibodies and substances containing two or more haptenic groups..... 2994
PAULING, L., PRESSMAN, D., AND IKEDA, C. Serological properties of simple substances (III) compn. of ppts. of antibodies and polyhaptenic simple substances; the valence of antibodies..... 3010
PAULSON, M. C. See Tarbell, D. S.
PEARL, I. A. Vanillin from lignin materials..... 1429
PEARSON, R. See Evans, W. V.
PEASE, R. N. Equil. and Kinetics of Gas Reacns. (book review), 3064; see Burnham, H. D.; Robertson, N. C.
PECK, R. L. Inhibition of proteolytic action of trypsin by soaps..... 487
PEDLOW, G. W., JR. See Whitmore, F. C.
PENNINGTON, D., SNELL, E. E., AND EAKIN, R. E. Crystalline avidin..... 469
PERRY, J. H. Chem. Engineers' Handbook (book review)..... 190
PETERS, C. F. See Snyder, H. R.
PFISTER, K., 3RD. See Huntress, E. H.
PFISTER, K. H. T. See Huntress, E. H.
PHILLIPS, B. A., WATSON, G. M., AND FELSING, W. A. Activity coeffs. of $SrCl_2$ by an isopiestic method..... 244
PHILLIPS, C. J. Glass: The Miracle Maker (book review)..... 729
PHILLIPS, M. A. *bis*-Benzimidazoles..... 187
PHILLIPS, R. F. See Adams, R.
PIERCE, A. E. See Northey, E. H.
PIERCE, J. S., SALSBURY, J. M., AND FREDERICKSEN, J. M. Local anesthetics (I) β-monoalkylaminoethyl esters of alkoxybenzoic acids..... 1691
PIERCE, J. S., SALSBURY, J. M., HADEN, W. W., AND WILLIS, L. H. Local anesthetics (II) alkoxy-

benzoates of 2-monoalkylamino-2-Me-1-propanols and 2-monoalkylamino-1-butanols..... 2884
PIERONEK, V. R. See Hennion, G. F.
PIGMAN, W. W., AND RICHTMYER, N. K. Influence of structural changes in the aglucons on the enzymic hydrolysis of alkyl β-D-glucosides, 369; action of almond emulsin on populin and on Ph 2,4,6-trimethyl-β-D-glucoside..... 374
PINES, H., GROSSE, A. V., AND IPATIEFF, V. N. Alkylation of paraffins at low temps. in presence of $AlCl_3$..... 33
PINGERT, F. P. See Allen, C. F. H.
PLATI, J. T. See Strain, W. H.
PLETCHER, D. E. See Wolfrom, M. L.
POLGÁR, A., AND ZECHMEISTER, L. Isomerization of β-carotene—isolation of a stereoisomer with increased adsorption affinity, 1856, (corrn.)..... 3071
POPKIN, A. H. See Whitmore, F. C.
PORTER, H. D. See Weissberger, A.
POWELL, G. See Bembry, T. H.; Block, P., Jr.
PREISLER, P. W., AND BERGER, L. Prepn. of tetrahydroxyquinone and rhodizonic acid salts from the product of oxidation of inositol with HNO_3.... 67
PRESSMAN, D. See Pauling, L.
PRESSMAN, D., BREWER, L., AND LUCAS, H. J. Hydration of unsatd. compds. (IX) oxonium complex const. of mesityl oxide, 1117; (X) role of oxonium complexes in hydration of mesityl oxide and dehydration of diacetone alc..... 1122
PRESSMAN, D., BROWN, D. H., AND PAULING, L. Serological properties of simple substances (IV) hapten inhibition of pptn. of antibodies and polyhaptenic simple substances..... 3015
PRESSMAN, D., AND LUCAS, H. J. Hydration of unsatd. compds. (XI) acrolein and acrylic acid... 1953
PRICE, C. C. Review of "High Polymeric Reacns., Their Theory and Practice" (Mark, Raff), 1015; see Fuson, R. C.
PRICE, C. C., CHAPIN, E. C., AND RIEGER, M. Reacn. of furoic acid with aromatic compds..... 2227
PRICE, C. C., AND DENO, N. C. Reacn. of furoic acid with tetralin..... 2601
PRICE, C. C., AND DURHAM, D. A. Polymerization of styrene catalyzed by *p*-bromobenzenediazonium hydroxide..... 2508
PRICE, C. C., AND FANTA, P. E. *sym-p,p'*-Dichlorotetraphenylethylene..... 2726
PRICE, C. C., AND HUBER, C. F. Reacn. of Me furoate with benzene and chlorobenzene..... 2136
PRICE, C. C., KELL, R. W., AND KREBS, E. Addn. polymerization catalyzed by substituted acyl peroxides..... 1103
PRICE, C. C., AND KNELL, M. Kinetics of the periodate oxidation of 1,2-glycols (II) ethylene glycol, pinacol and *cis-* and *trans*-cyclohexene glycols.... 552
PRICE, C. C., AND TOMISEK, A. J. *dl-* and *meso-*γ,γ'-Diphenyl-γ,γ'-suberodilactone..... 2727
PURVES, C. B. See Gardner, T. S.; Mahoney, J. F.; Michell, J. H.

QUARRELL, A. G. See Chalmers, B.
QUATTLEBAUM, W. M., JR., AND CORWIN, A. H. Synthesis of unsym. N-Me-dipyrrylmethanes..... 922
QUAYLE, O. R. See Owen, K.
QUAYLE, O. R., AND ROYALS, E. E. A kinetic study of the reacns. of *n*-BuBr with Na salts of phenol, thiophenol and *n*-Bu mercaptan..... 226

RAASCH, M. S. See Brode, W. R.
RAASCH, M. S., AND BRODE, W. R. Optically active phenylurethan anesthetic..... 1112
RABINOWITCH, E., AND STOCKMAYER, W. H. Assocn. of ferric ions with chloride, bromide and hydroxyl ions (a spectroscopic study)..... 335
RACHLIN, A. I. See Fuson, R. C.
RADFORD, H. D. See Nightingale, D.
RADIKE, A. See Billman, J. H.
RADLOVE, S. B. See Kass, J. P.
RAFF, R. See Mark, H.
RAINEY, W. T., JR. See Williams, J. W.
RAIZISS, G. W., AND FREIFELDER, M. N^1-Sulfanilylamino-alkyl-pyrimidines..... 2340
RALSTON, A. W. See Dorinson, A.; Hoerr, C. W.; Hoffman, E. J.
RALSTON, A. W., AND HOERR, C. W. Studies on high mol. wt. alphatic amines and their salts (VI) elec. conductivities of aq. soln. of the hydrochlorides of octyl-, decyl-, tetradecyl- and hexadecylamines..... 772
RALSTON, A. W., HOERR, C. W., AND HOFFMAN, E. J. Studies on high mol. wt. aliphatic amines and their salts (IV) elec. conductivities of aq. solns. of the hydrochlorides and acetates of dodecyl- and octadecylamines, 97; (VII) systems octylamine–, dodecylamine– and octadecylamine–water..... 1516
RANDALL, D. I. See Whitmore, F. C.
RANDALL, M., AND YOUNG, L. E. Elementary Phys. Chemistry (book review)..... 3059
RASMUSSEN, H. E. See Ewing, W. W.
RAY, W. A. See Jones, G.
REDEMANN, C. E. Peroxides in isopropanol..... 3049
REDLICH, O., AND BIGELEISEN, J. Molal vols. of solutes (VI) $KClO_3$ and HCl..... 758
REDLICH, O., AND NIELSEN, L. E. Molal vols. of solutes (VII) NaOAc and AcOH..... 761
REEVES, L. H. See Edwards, W. R., Jr.
REEVES, R. F., AND LINDWALL, H. G. Action of Grignard reagents on benzoylformanilides..... 1086
REID, E. E. Review of "Anhyd. $AlCl_3$ in Org. Chemistry" (Thomas), 1743; see Clayton, W. R.
REID, E. E., AND WILSON, E. Some mono- and dialkyl ethers of stilbestrol..... 1625
REIMER, M. Prepn. of phenylpropiolic acid..... 2510
REIMS, A. O. See Buchman, E. R.
RENFROW, W. B., JR. See Smith, L. I.
RENOLL, M. W. New method of synthesizing aliphatic difluorides, 1115; F derivs. of biphenyl... 1489
RENS, G. See Luyckx, A.
REYNOLDS, D. D., AND KENYON, W. O. Synthesis of some new glucose and gentiobiose derivs..... 1110
RHODES, F. H. Tech. Report Writing (book review)..... 3063
RHODES, T. J. Industrial Instruments for Measurement and Control (book review)..... 728
RICCI, J. E. See Selikson, B.
RICCI, J. E., AND NESSE, G. J. Soly. of KIO_3 and $Zn(IO_3)_2$ in dioxane–water mixts.; effect of sorting of solvent mols..... 2305
RICCI, J. E., AND WELTMAN, C. Some isotherms of the system Na_2CrO_4–$NaClO_3$–H_2O..... 2746
RICE, C. N. See Nahinsky, P.
RICE, F. O., AND MURPHY, M. T. Thermal decompn. of 5-membered rings..... 896
RICE, F. O., AND STALLBAUMER, A. L. Decompn. of cyclohexene oxide and 1,4-cyclohexadiene from the standpoint of the principle of least motion.... 1527
RICHTMYER, N. K. See Montgomery, E. M.; Pigman, W. W.
RICHTMYER, N. K., AND HUDSON, C. S. Oxidative degradation of L-glucoheptulose, 1609; a benzimidazole rule for detn. of configuration of aldonic acids and related compds..... 1612
RIDDLE, E. H. See Marvel, C. S.
RIEBSOMER, J. L., STAUFFER, D., GLICK, F., AND LAMBERT, F. Prepn. of substituted mandelic acids and their bacteriological effects (III)..... 2080
RIEGEL, B., DUNKER, M. F. W., AND THOMAS, McC. J. Prepn. and dehydration of 6-methoxy-*i*-norcholenyldiphenylcarbinol..... 2115
RIEGEL, B., GOLD, M. H., AND KUBICO, M. A. Method for synthesis of certain 2-substituted phenanthrenes..... 2221
RIEGEL, B., AND WITTCOFF, H. Prepn. of acetylsalicylyl disulfide and salicylyl disulfide..... 1486
RIEGER, M. See Price, C. C.
RIEMAN, W., III. See McComas, W. H., Jr.

RIENER, T. W. See Bruson, H. A.
RITTER, J. J., AND VLASES, G., JR. Inactivation in the camphene series..... 583
ROBERTS, J. D. See McMillan, W. G., Jr.
ROBERTS, J. D., YOUNG, W. G., AND WINSTEIN, S. Allylic rearrangements (XIII) kinetics and mechanisms of conversion of crotyl and methylvinylcarbinyl chlorides to acetates and Et ethers..... 2157
ROBERTS, R. M. Heat of org. reacns. (XII) reacn. between methemoglobin and salicylate, 1472; see Conn, J. B.; Haugaard, G.
ROBERTS, S. M. See Shive, B.
ROBERTSON, N. C., AND PEASE, R. N. Kinetics of thermal reacn. between H and cyanogen..... 1880
ROBESON, C. D. Crystalline natural α-tocopherol acetate, 1487; see Baxter, J. G.
ROBINSON, R. A., WILSON, J. M., AND AYLING, H. S. Activity coeffs. of some bivalent metal nitrates in aq. solns. at 25° from isopiestic vapor pressure measurements..... 1469
ROBINSON, R. J. See Zwicker, B. M. G.
ROBLIN, R. O., JR. See Anderson, G. W.; Bell, P. H.; English, J. P.; Winnek, P. S.
ROBLIN, R. O., JR., WINNEK, P. S., AND ENGLISH, J. P. Studies in chemotherapy (IV) sulfanilamidopyrimidines..... 567
ROE, C. P., AND EWART, R. H. Electrophoretic study of proteins in rubber latex serum..... 2628
ROEBUCK, J. R., MURRELL, T. A., AND MILLER, E. E. Joule–Thomson effect in CO_2..... 400
ROEPKE, R. R. See Bingham, E. C.
ROGERS, E. F. See Adams, R.
ROGERS, E. M. See Mantell, C. L.
ROHRER, C. S., LANFORD, O. E., AND KIEHL, S. J. Study of heterogeneous equil. in aq. solns. of the sulfates of tetravalent V at 30°..... 2810
ROHRMANN, E. See Marker, R. E.
ROLLEFSON, G. K. See Anderson, H. W.; Roth, W. L.
RONZIO, A. R. See Fisher, H. J.; Waugh, R. C.
ROPER, E. E. Review of "Temp. Measurement" (Weber)..... 475
ROSEN, L. J. See Bartlett, P. D.
ROSENBAUM, J. J., AND CASS, W. E. 2-Phenyloxazole; para-substituted derivs..... 2444
ROSENBERG, H. R. Chemistry and Physiol. of the Vitamins (book review)..... 2522
ROSENSTEIN, L. See Jasper, J. J.
ROSEVEARE, W. E. See Edwards, A. E.
ROSS, W. F. Reviews of "Advances in Enzymology and Related Subjects" (Nord, Werkman), 1744; "Annual Review of Biochemistry" Vol. XI (Luck, Smith), 2522; see Wood, T. R.
ROTH, W. L., AND ROLLEFSON, G. K. Photolysis of Me acetate, 490; catalysis of thermal decompn. of acetaldehyde by H_2S..... 1707
ROWLAND, C. S. See Whitmore, F. C.
ROWLAND, S. P. See Fuson, R. C.
ROWLEY, H. H., AND HUBBARD, W. N. Mutarotation of α-D-glucose in dioxane–water mixts. at 25°. 1010
ROYALS, E. E. See Quayle, O. R.
RUBEN, S. See Allen, M. B.; Harman, D.; Nahinsky, P.; Norris, T. H.
RUBEN, S., ALLEN, M. B., AND NAHINSKY, P. Tracer studies with radioactive C—exchange between acetic anhydride and NaAc..... 3050
RUBEN, S., KAMEN, M. D., ALLEN, M. B., AND NAHINSKY, P. Some exchange expts. with radioactive tracers..... 2297
RUDDY, A. W., STARKEY, E. B., AND HARTUNG, W. H. Diazonium borofluorides (III) their use in the Bart reacn..... 828
RUIGH, W. L. 7-Dehydrocampesterol, a new provitamin D, 1900; see Wintersteiner, O.
RUNDLE, R. E. See French, D.
RUOFF, P. M. See Hirschy, H. W.
RUSSELL, A., AND GULLEDGE, H. C. Vicinal substituted resorcinols (II) alkylresorcinols—synthesis of γ-*n*-hexyl, γ-*n*-heptyl and γ-*n*-octyl-resorcinols..... 1313
RUSSELL, A., AND HAPPOLDT, W. B., JR. Constitution of natural tannins (VIII) coloring matters derived from anthracene-9-aldehyde..... 1101
RUSSELL, A., AND TEBBENS, W. G., JR. Chem. constitution and the tanning effect (I) simple esters and polyesters of gallic acid..... 2274
RUSSELL, H., JR., OSBORNE, D. W., AND YOST, D. M. Heat capacity, entropy, heats of fusion, transition and vaporization and vapor pressures of Me mercaptan..... 165
RYAN, M. J. See Bartlett, P. D.

SAEGER, M. E. See Crawford, H. M.
SAFFER, A., AND DAVIS, T. W. Products from the Wurtz reacn. and mechanism of their formation, 2039, (corrn.)..... 3071
SAGENKAHN, M. See Schumann, S. C.
SAH, P. P. T. Synthesis of 4,4′-diamidinostilbene hydrochloride, 1487; see Fu, S.-C.
SALSBURY, J. M. See Pierce, J. S.
SAMPEY, J. R. See Hicks, E. M.
SAND, H. J. S. Electrochemistry and Electrochem. Analysis (book review)..... 2728
SARGENT, H., BUCHMAN, E. R., AND FARQUHAR, J. P. Constitution of pirylene: chem. evidence..... 2692
SARVER, L. A. See Yoe, J. H.
SATTLER, L. See Zerban, F. W.
SAUNDERS, R. H. See Murray, M. J.
SAUNDERS, R. H., MURRAY, M. J., AND CLEVELAND, F. F. Assocn. effects in Raman spectra of solns. of thiophenol in donor solvents..... 1230
SAVOY, C. M. S., AND ABERNETHY, J. L. Halogenation of certain esters in the biphenyl series (I) chlorination of 4-PhPhAc, 2219; (II) chlorination of 4-PhPh benzoate and 4-PhPh benzenesulfonate. 2719
SAYLES, D. C. See Kharasch, M. S.
SAYLOR, J. H. See Pauling, L.
SAYLOR, J. H., BAXT, V. J., AND GROSS, P. M. Soly. studies (VII) solubilities of some isomeric ketones in water..... 2742
SAYLOR, J. S. See Smull, J. G.
SAYWARD, J. M. See Kienle, R. H.
SCHAFFEL, G. S. See Stempel, G. H., Jr.
SCHALES, O. Prepn. and properties of renin..... 561
SCHAPIRO, D. See Bergmann, F.
SCHECHTER, M. S., AND HALLER, H. L. Identity of the red pigment in roots of *Tripterygium wilfordii* and *Celastrus scandens*..... 182
SCHENCK, L. M., AND HENZE, H. R. Sulfanilamido derivs. of N bases from Calif. petroleum..... 1499
SCHERTZ, G. L. See Marvel, C. S.
SCHIRMER, F. B., JR. See Steinman, R.
SCHIRMER, F. B., JR., AUDRIETH, L. F., GROSS, S. T., MCCLELLAN, D. S., AND SEPPI, L. J. Compn. and structure of Mo blue..... 2543
SCHLATTER, M. J. Reacn. between thioamides and primary amines, 2722; see Buchman, E. R.
SCHLESINGER, H. I. See Brown, H. C.
SCHMITT, F. O. See Hall, C. E.
SCHMUCK, R. F. See Trimble, H. M.
SCHOCH, T. J. Non-carbohydrate substances in cereal starches, 2954; fractionation of starch by selective pptn. with BuOH..... 2957
SCHOCH, T. J., WILSON, E. J., JR., AND HUDSON, C. S. Stability of β-methylmaltoside toward hot alkali. 2871
SCHOENHEIMER, R. Dynamic State of Body Constituents (book review)..... 2523
SCHOMAKER, V. See Spitzer, R.; Spurr, R.; Stevenson, D. P.
SCHOMAKER, V., AND SPURR, R. Structures of N_2O and of H azide..... 1184
SCHROEDER, O. C. See Cromwell, N. H.
SCHROEDER, W. A. Formation of pro-carotenoids in "monkey flowers" under some conditions, 2510; see Zechmeister, L.
SCHULTZ, E. See Arnold, R. T.

SCHULTZ, M. L., AND LILEK, E. F. Absorption spectra of some double salts containing $CoCl_2$..... 2748
SCHULTZE, H. C. See Bost, R. W.
SCHUMANN, S. C. See Aston, J. G.
SCHUMANN, S. C., ASTON, J. G., AND SAGENKAHN, M. Heat capacity and entropy, heats of fusion and vaporization and vapor pressures of isopentane, 1039, (corrn.)..... 3069
SCHWARTZ, L. See Mason, H. S.
SCHWENK, E., AND BLOCH, E. Prepn. of β-(2-Me-6-oxo-1-cyclohexen-1-yl) propionic acid, 3050; a new modification of Willgerodt's reacn..... 3051
SCHWOB, C., BIEGNER, J. E., CARSON, K. J., AND SCOTT, G. V. Catalytic properties of charcoal (IV) factors influencing the indophenol reacn..... 2276
SCOTT, A. F., AND BUNNETT, J. F. A dioxanate of IF_5..... 2727
SCOTT, A. W., AND ANDREWS, J. T. Some allyl nitrophenyl thiosemicarbazides and their anal. properties..... 2873
SCOTT, G. V. See Schwob, C.
SCOTT, L. D. See Audrieth, L. F.
SCOTT, S. L. See Fuson, R. C.
SEEGER, D. R., AND MACMILLAN, A. Further study of the cyclization of ureido derivs. of unsym. imino dibasic acids together with the synthesis of certain hydantoins and other related compds..... 1686
SEELIG, H., AND HULL, D. E. Exchange reacn. between simple alkyl iodides and iodide ion..... 940
SEGESSER, J. R. See Calvin, M.
SEGESSER, J. R., AND CALVIN, M. Prepn. of 4-nitrosalicylaldehyde..... 825
SEIDELL, A. Solubilities of Org. Compds. (book review)..... 1014
SELIKSON, B., AND RICCI, J. E. System $NaNO_3$–dioxane–H_2O at 25°..... 2474
SELTZ, H., AND DUNKERLEY, F. J. Thermodynamic study of the Sn–Bi system..... 1392
SELWOOD, P. W. See Byerly, W.; Morris, H.
SEPPI, L. J. See Schirmer, F. B., Jr.
SEWARD, R. P. Soly. of Na_2CO_3 in fused NaOH..... 1053
SEYER, W. F., AND LESLIE, J. D. Viscosity of *cis*- and *trans*-decahydronaphthalene..... 1912
SHABICA, A. C. See Marker, R. E.
SHACKLETON, J. W. See Marvel, C. S.
SHANHOLTZER, O. G. See Nightingale, D.
SHAPIRO, H. See Calingaert, G.
SHAPIRO, S. H. See McElvain, S. M.
SHARKEY, W. H. See Marvel, C. S.
SHAVEL, J., JR. See Folkers, K.
SHAW, E. N. See Thompson, A. F., Jr.
SHEFFIELD, E. See French, H. S.
SHEPHERD, R. G., BRATTON, A. C., AND BLANCHARD, K. C. Properties of the N–C–N system in N^1-heterocyclic sulfanilamides..... 2532
SHEPPARD, S. E., AND NEWSOME, P. T. Effect of solvents on absorption spectra of dyes (II) some dyes other than cyanines..... 2937
SHEPPARD, S. E., NEWSOME, P. T., AND BRIGHAM, H. R. Some effects of solvents on absorption spectra of dyes (I) chiefly polymethine dyes..... 2923
SHERWOOD, D. W., AND CALVIN, M. Resonance in substituted biphenyls..... 1350
SHIVE, B. See Wash, G.
SHIVE, B., HORECZY, J., WASH, G., AND LOCHTE, H. L. "Trans" - 2,2,6 - trimethylcyclohexanecarboxylic acid: a second solid naphthenic acid from Calif. petroleum..... 385
SHIVE, B., ROBERTS, S. M., MAHAN, R. I., AND BAILEY, J. R. N compds. in petroleum distillates (XXIII) structure of a $C_{16}H_{25}N$ base from Calif. petroleum..... 909
SHOMATE, C. H. See Southard, J. C.
SHRINER, R. L., AND GROSSER, F. Coumaran derivs. (IX) synthesis of 3,4,6,3′,4′-pentahydroxy-2-benzylcoumaran..... 382
SHRINER, R. L., AND STEPHENSON, R. W. Synthesis of tectorigenin dimethyl ether..... 2737
SHRINER, R. L., AND UPSON, R. W. *bis*-Benzimidazoles..... 187
SICKMAN, D. V. Review of "Equil. and Kinetics of Gas Reacns." (Pease)..... 3064
SIGERIST, H. E. Four Treatises of Theophrastus von Hohenheim Called "Paracelsus" (book review)..... 1237
SILVERMAN, A. Review of "Glass: The Miracle Maker" (Phillips)..... 729
SIMCHEN, A. E. See Bobtelsky, M.
SIMONS, J. H. See Sprauer, J. W.
SIMONS, J. H., AND WERNER, A. C. HF as a condensing agent (XVI) reacns. of CO..... 1356
SIMONSEN, J. L. See Owen, L. N.
SIMPSON, M. E. See Li, C.-H.
SIMPSON, S. G. Review of "Org. Reagents in Inorg. Analysis" (von Stein)..... 1984
SKEI, T. See Buchman, E. R.
SKELL, P., AND HAUSER, C. R. Reacns. of certain neopentyl systems with electrophilic reagents.... 2633
SKINNER, G. S., COGHLAN, C. A., AND BERLIN, A. S. *p*-Bromophenylhydroxymaleic imide..... 2600
SLOAT, T. K. See Whitmore, F. C.
SLOATMAN, W. S. See Whitmore, F. C.
SMILEY, W. G., AND SMITH, A. K. Electrode polarization in dielec. const. measurements..... 624
SMITH, A. K. See Smiley, W. G.
SMITH, C. M. See Adams, R.
SMITH, C. S. See Wolfrom, M. L.
SMITH, E. A. See Conn, J. B.
SMITH, E. R., AND TAYLOR, J. K. Change in potential of Ag–AgCl electrodes with time..... 3053
SMITH, G. McP. See Geyer, B. P.
SMITH, H. A., AND MYERS, R. R. Acid catalyzed hydrolysis of Ph substituted aliphatic esters..... 2362
SMITH, J. H. C. See Luck, J. M.
SMITH, L. E. See Nelson, O. A.
SMITH, L. E., AND NELSON, O. A. F. p. of phenothiazine..... 461
SMITH, L. I. Org. Syntheses (book review), 3063; review of "Chemistry and Physiol. of the Vitamins" (Rosenberg)..... 2522
SMITH, L. I., AND AUSTIN, F. L. Reacn. between quinones and enolates (XVI) dibromo-*o*-xyloquinone and Na malonic ester..... 528
SMITH, L. I., AND CARLIN, R. B. 3-Acetoxy-6-hydroxy-2,4,5-trimethylbenzylacetoacetic ester, and its transformation into chromene and chroman derivs., 435; structure of the chloromethylation product of trimethylhydroquinone diacetate.. 524
SMITH, L. I., KOLTHOFF, I. M., AND SPILLANE, L. J. Chemistry of vitamin E (XXXVII) amperometric titration of α-tocopherol with auric chloride at the dropping Hg electrode..... 646
SMITH, L. I., AND MILLER, H. C. Chemistry of vitamin E (XXXIII) a new synthesis of 6-hydroxychromans, including α-tocopherol..... 404
SMITH, L. I., AND RENFROW, W. B., JR. Chemistry of vitamin E (XXXIV) the 3 dimethylethyltocols. 445
SMITH, L. I., RENFROW, W. B., JR., AND OPIE, J. W. Chemistry of vitamin E (XXXVIII) α-tocopheramine, a new vitamin E factor, 1082; (XXXIX) Ca α-tocopheryl succinate..... 1084
SMITH, L. I., SPILLANE, L. J., AND KOLTHOFF, I. M. Chemistry of vitamin E (XXXV) behavior of tocopherols at dropping Hg electrode, 447; (XXXVI) behavior at dropping Hg electrode of quinones related to vitamin E..... 644
SMITH, L. I., AND SPRUNG, J. A. Chemistry of vitamin E (XXXI) 3,5-dinitrobenzazide as a reagent for prepn. of derivs. of tocopherols..... 433
SMITH, N. O. Hydration of $Al_2(SO_4)_3$..... 41
SMITH, R. A. See Noller, C. R.
SMITH, R. K. Olefin rearrangements—equil. of olefins from pinacolyl alc..... 1733
SMITH, W., AND WARING, C. E. Improved method for prepn. of benzenediazonium salts..... 469

SMULL, J. G., AND SAYLOR, J. S. Alkylation of linseed oil ... 3054
SMYTH, C. P. See Baker, W. O.; Conner, W. P.; Hurdis, E. C.; Oesper, P. F.; Turkevich, A.
SNELL, E. E. See Pennington, D.
SNYDER, H. R. See Fuson, R. C.
SNYDER, H. R., ANDREEN, J. H., CANNON, G. W., AND PETERS, C. F. Convenient synthesis of *dl*-methionine ... 2082
SOBEL, A. E., KAYE, I. A., AND SPOERRI, P. E. Steryl sulfates (III) prepn. of 3,5,6-cholestantriol-I ... 471
SOBEL, A. E., AND SPOERRI, P. E. Steryl sulfates (II) isolation and sepn. of sterols, 361; (IV) thermal decompn. of Ca cholesteryl sulfate ... 482
SOFFER, M. D. See Campbell, W. P.
SOLDATE, A. M. See McBain, J. W.
SÓLYOM, G. See Zechmeister, L.
SONNEBORN, H., III, AND WISELOGLE, F. Y. Divalent N (II) action of NO on pentaphenylethane. 860
SOROOS, H. See Calingaert, G.
SORUM, C. H. Review of "Introductory College Chemistry" (Deming, Hendricks) ... 3064
SOUTHARD, J. C., AND MOORE, G. E. High-temp. heat content of Mn_3O_4, $MnSiO_3$ and Mn_3C ... 1769
SOUTHARD, J. C., AND SHOMATE, C. H. Heat of formation and high-temp. heat content of MnO and $MnSO_4$—high temp. heat content of Mn ... 1770
SOUTHWICK, P. L. See Fuson, R. C.
SOWDEN, J. C., AND FISCHER, H. O. L. *l*-Glycidol ... 1291
SPECK, S. B. See Fuson, R. C.
SPEER, R. J. See Henze, H. R.
SPENCER, H. M., AND FLANNAGAN, G. N. Empirical heat capacity eqs. of gases ... 2511
SPENCER, H. M., AND SPICER, W. M. Heat capacities of red and yellow Pb monoxides at high temps ... 617
SPICER, W. M. See Spencer, H. M.
SPIES, J. R., AND UMBERGER, E. J. Chemistry of allergens (VI) chem. compn. and properties of an active carbohydrate-free protein from cottonseed ... 1889
SPILLANE, L. J. See Smith, L. I.
SPITZER, R., HOWELL, W. J., JR., AND SCHOMAKER, V. Electron diffraction investigation of mol. structures of $SiBr_4$, tribromosilane and dibromodifluorosilane ... 62
SPOERRI, P. E. See Sobel, A. E.
SPRANG, C. A., AND DEGERING, E. F. Utilization of aliphatic nitro compds. (III) nitroalcs. prepared from aldehydes containing no other functional groups, 1063; (IV) nitrodiols (nitroglycols) prepared from simple aldehydes ... 1735
SPRAUER, J. W., AND SIMONS, J. H. Kinetics of the HF catalyzed reacn. between toluene and *t*-BuCl ... 648
SPRULES, F. J. See Adams, R.
SPRUNG, J. A. See Smith, L. I.
SPUHLER, F. J. See Jones, J. H.
SPURR, R. See Schomaker, V.
SPURR, R., AND SCHOMAKER, V. Constitution of pirylene: electron diffraction investigation ... 2693
STAGNER, B. A. See Kalichevsky, V. A.
STALLBAUMER, A. L. See Rice, F. O.
STALLCUP, W. D. See Fuguitt, R. E.; Williams, D.
STALLCUP, W. D., AND HAWKINS, J. E. Reacns. of β-pinene (II) with SeO_2 in AcOH ... 1807
STANFIELD, J. A. See Wood, J. H.
STANLEY, W. M. Concn. and purification of tobacco mosaic virus by means of Sharples super-centrifuge ... 1804
STARKEY, E. B. See Ruddy, A. W.
STAUFFER, D. See Riebsomer, J. L.
STAUFFER, D. A. See Hazlet, S. E.
STAVELY, H. E. Catalytic reduction of cholesterol α-oxide ... 2723
STEADMAN, T. R. See Campbell, W. P.
STEIN, C. W. C., AND DAY, A. R. Reacns. of retenequinonimine and phenanthraquinonimine with aldehydes—a new example of an aldol-type of condensation, 2567; reacns. of retenequinonimine and phenanthraquinonimine with Schiff bases—new example of an aldol-type of condensation ... 2569
VON STEIN, P. Org. Reagents in Inorg. Analysis (book review) ... 1984
STEIN, W. H., MOORE, S., AND BERGMANN, M. Sp. rotation of *l*-tyrosine ... 724
STEINMAN, H. G. See Doak, G. O.
STEINMAN, H. G., AND DAWSON, C. R. On the mechanism of the ascorbic acid–ascorbic acid oxidase reacn.—the H_2O_2 question ... 1212
STEINMAN, R., SCHIRMER, F. B., JR., AND AUDRIETH, L. F. Prepn. and phys. properties of trimeric phosphonitrilic chloride ... 2377
STEKOL, J. A. Se tetracysteine ... 1742
STELLER, J. S. See Wiley, J. W.
STEMPEL, G. H., JR., AND SCHAFFEL, G. S. Use of phenylhydrazine to characterize org. acids ... 470
STENGER, V. A. See Kolthoff, I. M.
STEPHENSON, R. W. See Shriner, R. L.
STEVENS, J. R., BEUTEL, R. H., AND CHAMBERLIN, E. 3,4-Substituted pyridines (I) synthesis of 3-vinyl-4-methylpyridine, 1093, (corrn.) ... 3071
STEVENS, P. G., AND ERICKSON, J. L. E. American musk (I) chem. constitution of the musk of the La. muskrat ... 144
STEVENS, P. G., AND MOWAT, J. H. Action of Na on hexamethylacetone ... 554
STEVENSON, A. C. See Bachmann, W. E.
STEVENSON, D. P., AND HIPPLE, J. A., JR. Ionization and dissocn. by electron impact: *n*-butane, isobutane and ethane, 1588; ionization and dissocn. by electron impact: *n*-PrCl and *t*-BuCl, 2766; ionization and dissocn. by electron impact: isobutylene, propane and propylene ... 2769
STEVENSON, D. P., AND SCHOMAKER, V. Note on the structures of Ga and In trihalides ... 2514
STEWART, H. W. See Adams, R.
STEWART, P. B. See Kobe, K. A.
STEWART, T. D. See Harman, D.
STIMSON, M. M. Ultraviolet absorption spectra of nitrogenous heterocycles (IV) effect of *p*H and irradiation on spectra of isoguanine and 2-hydroxy-6,8-diaminopurine ... 1604
STOCKMAYER, W. H. See Beattie, J. A.; Rabinowitch, E.
STONEHILL, H. I., AND BERRY, M. A. Revised consts. for the Debye–Hückel theory ... 2724
STORCH, H. H., HAWK, C. O., AND O'NEILL, W. E. Kinetics of H consumption, O elimination and liquefaction in coal hydrogenation—nature of the catalytic reacns ... 230
STOUT, J. W., AND ADAMS, H. E. Magnetism and the 3rd law of thermodynamics—heat capacity of manganous fluoride from 13 to 320 °K ... 1535
STRAIN, H. H. Chromatographic Adsorption Analysis (book review) ... 1013
STRAIN, H. H., AND MANNING, W. M. Occurrence and interconversion of various fucoxanthins ... 1235
STRAIN, W. H., PLATI, J. T., AND WARREN, S. L. Iodinated org. compds. as contrast media for radiographic diagnoses (I) iodinated aracyl esters ... 1436
STRONG, F. M. See Feeney, R. E.
STROSS, F. H., AND EVANS, R. J. Some phys. consts. of N-octyl-, N-dodecyl- and N-cetyl-piperidine ... 2511
STUCKWISCH, C. G. See Gilman, H.
STURTEVANT, J. M. Sapon. of acetylsalicylic acid at 35°, 77; gal. investigations of org. reacns. (IV) heats of ionization of *dl*-alanine at 25°, 762; see Berry, K. L.
SUEN, T.-J., AND FAN, S. Catalytic hydrogenation of heptaldehyde in vapor phase ... 1460
SUGIHARA, J. M. See Mackinney, G.
SULLIVAN, M. X. See Irreverre, F.
SULLIVAN, W. N. See LaForge, F. B.
SUMPTER, W. C. Reacn. of PhMgBr with N-phenylisatin ... 1736
SUTER, C. M. See Bair, R. K.; Campaigne, E.
SUTER, C. M., AND WESTON, A. W. α-β-Dialkyl-

phenethylamines—alkylation of Ph acetone, 533; physiol. active phenethylamines containing a *t*-hydroxyl ... 2451
SUTHERLAND, L. H. See Whitmore, F. C.
SWAIN, R. E. Review of "Du Pont—One Hundred and Forty Years" (Dutton) ... 3064
SWIFT, E., JR. Ds. of some aliphatic amines, 115; reviews of "Exptl. Phys. Chemistry" (Palmer), 3065; "Practical Phys. Chemistry" (Findlay) ... 3065
SWIFT, E. H. Review of "Volumetric Analysis" (Kolthoff, Stenger), 2730; see Noyes, A. A.
SWIFT, L. J., AND WALTER, E. D. Isolation of lupeol from the osage orange (*Maclura pomifera* Raf.) ... 2539

TARBELL, D. S., MALLATT, R. C., AND WILSON, J. W. Acidic and basic catalysis in urethan formation ... 2229
TARBELL, D. S., AND PAULSON, M. C. Attempted asymmetric syntheses involving the Grignard reagent in optically active solvents ... 2842
TARBELL, D. S., AND WILSON, J. W. Rearrangement of O-crotyl-3,5-dichlorosalicylic acid and related compds., 607; rearrangement of 4-crotyloxy-3,5-dichlorobenzoic acid ... 1066
TATILBAUM, A. See Worrall, D. E.
TAUBE, H. Production of at. I in reacn. of peroxides with I^-, 161; reacns. in solns. containing O_3, H_2O_2, H^+ and Br^-—sp. rate of the reacn. $O_3 + Br^- \rightarrow$.. 2468
TAUBER, H., LAUFER, S., AND GOLL, M. Color test for citrinin and a method for its prepn. ... 2228
TAYLOR, H. S., AND GLASSTONE, S. A Treatise on Phys. Chemistry. Atomistics and Thermodynamics (book review) ... 1743
TAYLOR, J. K. See Smith, E. R.
TAYLOR, T. I. See Huggett, C.
TEBBENS, W. G., JR. See Russell, A.
TERRY, D. H. See Lutz, R. E.
THEOBALD, C. W. See Adams, R.
THOMAS, C. A. Anhyd. $AlCl_3$ in Org. Chemistry (book review) ... 1743
THOMAS, D. G. See Bachmann, W. E.
THOMAS, D. S. JR. See Weissberger, A.
THOMAS, E. D. See Lochte, H. L.
THOMAS, L. B., AND OLMER, F. G. Accommodation coeff. of Hg on Pt and the heat of vaporization of Hg ... 2190
THOMAS, McC. J. See Riegel, B.
THOMPSON, A. F., JR., AND MARGNETTI, C. Decompn. of certain acetylenic carbinols ... 573
THOMPSON, A. F., JR., AND SHAW, E. N. Partial reduction of acetylenes to olefins using an Fe catalyst (II) enyne and dienyne reduction ... 363
THORPE, J. F., AND WHITELEY, M. A. Thorpe's Dictionary of Applied Chemistry (book review) ... 2237
THORPE, M. A. See Wallingford, V. H.
TICHENOR, R. L. See Kistiakowsky, G. B.; Mead, D. J.
TILDEN, E. B. See McClenahan, W. S.
TILDEN, E. B., ADAMS, M., AND HUDSON, C. S. Purification of the amylase of *Bacillus macerans* .. 1432
TIPSON, R. S., AND CRETCHER, L. H. Cinchona alkaloids in pneumonia (X) some ethers of 6′-(β-thiolethyl)-apocupreine ... 1162
TOBIE, W. C., AND AYRES, G. B. Improved procedure for prepn. of glycine ... 725
TODD, D. See Campbell, W. P.; Hasselstrom, T.
TOENNIES, G., AND HOMILLER, R. P. Oxidation of amino acids by H_2O_2 in formic acid ... 3054
TOETTCHER, F. C. See Long, E. A.
TOMSICEK, W. J. See Larson, W. D.; Price, C. C.
TORIBARA, T. Y. See Willard, H. H.
TOTTER, J. R. See Darby, W. J.
TOY, A. D. F. See Audrieth, L. F.
TRANSUE, L. F., WASHBURN, E. R., AND KAHLER, F. H. Direct measurement of spreading pressures of volatile org. liquids on water ... 275
TRIMBLE, H. M., ENGLE, C. J., BROWN, R. A., AND SCHMUCK, R. F. Sp. heats of morpholine and its aq. solns. ... 679
TROYAN, J. E. D. and refractive index of cumene ... 3056
TSHIN, S.-Y. See Chi, Y.-F.
TURK, A. See Henne, A. L.
TURKEVICH, A., AND SMYTH, C. P. Dielec. behavior, supercooling and vitrification of certain chlorobutanes and chloropentanes ... 737
TURKEVICH, J., OESPER, P. F., AND SMYTH, C. P. Dipole moment of a free radical ... 1179
TURNBULL, D. See Maron, S. H.
TURNER, D. L. See Marker, R. E.
TWYMAN, F. Spectrochem. Analysis of Metals and Alloys (book review) ... 1745
TYSON, G. N., JR. See Wiley, J. W.

ULICH, H., AND CRUSE, K. Kurzes Lehrbuch der physik. Chemie (book review) ... 475
ULSHAFER, P. R. See Marker, R. E.
UMBERGER, E. J. See Spies, J. R.
UNGNADE, H. E., AND HENICK, A. S. Prepn. of *m*-hydroxybenzoic acid ... 1737
UNRUH, C. C., AND KENYON, W. O. Investigation of properties of cellulose oxidized by NO_2 (I) ... 127
UPSON, R. W. See Shriner, R. L.
UREY, H. C. See Leifer, E.

VAN ALLAN, J. See Allen, C. F. H.
VAN ORDEN, H. O. See Hazlet, S. E.
VERNON, A. A., and MASTERSON, J. P. Soly. effect in solvents of low dielec. const. (II) a study of the soly. effect in benzene ... 2822
VICKERY, H. B. Review of "The Dynamic State of Body Constituents" (Schoenheimer) ... 2523
DU VIGNEAUD, V., HOFMANN, K., AND MELVILLE, D. B. Structure of biotin ... 188
VINCENT, W. B., AND HOARD, J. L. Structures of complex fluorides—Rb hexafluogermanate ... 1233
VINOGRAD, J. R., AND MCBAIN, J. W. Diffusion of electrolytes and of the ions in their mixts. (corrn.) . 3067
VIOHL, P. See Corwin, A. H.
VLASES, G., JR. See Ritter, J. J.
VOLMAN, D. H. Vapor phase photodecompn. of Me formate ... 1820
VOSBURGH, W. C. See Gould, R. K.

WAGNER, R. B. See Marker, R. E.
WAISBROT, S. W. See Wolfrom, M. L.
WAITKINS, G. See McCrosky, C. R.
WALDBAUER, L. Reviews of "Textbook of Quant. Analysis" (Hall), 190; "The Spectrochem. Analysis of Metals and Alloys" (Twyman) ... 1745
WALDMAN, E. See Kremer, C. B.
WALKER, J. W. See Noller, C. R.
WALL, F. T. Intramol. condensations in polymers, 269; distribution of benzoic acid between water and benzene ... 472
WALLACE, E. G. See Wolfrom, M. L.
WALLACE, W. P., AND HENZE, H. R. Keto ethers (X) 1-methoxyethyl alkyl ketones ... 2882
WALLINGFORD, V. H. See Homeyer, A. H.
WALLINGFORD, V. H., AND JONES, D. M. Alkyl carbonates in synthetic chemistry (IV) alkylation of malonic esters by alkyl carbonates ... 578
WALLINGFORD, V. H., JONES, D. M., AND HOMEYER, A. H. Alkyl carbonates in synthetic chemistry (III) condensation with nitriles—synthesis of α-cyano esters ... 576
WALLINGFORD, V. H., THORPE, M. A., AND HOMEYER, A. H. Alkyl carbonates in synthetic chemistry (V) alkyl carbonates as solvents for metalation and alkylation reacns ... 580
WALTER, E. D. See Swift, L. J.
WALTERS, P. M. See McElvain, S. M.
WALTON, J. H. See Nichols, A. R., Jr.
WARD, J. J. See Weiler, J. F.
WARD, M. L. See Fuson, R. C.
WARING, C. E. See Smith, W.

WARNEKE, F. E. See Crawford, H. M.
WARNER, R. C. See McMeekin, T. L.
WARREN, S. L. See Strain, W. H.
WASH, G. See Shive, B.
WASH, G., SHIVE, B., AND LOCHTE, H. L. Normal and abnormal alkylation of 2-phenylcyclopentyl Me ketone (corrn.) 3069
WASHBURN, E. R. See Transue, L. F.
WASHBURN, E. R., BROCKWAY, C. E., GRAHAM, C. L., AND DEMING, P. Ternary systems involving cyclohexane, water, and isopropyl and *n*-propyl alcs. 1886
WATSON, G. M. See Felsing, W. A.; Phillips, B. A.
WATT, G. W. See Knowles, C. M.; Lemons, J. F.; Moore, T. E.
WATTERS, G. G. See Brewster, C. M.
WAUGH, R. C., EKELEY, J. B., AND RONZIO, A. R. The glyoxalines (II) a study of the reacn. between benzamidine and phenylglyoxal 2028
WAWZONEK, S. See Laitinen, H. A.
WAWZONEK, S., AND LAITINEN, H. A. Reduction of unsatd. hydrocarbons at the dropping Hg electrode (II) aromatic polynuclear hydrocarbons 2365
WAY, E. L., AND ONETO, J. F. Sulfophenylarsonic acids and certain of their derivs. (VI) derivs. of *p*-sulfonamidophenylarsonic acid 1287
WEBER, R. L. Temp. Measurement (book review) .. 475
WEIJLARD, J. Cocarboxylase and related esters 2279
WEIJLARD, J., AND ERICKSON, A. E. N-Allylnormorphine 869
WEILER, J. F., WARD, J. J., AND HOWARD, H. C. Mol. wts. of hydrogenolysis products from a Pittsburgh seam bituminous coal 734
WEINGARTNER, H. C. See Johnstone, H. F.
WEISER, H. B., MILLIGAN, W. O., AND COOK, E. L. Hydrous $Cu(OH)_2$ and basic cupric sulfates 503
WEISSBERGER, A., AND GLASS, D. B. Reacn. of β-isodurylaldehyde cyanohydrin with PhMgBr 1724
WEISSBERGER, A., AND PORTER, H. D. Investigation of pyrazole compds. (I) reacn. product of phenylhydrazine and Et cyanoacetate 2133
WEISSBERGER, A., AND THOMAS, D. S., JR. Oxidation processes (XIV) effect of Ag on autoxidation of some photographic developing agents 1561
WEISSMAN, S. I., AND LIPKIN, D. Electromagnetic mechanism of the β-phosphorescence of fluorescein in acid solns 1916
WELLDON, P. B. See Fuson, R. C.
WELSH, L. H., AND KEENAN, G. L. Polymorphism of *d*-galactose diethylmercaptal pentaacetate 183
WELTMAN, C. See Ricci, J. E.
WENNER, R. R. Thermochem. Calcns. (book review) 1237
WERKMAN, C. H. See Nord, F. F.
WERNER, A. C. See Simons, J. H.
WERTHEIM, E. Introductory Org. Chemistry (book review) 3063
WESNER, M. M. See Chakravorty, P. N.
WEST, E. S. Phys. Chemistry for Students of Biochemistry and Medicine (book review) 3061
WESTHEIMER, F. H. See Grigsby, W. E.
WESTLAKE, H. E., JR., AND DOUGHERTY, G. Use of Bunte salts in synthesis (III) prepn. of aliphatic disulfides 149
WESTON, A. W. See Suter, C. M.
WHALEY, A. M. See Henne, A. L.
WHELAND, G. W. Quantum mechanical investigation of orientation of substituents in aromatic mols. 900
WHETSTONE, R. R. See Linstead, R. P.
WHITCHER, W. J. See Jacobs, T. L.
WHITE, E. V. Constitution of arabo-galactan (II) isolation of heptamethyl- and octamethyl-6-galactosidogalactose through partial hydrolysis of methylated arabogalactan, 302; (III) location of the arabinose component, 1507; (IV) structure of the repeating unit, 2838, (corrn.) 3069
WHITE, J. W., JR., AND ZSCHEILE, F. P. Studies on carotenoids (III) distribution of pure pigments between immiscible solvents 1440
WHITE, J. W., JR., ZSCHEILE, F. P., AND BRUNSON, A. M. Carotenoids of yellow corn grain 2603
WHITELEY, M. A. See Thorpe, J. F.
WHITMAN, G. M. See Adkins, H.
WHITMORE, F. C., AND BLOCK, L. P. Grignard reacns. (XV) sterically hindered aliphatic carbonyl compds. (V) enolization studies (I) 1619
WHITMORE, F. C., COSBY, J. N., SLOATMAN, W. S., AND CLARKE, D. G. Higher hydrocarbons (II) five 11-substituted heneicosanes 1801
WHITMORE, F. C., AND FORSTER, W. S. Grignard reacns. (XVII) reacns. of esters and acid chlorides with Grignard reagents 2966
WHITMORE, F. C., AND GEORGE, R. S. Abnormal Grignard reacns. (X) enolizing and reducing action of Grignard reagents upon diisopropyl ketone 1239
WHITMORE, F. C., AND LESTER, C. T. Abnormal Grignard reacns. (XII) sterically hindered aliphatic carbonyl compounds (II) ketones containing the dineopentylcarbinyl group, 1247; (XIII) (III) compds. derived from the BrMg enolates of alkyl dineopentylcarbinyl ketones 1251
WHITMORE, F. C., AND LEWIS, C. E. Abnormal Grignard reacns. (XIV) sterically hindered aliphatic carbonyl compds. (IV) Me triethylcarbinyl ketone and its BrMg enolate, 1618; (XVI) 2964
WHITMORE, F. C., MEYER, R. E., PEDLOW, G. W., JR., AND POPKIN, A. H. Reducing action of primary Grignard reagents with trimethylacetyl chloride (corrn.) 3067
WHITMORE, F. C., AND RANDALL, D. I. Abnormal Grignard reacns. (XI) sterically hindered aliphatic carbonyl compds. (I) ketones containing the Me-*t*-butylneopentylcarbinyl group and their BrMg enolates 1242
WHITMORE, F. C., ROWLAND, C. S., WRENN, S. N., AND KILMER, G. W. Dehydration of alcs. (XIX) *t*-amyl alc. and the related dimethylneopentyl carbinol 2970
WHITMORE, F. C., AND SLOAT, T. K. Grignard reacns. (XVIII) reacns. of benzylmagnesium chloride 2968
WHITMORE, F. C., SUTHERLAND, L. H., AND COSBY, J. N. Higher hydrocarbons (I) 7 alkyl substituted docosanes 1360
WHITMORE, F. C., AND ZOOK, H. D. Formation of cyclopropanes from monohalides (III) action of Na alkyls on aliphatic chlorides—relation to the Wurtz reacn. 1783
WHITMORE, W. F., AND GEBHART, A. I. Prepn. of α- and β-indanol and some of their derivs. from indene 912
WHITNEY, R. B. See Grahame, D. C.
WHITSON, J. See Marvel, C. S.
WIIG, E. O. Review of "Photochemistry of Gases" (Noyes, Leighton) 476
WIKHOLM, D. M. See Frank, R. L.
WILDS, A. L. Synthesis of 2′-ketodihydro-1,2-cyclopentenophenanthrene and derivs. of phenanthro-[1,2-*b*]furan, 1421; see Bachmann, W. E.
WILES, Q. T. See Cromwell, N. H.
WILEY, J. W., TYSON, G. N., JR., AND STELLER, J. S. Configuration of complex kojates formed with some transition elements as detd. by magnetic susceptibility measurements 963
WILKERSON, A. S. Optical properties of 2-sulfanilamidopyrimidine (sulfadiazine) 2230
WILLARD, H. H. Review of "*p*H and Electro Titrations" (Kolthoff, Laitinen) 1016
WILLARD, H. H., AND TORIBARA, T. Y. Prepn. and properties of K oxalatostannate, 1759; study of complex dioxalatothiometastannates 1762
WILLARD, J. E. See Bohlman, E. G.
WILLIAMS, D. Infra-red spectra of ammonium halides 857
WILLIAMS, D., AND STALLCUP, W. D. Spectroscopic evidence of intermol. transfer of protons 2684

WILLIAMS, G. E., AND GILBERT, E. C. Vapor pressure of phenylhydrazine as a function of temp..... 2776
WILLIAMS, J. W., RAINEY, W. T., JR., AND LEOPOLD, R. S. Identification of amides through the Hg derivs..... 1738
WILLIAMS, M. B. See Hoard, J. L.
WILLIAMS, M. B., AND HOARD, J. L. Structures of complex fluorides—K oxyhexafluocolumbate, K_2CbOF_6..... 1139
WILLIAMS, R. B. Heats of catalytic hydrogenation in soln. (I) apparatus, technique, and the heats of hydrogenation of certain pairs of stereoisomers.... 1395
WILLIAMS, R. J. An Introduction to Org. Chemistry (book review), 728; see Cheldelin, V. H.
WILLIAMS, W. W. See Brooker, L. G. S.
WILLIAMSON, P. M. See Lemons, J. F.
WILLIS, L. H. See Pierce, J. S.
WILLISTON, A. F. See Foster, L. S.
WILSON, E. See Reid, E. E.
WILSON, E. B. Review of "The Nature of Thermodynamics" (Bridgman)..... 2524
WILSON, E. J., JR. See Fry, E. M.; Schoch, T. J.
WILSON, J. M. See Robinson, R. A.
WILSON, J. W. See Tarbell, D. S.
WILSON, W. K., MASON, C. M., HICKEY, J. W., AND MACK, J. H. Magnetic rotation of Ce salts in aq. soln..... 412
WILT, M. H. See Yohe, G. R.
WINBERG, H. E. See Hurd, C. D.
WINNEK, P. S. See Anderson, G. W.; Roblin, R. O., Jr.
WINNEK, P. S., ANDERSON, G. W., MARSON, H. W., FAITH, H. E., AND ROBLIN, R. O., JR. Studies in chemotherapy (V) sulfanilylcyanamide and related compds..... 1682
WINSCHE, W. E. See Johnstone, H. F.
WINSLOW, E. H., AND LIEBHAFSKY, H. A. Crude B—analysis and compn..... 2725
WINSTEIN, S. Role of neighboring groups in replacement reacns. (III) retention of configuration in reacn. of 3-bromo-2-butanols with PBr_3, 2791; (IV) identity of various prepns. of 1,2-dibromocyclohexane, 2792; see Roberts, J. D.
WINSTEIN, S., AND BUCKLES, R. E. Role of neighboring groups in replacement reacns. (I) retention of configuration in reacn. of some dihalides and acetoxyhalides with AgAc, 2780; (II) effects of small amts. of water on the reacn. of AgAc with some butene and cyclohexene derivs..... 2787
WINSTEIN, S., HESS, H. V., AND BUCKLES, R. E. Role of neighboring groups in replacement reacns. (V) effect of neighboring acetoxy group on the course of replacement of the tosylate group of *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate.... 2796
WINSTEIN, S., AND WOOD, R. E. Dielec. consts. of some pairs of diasteromers (corrn.)..... 3067
WINTERSTEINER, O., AND RUIGH, W. L. 7-Benzoxysterols and their use in prepn. of 7-dehydrosterols, 1177; on the epimeric 7-hydroxycholesterols..... 2453
WISELOGLE, F. Y. See Sonneborn, H., III.
WITTBECKER, E. L. See Marker, R. E.
WITTCOFF, H. See Riegel, B.
WITTLE, E. L. See Marker, R. E.
WITZEMANN, E. J. See Lehninger, A. L.
WOLFE, J. K., HANN, R. M., AND HUDSON, C. S. 1,2,3,4-Dibenzylidene-D-sorbitol..... 1493
WOLFROM, M. L., AND KOHN, E. J. Crystalline xylitol..... 1739
WOLFROM, M. L., AND MAHAN, J. Osage orange pigments (IX) improved sepn.; establishment of the isopropylidene group..... 308
WOLFROM, M. L., AND MOFFETT, S. M. Osage orange pigments (X) oxidation..... 311
WOLFROM, M. L., AND MORGAN, P. W. O-Pentaacetyl-*d*-gluconates of polyhydric alcs. and cellulose, 2026, (corrn.)..... 3071
WOLFROM, M. L., SMITH, C. S., PLETCHER, D. E., AND BROWN, A. E. β-Form of the Cori ester (*d*-glucopyranose 1-phosphate)..... 23
WOLFROM, M. L., WAISBROT, S. W., AND BROWN, R. L. Action of diazomethane on acyclic sugar derivs. (II), 1701; (III) new synthesis of ketoses and of their open chain (keto) acetates..... 2329
WOLFROM, M. L., WALLACE, E. G., AND METCALF, E. A. Transformation of tetramethylglucoseen-1,2 into 5-(methoxymethyl)-2-furaldehyde..... 265
WOLLNER, H. J., MATCHETT, J. R., LEVINE, J., AND LOEWE, S. Isolation of a physiol. active tetrahydrocannabinol from *Cannabis sativa* resin..... 26
WOOD, J. H., AND STANFIELD, J. A. Synthesis of 2,7-naphthalenedialdehyde; an attempted synthesis of coronene..... 2343
WOOD, R. E. See Winstein, S.
WOOD, T. R., AND ROSS, W. F. Does the parathyroid hormone influence phosphatase activity?. 2759
WOODRUFF, E. H. Phenethylamines (IV) dimethoxy and dihydroxyphenyl-*n*-propylamines (β-Me-β-phenethylamines)..... 2859
WOODWARD, R. B. Structure and absorption spectra (III) normal conjugated dienes, 72; (IV) further observations on α,β-unsatd. ketones, 76; mechanism of the Diels–Alder reacn..... 3058
WORRALL, D. E., AND TATILBAUM, A. Nitrovinylnaphthalene..... 1739
WORTH, H. J., AND HAENDLER, H. M. Addn. compds. of tetrahydrothiopyran..... 1232
WRENN, S. N. See Whitmore, F. C.
WYMAN, J., JR. See Marcy, H. O., 3rd.

YACKEL, E. C., AND KENYON, W. O. Oxidation of cellulose by NO_2..... 121
YAGER, W. A. See Baker, W. O.
YAGER, W. A., AND BAKER, W. O. Relation of dielec. properties of structure of crystalline polymers (I) polyesters..... 2164
YOE, J. H., AND BOYD, G. R., JR. 2-Thio-5-keto-4-carbethoxy-1,3-dihydropyrimidine and related compds..... 1511
YOE, J. H., AND SARVER, L. A. Org. Anal. Reagents (book review)..... 2518
YOHE, G. R., AND WILT, M. H. Oxidizing power of Ill. coal (II) effects of extended time..... 1809
YOKLEY, O. E. See Huggins, K. A.
YOST, D. M. See Osborne, D. W.; Russell, H., Jr.
YOUNG, F. E., AND HILDEBRAND, J. H. Heat of fusion and heat capacities of solid and liquid white P..... 839
YOUNG, H. A. See Young, M. B.
YOUNG, L. E. See Randall, M.
YOUNG, M. B., AND YOUNG, H. A. Absorption of O by glutathione in alkaline solns. (I) kinetics of the reacn. at *p*H 9 to 11..... 2282
YOUNG, R. C., AND HASTINGS, T. J., JR. Anhyd. $TaBr_3$..... 1740
YOUNG, W. G. See Roberts, J. D.

ZECHMEISTER, L. See LeRosen, A. L.; Polgár, A.
ZECHMEISTER, L., AND CHOLNOKY, L. Principles and Practice of Chromatography (book review)... 2729
ZECHMEISTER, L., AND LEROSEN, A. L. Stereoisomeric diphenyloctatetraenes..... 2755
ZECHMEISTER, L., AND MCNEELY, W. H. Sepn. of *cis* and *trans* stilbenes by application of the chromatographic brush method..... 1919
ZECHMEISTER, L., MCNEELY, W. H., AND SÓLYOM, G. Chromatography of *cis* and *trans* benzoin and anisoin oximes with application of the brush method..... 1922
ZECHMEISTER, L., AND SCHROEDER, W. A. Pro-γ-carotene..... 1173
ZELLER, M. M. See Davidson, A. W.

ZERBAN, F. W. See Browne, C. A.
ZERBAN, F. W., AND SATTLER, L. *d*-Allulose and some methylated derivs. 1740
ZIEGLER, W. T., AND ANDREWS, D. H. Heat capacity of benzene-d_6. 2482
ZIERING, A. See Niederl, J. B.
ZINN, J. B. Review of "General Chemistry" (Holmes). 3066
ZLOTOWSKI, I., AND KOLTHOFF, I. M. Validity of Ilkovic eq. in polarographic analysis of alkali metals and characteristics of alkali waves in various media. 1297
ZOOK, H. D. See Whitmore, F. C.
ZSCHEILE, F. P. See White, J. W., Jr.
ZWICKER, B. M. G., AND ROBINSON, R. J. Electrolytic reduction of strychnine. 790

Subject Index to Volume LXIV, 1942

ABSORPTION. (See also *Adsorption; Rays; Sorption.*) of unsym. cyanines, 199; O, induced by ether linkages, 1354; and re-emission of light by crystal violet ion isomers, 1774; of O by glutathione in alkaline solns. 2282
Absorption Spectra. See *Spectra.*
Accommodation coefficient, of Hg on Pt. 2190
Acenaphthene, derivs. of, 1666; amylsodium–, reacn., 2250, (corrn.) 3073
Acetaldehyde, photolysis of I mixts. and, 889, 893; thermal decompn. of, 994; thermal decompn. of, by H_2S 1707
Acetals, ketene, 254, 260, 1059, 1966, 2525; a hemi-, derived from starch oxidized with periodate 585
m-Acetamidophenyl allyl ether, thermal rearrangement of 1023
Acetic acid, photolysis of Me acetate, 490; mol. vol. of, 761; dropping Hg electrode in, 1303, 2177; plumbic acid–anhyd., solns., 1523; relative acid strengths of formic, propionic and, 2065; structure of copolymers of vinyl ester of, 2356; acylation of *t*-Bu ester of, 2714; reacn. of some dihalides and acetoxyhalides with AgAc, 2780; effect of water on reacn. of AgAc with butene and cyclohexene derivs., 2787; radioactive C as tracer in exchange between acetic anhydride and NaAc 3050
Acetic acid, hindrance in synthesis of Me-*t*-Bu-, and MeEtPr-, 300; temp. effect on surface tension and d. of some halogen substituted, 2078; bromination of 4-PhPh chloroacetate, 2449; synthesis of stilbene-2-, 2962; reacns. of trimethylacetyl chloride and Me trimethylacetate and *t*-butylacetyl chloride and Me *t*-butylacetate with Et, *n*-Pr, *i*-Pr, *n*-Bu and *i*-Bu Grignard reagents 2966
Acetic anhydride, radioactive C as tracer in exchange between, and NaAc 3050
Acetoacetic acid, 3-acetoxy-6-hydroxy-2,4,5-trimethylbenzyl-, ester, and transformation into chromene and chroman derivs., 435; introduction of *t*-Bu group into Et ester of 728
Acetone, alkylation of Ph, 533; action of Na on Me_4- 554
Acetonebenzil, products from anhydr- 2120, 2123
Acetone-sugars. (See under names of corresponding *sugars.*)
Acetonitrile, prepn. of orthoesters from, 1825; acylation of, with Et *n*-butyrate 2720
Acetophenone, water effects on photochem. bromination of, 887; prepn. of substituted, 1413; effect of metallic halides on reacn. of Grignard reagents with benzal-, 2972; *o*-benzyloxy- 3051
Acetyl chloride, reducing action of primary Grignard reagents with Me_3-, (corrn.) 3064
Acetylene, hydrogenation of 1407
Acetylene glycols. See *Glycols.*
Acetylenes, acetylenic ethers, 223, 2635; reduction to olefins, 363; acetylenic analog of neopentyl bromide, 543; decompn. of certain, carbinols, 573; catalytic addn. reacns. of, alcs., 1220; reduction of Ph substituted, at dropping Hg electrode, 1765; hydrogenation of disubstituted, 2505; halogen derivs. of phenoxy- 2635
Acetyl groups, distribution of, in cellulose acetate 1539
Acid anhydrides. See *Anhydrides.*
Acid chlorides. See *Chlorides.*
Acidity scale, extension of the 1861
Acids. (See also *Amino acids; Fatty acids; Hydrogen ion; Titration.*), new, synthesis, 300; phenylhydrazine in characterizing org., 470; potentiometric titration of dibasic, 1153; reacn. of Grignard reagents with esters of highly hindered, 1450; catalyzed hydrolysis of Ph substituted aliphatic esters, 2363; initial step in action of, on tetraarylhydrazines, 2808; mixed heteropoly, catalysts for vapor phase air oxidation of naphthalene 2917
Acid strength, relative, of formic, acetic and propionic acids in alcs. and dioxane–H_2O mixts. 2065
Acridine, synthesis of some Me benz-, by cyclization. 2894
Acrolein, hydration of 1953
Acrylic acid, elec. properties of meth- and chloracrylates, 2389; copolymerization of alkyl acrylates, 1675; resolution of β-chloro-β-(2-methoxy-4,6-dimethyl-5-chlorophenyl)-α-methyl-, and the corresponding, 1786; β-bromo-β-(2-alkoxynaphthyl)-α-alkyl-, 1791; substituted β-(2,7-dimethoxy-1-naphthyl)-α-methyl-, 1795; hydration of 1953
Acrylonitrile, chemistry of 2457, 2850
Activity, theory or relation of structure to, of sulfanilamide type compds 2905
Activity coefficient, of $SrCl_2$, 244; of Rb and Cs sulfates, 550; of methylamine hydrochlorides, 965; of selenic acid, 1054; of $PbBr_3$, 1136; of bivalent metal nitrates, 1469; of undissociated part of weak acids, (corrn.) 3069
Acylation, of 1,4-dimesityl-1,2,4-butanetrione enol, 1375; of anions of certain alkyl esters with Ph esters, 2271; Friedel–Crafts, of some sterically hindered alkylbenzenes, 2421; para, of polyalkylbenzophenones by aryl 2,4,6-trialkylbenzoates, 2573; acetonitrile with Et *n*-butyrate 2720
Adhesion, energy of, of crystalline powders 1195
Adsorption. (See also *Absorption; Chromatography; Sorption.*) N, in NH_3 decompn., 751; of H on ThO_2, 1731; azoyl derivs. of sugars and sepn. by chromatographic, 1501; of org. compds., 1513; of palmitic acid by some starches, 2144; at crystalline solid surfaces, 2383; of gases at low temp. and pressure on smooth Ag, 2545; of Co ions on TiO_2 2820
Aglucon, structural changes in, on enzymic hydrolysis of alkyl β-D-glucosides 369
Agricultural chemistry, Liebig and after Liebig (book review) 2237
Alanine, ds. and sp. heats of aq. solns. of *dl*-α-, β-, and lactamide, 191; heats of ionization of *dl*-, 762; 3 isomeric *dl*-β-pyridyl-, 1678; polycondensation of, Et ester 2268
Alcohols, identification in aq. soln., 179; nitro-, from aldehydes, 1063; alkanolamines, 1089; oxonium complexes in dehydration of diacetone, 1122; catalytic addn. reacns. of acetylenic, 1220; chloronitroanilino alkanols, 1285; $PbAc_4$ cleavage of cyclic α-keto-, 1416; synthesis of 2-alkylaminoethanols from ethanolamine, 1503; condensation of *s*-aliphatic, with benzene with $AlCl_3$, 1576; identification of, with S-benzylthiuronium chloride, 1978; O-pentaacetyl-*d*-gluconates of polyhydric, 2026, (corrn.) 3071; methylphenylcarbinol prepared by Grignard reacn., 2842; alkoxybenzoates of 2-monoalkylamino-2-Me-1-propanols and 2-monoalkylamino-1-butanols as local anesthetics, 2884; vinyl, 2886, 2888; dehydration of, 2970; batyl 3045
Aldehydes, bimol. reduction of hindered, 30; new synthesis of phthal-, 315; condensations with, 451; N-methylformanilide synthesis of, 1666; photolysis of aliphatic, 889, 893; elimination of HBr from acetals of α-bromo-, 1966; reacns. of retene- and phenanthraquinonimine with 2567
Aldol condensation. See *Condensation.*
Aldonic acids, benzimidazole rule for configuration of. 1612
Aleuritic acid, 8,9,15-trihydroxypentadecylamine from 1902

Alfalfa seed oil, sterols of..... 2488
Alkalies. (See also *Bases; Indicators; Titration.*) effect of, promoter on decompn. of NH_3, 745; action on cyclohexenecarbonals..... 1497
Alkali metals, polarographic analysis of..... 1297
Alkaloid, of *Crotalaria grantiana*, 571; from *Lycopodium saururus*, 968; cinchona, in pneumonia, 1162; of papaveraceous plants, 1659; erythrina, 1892, 2146; identification of, in *Fagara coco*, 2326; structure of riddelliine..... 2760
Alkanes. (See also *Paraffins.*) α-thienylamino-, 477; configurations of diasteromeric dibromo-, 601, (corrn.) 3069; 1,1,1-trichloro-2-hydroxy-3-nitro-, and their reduction products..... 2515
Alkanolamines. See *Alcohols.*
Alkylation, of paraffins with $AlCl_3$, 33; of malonic esters by alkyl carbonates, 578; alkyl carbonates as solvents for, reacns., 580; of benzene with acid catalysts, 1032; of *m*-xylene, 1662; of α-naphthoquinones with tetravalent Pb esters, 2043; of para quinones with acyl peroxides, 2060; BF_3 catalyzed, of halobenzenes, 2751; of amines, 2977; of linseed oil..... 3054
Alkyl carbonates. See under *Carbonic acid.*
Allergens, chemistry of..... 1889
d-Allulose, and some methylated derivs..... 1740
Allyl chloride, Br–, reacn..... 709
Allyl ether, thermal rearrangement of *m*-acetamidophenyl-..... 1023
Allylic rearrangements..... 2157
Allyl nitrophenyl thiosemicarbazides, and their anal. properties..... 2873
Aloins, chemistry of the..... 1378
Alumina, Cu–, catalysts in hydrogenation of alkyl Ph ketones..... 520
Aluminum, polymerization of some Me_3-, derivs., 316; $AlCl_3$–Al catalyst in benzoylation..... 878
Aluminum chloride. (See also *Friedel–Crafts reaction.*) alkylation of paraffins with, 33; Anhyd., in Org. Chemistry (Thomas, book review), 1743; in condensation of *s*-aliphatic alcs. with benzene, 1576; elec. moment of, 2076; in condensation of Me dipropyl carbinols with phenol..... 2655
Aluminum sulfate, hydration of..... 41
Alums, crystal-chem. studies of the..... 1819
Amides. (See also *Sulfonamides.*) identification of, through Hg derivs., 1738; dielec. properties and structure of linear poly-, 2171; macromol. disorder in linear poly-, 2399; reacn. between thio-, and primary amines..... 2722
Amidophosphoric acid, N-substituted derivs. of Ph esters of di-, and..... 1337
Amines, ds. of some aliphatic, 115; α-thienylaminoalkanes, 477; specificity study of "azol-esterases," 564; conductivities of high mol. wt. aliphatic, 772; alkanol-, 1089; amines high mol. wt. aliphatic, and their salts, 97, 498, 1516, 2067, 2824; color reacns. of sympathomimetic, with diazonium compds., 1319; optically active vasopressor, 1449; restricted rotation in aryl, 1475; (corrn.), 3069; esters of *s*-hydroxyaralkylalkyl-, 2263; basicity studies of *t*-vinyl, 2588; reacn. between thioamides and primary, 2722; phenethyl-, 2859; prepn. of mixed, *s*-aliphatic, RR'NH, 2878; catalytic interchange of groups in aliphatic, 2920; alkylation of..... 2977
Amino acids, as growth stimulants for *Lactobacillus casei*, 881; bis, derivs., 1286; dielec. increments of, polypeptides, 1379; polycondensation of α-, esters, 2264, 2268; basic, in strains of tobacco mosaic virus, 2734; oxidation of, by H_2O_2 in formic acid..... 3054
Amino alcohols. See *Alcohols.*
Amino ketones. See *Ketones.*
Ammonia, electrolyte influence on ammonolysis by, 467; effect of alkali promoter on decompn. of, 745, 751; effect of strong elec. fields on radiochem. decompn. of gaseous..... 1908
Ammonium compounds, structure of $(NH_4)_2SiF_6$-, NH_4F, 633; infrared spectra of, halides, 857; thermal decompn. of *trans*-1,2-cyclobutane-*bis*-(trimethylammonium) hydroxide..... 2701
Ammonium nitrate, systems: $LiNO_3$–, and $LiNO_3$–H_2O–..... 2680
Ammonolysis, electrolyte influence on, by NH_3..... 467
Ammono phosphoric acids, aquo.....1337, 1553
Ampholytes, adsorption of, on an activated charcoal. 1513
t-Amyl alcohol, and the related dimethylneopentylcarbinol..... 2970
Amylase, purification of, of *Bacillus macerans*, 1432; products from starch by action of, of *Bacillus macerans*..... 2139
Amylcaine hydrochloride, dimorphism of..... 1227
Amylsodium, pyrolysis of, 2247; reacn. with naphthalene, acenaphthene and decalin, 2250, (corrn.).. 3073
Amyl sulfide, synthesis of *p*-hydroxyphenyl..... 2322
Analysis. (See also *Polarography; Titration.*) nephelometric detn. of low solubilities, 101; amperometric titration of α-tocopherol, 646; polarographic study of *o*-phthalic acid and phthalates, 660; potentiometric titration of dibasic acids, 1153; polarographic, of alkali metals, 1297; detn. of Na, 1814; method for standardization of chromatographic..... 1905
Analysis, books, Textbook of Quant. (Hall, book review), 190; Quant. (Kanning, book review), 1012; Chromatographic Adsorption (Strain, book review), 1013; Phys. and Chem. Methods of Sugar (Browne, Zerban, book review), 1014; *p*H and Electro Titrations (Kolthoff, Laitinen, book review), 1016; Qual. (Anderson, Hazlehurst, book review), 1491; Ionic Equil. as Applied to Qual. (Hogness, Johnson, book review), 1492; Spectrochem., of Metals and Alloys (Twyman, book review), 1745; Polarographic Method of (Müller, book review), 1983; Org. Reagents in Inorg. (von Stein, book review), 1984; Org. Anal. Reagents (Yoe, Sarver, book review), 2518; A Course of Instruction in the Qual. Chem., of Inorg. Substances (Noyes, Swift, book review), 2522; Electrochemistry and Electrochem. (Sand, book review), 2728; Polarography. Polarographic, and Voltammetry. Amperometric Titrations (Kolthoff, Lingane, book review), 2728; Micromethods of Quant. Org. (Niederl, Niederl, book review), 2729; Volumetric (Kolthoff, Stenger, book review), 2730; Introduction to Semimicro Qual. Chem. (Curtman, book review), 3060; Introduction to Microtechnique of Inorg. (Benedetti-Pichler)..... 3061
Androsterone, conversion of 5-pregnen-3(β)-ol-20-one to dehydroiso-..... 1276
Anesthetics, optically active phenylurethan, 1112; local, 1691, 2884; esters of pyridinecarboxylic acids as local..... 1721
Anhydracetonebenzil, products from.....2120, 2123
Anhydrides, heats of hydrolysis of some acid..... 1747
Anilides, action of Grignard reagents on benzoylform-, 1086; N-Me-formanilide synthesis of aldehydes..... 1666
Anilino alkanols, chloronitro-..... 1285
Anisoin oxime, chromatography of *cis* and *trans*..... 1922
Anisole, partial pressure of HCl from solns. in..... 951
Anisoles, syntheses of some substituted..... 1315
p-Anisyl ketone, γ-phenoxypropyl..... 186
Anthochlor pigments..... 1704
Anthracene-9-aldehyde, coloring matters derived from..... 1101
Anthraquinone, formation of, from *o*-benzoylbenzoic acid..... 2324
Anthrones, reacn. of Grignard reagents with acyloxy-. 376
Antibodies, pptn. reacns. between, and polyhaptenic substances, 2994; compn. of ppts. of, 3010; hapten inhibition of pptn. of..... 3015
Antimony, elec. moments of, trihalides in dioxane, 614; cyanates and thiocyanates of..... 1757
Antioxidants, and autoxidation of fats..... 2337
Apocupreine, ethers of 6'-(β-thiolethyl)-..... 1162

D-Arabinose, synthesis of 5-D-glucosido-..... 2731
Arabo-galactan, constitution of, 302; (corrn. 3069), 2838; arabinose component of..... 1507
Aracyl esters, iodinated, for radiography..... 1436
Argentine plants, studies on.....968, 2326
Arndt–Eistert reaction, mechanism of..... 3043
Arsenic compounds, parameters in K dihydrogen arsenate and Ag arsenate, 354; elec. moments of, trihalides in dioxane, 614; arsonic acids, 828; As cyanates and thiocyanates, 1757; serological properties of.....2994, 3003
Arsenious acid, reduction of V_2O_5 by..... 1462
Arsine oxides, of naphthalene and biphenyl..... 1064
Arsonic acids, sulfophenyl-, and derivs..... 1287
Aryl amines. See *Amines*.
Ascorbic acid, mechanism of, oxidase–, reacn..... 1212
1(−)-Asparagine, reacn. of formaldehyde with..... 2899
Atomic weight, of Pb..... 3047
Atoms, Treatise on Phys. Chemistry. Atomistics and Thermodynamics (Taylor, Glasstone, book review)..... 1743
Autoxidation. See *Oxidation*.
Avidin, crystalline..... 469
Azo derivatives, insecticidal properties of certain, of 3,2′-nicotyrine..... 2835
Azoyl derivatives, of sugar..... 1501

BACILLUS. (See also *Bacteria*.) growth stimulating substances for *Lactobacillus casei*, 881; purification of the amylase of, *macerans*, 1432; products from starch by action of amylase of, *macerans*, 2139; action of, *macerans* on a corn starch component.... 3044
Bacteria. (See also *Bacillus*.) synthesis of dextran from sucrose, 1959; activity of substituted mandelic acids..... 2080
Barbaloin..... 2516
Barbituric acids, α-alkoxyvinyl- and α-alkoxyethyl-, 1831; some N-substituted, 2233; some N-aralkyl, 2514; some new thiazolidinopyrimidines of, type.. 2709
Barium chloride, activity coeffs. of..... 244
Bart reaction, use of diazonium borofluorides in..... 828
Bases. (See also *Alkalies; Alkaloids; Amines; Cations; Indicators; Nitrogen compounds; Schiff bases; Titration*.) ionic competition in, exchange reacns..... 954
Batyl alcohol..... 3045
Beidellite membranes, and detn. of Na..... 1814
Benzacridine, synthesis of some Me, by cyclization... 2894
Benzalacetophenone, effect of metallic halides on reacn. of Grignard reagents with..... 2972
21-Benzal-5-pregnen-3(β)-ol-20-one, and allied compds..... 1282
Benzamidine, phenylglyoxal–, reacn..... 2028
1,2-Benzanthracene, soly. of 10-Et-, 101; synthesis of 4,10-ace-..... 802
Benzazide, 3,5-dinitro-, in prepn. of tocopherols..... 433
Benzene, alkylation of, with acid catalysts, 1032; $AlCl_3$ in condensation of *s*-aliphatic alcs. with, 1576; reacn. of Me furoate with, and chloro-, 2136; heat capacity of, 2375; study of soly. effect in..... 2822
Benzene, chemistry of *o*-diphenyl-, 1365; vapor dipole moments of some substituted, 2212; Friedel–Crafts acylations of some sterically hindered alkyl-, 2421; rearrangement of 1,1,3,3,5,5-hexamethylcyclohexatriol to hexamethyl-, 2461; halogenation of *m*-diphenyl-, 2485; some BF_3 catalyzed alkylations of halo-, 2751; studies in methylenedioxy-, series, 2983; prepn. of 5-alkoxy-4-N-succinyl-4-amino-1,3-dimethyl-, (corrn.)..... 3069
Benzene-d_6, heat capacity of..... 2482
Benzene derivatives, nuclear substitution of, 297; elec. moments of..... 768
Benzenediazonium compounds, prepn. of, salts, 469; *p*-bromo-, hydroxide in polymerization of styrene.. 2508
Benzenesulfonic acid, N,N′-piperazinium bis-(2-Me-5-isopropylbenzenesulfonate), 1741; chlorination of 4PhPh ester of..... 2719
Benzenesulfonyl urea, prepn. of *p*-amino-..... 2225
9,10-*o*-Benzenoanthracene..... 2649
Benzfluorenes, synthesis of some Ph di-, by cyclization..... 2894
Benzil, products from anhydracetone-.....2120, 2123
Benzilic acid, amino-, piperidino- and morpholinoethyl and propyl esters of, and their mydriatic activity.....428, 431
Benzimidazole, *bis*-, 187; rule for configuration of aldonic acids..... 1612
Benzoic acid, distribution of, between water and benzene, 472; substituted amides of 2,4,6-Me_3-, 726; rearrangement of 4-crotyloxy-3,5-dichloro-, 1066; β-monoalkylaminoethyl esters of alkoxy-, 1691; prepn. of *m*-hydroxy-, 1737; synthesis of 2-(2′-methoxybenzoyl)-, 2226; nitration of 4-PhPh ester of, 2505; para acylation of polyalkylbenzophenones by aryl 2,4,6-trialkyl- esters of, 2573; chlorination of 4-PhPh ester of, 2719; alkoxybenzoates of 2-monoalkylamino-2-Me-1-propanols and 2-monoalkylamino-1-butanols as local anesthetics, 2884; identification of *o*- and *p*-sulfo-, as their S-benzylthiuronium salts..... 3040
Benzoin oxime, chromatography of *cis* and *trans*.... 1922
Benzonitrile, behavior of 3,4,5-trimethoxy- toward Grignard reagents..... 2085
Benzophenone, oxidation of, oxime, 1453; para acylation of polyalkyl-, by aryl 2,4,6-trialkylbenzoates, 2573; effect of metal halides on reacn. of Grignard reagents with..... 2972
Benzopyrans, *d*- and *l*-1-hydroxy-3-*n*-amyl-6,9,9-trimethyl-7,8,9,10-tetrahydro-6-di-..... 2087
Benzo(f)quinolines, 5- and 1-amino-, 540, (corrn.).... 3069
7-Benzoxysterols, and use in prepn. of 7-dehydro-.... 1177
Benzoylation, Al–$AlCl_3$ catalyst in..... 878
o-Benzoylbenzoic acid, mechanism for formation of anthraquinone from..... 2324
Benzoyl chloride, action on Et β-diethylaminocrotonate..... 612
Benzoyleneureas, synthesis of amino-..... 2644
Benzoylethylamine, condensations with..... 451
Benzoylformanilides, action of Grignard reagents on. 1086
Benzoylmesitoylmethane, properties of *o*-methoxy-.. 2262
3,4-Benzpyrene, soly. of..... 101
Benzylidene aminomorpholine compounds..... 2502
Benzylidene-dulcitol, structure of di-*o*-nitro-..... 1614
Benzylmagnesium chloride, reacns. of..... 2968
Benzyl nitrate, reacn. velocity with water and hydroxyl ion..... 1928
Beryllium iodide, catalytic decompn. of H_2O_2 by basic, hydrosols..... 1340
Bethogenin, a new sapogenin..... 2581
Biacetyl, production of radicals by illumination of... 717
Bile acids, dipole moments of some..... 1941
Biochemistry, Practical Methods in (Koch, book review), 189; Mechanism of Biol. Oxidations (Green, book review), 1236; Annual Review of (Luck, Smith, book review), 2522; The Dynamic State of Body Constituents (Schoenheimer, book review), 2523; Phys. Chemistry for Students of, and Medicine (Ferry, book review)..... 3061
Bio-reduction, of steroids..... 1653
Biotin, structure of, 188; X-ray diffraction measurements on..... 1742
Biphenyl, arsine oxides of, 1064; resonance in substituted, 1350; F derivs. of, 1489; effect of, group in dissocn. of hexaarylethanes, 1824; nitration of halo-, 1848; halogenation of esters in, series, 2219, 2719; nitration of certain dinitro-, 2225; 4-nitrodiphenyl ether-4′-sulfonyl chloride..... 3056
Biphenylene, 1,8-dimethyl and 2,7-dimethoxy-..... 1698
Bismuth, oxidation of triethylbismuth, 392; thermodynamics of Sn–, system..... 1392
Blood, rheology of..... 1204
Bonds, conjugated diolefins by double, displacement, 826; addn. of HF to triple..... 2289
Boron, anal. and compn. of crude..... 2725
Boron bromide, cleavage of ethers with..... 1128

Boron chloride, reacn. with *p*-toluidine, 1584; elec. moment of... 2976
Boron compounds, stereochemistry of B coördination compds. of B, 325; N–org., 1584; oxidation of *n*-BuB oxide... 1811
Boron fluoride, introduction of *t*-Bu group into Et acetoacetate by means of, 728; use of diazonium borofluorides in Bart reacn., 828; systems with, 2198; steric strains as a factor in the relative stability of some etherates of, 2557; structure of $B(CH_3)_2F$ and BCH_3F_2, 2686; some, catalyzed alkylations of halobenzenes... 2751
Bridge compounds. See *Cyclic compounds.*
Bromate, reduction at dropping Hg electrode... 1044, 1970
Bromide ions, and the Br–ethylene reacn... 697
Bromination. (See also *Halogenation.*) water in photochem., of acetophenone, 887; of 4-PhPh chloroacetate... 2449
Bromine, addn. in presence of bromide ions to ethylene derivs., 697; vinyl bromide–, and allyl chloride–, reacns., 704; addns. in AcOH, 709; addn. to 1-*p*-bromophenyl-4-Ph-1,3-butadiene, 1160; reacns. of, with CCl_4 and tetrachloroethylene, 1342; sp. rate of the reacn. $O_3 + Br^- \rightarrow$. 2468
Bromoalkanes, configurations of some diastereomeric di-... 601
Bromo-*o*-xyloquinone, di-, and Na malonic ester... 528
Brucine, as reagent for partially resolving bromoalkanes, 601, (corrn.)... 3069
Bunte salts, use in synthesis... 149
Butadienes, substituted diphenyl-... 1160
Butanes, dielec. behavior of chloro-, 737; reacns. of AgAc with -3-bromo-, *dl*-2,3-dibromobutanes, 2780, 2787
n-Butane, ionization and dissocn. by electron impact in... 1588
1,2,4-Butanetrione enol, acylation of 1,4-dimesityl-, 1375; prepn. and alkylation of 1,4-dimesityl-3-Me-... 2423
2-Butanol, action of HF, H_2SO_4 and H_3PO_4 on optically active, 1025; reacn. of 3-bromo-, with PBr_3... 2791
Butanol lignin, acid hydrolysate of... 22
Butene derivatives, effect of water on reacn. of AgAc and... 2787
t-Butylacetic acid, acylation of Et ester of... 2714
Butyl alcohol, fractionation of starch by selective pptn. with... 2957
n-Butylamines, rapid prepn. of N-alkyl-... 2878
n-Butyl bromide, reacns. with Na salts of phenol, thiophenol and *n*-Bu mercaptan... 226
t-Butyl chloride, kinetics of toluene–, reacn., 648; ionization and dissocn. of, by electron impact... 2766
n-Butylhydroxylamine, N,N-di-, and its oxalate... 3057
n-Butyl methyl ketone, photochem. decompn. of... 2676
t-Butyl nitrate, reacn. velocity of, with water and hydroxyl ion... 1928
n-Butyl thiol, kinetics of *n*-BuBr–, reacn... 226
n-Butyric acid, α-bromo-β-methoxy-, 1223; acylation of acetonitrile with Et ester of... 2720
n-Butyrylacetic acid, by alcoholysis of a ketonitrile... 2720

CADALENE, oxidation of... 425
Cadinene, structure of... 417
Cafesterol, chem. behavior of... 2235
Calcium, X-ray study of Sr–, alloy series... 1226
Calcium cholesteryl sulfate, thermal decompn. of... 482
Calcium cyanamide, crystal structure of... 1730
Calcium nitrate, system: $Sr(NO_3)_2$–H_2O–... 1301
Calcium oxalate, effect of *p*H on soly. of, 2948; soly. of, monohydrate, in water and salt solns... 2946
Calcium α-tocopheryl succinate... 1084
Calorimeters, comparison of flow, for org. vapors... 2372
Calorimetry, investigation of org. reacns... 762
Campesterol, 7-dehydro-, a new provitamin D... 1900
Camphene series, inactivation in... 583
Camphor, configuration of bis-formyl, -ethylenediamine-Ni... 1924
Cannabinol, a physiol. active tetrahydro-, 26; tetrahydro-, homologs and analogs with marihuana activity, 694, 2653; some analogs of synthetic tetrahydro-, 2031; optically active synthetic tetrahydro-... 2087
Cannizzaro reaction, novel type of... 872
Capillarity, thermodynamic theory of electro-... 1548
Caproic acid, *n* of normal satd. fatty acids from, to stearic... 2739
Carbinols. (See also *Alcohols; Methanol.*) formation of phenolphthalein, 2312; $AlCl_3$ in condensation of Me dipropyl, with phenol... 2655
Carbohydrates. (See also *Sugars.*) studies on reacns. relating to... 1957, 1959
Carbon, N–C–C system in N^1-heterocyclic sulfanilamides, 2532; radioactive, as tracer in exchange between acetic anhydride and NaAc... 3050
Carbon acids, synthesis and oxidation of several 3... 2299
Carbon dioxide, Joule–Thomson effect in... 400
Carbonic acid, alkyl carbonates in synthetic chemistry... 576, 578, 580
Carbon monoxide, HF as condensing agent for, 1356; sorption of, by metals... 2610
Carbon tetrachloride, dielec. const. of, 117; reacn. of Br with... 1342
Carbonyl compounds, ketene diethylacetal reacn. with α,β-unsatd., 260; identification through conversion to hydantoins, 522; Raman spectra of, 1181; steric hindrance in, 1242, 1247, 1251; bridge compds., 1260; catalytic reduction of some, 1456; sterically hindered aliphatic, 1618, 1619, 2964; behavior of, bridge compds. with alkaline H_2O_2, 2439; mechanism of reacn. between hindered, and Grignard reagent... 2875
Carboxylation... 329, 333, 1621, 2975
Carboxylic acid, di-, derivs. of sulfonamides... 1572
Carcinogenic hydrocarbons, water soly. of... 108
Carotene, pro-γ-, 1173; isomerization of β-, 1856, (corrn.)... 3071
Carotenoids, isolation of prolycopene, 1075; studies on, 1440; formation of pro-, in "monkey flowers" under some conditions, 2510; of yellow corn grain... 2603
Carvacrolphthalein... 2538
Casein, glutamic acid from... 2035
Catalysis, reacn. in coal hydrogenation, 230; Inorg. and Org. (Berkman, Morrell, Egloff, book review), 474; HF in toluene–*t*-BuCl reacn., 648; halide ion, addn. reacn., 704; effect on oxidation products of hydroxylamine, 731; addn. polymerization, by substituted acyl peroxides, 1103; addn. reacns. of acetylenic alcs., 1220; decompn. of H_2O_2 by basic BeI_2 hydrosols, 1340; heat of catalytic hydrogenation, in soln., 1395; base-, cleavage of methylenedioxy rings, 1410; reduction of some carbonyl compds., 1456; hydrogenation of heptaldehyde in vapor phase, 1460; of thermal decompn. of acetaldehyde by H_2S, 1707; conversion of para-H on Ni, Pt and Pd, 1594; stereochemistry of, hydrogenation, 1985, 1991, 2003, 2006, 2009, 2014 (corrn, 3071), 2022; acidic and basic, in urethan formation, 2229; properties of charcoal, 2276; acid, hydrolysis of Ph substituted aliphatic esters, 2362; effect of electrolytes on solvolytic reacns., 2498; hydrogenation of cystine, 2721; reduction of cholesterol α-oxide... 2723
Catalysts, $AlCl_3$ in alkylation of paraffins, 33; Fe, in partial reduction of acetylenes to olefins, 363; metallic chlorides in Friedel–Crafts ketone synthesis, 464; Cu–alumina, in hydrogenation of alkyl Ph ketones, 520; effect of alkali promoter on decompn. of NH_3 over Fe, 745, 751; Al–$AlCl_3$, in benzoylation, 878; acid, in alkylation of benzene, 1032; non-peroxide, for SO_2–olefin reacn., 1229; $AlCl_3$ in condensation of *s*-aliphatic alcs. with benzene, 1576; for peroxide decompn., 2492; *p*-bromobenzenediazonium hydroxide in polymerization of styrene, 2508; $AlCl_3$ in condensation of Me dipropyl carbinols with phenol, 2655; some BF_3, alkylations of halobenzenes, 2751; mixed heteropoly acid, for vapor phase air oxidation of naph-

thalene, 2917; interchange of groups in aliphatic amines ... 2920
Catnip, nepetalic anhydride in, oil ... 1828
Celastrol, identity of ... 182
Cellobiose, synthesis of ... 1289
Cells, potentials of KCl transference ... 513
Cellulose, ethoxyl group in Et, 9; Me and other ethers of, 15; oxidation of, by NO_2, 121, 127; O-pentaacetyl-*d*-gluconates of, 2026, (corrn.) ... 3071
Cellulose acetate, distribution of acetyl groups in ... 1539
Cellulose esters, crystallinity of ... 776
Centrifuge, concn. of tobacco mosaic virus by Sharples super- ... 1804
Cerium salts, magnetic rotation of ... 412
Cesium cobaltous chlorides, absorption spectra of 2 .. 2748
Cesium sulfate, activity coeff. of ... 550
N-Cetylpiperidine, phys. consts. of ... 2511
Charcoal, adsorption of ampholytes on an activated charcoal, 1513; catalytic properties of ... 2276
Chaulmoogryl quaternary salts ... 2514
Chemical constitution, and the tanning effect ... 2274
Chemical engineering, Chem. Engineers' Handbook (Perry, book review) ... 190
Chemistry, Principles of General (Brinkley, book review), 474; Thorpe's Dictionary of Applied (Thorpe, Whiteley, book review), 2237; Chem. Dictionary (Campbell, book review), 2519; Tech. Report Writing (Rhodes, book review), 3063; Introductory College (Deming, Hendricks, book review), 3064; General (Holmes, book review) ... 3066
Chemotherapy, studies in ... 567, 1682, 2902, 2905
Chlorides, metallic, in Friedel–Crafts ketone synthesis, 464; action of Na alkyls on aliphatic, 1783; reacn. of acid, with Grignard reagents, 2966; introduction of the —COCl group into alicyclic and aliphatic acid ... 2975
Chlorination. (See also *Halogenation.*) of 1,1,1-trifluoropropane, 1157; of 4-PhPhAc ... 2219
Chlorine compounds, chloromethylation of trimethylhydroquinone diacetate ... 524
Chloroethyl ether, partial pressure of HCl from solns. in β,β'-di- ... 951
Chloroformyl group, introduction of, into alicyclic and aliphatic acid chlorides ... 2975
Chlorogenin, configuration of the hydroxyl groups in, 221; structure of side-chain of ... 809
Chlorohydrin, reacn. of epi-, with Grignard reagent .. 484
Chlorophyll, radioactive H in, photosynthesis ... 3037
Cholanic acid, 3(α),11,12-trihydroxy- ... 1228
etio-Cholan-3(β)-ol-17-one, conversion of pregnan-3-(β)-ol-20-one to ... 817
Cholestadienes, prepn. of $\Delta^{6,8(14)}$-, $\Delta^{7,9(11)}$-, $\Delta^{7,14}$- and $\Delta^{8,14}$- ... 140, 471
3,5,6-Cholestantriol-I, prepn. of ... 2723
Cholesterol α-oxide, catalytic reduction of ... 2453
Cholesterols, epimeric 7-hydroxy- ... 2317
Cholesteryl oxides, studies on ... 1941
Cholic acids, moments of ... 1941
Chroman, transformation of 3-acetoxy-6-hydroxy-2,4,5-trimethylbenzylacetoacetic ester to, derivs., 435; synthesis of 6-hydroxy- ... 440
Chromatography. Adsorption Analysis (Strain, book review), 1013; azoyl derivs. of sugars and sepn. by, adsorption, 1501; analysis of erythrina alkaloids, 1892; method for standardization of, analysis, 1905; sepn. of *cis* and *trans* stilbenes and benzoin and anisoin oximes by, brush method, 1919, 1922; Principles and Practice of (Zechmeister, Cholnoky, book review) ... 2729
Chromene derivatives, transformation of 3-acetoxy-6-hydroxy-2,4,5-trimethylbenzylacetoacetic ester to ... 435
Chromium compounds, sp. gr. of $Na_2Cr_2O_7$, solns., 175; isotherms of the system Na_2CrO_4–$NaClO_3$–H_2O 2746
Cinchona alkaloids, in pneumonia ... 1162
Cinchoninic acid, keto and mercapto derivs. of, from rhodanine-oxindoles ... 1669
Cinnamic acid, derivs. of ... 2859
Citrinin, polarographic detn. of, 1490; color test for, and prepn. of ... 2228
Claisen rearrangement. See *Rearrangement.*
Cleavage. (See also *Hydrolysis; Reactions.*) base-catalyzed, of methylenedioxy rings ... 1410
Cleavage, reductive, of dioxolones by the Grignard reagent ... 1567
Clionasterol, location of double bond in ... 473
Coal, catalytic reacn. in, hydrogenation, 230; mol. wts. of hydrogenation products of bituminous, 734; oxidizing power of air exposed ... 1809
Cobalt compounds, as catalysts ... 2492
Cobalt ions, adsorption of simple and complex, on TiO_2 ... 2820
Cobaltous chloride, absorption spectra of some double salts containing ... 2748
Cobalt oxides, reacns. of, (II) and (III) in liquid NH_3 ... 2772
Cocarboxylase, and related esters ... 2279
Collagen, X-ray diffraction spacing of, 727; electron microscope observations of ... 1234
Colloid science, Advances in (Kraemer, Bartell, Kistler, book review) ... 2521
Color, and constitution ... 199
Columbium compounds, structure of K_3CbOF_6 ... 1139
Compressibility, of isobutene ... 548
Condensations, 2271, 2714; intramol. aldol, in unsatd. ketone polymers, 177; intramol., in polymers, 269; HF as agent for, 1356; by Na, 2239, 2240, 2242, 2247, 2250 (corrn., 3073); poly-, of α-amino acid esters, 2264, 2268; new example of aldol. ... 2567, 2569
Conductivity, of KIO_3, 7; of dodecyl- and octadecylamines, 97; anomalies in, measurements with H_2O_2, 454; of aq. alkali hydroxides, 621; sp., of chlorobutanes and chloropentanes, 737; of high mol. wt. aliphatic amines and salts, 772; studies, 1544, 1635; temp. coeff. of, of KCl solns ... 2517
Contact angles, reproducible, on reproducible metal surfaces ... 494, 1530, 1641
Copper, alumina–, catalysts in hydrogenation of alkyl Ph ketones, 520; a, bearing protein in cow's milk, 1616; sorption of CO on ... 2610
Copper hydroxide, hydrous and basic cupric sulfates . 503
Copper(II) ions, of diethylenetriamine ... 686
Copper sulfates, hydrous $Cu(OH)_2$ and basic cupric sulfates ... 503
Cori ester, β-form of ... 23
Corn sirup, structure of dextrins isolated from ... 2331
Coronene, ultraviolet absorption spectra of, 1485; attempted synthesis of, from Cu and 2,7-polythionaphthalenedialdehyde ... 2343
Cosmos sulphureus, pigments of ... 1704
Cotton, American, Handbook (Merrill, Macormac, Mauersberger, book review) ... 1014
Cottonseed, chemistry of allergens from ... 1889
Coumaran derivatives ... 382
Coumaran series, orientation studies in ... 1315, 2986
Coumarones, 5-aminocoumarone-2,3-dicarboxylic acid cyclohydrazide ... 86
Cresol, formation of diphenylmethyl ether of *o*-, 2154; effect of *p*-, concn. on cresolase activity of tyrosinase ... 2344
Cresolase, factors influencing, activity of tyrosinase .. 2344
Critical constants, of isobutene, 546; eq. of state for gases at high pressures involving only ... 2195
Crotalaria grantiana, alkaloid of ... 571
Crotaline, structure of mono-, 2593, 2597; (corrns.) .. 3067
Crotonic acid, action of benzoyl chloride on Et β-diethylaminocrotonate ... 612
Crotoxin, electrophoresis of ... 1586
Crotyl chloride, conversion to acetate and Et ether ... 2157
O-Crotyl-3,5-dichlorosalicylic acid, rearrangement of. 607
4-Crotyloxy-3,5-dichlorobenzoic acid, rearrangement of ... 1066
Crystallinity, of cellulose esters ... 776
Crystal structure. (See also *Isomerism; Molecules.*) of diphenylselenium dichloride, 508; of Ca cyanamide, 1730; of β-glycylglycine ... 2236

Crystal study, of alums ... 1819
Crystal violet ion, isomers of ... 1774
Cumene, d. and refractive index of ... 3056
Cyanamide, sulfanilyl-, and related compds ... 1682
Cyanic acid, synthesis of α-, esters, 576; cyanates and thiocyanates of Pb, As and Sb, 1757; kinetics of transformation of hydrazine cyanate into semicarbazide ... 2777
Cyanides, reduction of complex Ni, 1187; reduction of complex ... 2715
Cyanine dyes, effect of solvents on absorption spectra of polymethine dyes ... 2923
Cyanines, absorption of unsym ... 199
Cyanoacetic acid, reacn. product of phenylhydrazine and Et ester of ... 2133
Cyanoethylation, of active methylene group of acrylonitrile ... 2457
Cyanogen, kinetics of thermal reacn. of H and ... 1880
Cyanohydrin, reacn. of β-isodurylaldehyde, with PhMgBr ... 1724
Cyanostilbenes, unsym., 885; sym ... 2486
Cyclic compounds, photochem. decompn. of, ketones, 80; 5-aminocoumarone-2,3-dicarboxylic acid cyclohydrazide, 86; carbonyl bridge compds., 1260; synthesis of condensed, 1311; $PbAc_4$ cleavage of cyclic α-keto alcs., 1416; detn. of bridge structure of dipyrrylmethanes ... 2098, 2106
Cyclization, of β-styrylacetaldehyde, 1007; of ureido derivs. of iminodibasic acids, 1686; mechanism of reactions, 2894; derivatives, 2696, 2701, 2703; structure of methylene- ... 1142
β-Cyclogeraniol ... 1979
Cycloheptadecanol, in American musk ... 144
Cyclohexadiene, decompn. of 1,4-, 1527; dehydration of 1,5-hexadiene-3-ol to 1,3,5-hexatriene and 1,3- ... 1978
Cyclohexane, ternary systems of water, propyl alcs. and, 1886; heat capacity of Me-, and, 2375; reacn. of AgAc with bromo-, 2780, 2787; identity of various prepns. of 1,2-dibromo- ... 2792
Cyclohexanecarboxylic acid, "trans"-2,2,6-Me_3- ... 385
Cyclohexanol, dipole moments of ... 1982
Cyclohexanone, dipole moments of ... 1982
Cyclohexatriol-2,4,6, rearrangement of 1,1,3,3,5,5-hexamethyl-, to hexamethylbenzene ... 2461
Cyclohexene, periodate oxidation of *cis*- and *trans*-, glycols, 552; heat capacity of, 2375; effect of water on reacn. of AgAc and, derivs ... 2787
Cyclohexene oxide, decompn. of ... 1527
Cyclohexenecarbonals, action of alkali on ... 1497
Cyclohexen-1-yl)-propionic acid, prepn. of β-(2-Me-6-oxo-1- ... 3050
p-Cyclohexylphenyl-phenylsulfone ... 1489
Cyclohexyl *p*-toluenesulfonate, solvolysis of *trans*-2-acetoxy- ... 2796
Cyclopentadecanol, in American musk ... 144
Cyclopentadiene, vapor pressure of di- ... 2501
Cyclopentadienone, reacns. with Ph_4^- ... 604
Cyclopentane derivatives, pyrolysis of ... 897
Cyclopentane-1,1′-tetralin, spiro- ... 1719
1,2-Cyclopentenonaphthalene, 3′-keto-2-Me-6-hydroxy-1,2,3,4-tetrahydro- ... 94
1,2-Cyclopentenophenanthrene, 2′-ketodihydro- ... 1421
Cyclopentyl phenyl ketone, alkylation of 2-Me-, (corrn.) ... 3069
Cyclopropanes, formation from monohalides ... 1783
β′-Cymoxydiethyl ether, some quaternary salts from β-dimethylamino- ... 2232
Cysteine, Se tetra- ... 1742
Cystine, N,N′-di-acetylsulfanilyl-*l*-, and N,N′-disulfanilyl-*l*-, 1488; catalytic hydrogenation of ... 2721

DEAMINATION, of 5-amino-8-nitroisoquinoline ... 2442
Debye–Hückel theory. (See also *Ionization.*) revised consts. for ... 2724
Decalin, magnetic susceptibilities of *cis* and *trans*, 717; amylsodium–, reacn., 2250, (corrn.) ... 3073
Decomposition. See *Pyrolysis.*
Decylamines, conductivities of do- and octa- ... 97
n-Decylsodium, prepn. of ... 2239
Dehydration, of alcs ... 2970
Dehydrogenation, studies in ... 1719
Density, temp. and compn. coeffs. of, of MeOH–dioxane system ... 1207
Detergents, effect of, on soly. of propylene vapor in H_2O, 1556, (corrn.) ... 3071
Deuterium, carbonyl reductions with, 1456; use of, as tracer in Claisen rearrangement, 2302; prepn. of ... 2613
Deuterium chloride, prepn. of ... 2223
Deuterium compounds, prepn. of, of pyrrole, 1543; heat capacity of benzene-d_6, 2482; prepn. of *d*-1-deutero-2-methylbutane ... 2563
Deuterium oxide, H exchange with ... 2503
Dextran, bacterial synthesis of, from sucrose ... 1959
Dextrins, mol. wt. of Schardinger α- and β-, 1651; structure of, isolated from corn sirup ... 2331
Diazomethane, action of, on acyclic sugar derivs. 1701, 2329
Diazonium borofluorides, use in the Bart reacn ... 828
Diazonium compounds, color reacns. of sympathomimetic amines with ... 1318
Diazonium salts, prepn. of benzene- ... 469
Diazotization, of nitrobenzene, 19; of an aminoarylead compd ... 1007
Dibenzylidene dulcitol, structure of 1,3,4,6-, 132; a new, (2,3,4,5), 136; a second 2,3,4,5- ... 137
Dielectric constant, of CCl_4, 117; electrode polarization in, measurements, 624; soly. effect in solvents of low ... 2822
Dielectrics, studies on muscle hemoglobin, 638; behavior of chlorobutanes and chloropentanes, 737; (Vol. XL, N. Y. Acad. Sci., book review), 1238; investigation of polypeptides, 1379, 1870; relation of, properties to structure of crystalline polymers, 2164, 2171; behavior of *i*-Bu and *i*-amyl bromides, (corrn.) 3067; consts. of some pairs of diasteromers, (corrn.) ... 3067
Diels–Alder reaction, mechanism of ... 3058
Diene synthesis, mechanism of "aromatizing," reacns. in nitrobenzene ... 176
Dienes, absorption spectra of normal conjugated, 72; condensation with cyclic 1,3-diene systems ... 604
Dienyne, reduction, 363; ring synthesis by the, double addn. reacn ... 1311
Diffraction. See *Electron; Rays, Roentgen.*
Diffusion, in and through Solids (Barker, book review) ... 1013
Digitogenin, position of hydroxyl groups in ... 1843
Diketene, dipole moments of, and related compds ... 768
Dimethyl ether, thermal decompn. of ... 994
Dimethyl sulfide, thermodynamics of ... 169
Dimorphism. (See also *Polymorphism.*) of amylcaine hydrochloride ... 1227
Dineric distribution, new method for detg ... 347
Diols, nitro-, from simple aldehydes ... 1735
Diosgenin, new sources of ... 1283
Dioxane, elec. moments of org. Hg halides in, 830; temp. and compn. coeffs. of d., refractive index and viscosity of MeOH–, system, 1207; b. p.–compn. data of MeOH–, system, 1231; acid strengths in H_2O–, mixts., 2065; elec. moments of inorg. halides in, 2076; soly. of KIO_3 and $Zn(IO_3)_2$ in water–, mixts., 2305; system: $NaBO_3$–H_2O–, 2474; a dioxanate of IF_5 ... 2727
Dioxolane, rates of O absorption by, and Me- ... 1354
Dioxolones, reductive cleavage of, by Grignard reagent ... 1567
Diphenic acids, hydrogenation of, 1985; prepn. of the 6 inactive, 1991; optically active, 2003; hexahydro-, 2006; assignment of *cis*- and *trans*-configurations in perhydro-, 2009, (corrns.), 3071; fluorenones and ... 2845
Diphenylamine, f. ps. of binary mixts. of ... 1057
Diphenylmethyl ether, formation and rearrangement of, of *o*-cresol ... 2154
Dipole moment. See *Electric moment.*

Dispersion, of simple amino acid polypeptides, 1870; molar, of free and bonded ions..... 3023
Dissociation, ionization and, by electron impact in *n*-butane, isobutane and ethane, 1588; of *n*-PrCl and *t*-BuCl, 2766; of isobutylene, propane and propylene, 2769; of hexaarylethanes, 1824, 2227; photo-, in rigid solvents..... 2801
Dissociation constant, of α-nitrotetronic acid, 1948; of diphenylselenium dibromide and diiodide..... 2672
Disulfides, Bunte salts for syntheses of aliphatic.... 149
Dithionite ion, thermodynamics of..... 398
Docosanes, 7 alkyl substituted..... 1360
Dodecylamine, H_2O–, system, 1516; surface tension of aq. solns. of, acetate, 2067; behavior of, salts in water, EtOH and benzene..... 2824
N-Dodecylpiperidine, phys. consts. of..... 2511
Dulcitol, structure of 1,3:4,6-dibenzylidene-, 132; a new dibenzylidene, (2,3,4,5-dibenzylidene-,), 136; a second 2,3,4,5-dibenzylidene-, 137; structure of dimethylene, 986; structure of di-*o*-nitrobenzylidene-..... 1614
Du Pont, One Hundred and Forty Years (Dutton, book review)..... 3064
Dyes, resonance as a classification basis for, 199; from anthracene-9-aldehyde, 1101; isomers of crystal violet ion, 1774; effects of solvents on absorption spectra of.....2923, 2937

ELECTRICAL methods, Phys. Examn. of Metals (Chalmers, Quarrell, book review)..... 2519
Electrical properties, of solids.....283, 2389
Electric moments, of 5 org.-metallic halides, 173; of inorg. halides in dioxane, 614; of diketene and related compds., 768; of org. mercuric halides in dioxane, 830; reduction by steric hindrance of, of di-*t*-butylhydroquinone, 937; and resonance in heterocyclic mols. containing N and S, 1130; of a free radical, 1179; of some bile acids, 1941; of urea and thiourea, 1944, (corrn.) 3071; of α-nitrotetronic acid, 1948; of cyclohexanol and cyclohexanone in dioxane, 1982; of inorg. halides in dioxane, 2076; vapor, of some substituted benzenes, 2212; in nitroethane and some chloronitroparaffins, 2829; solvent polarization error and its elimination in calculating, 2988; of *ms*-tetraphenylporphine..... 2993
Electrocapillarity, thermodynamic theory of, 1548; and theory of maxima of dropping Hg electrode.. 2177
Electrochemistry, and Electrochem. Analysis (Sand, book review)..... 2728
Electrodes. (See also *Polarization; Potential electric.*) behavior of tocopherols at dropping Hg, 447; standard potential of Ag–AgBr, in MeOH, 517; polarization in dielec. const. measurements, 624; quinone behavior at dropping Hg, 644; amperometric titration of α-tocopherol at dropping Hg, 646; electroreduction of water at dropping Hg, 833; reduction of perrhenate ion at dropping Hg, 1001; reduction of iodate and bromate at dropping Hg, 1044; potential of ytterbic–ytterbous ion, 1133; dropping Hg, in AcOH, 1303; molal, potential of Ag–AgCl, 1478; reduction of unsatd. hydrocarbons at dropping Hg, 1765, 2365; reduction of iodate and bromate at dropping Hg, 1970; dropping Hg, in AcOH, 2177; e. m. f. of HgBr, 3021; change in potential of Ag–AgCl, with time..... 3053
Electrolysis. (See also *Cells; Electrodes; Oxidation; Reduction.*) reduction of strychnine..... 790
Electrolytes. (See also *Acids; Bases; Conductivity; Ionization.*) influence of, on ammonolysis by NH_3, 467; thermodynamics of bi-univalent, 1136; catalytic effect of, on solvolytic reacns., 2498; surface tensions of, solns. as function of concn., 2744; diffusion of, and ions in their mixts., (corrn.)..... 3067
Electromagnetism, mechanism of the beta phosphorescence of fluorescein in acid soln..... 1916
Electromotive force. See *Potential, electric.*
Electron. (See also *Ions; Molecules.*) microscope observations of collagen, 1234; low, levels in Eu ion, 1346; ionization and dissocn. by, impact, in *n*-butane, isobutane and ethane, 1588; of *n*-PrCl and *t*-BuCl, 2766, of propylene, isobutylene and propane, 2769; Microscope (Burton, Kohl, book review)..... 3060
Electron diffraction, investigation of mol. structures of $SiBr_4$, tribromosilane and dibromodifluorosilane, 62; of methylenecyclobutane and hexamethylethane, 1142; of N_2O and H azide, 1184; of propargyl halides, 1753; study of $B(CH_3)_2F$ and BCH_3F_2, 2686; investigation of pirylene, 2693; of Me isocyanide..... 2952
Electrophilic reagents, reacns. of certain neopentyl systems with..... 2633
Electrophoresis, of interstitial cell hormone, 367; effect of urea on, patterns of serum proteins, 1090; of crotoxin, 1586; study of proteins in rubber latex serum..... 2628
Emersion, energy of, of crystalline powders..... 1195
Emulsin, almond, action on Ph 2,4,6-Me_3-β-D-glucoside..... 374
Enediols, 2152, 2891; effect of methoxyl toward stabilizing, 2258; prepn. of a..... 2260
Energy. (See also *Heat.*) free, of HNO_3 gas, 48, (corrn.) 3069; of immersion, of crystalline powders, 1190; of adhesion and emersion of crystalline powders, 1195; binding, between a crystalline solid and a liquid, 1195; states of solids, 1346; apparent, of the N–N bond from heats of combustion, 2369; changes at crystalline solid surfaces..... 2383
Enolates, quinone, reacn..... 528
Enolization. See *Isomerization.*
Entropy, of HNO_3, 48, (corrn.) 3069; of Me mercaptan, 165; of dimethyl sulfide, 169; of solution of HCl, 951; of isopentane, 1039, (corrn.)..... 3069
Enyne, reduction..... 363
Enzymes. (See also *Amylase.*) hydrolysis of alkyl β-D-glucosides, 369; almond emulsin and populin action on Ph 2,4,6-Me_3-β-D-glucoside, 374; specificity studies of "azol-esterases," 564; und ihre Wirkungen (Oppenheimer, book review), 1014; ascorbic acid–ascorbic acid oxidase reacn., 1212; *Bacillus macerans* amylase, 1432; A Symposium on Respiratory (book review), 2520; phosphatase activity of parathyroid hormone, 2759; action of *macerans*, on a corn starch component..... 3044
Enzymology, Advances in, and Related Subjects (Nord, Werkman, book review)..... 1744
Equation of state, for gaseous isobutene, 548; for gases at high pressures, 2195; of gaseous mixts... 2816
Equilenone, 6-hydroxy-1,2,3,4-tetrahydro-17-..... 536
Equilibrium. (See also *Pressure.*) vapor phase esterification..... 36
Erythraline, constitution of..... 2146
Erythramine, constitution of..... 2146
Erythratine, constitution of..... 2146
Erythrina alkaloids.....1892, 2146
Esterification, vapor phase, equil..... 36
Esters, chain structures of linear poly-, 154; specificity studies of "azol-esterases," 564; prepn. of ortho-, 1825; dielec. properties and structure of poly-, 2164; reacn. of, with Grignard reagents.... 2966
Estrogens, synthesis of an analog of the sex hormones. 94
Estrone, phenolic B ring, isomer, 536; synthesis of a stereoisomer of, 974; derivs. of, containing O at position 16..... 2235
Ethane, ionization and dissocn. by electron impact in, 1588; dissocn. of hexaaryl-, 1824, 2227; prepn. of polyethoxy-, and bromo derivs., 1963; dipole moment, induction and resonance in..... 2829
Ethanolamine, action of mono-, on Et bromomalonate, 1010; synthesis of 2-alkylaminoethanols from, 1503, (corrn.)..... 3071
Etherates, of BF_3..... 2557

Ethers, Me and other, of cellulose, 15; acetylenic, 223, 2635; cleavage of, with BBr_3, 1128; keto, 1222, 2882
Ethoxyl groups, in ethylcellulose ... 9
Ethyl alcohol, reduction of V_2O_5 by ... 1462
Ethylene, halogen addn. to, derivs., 697, 704, 709; reacn. of Br with tetrachloro-, 1342; hydrogenation of ... 1404
Ethylenediamine, configuration of bis-formylcamphor-, -Ni, 1924; N,N-dimethyl-, and derivs.. 2232
Ethylene glycol. See *Glycol.*
Ethylenetriamine, Cu(II) and Ni(II) complex ions of di- ... 686
Europium ion, evidence for low electronic levels in.. 1346
Europium sulfate octahydrate, heat capacity of ... 1346
Expansion, linear thermal coeff., of alums ... 1819

FAGARA COCO (Gill) Engl., identification of alkaloids in ... 2326
Fagarine, isolation of ... 2326
Fats, seed, of *Litsea longifolia* Bth. & Hk., 1079; antioxidants and autoxidation of ... 2337
Fatty acids. (See also *Acids.*) branched-chain, 1106; nature of, associated with starch, 2144; refractive indices and ds. of normal satd., in liquid state, 2739; of cereal starches ... 2954
Ferruginol, structure of ... 928
Fiber patterns, chain structure of trimethylene glycol series ... 154
Fibrinogen, on blood plasma fluidity ... 1204
Films. (See also *Adsorption, Surface.*) water soly. of carcinogenic hydrocarbons, 108; of amine hydrochlorides, 498; pressure–area–temp. and energy relations of monolayers of octadecanenitrile, 1600; sol. and insol., of amine acetates... 2067
Flavianates, soly. of, of certain org. bases in H_2O, EtOH and *n*-BuOH ... 2507
Fluidity, effect of fibrinogen on, of blood plasma.... 1204
Fluorenes, synthesis of some Me dibenz-, by cyclization ... 2894
Fluorenones, and diphenic acids ... 2845
Fluorenone-spirohydantoin, alkaline hydrolysis of.. 689
Fluorescein, beta phosphorescence of ... 1916
Fluorescence, Chem. and their Applications (de Ment, book review) ... 1983
Fluorides, structures of complex, 633, 1139, 1233; use of diazonium boro-, in Bart reacn., 828; synthesis of aliphatic di-, 1115; heat capacity of manganous ... 1535
Fluorine derivatives, of biphenyl ... 1489
Fluorobenzene, heat capacity of ... 2375
Fluorochlorobromomethane ... 1599
Fluoropropane, chlorination of 1,1,1-tri- ... 1157
Formaldehyde, from the aloins, 1378; reduction of V_2O_5 by, 1462; reacn. of, with 1(−)-asparagine.. 2899
Formanilides, action of Grignard reagents on benzoyl-, 1086; N-Me-, synthesis of aldehydes... 1666
Formic acid, prepn. of tri-*m*-nitrophenyl orthoformate, 186; furfuryl formate, 1583; vapor phase photo decompn. of Me ester of, 1821; relative acid strengths of acetic, propionic and, 2065; oxidation of amino acids by H_2O_2 in ... 3054
Free energy. See *Energy.*
Freezing points, of binary mixts. of diphenylamine.. 1057
Friedel–Crafts reaction, metallic chlorides as catalysts for, of ketones, 464; Al–$AlCl_3$ catalyst in, 878; acylations of some sterically hindered alkylbenzenes ... 2421
Fructosan, a new, isolated from *Yucca mohavensis*, Sarg ... 2501
d-Fructose-1,6-diphosphate, prepn. of, by means of baker's yeasts ... 2722
L-Fucitol, structure of diacetone- ... 982
Fucosterol, structure of ... 1732
Fucoxanthins, interconversion of ... 1235
Fumaric acid, synthesis and oxidation of, with radiocarbon ... 948
Furaldehyde, transformation of Me_4-glucoseen-1,2 into 5-(methoxymethyl)-2- ... 265
Furan, synthesis of phenanthro(1,2-*b*)-, derivs., 1421; halogen compds. derived from 4-Me-2,5-diphenyl-, 2583; conversion of unsatd. 1,4-diketones into... 2585
Furanones, conversion of unsatd. 1,4-diketones into hydroxy- ... 2585
Furfural, from the aloins ... 1378
Furfuryl formate ... 1583
Furoic acid, reacn. of Me ester of, with benzene and chlorobenzene, 2136; reacn. with aromatic compds., 2227; reacn. with tetralin ... 2601

GALACTAN, constitution of arabo-, 302, (corrn., 3069) ... 1507, 2838
D-Galactosan<1,5>β<1,6>, studies on ... 2435
Galactose, polymorphism of *d*-, diethylmercaptal pentaacetate, 183; ioslation of hepta- and octamethyl-6-galactosido-, through partial hydrolysis of methylated arabogalactan, 302; rate of reacn. of diacetone, with *p*-toluenesulfonyl chloride in pyridine soln ... 2463
Gallic acid, esters of ... 2274
Gallium trihalide, structure of ... 2514
Gases, Photochemistry of (Noyes, Leighton, book review), 476; empirical heat capacity eqs. of, 2511; War—Their Identification and Decontamination (Jacobs, book review), 2519; adsorption of some, at low temp. and pressure on Ag, 2545; 2nd virial coeffs. of, mixts ... 2816
Gelatin, tanning of, 868; effect of, concn. on cresolase activity of tyrosinase ... 2344
Gentiobiose derivatives, new ... 1110
Geraniol, condensation of β-cyclo-, with leucoisonaphthazarin ... 1979
Germanium compounds, Rb_2GeF_6 ... 1233
Germanium tetrachloride, elec. moment of, 2076; prepn. of ... 3042
Glass, the Miracle Maker (Phillips, book review)... 729
Globulin, hydration of β-lacto-, crystals, 2393; X-ray and optic measurements on β-lacto-, 2504; digestion of β-lacto-, by pepsin ... 2664
L-Glucoheptulose, studies on, 1606; oxidative degradation of ... 1609
d-Gluconic acid, O-pentaacetyl-*d*-gluconates of polyhydric alcs. and cellulose, 2026, (corrn.) ... 3071
Glucononitriles, absorption spectra and X-ray study of isomeric ... 1950
d-Glucopyranose 1-phosphate, the Cori ester ... 23
Glucose, mutarotation in aq. MeOH mixts., 236; mutarotation of α-D-, in dioxane–water mixts., 1010; new, derivs., 1110; sulfanilyl-2-amino-α-D-, 1371; rate of reacn. of diacetone, with *p*-toluenesulfonyl chloride in pyridine soln ... 2463
Glucoseen-1,2, transformation of Me_4-, into 5-(methoxymethyl)-2-furaldehyde ... 265
Glucosides, enzymic hydrolysis of alkyl β-D-, 369; almond emulsin and populin action on Ph 2,4,6-Me_3-β-D-, 374; rotational relationships of alkyl, 1482; fractionation of partially methylated ... 1957
5-D-Glucosido-D-arabinose, synthesis of ... 2831
Glutamic acid, γ-alkylamides of, 1021; optical configuration of, from casein hydrolyzates ... 2035
Glutathione, absorption of O by, in alkaline solns... 2282
l-Glycidol ... 1291
Glycine, prepn. of, 725; di-, halogen acid addn. products, 1286; crystal structure of β-glycyl-, 2236; polycondensation of, esters ... 2264
Glycogen, phys. chem. characteristics of ... 2349
Glycol, chain structure of trimethylene, series, 154; kinetics of periodate oxidation of 1,2-, 552; esters of thiodi-, 908; nitro-, from simple aldehydes, 1735; α-*o*-methoxyphenol-β-mesitoyl-, 2260; vinylogs of acetylene and ethylene ... 2891
Glycosides, prepn. and rearrangement of Ph-, 690; synthesis of phenolic ... 2419
Glyoxal, benzamidine–Ph, reacn ... 2028
Glyoxalines, 1434, 2028; complex formations between I_2 and μ-mercaptodihydro- ... 2706
Gold, contact angles of water against Ag and, 494;

interfacial contact angles between water and org. liquids on, surfaces....1530, 1641
Gold compounds, with α-tocopherol.... 642
Grantianine.... 571
Grignard reactions, abnormal, 1239, 1242, 1247, 1251, 1618, 1619, 2964, 2966, 2968; factors detg. the course and mechanism of.... 2972
Grignard reagents. (See also *Magnesium compounds.*) reacn. with acyloxyanthrones, 376; reacn. of epichlorohydrin with, 484; action of, on benzoylformanilides, 1086; action on certain pentacenequinones, 1253; reacn. of, with esters of highly hindered acids, 1450; reductive cleavage of dioxolones by, 1567; behavior of pyrogallol trimethyl ether and 3,4,5-trimethoxybenzonitrile toward, 2085; attempted asymmetric syntheses involving, in optically active solvents, 2842; ionic nature of, 2865; mechanism of reacn. between hindered carbonyl compds. and, 2875; reducing action of primary and secondary, with trimethylacetyl chloride, (corrn.).... 3067
Guanidine, some mono- and disubstituted.... 2231

HALIDE ion, catalyzed halogen–ethylene reacn.... 704
Halides. (See also *Bromides; Chlorides; Halogen compounds; Iodides.*) mol. structures of some Si poly-, 62; dipole moments of org.-metallic, 173; ketene diethylacetal reacn. with org., 254; elec. moments of some inorg., in dioxane, 614, 2076; radio halogen exchanges in P, 850; infrared spectra of ammonium, 857; formation of cyclopropanes from mono-, 1783; retention of configuration in reacn. of some di-, and acetoxy-, with AgAc, 2780; effect of metallic, on reacn. of Grignard reagents with benzalacetophenone and benzophenone.... 2972
Haloform, mechanism of, reacn.—prepn. of mixed.. 1413
Halogenation, of esters in the biphenyl series, 2219, 2719; of *m*-diphenylbenzene.... 2485
Halogens, addn. to ethylene derivs., 697, 704, 709; compds. derived from 4-Me-2,5-diphenylfuran, 2583; derivs. of phenoxyacetylene, 2635; BF_3 catalyzed alkylations of halobenzenes.... 2751
Haptenic substances, pptn. reacns. between antibodies and poly-, 2994; pptn. reacns. of poly-, 3003; compn. of simple poly-, 3010; hapten inhibition of pptn. of simple poly-.... 3015
Heat capacity, of HNO_3, 48, (corrn.) 3069; of Me mercaptan, 165; of dimethyl sulfide, 169; data for 2,2,4-trimethylpentane, 179; of *dl*-α-alanine, β-alanine and lactamide, 191; of red and yellow Pb monoxides, 617; of Ni nitrate hexammoniate, 629; of morpholine and its aq. solns., 679; of white P, 839; hysteresis of liquid isopentane, 1034; of isopentane, 1039, (corrn.) 3069; of org. vapors, 1224; of Eu sulfate octahydrate, 1346; of manganous fluoride, 1535; high temp., of Mn_3O_4, $MnSiO_3$ and Mn_3C, 1769; high-temp., of MnO and $MnSO_4$, 1770; of org. vapors, 2372, 2375; of benzene-d_6, 2482; empirical, eqs. of gases, 2511; at low temps. of anhyd. sulfates of Fe, Mg, Mn and K.... 2949
Heat of combustion, apparent energy of the N–N bond calcd. from.... 2369
Heat of dilution, of HNO_3, 48, (corrn.) 3069; of $Mn(NO_3)_2$–H_2O system.... 1445
Heat of formation, of MnO and $MnSO_4$.... 1770
Heat of fusion, of Me mercaptan, 165; of dimethyl sulfide, 169; of white P, 839; of isopentane, 1039, (corrn.).... 3069
Heat of hydrogenation, catalytic, of pairs of stereoisomers.... 1395
Heat of hydrolysis, of some acid anhydrides.... 1747
Heat of ionization, of *dl*-alanine.... 762
Heat of reaction, org.....1472, 1747, 2664
Heat of solution, of HCl, 951; of $Mn(NO_3)_2$–H_2O system.... 1445
Heat of transition, of Me mercaptan, 165; of Ni nitrate hexammoniate.... 629
Heat of vaporization, of Me mercaptan, 165; of dimethyl sulfide, 169; of isopentane, 1039, (corrn.) 3069; of Hg.... 2190
Hemoglobin, dielec. studies on muscle.... 638
Hemorrhage. (See also under *Vitamin K.*) anti-, activity of sulfonated derivs. of 2-Me-naphthalene, 1096; water-soluble compds. with anti-, activity. 2657
Heneicosanes, five 11-substituted.... 1801
Heptaldehyde, catalytic hydrogenation of, in vapor phase.... 1460
Heptulose, studies on L-gluco-, 1606; oxidative degradation of L-gluco-.... 1609
1,5-Hexadiene-3-ol, dehydration to 1,3,5-hexatriene and 1,3-cyclohexadiene.... 1978
Hexamethylethane, structure of.... 1142
1,3,5-Hexatriene, dehydration of 1,5-hexadiene-3-ol to, and 1,3-cyclohexadiene.... 1978
Hindrance, in AcOH synthesis.... 300
Histamine, relation between structure and, -like activity.... 2288
History of chemistry, Torch and Crucible (French, book review), 729; Four Treatises of Theophrastus von Hohenheim Called "Paracelsus" (Sigerist, book review), 1237; Tools of the Chemist (Child, book review), 1982; The Stone that Burns (Haynes, book review), 2521; Du Pont—One Hundred and Forty Years (Dutton, book review).... 3064
Hormones, synthesis of analog of the sex, 94; phys.-chem. of interstitial cell, from sheep pituitary gland, 367; phosphatase activity of parathyroid. 2759
Hunnemanine, a new alkaloid from *Hunnemannia fumariaefolia Sweet*.... 1659
Hydantoins, identification of carbonyl compds. as, 522; alkaline hydrolysis of fluorenone-spiro-, 689; from phenylglyoxal and urea reacn., 1434; containing a tetrahydropyranyl substituent, 1672; cyclization of ureido derivs. of iminodibasic acids and synthesis of, 1686; 5,5-dimethyl-, containing a —NRR′ substituent.... 2881
Hydration, of $Al_2(SO_4)_2$, 41; of unsatd. compds., 1117, 1122, 1953; of isobutene in dil. HNO_3, 1938; of β-lactoglobulin crystals.... 2393
Hydrazides, 5-aminocoumarone-2,3-dicarboxylic acid cyclo-.... 86
Hydrazine cyanate, kinetics of transformation of, into semicarbazide.... 2777
Hydrazines, initial step in action of acids on tetraaryl-.... 2808
Hydrocarbons, soly. of carcinogenic, in water, 108; reacn. of oxalyl chloride with paraffin, 329; and unsatd., 333; higher, 1360, 1801; reduction of unsatd., at dropping Hg electrode.....1765, 2365
Hydrochloric acid, molal vol. of, 758; partial pressure of, from org. solvents, 951; soly. relations of HgO in.... 2380
Hydrochlorides, films of amine.... 498
Hydrocyanic acid, structure of.... 722
Hydrofluoric acid, catalyzed reacn. between toluene and *t*-BuCl, 648; action on 2-butanol, 1025; as condensing agent, 1356; addn. of, to the triple bond.... 2289
Hydrogel, of zirconia.... 110
Hydrogen. (See also *Deuterium; Dehydrogenation; Hydrogenation.*) catalytic conversion of para-, on Ni, Pt and Pd, 1594; kinetics of thermal reacn. of cyanogen and, 1880; adsorption of, on ThO_2, 1731; new method for estimation of active, 2098; tracer studies with radioactive, 2293, 2294, 3037; exchange with D_2O and T_2O, 2503; effect of certain factors in sepn. of, isotopes.... 2613
Hydrogenation. (See also *Reduction.*) of β-iminonitriles, 150; catalytic reacn. in coal, 230; catalytic, of alkyl Ph ketones, 520; mol. wts. of, products of bituminous coal, 734; gaseous, and polymerization reacns., 1404; catalytic, of heptaldehyde, 1460; stereochemistry of catalytic,

1985, 1991, 2003, 2006, 2009, 2014 (corrns. 3071), 2022; of disubstituted acetylenes, 2505; catalytic, of cystine ... 2721
Hydrogen azide, structure of ... 1184
Hydrogen chloride. See *Hydrochloric acid.*
Hydrogen cyanide. See *Hydrocyanic acid.*
Hydrogen fluoride. See *Hydrofluoric acid.*
Hydrogen ion concentration, the acidity scale, 1861; effect of *p*H on soly. of Ca oxalate ... 2948
Hydrogen peroxide, anomalies in conductivity measurements with, 454; action on pseudosapogenin acetates and pregnenolones, 468; reacns. involving O, amalgams and, 852; production by oxidase, 1212; BeI_2 hydrosols in decompn. of, 1340; behavior of carbonyl bridge compds. with alkaline, 2439; reacns. in solns. containing O_3, H^+ and Br^-, and, 2468; oxidation of amino acids by ... 3054
Hydrogen sulfide, catalysis of thermal decompn. of acetaldehyde by ... 1707
Hydrolysis, enzymic, of alkyl β-D-glucosides, 369; alkaline, of fluorenone-spirohydantoin, 689; consts. for In tribromide and triiodide, 953; acid catalyzed, of Ph substituted aliphatic esters ... 2362
Hydroquinone, chloromethylation of trimethyl-, diacetate, 524; reduction of dipole moment in di-*t*-butyl- ... 937
Hydroxyl, attempt to detect free, as an intermediate in photochem. reacns ... 2499
Hydroxylamine, effect of catalysis on oxidation products of ... 731

ILKOVIČ equation, validity of, in polarographic analysis of alkali metals ... 1297
Imidazole, prepn. of 4(5)-hydroxymethyl-, 463; tautomeric character of, ring ... 1167
Imino acids, cyclization of ureido derivs. of dibasic ... 1686
β-Iminonitriles, hydrogenation of ... 150
Immersion, energy of, of crystalline powders ... 1190
Indanol, α- and β-, from indene ... 912
Indanone derivatives, prepn. of ... 2439
Indene, α- and β-indanol from, 912; vapor pressure of ... 2501
Indenones, structure of certain highly arylated, and their behavior with Br_2 ... 2127
Indium, chemistry of ... 953
Indium trihalide, structure of ... 2514
Indium salicylates, basic ... 2234
Indophenol, charcoal as a factor influencing the, reacn ... 2276
Industrial chemistry, Industrial Instruments for Measurement and Control (Rhodes, book review) ... 728
Inorganic chemistry, Technology (Badger, Baker, book review), 1237; A Course of Instruction in the Qual. Chem. Analysis of Inorg. Substances (Noyes, Swift, book review) ... 2522
Inositol, tetrahydroxyquinone and rhodizonic acid salts from oxidation of, with HNO_3 ... 67
Insecticide, principle in bark of southern prickly ash, 187; properties of certain azo derivs. of 3,2′-nicotyrine ... 2835
Invertase activity, in identical liquid and frozen mixts ... 2577
Iodate, mobility of ion, 7; reduction at dropping Hg electrode, 1044; reduction in neutral and basic media ... 1970
Iodides. (See also *Halides.*) transference no. of KI, 682; exchange reacn. between alkyl, and iodide ion ... 940
Iodine. (See also *Halogens.*) production of at., in reacn. of peroxides with I, 161; transference nos. of KO from e. m. f. of iodide–, gravity cells, 682; addns. in glacial AcOH, 709; photolysis of acetaldehyde and, mixts., 889, 893; complex formations between, and μ-mercapto-dihydroglyoxalines ... 2706
Iodine compounds. (See also *Iodides.*) 3′,5′-diiodothyronine, 1070; kinetics and mechanism of 2,6-diiodotyrosine formation, 1147; iodinated aracyl esters for radiography, 1436; synthesis of radioactive MeI, 2293; soly. of KIO_3 and $Zn(IO_3)_2$ in dioxane–water mixts., 2305; the monoiodo deriv. of *m*-diphenylbenzene, 2485; photoöxidation of MeI ... 2500
Iodine monochloride, system KCl– ... 2620
Iodine pentafluoride, a dioxanate of ... 2727
Ionic equilibrium, as Applied to Qual. Analysis (Hogness, Johnson, book review) ... 1492
Ionization. (See also *Conductivity; Debye–Hückel theory.*) secondary, of selenic acid, 1054; consts. of propionic acid, 1480; and dissocn. by electron impact in *n*-butane, isobutane and ethane, 1588; of *n*-PrCl and *t*-BuCl, 2766; of propylene, propane and isobutylene, 2769; revised consts. for the Debye–Hückel theory, 2724; const. of morpholine ... 3043
Ions. (See also *Activity coefficient; Electrolytes; Reaction velocity.*) assocn. of ferric, with chloride, bromide and hydroxyl, 335; apparent volumes of individual, in aq. soln., 668; ionic competition in base-exchange reacns., 954; complex, 1630; limiting ionic mobilities of univalent, 1635; ionic nature of the Grignard reagent, 2865; molar dispersion and refraction of free and bonded, 3023; diffusion of electrolytes and, in their mixts., (corrn.) ... 3067
Iron, ferric ion reacn. with orthophosphate and thiocyanate, 291; catalysts in decompn. of NH_3. 741, 745
Iron chloride, system: $FeCl_3$–NaCl, 241; elec. moment of $FeCl_3$ ... 2076
Iron compounds, assocn. of ferric ions with chloride, bromide and hydroxyl ions ... 335
Iron oxide, reacn. of, (II) in liquid NH_3 ... 2772
Iron sulfate, sp. heat of $FeSO_4$ ... 2949
Isatin, reacn. of PhMgBr with N-Ph- ... 1736
Isoamyl bromide, dielec. behavior of, (corrn.) ... 3067
Isobutane, ionization and dissocn. by electron impact in ... 1588
Isobutene, photochemistry of, 1; vapor pressures and crit. consts. of, 546; compressibility of and an eq. of state for gaseous, 548; hydration in dil. HNO_3 ... 1938
Isobutyl bromide, dielec. behavior of, (corrn.) ... 3067
Isobutylene, ionization and dissocn. of, by electron impact ... 2769
Isocyanide, mol. structure of Me ... 2952
β-Isodurylaldehyde cyanohydrin, reacn. with Ph-MgBr ... 1724
Isoguanine, absorption spectra of ... 1604
Isomerism. (See also *Rearrangement.*) diastereo-, of the 9,10,12-trihydroxystearic acids and the geometric configurations of ricinoleic and ricinelaidic acids ... 2253
Isomerization. (See also *Rearrangement.*) studies of sterically hindered carbonyl compds., 1619; of β-carotene, 1856, (corrn.) 3071; in the Reformatsky reacn ... 2131
Isomers, heats of hydrogenation of pairs of stereo-, 1395; stereo-, of diphenyloctatetraenes, 2755; dielec. consts. of some pairs of diastereomers (corrn.) ... 3067
Isonaphthazarin, condensation of β-cyclogeraniol with leuco- ... 1979
Isopentane, heat capacity and vapor pressure hysteresis of liquid, 1034; thermodynamics of, 1039, (corrn.) ... 3069
Isopropanol, peroxides in ... 3049
Isopropenyl ketone, polymer of Me, 92; phys. consts. of Me ... 2224
Isopropyl alcohol, ternary systems of cyclohexane, water and ... 1886
Isopropylamine, characteristics of β-(2,5-dimethoxyphenyl)-β-hydroxy-, hydrochloride ... 3040
Isopropylidene-L-fucitol, 2,3,4,5-di- ... 982
Isopropylidene group, in osage orange pigments ... 308
Isopropyl ketone, enolizing and reducing action of Grignard reagents on di- ... 1239
Isoquinalaldehyde, condensation reacns. of ... 2430

Isoquinoline, derivs. of amino-, 783; deamination of 5-amino-8-nitro- 2442
Isotopes. (See also *Deuterium; Radiocompounds.*) chem. sepn. of 2613

JOULE–Thomson effect, in CO_2 400

KETENE, action on 5,5-dibromoxyhydrouracil, 306; condensation products of, with ketones 2216
Ketene acetals 254, 260, 1059, 1966, 2525
α-Keto alcohols, $PbAc_4$ cleavage of cyclic 1416
2′-Ketodihydro-1,2-cyclopentenophenanthrene 1421
β-Keto esters, prepn. of some 2271
Keto ethers 1222, 2882
Ketones, α,β-unsatd., 76; photochem. decompn. of cyclic, 80; polymer of Me isopropenyl, 92; intramol. aldol condensation in unsatd., polymers, 177; γ-phenoxypropyl *p*-anisyl, 186; 3,6-diketo sterols and their reduction products, 219; catalytic hydrogenation of alkyl Ph, 520; enolizing and reducing action of Grignard reagents on diisopropyl 1239; Me-*t*-butylneopentylcarbinyl, 1242; containing the dineopentylcarbinyl group, 1247; Grignard derivs. of alkyl dineopentylcarbinyl, 1251; parachors of normal, 1294; Me triethylcarbinyl, 1618; use of alkoxy, in quinoline synthesis, 1897; condensation products of ketene with, 2216; stereoisomeric bromo 1,4-dimesityl unsatd. 1,4-di-, 2426; amino alcs. and 1,3-diamino compds. from β-amino, 2432; ortho alkylation and arylation of mesitylaryl, 2446; conversion of unsatd. 1,4-di-, into furans and hydroxyfuranones, 2585; photochem. decompn. of *n*-Bu Me, 2676; solubilities of some isomeric, in water, 2742; reacns. of acrylonitrile with, 2850; reacn. of *n*-BuMgBr with some aromatic, 2862; 1-methoxyethyl alkyl, 2882; alkylation of 2-methylcyclopentyl Ph (corrn.) 3069
Keto-sarsasapogenin 813
Ketoses, new synthesis of, and their open chain (keto) acetates 2329
Kojic acid, magnetic susceptibility of metallic salts of 963

LACTAMIDE, d. and sp. heat of 191
Lactobacillus casei, growth stimulating substance for. 881
β-Lactoglobulin, hydration of, crystals, 2393; X-ray and optic measurements on, 2504; digestion of, by pepsin 2664
Lactose, syntheses of, and its epimer, 1490; syntheses of epi-, and 1852
Lead, alkylation of α-naphthoquinones with esters of tetravalent, 2043; at. wt. of 3047
Lead bromide, activity coeffs. of 1136
Lead compounds, disproportionation of R_6Pb_2 compds., 462; diazotization of an aminoaryl, 1007; plumbic acetate–anhyd. AcOH solns. 1523
Lead oxides, heat capacities of red and yellow Pb monoxides at high temps., 617; studies of 1637
Lead tetraacetate, cleavage of cyclic α-keto alcs., 1416; methylation of aromatic nitro compds. with. 2052
Lepidine, nitration of, and 2-chloro- 2417
Leuconostoc mesenteroides, dextran synthesized by action of, on sucrose 1959
Liebig, and after Liebig (book review) 2237
Lignin, hydrolytic derivs. of, volatile compds., 22; vanillin from, materials 1429
Linoleic acid, conjugated material formed in bleaching of, 988; a new 1580
Linseed oil, alkylation of 3054
Liquid. (See also *Fluidity.*) direct measurement of spreading pressures of volatile org., on water 274
Lithium hydroxide, conductance of aq. 621
Litsea longifolia Bth. & Hk., seed fat of 1079
Lithium nitrate, systems: NH_4NO_3–, and NH_4NO_3–H_2O– 2680
"Luminol," synthesis of dihydroxyquinoxalines isomeric with 2644
Lupeol, isolation from osage orange 2539
Lycopene, pro- 1075
Lycopodium saururus, alkaloids from 968

MACROMOLECULAR disorder, in linear polyamides 2399
Magnesium compounds. (See also *Grignard reagents.*) reacn. of epichlorohydrin with EtMgBr, 484; BrMg enolates of Me-*t*-butylneopentylcarbinyl ketones, 1242; Grignard derivs. of BrMg enolates of alkyl dineopentylcarbinyl ketones, 1251; reacn. of β-isodurylaldehyde cyanohydrin with PhMgBr, 1724; reacn. of PhMgBr with N-phenylisatin, 1736; composition of alkylmagnesium chloride solns. in Et ether, 2509; reacn. of *n*-BuMgBr with some aromatic ketones, 2862; reacns. of benzylmagnesium chloride 2968
Magnesium sulfate, surface tension of, solns., 2744; sp. heat of, at low temp. 2949
Magnetic susceptibility, of *cis*- and *trans*-decalin, 717; of complex kojates 963
Magnetic rotation. See *Optical rotation.*
Magnetism, and the 3rd law of thermodynamics 1535
Maleic acid, copolymerization of alkyl maleates 1675
Maleic imide, *p*-bromophenylhydroxy- 2600
Malonic acid, dibromo-*o*-xyloquinone and Na, ester, 528; alkylation of, esters by alkyl carbonates, 578; action of monoethanolamine on Et bromomalonate, 1010; malonic ester synthesis and Walden inversion 2606
Maltoside, stability of β-Me-, toward hot alkali 2871
Mandelic acids, prepn. and bacteriology of substituted 2080
Manganese, high-temp. heat content of 1770
Manganese compounds, high-temp. heat content of Mn_3O_4, $MnSiO_3$ and Mn_3C, 1769; heat of formation and high-temp. heat content of MnO and $MnSO_4$ 1770
Manganese sulfate, sp. heat of, at low temp. 2949
Manganous fluoride, heat capacity of 1535
Manganous hydroxide, autoxidation of 1866
Manganous nitrate, temp.–compn. and vapor pressure–temp. relations of H_2O–, system 1443, 1445
Mannich reaction, prepn. of β-keto amines by 451
D-Manno-D-gala-heptose, and derivs. 247
D-Mannosan<1,5>β<1,6>, anhydro deriv. of, 925; from β-phenyl-D-mannoside 1483
Marihuana activity, tetrahydrocannabinol homologs and analogs with 694, 2653
Mass spectra, of *n*-PrCl and *t*-BuCl, 2766; of isobutylene, propane and propylene 2769
Mass spectrometer, kinetics of gaseous reacns. by means of 994
Medicinal Products, Chemistry of Org. (Jenkins, Hartung, book review) 1012
Medicine, Phys. Chemistry for Students of Biochemistry and (Ferry, book review) 3061
Menschutkin reaction, study of, using radioactive H as tracer 2294
Mercapto-thiazolines, Ph- 2487
Mercuric oxide, soly. relations of, in HCl 2380
Mercurous bromide, e. m. f. of, electrode 3021
Mercury, accommodation coeff. of, on Pt, and heat of vaporization of, 2190; attachment and detachment of dropping, under various conditions 2553
Mercury compounds, elec. moments of org. Hg halides in dioxane, 830; reacns. involving O, H_2O_2 and, 852; identification of amides through the Hg derivs. 1738
Mercury electrode, dropping, behavior of tocopherols at, 447; quinone behavior at, 644; amperometric titration of α-tocopherol at, 646; electroreduction of water at, 833; reduction of perrhenate ion at, 1001; reduction of iodate and bromate at, 1044; in AcOH, 1303, 2177; reduction of unsatd. hydrocarbons at, 1765, 2365; reduction of iodate and bromate at. 1970
Mercury (II) salts, reacns. between *sym*-diphenyltriazene and 935

Mesidine, prepn. of N-succinyl-N-Et-3-bromo-, (corrn.) 3069
β-Mesitoylacetylene glycol, prepn. of α-*o*-methoxyphenyl- 2260
Mesitoyl compounds, reacn. with Grignard reagents. 1450
Mesitoylmethane, properties of *o*-methoxybenzoyl- 2262
Mesityl aryl ketones, ortho alkylation and arylation of 2446
Mesityl-1,2,4-butanetrione enol, acylation of 1,4-di- 1375
Mesitylene derivatives, 2573; Raman spectra of 1181
Mesityl ketones, stereoisomeric bromo 1,4-dimesityl unsatd. 1,4-diketones 2426
Mesityl-3-methyl-1,2,4-butanetrione enol, prepn. and alkylation of 1,4-di- 2423
Mesityl oxide, oxonium complex const. of, 1117; hydration of 1122
Mesityl-1-propen-1-ols, isomeric bromo-1,2-di- 2888
Metalation, alkyl carbonates as solvents for, reacns. 580
Metal nitrates, activity coeffs. of bivalent 1469
Metals, reproducible contact angles on reproducible, surfaces, 494; Phys. Examn. of, Vol. II, Elec. Methods (Chalmers, Quarrell, book review), 2519; chem. sepn. of H isotopes by addn. of, to water, acids and bases 2613
Metanilamide, soly. of 2464
Methane, fluorochlorobromo- 1599
Methanol, standard potential of Ag–AgBr electrode in, 517; periodate oxidized starch reacn. with, 589; temp. and compn. coeffs. of d., refractive index and viscosity of dioxane–, system, 1207; b. p.–compn. data of dioxane–, system 1231
Methemoglobin, heat of org. reacn. between, and salicylate 1472
Methene, di-N-methyldipyrryl- 593
dl-Methionine, synthesis of 2082
Methoxyl, effect of, toward stabilizing ene-diols 2258
Methylamine hydrochlorides, activity coeffs. of 965
Methyl alcohol. See *Methanol.*
Methylation, of aromatic nitro compds. with $PbAc_4$ 2052
Methylenecyclobutane, structure of 1142
Methylenedioxybenzene series, studies in 2983
Methylenedioxy rings, base-catalyzed cleavage of 1410
Methyl iodide, photooxidation of 2500
Methyl isopropenyl ketone, phys. consts. of 2224
Methyl mercaptan, thermodynamics of 165
Microchemistry, Micromethods of Quant. Org. Analysis (Niederl, Niederl, book review), 2729; Introduction to Microtechnique of Inorg. Analysis (Benedetti-Pichler, book review) 3061
Microscope, Electron (Burton, Kohl, book review) 3060
Milk, a Cu bearing protein from cow's 1616
Mimulus longiflorus Grant, formation of pro-carotenoids in 2510
Mineral membranes, electrochem. properties of 1814
Molecular volume, of *dl*-α-alanine, β-alanine and lactamide, 191; apparent, of individual ions, 668; of solutes, 758, 761; apparent, of aq. H_2SO_4 solns., 1878; partial, of $NiSO_4$ solns. 2379
Molecular weight, of polynuclear aromatic compds., 425; mechanical properties of substances of high, 1323, 1330; random reorganization of, distribution in linear condensation polymers 2205
Molecules. (See also *Crystal Structure; Polarization.*) bi-, reduction of hindered aldehydes, 30; structures of some Si polyhalides, 62; intra-, condensations in polymers, 269; orientation of substituents in aromatic, 900; dipole moment and resonance in heterocyclic, containing N and S, 1130; viscosity of dil. solns. of long-chain, 2716; dissocn. of org., into radicals and ions, 2801; structure of Me isocyanide, 2952; size distribution in linear condensation polymers, (corrn.) 3067; vitrification and crystallization of org., (corrn.) 3067
Molybdenum blue, compn. and structure of 2543
Molybdenum compounds, catalyst from, in oxidation of naphthalene 2917
Morphine, N-allylnor- 869
Morpholine, sp. heats of, and aq. solns., 679; some reacns. of, 2506; ionization const. of, in water, 3043; deriv. of 3051
Morpholine compounds, benzylidene amino- 2502
4-Morpholinealkyl esters, and amides possessing antispasmodic activity 970
β-Morpholinobenzilacetone, prepn. of 2432
Musk, chem. constitution of American 144
Mutarotation, of glucose in aq. MeOH solns., 236; of α-D-glucose in dioxane–water mixts. 1010
Mydriatics, synthetic 428, 431

NAPHTHALENE, derivs. of, 94; cadinene derivs., 417; oxidation of some, 425; polyphenyl, 557, 559; 1,2-diphenyl-3,4-dihydro-, 727; derivatives, 974; arsine oxides of, 1064; antihemorrhagic activity of sulfonated derivs. of 2-Me-, 1096; prepn. and resolution of N-succinyl-1-Me-amino-2-Me-, and N-succinyl-1-Me-amino-4-chloro-2-Me-, 1475; nitrovinyl-, 1739; viscosity of *cis-* and *trans*-decahydro-, 1912; enolization of some keto-, derivs., 2131; amylsodium–, reacn., 2250, (corrn.) 3073; reduction of, derivs., 2365; mixed heteropoly acid catalysts for vapor phase air oxidation of 2917
2,7-Naphthalenedialdehyde, synthesis of 2343
2,3-Naphthalic acid, diethyl 1,4-dihydroxy-, ester 798
Naphthenic acid, "trans"-2,2,6-Me_3-cyclohexanecarboxylic acid from petroleum 385
Naphthohydroquinones, water-soluble compds. with antihemorrhagic activity 2657
1-Naphthol, derivs. of 2-propionyl- 2578
Naphthoquinones, identity of red pigments in roots of *Tripterygium wilfordii* and *Celastrus scandens* as, 182; 2-Me-1,4-, derivs., 725; alkylation of α-, with tetravalent Pb esters 2043
Naphthyl groups, effect of, in dissocn. of hexaarylethanes 1824
Naphthylidene sulfanilamide derivatives, certain 2230
Neopentyl bromide, acetylenic analog of 543
Neopentylcarbinol, *t*-amyl alc. and the related dimethyl- 2970
Neopentylcarbinyl ketones, Me-*t*-Bu-, 1242; di-, 1247; Grignard derivs. of alkyl di- 1251
Neopentyl systems, reacns. of certain, with electrophilic reagents 2633
Nepetalic anhydride, in catnip oil 1828
Nephelometry, detn. of low solubilities 101
Nickel, absorption spectra of para- and diamagnetic, complexes, 181; catalytic conversion of para-H on, 1594; configuration of org. coördination compds. of 1924
Nickel cyanides, reduction of complex 1187
Nickel(II) ions, of diethylenetriamine 686
Nickel nitrate hexammoniate, heat capacity and heat of transition of 629
Nickel sulfate, partial molal volumes of, solns. 2379
3,2′-Nicotyrine, insecticidal properties of certain azo derivs. of 2835
Nitrates, activity coeffs. of bivalent metal 1469
Nitration, of halobiphenyls, 1848; of certain dinitrobiphenyls, 2225; of lepidine and 2-chlorolepidine, 2417; of 4-PhPh benzoate 2505
Nitric acid, thermodynamic study of, 48, (corrn.) 3069
Nitriles, hydrogenation of β-imino-, 150; condensation of alkyl carbonates with, 576; absorption spectra and X-ray examn. of isomeric glucono-, 1950; chemistry of acrylo- 2457, 2850
Nitrobenzene, diazotization of, 19; mechanism of "aromatizing" diene reacns. in 176
Nitro compounds, Raman spectra of, 1181; utilization of aliphatic, 1063, 1735; methylation of aromatic, with $PbAc_4$, 2052; dipole moment, induction and resonance in nitroethane and some chloronitroparaffins 2829
Nitrogen, thermodynamics of, at high pressures, 44; adsorption in NH_3 decompn., 751; divalent, 860; dipole moment and resonance in heterocyclic mols. containing, 1130; sulfanilamido derivs. of, petroleum bases, 1499; org. B–, compds., 1584; N–C–N

system in N^1-heterocyclic sulfanilamides, 2532; apparent energy of the N–N bond from heats of combustion ... 2369
Nitrogen compounds, in petroleum distillates, 909, 2753; prepn. and properties of trimeric phosphonitrilic chloride, 2377; An Outline of Org. (Degering, Bordenca, Gwynn, book review) ... 2729
Nitrogen oxides, oxidation of cellulose by NO_2, 121, 127; action of NO on pentaphenylethane, 860; structure of N_2O ... 1184
Nitromethane, heat capacity of ... 1224
Nitroparaffins, surface tensions, densities and parachors of aliphatic ... 2540
i-Norcholenyldiphenylcarbinol, prepn. and dehydration of 6-methoxy- ... 2115

10,12-**O**CTADECADIENOIC acid-1, solid ... 1580
Octadecanenitrile, pressure–area–temp. and energy relations of monolayers of ... 1600
Octadecanoic acid, synthesis of 17-Me- ... 1106
Octadecenoic acids, derivs. of ... 1061
Octadecylamine, H_2O–, system ... 1516
$\Delta^{9,10}$-Octalin, oxidation product of ... 720
Octane, heat capacity of an, 179; compressibility of liquid *n*- ... 1822
Octatetraenes, stereoisomeric diphenyl- ... 2755
Octene-2, 3,7-dimethyl- ... 1484
Octylamine, conductivity of, 772; H_2O–, system ... 1516
N-Octylpiperidine, phys. consts. of ... 2511
n-Octyl sodium, prepn. of ... 2239
Oils, conjugated material formed in bleaching vegetable, 988; sterols of alfalfa seed ... 2488
Olefins, reduction of acetylenes to, 363; conjugated di-, by double bond displacement, 826; nonperoxide catalysts for SO_2–, reacn., 1229; rearrangements, 1733; reduction of Ph substituted, at dropping Hg electrode, 1765; restricted rotation in aryl ... 1786, 1791, 1795
Optically active compounds, vasopressor amines, 1449; attempted asymmetric syntheses involving the Grignard reagent in, solvents ... 2842
Optical rotation. (See also *Mutarotation.*) of aq. Ce salts, 412; temp. effects on validity of Hudson's rules of iso-, 1626; of *d*-1-deutero-2-methylbutane, 2563; configuration of glutamic acid ... 2035
Organic chemistry, A Brief Course in (Fuson, Connor, Price, Snyder, book review), 189; Theory of (Branch, Calvin, book review), 474; Introduction to (Williams, book review) 728; Organic Reactions, Vol. I (Adams, book review), 3062; Org. Syntheses (Smith, book review), 3063; A Shorter Course in (Colbert, book review), 3063; Introductory (Wertheim, book review) ... 3063
Organic compounds, Solubilities of (Seidell, book review), 1014; identification of, 1017; adsorption of, 1513; Reagents in Inorg. Analysis (von Stein, book review) ... 1984
Organic Syntheses, Coll. Vol. I (Gilman, Blatt, book review) ... 1492
Orthanilamide, soly. of ... 2464
Orthoformic acid, prepn. of tri-*m*-nitrophenyl orthoformate ... 186
Orthophosphoric acid, reacn. of ferric ion with ... 291
Osage orange pigments ... 308, 311
Osage orange, isolation of lupeol from ... 2539
Ouabain, structure of ... 720
Oxalic acid, reduction of V_2O_5 by, 1462; activity coeffs. of (corrn.) ... 3069
Oxalyl chloride, reacn. with paraffin hydrocarbons, 329; and unsatd. carbons, 333; peroxide-catalyzed reacn. of, with side-chains of aralkyl hydrocarbons. 1621
Oxazole, 2-Ph-, and derivs., 785; *p*-substituted derivs. of 2-Ph- ... 2444
Oxidation. (See also *Dehydrogenation.*) of Et cellulose, 9; of, ethers, 15; of cellulose by NO_2, 121, 127; of osage orange pigments, 311; of vitamin C, 358; of triethylbismuth, 392; of polynuclear aromatic compds., 425; periodate, of 1,2-glycols, 552; starch, with periodic acid, 585; catalysis in, of hydroxylamine, 731; of β-pinene with SeO_2, 1008; enzymatic, of ascorbic acid, 1212; Mechanisms of Biol. (Green, book review), 1236; of benzophenone oxime, 1453; processes, 1561; auto-, of $Mn(OH)_2$, 1866; antioxidants and auto-, of fats, 2337; oxidative cleavage of vinyl alcs., 2886; mixed heteropoly acid catalysts for vapor phase air, of naphthalene, 2917; of amino acids by H_2O_2 in formic acid ... 3054
Oxidizing power, of air exposed coal ... 1809
Oxime, oxidation of benzophenone ... 1453
Oxindoles, synthesis from rhodanine-, of keto and mercapto derivs. of cinchoninic acid ... 1669
Oxonium complex constant, of mesityl oxide ... 1117, 1122
Oxygen. (See also *Oxidation.*) reacns. involving amalgams, H_2O_2 and, 852; absorption induced by ether linkages, 1354; absorption of, by glutathione in alkaline solns., 2282; sp. rate of the reacn. $O_3 + Br^- \rightarrow$ ... 2468

PALLADIUM, catalytic conversion of para-H on ... 1594
Palmitic acid, adsorption of, by potato and corn and rice starches ... 2144
Paracelsus, Four Treatises of Theophrastus von Hohenheim Called (Sigerist, book review) ... 1237
Parachors, study of org., 1294; of aliphatic nitroparaffins ... 2540
Paraffins. (See also *Alkanes; Hydrocarbons.*) alkylation of, with $AlCl_3$, 33; surface tensions, densities and parachors of aliphatic nitro-, 2540; dipole moment, induction and resonance in chloronitro- ... 2829
Parathyroid, phosphatase activity of, hormone ... 2759
Peimine, prepn. of (corrn.) ... 3069
Peiminine, prepn. of (corrn.) ... 3069
Pentacene, synthesis of 6,13-diphenyl- ... 1253
Pentacenequinone, Grignard reagent action on ... 1253
Pentadecylamine, 8,9,15-trihydroxy-, from aleuritic acid ... 1902
1,3-Pentadiene, prepn. of 4-Me- ... 787
Pentane, heat capacity data for gaseous 2,2,4-Me_3-, 179; dielec. behavior of chloro-, 737; prepn. of *d*-1-deutero-2-Me butane and study of its optical rotation ... 2563
Pentryl analogs, intermediates of ... 1285
Pepsin, digestion of β-lactoglobulin by ... 2664
Peptides, dielec. increments of amino acid poly-, 1379; dielec. investigation of poly-, 1870; some diamino ... 2231
Perinaphthane derivatives, reacns. of ... 917
Periodate oxidation, of 1,2-glycols ... 552
Periodic acid, starch oxidation with ... 585, 589
Peroxides, reacn. with I^- to form at. I, 161; addn. polymerization catalyzed by substituted acyl, 1103; alkylation of para quinones with acyl, 2060; catalysts for, decompn. ... 2492
Perrhenic acid, reduction of perrhenate ion ... 1001
Petroleum. (See also *Hydrocarbons.*) second solid naphthenic acid from, 385; distillates, N compds. in, 909, 2753; sulfanilamido derivs. of N bases from, 1499; Chem. Refining of (Kalichevsky, Stagner, book review) ... 3062
Pfitzinger reaction, use of alkoxy ketones in quinoline synthesis by ... 1897
Phase transitions ... 629
Phenanthraquinone, complete hydrogenation of ... 2022
Phenanthraquinonimine, reacn. with aldehydes, 2567; reacn. with Schiff bases ... 2569
Phenanthrene, soly. of, 101; oxidation of, 425; derivatives, 536, 974; hydrogenation of derivs ... 1985
Phenanthrenes, 9-vinyl-, 69; synthesis of 3-acetyl-1-Me-, 1225; synthesis of 2′-ketodihydro-1,2-cyclopenteno-, and derivs. of phenanthro(1,2-*b*)furan, 1421; stereoisomeric forms of the perhydro-, ring, 2014, (corrn.) 3071; enolization of some keto-, derivs., 2131; synthesis of certain 2-substituted, 2221; structure of Skita's "decahydro-9,10-dihydroxy-" ... 3046
9-Phenanthrol, hydrogenation of, 2014, (corrn.) ... 3071

Phenethylamines, 2859; α,β-dialkyl-, 533; physiol. active, containing a *t*-hydroxyl ... 2451
Phenol, kinetics of *n*-BuBr–, reacn., 226; compd. formation between the isomeric phenyl-, and pyridine, 2625; $AlCl_3$ in condensation of Me dipropyl carbinols with, 2655; nitro-4-phenyl- ... 3057
Phenolphthalein, kinetics and equil. of carbinol formation of ... 2312
Phenothiazine, vapor pressure of ... 3035
Phenylacetone, alkylation of ... 533
Phenyl amyl sulfide, synthesis of *p*-hydroxy- ... 2322
Phenylethane, action of NO on penta-, 860; synthesis of di-, derivs. related to materials occurring naturally ... 2962
Phenylethylene, *sym*-*p*,*p*'-dichlorotetra- ... 2726
Phenylhydrazine, use of, in characterizing org. acids, 470; reacn. product of, and Et cyanoacetate, 2133; vapor pressure of, as function of temp., 2776; photodissocn. of, in a rigid solvent ... 2801
p-Phenylphenacyl acid, esters of octadecenoic acids .. 1061
p-Phenylphenacyl bromide, sulfonium derivs. of 1165
Phenylphenols, nitro-4- ... 3057
4-Phenylphenylacetic acid, chlorination of ... 2219
4-Phenylphenyl benzenesulfonate, chlorination of ... 2719
4-Phenylphenyl benzoate, nitration of, 2505; chlorination of ... 2719
4-Phenylphenyl chloroacetate, bromination of ... 2449
Phenylsulfone, *p*-cyclohexylphenyl- ... 1489
Phosphatase, activity of the parathyroid hormone .. 2759
Phosphine, prepn. and properties of Me_2- ... 718
Phosphonic acids, prepn. of *bis*-aryl- ... 2982
Phosphonitrilic chloride, prepn. and properties of trimeric ... 2377
Phosphorescence. (See also *Fluorescence.*) beta, of fluorescein in acid soln ... 1916
Phosphoric acid, action of, on 2-butanol, 1025; aquo ammono ... 1337, 1553
Phosphorus, heat of fusion and heat capacities of white, 839; cyanates and thiocyanates of ... 1757
Phosphorus halides, elec. moments of P trihalides in dioxane, 614; radio halogen exchanges in ... 850
Phosphoryl triamide, N-substituted derivs. of, and thio-, as H bonding agents ... 1553
Phosphorus tribromide, reacn. of 3-bromo-2-butanols with ... 2791
Photoactivation, of adsorption of H on ThO_2 ... 1731
Photochemistry. (See also *Bromination; Chlorination; Hydrolysis; Oxidation; Photolysis; Rays; Reduction.*) of isobutene, 1; decompn. of cyclic ketones, 80; reacn. of oxalyl chloride with paraffin hydrocarbons, 329; of Gases (Noyes, Leighton, book review), 476; water effects in bromination of acetophenone, 887; attempt to detect free hydroxyl as an intermediate in, reacns., 2499; studies, 2676; reversible, processes in rigid media ... 2801
Photodecomposition, vapor phase, of Me formate ... 1820
Photographic developers, effect of Ag on autoxidation of ... 1561
Photolysis. (See also *Light, Photochemistry.*) of Me acetate, 490; of diacetyl, 717; of aliphatic aldehydes ... 889, 893
Photoöxidation, of MeI ... 2500
Photosynthesis, radioactive H in chlorophyll ... 3037
Phthalaldehydes, new synthesis of ... 315
Phthalein, carvacrol- ... 2538
o-Phthalic acid, polarographic study of, and phthalates, 660, (corrn.) ... 3069
Phthalic anhydride, Δ^4-tetrahydro-, in synthesis of 4,10-ace-1,2-benzanthracene ... 802
Physical chemistry, Kurzes Lehrbuch der (Ulich, Cruse, book review), 475; an Introduction (Moelwyn-Hughes, book review), 730; Treatise on (Taylor, Glasstone, book review), 1743; Elementary (Randall, Young, book review), 3059; chemistry (Gucker, Meldrum, book review), 3059; for Students of Biochemistry and Medicine (Ferry, book review), 3061; Exptl. (Palmer, book review), 3065; Practical (Findlay, book review) ... 3065
β-Picrylhydrazine, dipole moment of α,α-diphenyl- .. 1179
Pigments. (See also *Colors; Dyes.*) osage orange, 308, 311; distribution of carotenoid, 1440; anthochlor ... 1704
Pinacol, periodate oxidation of ... 552
Pinacolyl alcohol, equil. of olefins from ... 1733
Pinene, oxidation of β-, with SeO_2, 1008; reacns. of β-, 1807; system α- and β- ... 2978
Pine tar, resin acids from ... 871
N,N' - Piperazinium bis - (2 - methyl - 5 - isopropylbenzenesulfonate) ... 1741
Piperidines, some phys. consts. of N-octyl-, N-dodecyl- and N-cetyl- ... 2511
β-Piperidinobenzilacetone, prepn. of ... 2432
Piperonylamides, N-substituted ... 1741
Pirylene, constitution of ... 2692, 2693
Pituitary glands, phys.-chem. of the interstitial cell hormone from sheep ... 367
Platinum, catalytic conversion of para-H on, 1594; accommodation coeff. of Hg on, 2190; sorption of CO on ... 2610
Podocarpic acid, structure of ... 928
Poison ivy, toxic principles of ... 3058
Polarization. (See also *Electric moments.*) electrode, in dielec. const. measurements, 624; solvent, error in dipole moments ... 2988
Polarography, study of *o*-phthalic acid and phthalates, 660, (corrn.) 3069; investigation of Re compds., 1001, 2182; analysis of alkali metals, 1297; detn. of citrinin, 1490; reduction of Ph substituted olefins and acetylenes, 1765; Method of Analysis (Müller, book review), 1983; reduction of aromatic polynuclear hydrocarbons, 2365; Polarography, Analysis and Voltammetry. Amperometric Titrations (Kolthoff, Lingane, book review) ... 2728
Polymerization. (See also *Condensation.*) of trimethylaluminum derivs., 316; addn., catalyzed by substituted acyl peroxides, 1103; gaseous hydrogenation and, reacns., 1404; co-, of alkyl acrylates and maleates, 1675; of styrene catalyzed by *p*-bromobenzenediazonium hydroxide ... 2508
Polymers, structure of vinyl, 92; intramol. condensations in, 269; High, Reacns., Their Theory and Practice (Mark, Raff, book review), 1015; theory of solns. of high, 1712; temp. and solvent effects on viscosity of high, 1557; relation of dielec. properties to structure of crystalline, 2164, 2171; random reorganization of mol. wt. distribution in linear condensation polymers, 2205; structure of co-, of vinyl chloride and acetate, 2356; mol. size distribution in linear condensation (corrn.) ... 3067
Polypeptides. See *Peptides.*
Polyvinyl chloride, viscosities of, solns., 277; elec. properties of plasticized ... 283
Populin, action on Ph 2,4,6-Me_3-β-D-glucoside ... 374
Porphine, dipole moment of *ms*-Ph_4- ... 2993
Potassium chlorate, molal vol. of ... 758
Potassium chloride, potentials of, transference cells, 513; limiting equivalent conductances of, in H_2O, 1544; relative surface tension of, solns. by a differential bubble pressure method, 2476; temp. coeff. of the conductance of, solns., 2517; system ICl– ... 2620
Potassium dihydrogen arsenate, parameters in ... 354
Potassium hydroxide, conductance of aq ... 621
Potassium iodate, conductance of, 7; soly. in dioxane–water mixts ... 2305
Potassium iodide, transference nos. of ... 682
Potassium oxalatostannate, prepn. of ... 1759
Potassium oxyhexafluocolumbate, structure of ... 1139
Potassium sulfate, sp. heat of, at low temp ... 2949
Potentials. (See also *Cells.*) of KCl transference cells, 513; standard, of Ag–AgBr electrode in MeOH, 517; transference nos. of KO from e. mf. f. of iodide–I gravity cells, 682; molal electrode, of Ag–AgCl electrode, 1478; of ytterbic–ytterbous ion electrode, 1133, (corrn.) 3071; oxidation–reduction,

of thallous–thallic salts in aq. HCl solns., 1644; elimination of liquid junction, 2071; e. m. f. of HgBr electrode, 3021; change in, of Ag–AgCl electrodes with time ... 3053
Potentiometry, *p*H and Electrotitrations (Kolthoff, Laitinen, book review), 1016; titration of dibasic acids in dioxane–water mixts. ... 1153
Powders, energy of immersion of crystalline, 1190; energy of adhesion and emersion of crystalline ... 1195
Precipitation, fractionation of starch by selective, with BuOH ... 2957
Pregnanetriol, 20-Me-, and related compds. ... 481
Pregnanol-3(β),21-diol-20-one, conversion of 17,21-dibromopregnan-2(β)-ol-20-one to ... 213
Pregnan-3(β)-ol-20-one, 17-bromo-, 210; rearrangement of 17-bromo-, 216; conversion to *etio*-cholan-3(β)-ol-17-one, 817; 17-Me-, 1273; rearrangement of 16,17-dibromo- ... 2093
allo-Pregnan-3(β)-ol-20-one acetate, rearrangement of 17,21-dibromo- ... 2089
Pregnanolones, hypoiodate oxidation of ... 1842
allo-Pregnanone-20, 17-bromo-, and 17,21-dibromo- ... 822
5-Pregnen-3-(β)-ol-20-one, conversion to dehydroisoandrosterone, 1276; 21-benzal- ... 1282
Pregnenolones, H_2O_2 action on, 468; some 16-alkyl-, 1280; hypoiodate oxidation of ... 1842
Pressures, thermodynamics of N at high, 44; direct measurement of spreading, of volatile org. liquids on water, 274; eq. of state for gases at high ... 2195
Pro-γ-carotene ... 1173
Progesterones, some 16-alkyl- ... 1280
Prolycopene ... 1075
Propane, chlorination of 1,1,1-trifluoro-, 1157; ionization and dissocn. of, by electron impact ... 2769
Propargyl halides, electron diffraction of ... 1753
Propiolic acid, prepn. of Ph- ... 2510
Propionic acid, ionization consts. of, in MeOH and EtOH–H_2O mixts., 1480; relative acid strengths of formic, acetic and, 2065; acylation of *t*-Bu ester of, 2714; prepn. of β-(2-Me-6-oxo-1-cyclohexen-1-yl)- ... 3050
Propionylacetic acid, new method for prepn. of Et ester of ... 2271
2-Propionyl-1-naphthol, derivs. of ... 2578
Propoxymethyl alkyl ketones ... 1222
Propyl alcohol, ternary systems of cyclohexane, water and ... 1886
n-Propylamines, dimethoxy and dihydroxyphenyl- ... 2859
Propyl carbinols, condensation of Me di-, with phenols in presence of $AlCl_3$ ... 2655
n-Propyl chloride, ionization and dissocn. of, by electron impact ... 2766
Propylene, hydrogenation of, 1404; soly. of, vapor in H_2O as affected by typical detergent, 1556, (corrn.) 3071; ionization and dissocn. of, by electron impact ... 2769
n-Propylketene diethylacetal, iso-, and ... 1966
Proteins, prepn. of renin, 561; effect of urea on electrophoretic patterns of serum, 1090; electrophoresis of crotoxin, 1586; Cu bearing, from cow's milk, 1616; Amphoteric Properties of (Cannon, book review), 2237; electrophoretic study of, in rubber latex serum ... 2628
Protons, spectroscopic evidence of intermol. transfer of ... 2684
Purine, absorption spectra of 2-hydroxy-6,8-diamino- ... 1604
Pyran, addn. compds. of tetrahydrothio-, 1232; *d*- and *l*-1-hydroxy-3-*n*-amyl-6,9,9-trimethyl-7,8,-9,10-tetrahydro-6-dibenzo- ... 2087
Pyranyl, hydantoins containing a tetrahydro-, substituent ... 1672
Pyrazole-3-carboxylic acid, 1-carbamyl-5-Me- ... 2507
Pyrazole compounds, investigation of ... 2133
Pyrene, some reacns. of, (corrn.) ... 3067
Pyridinecarboxylic acids, esters of, as local anesthetics ... 1721
Pyridines, 3,4-substituted, 1093, (corrn.) 3071; substituted 2-sulfonamido-5-amino-, 1695; rates of reacn. of diacetone-glucose, -galactose and -sorbose with *p*-toluenesulfonyl chloride in, soln., 2463; compd. formation between the isomeric phenylphenols and ... 2625
Pyridinium salts, prepn. of *p*-nitrobenzyl-, of sulfonic acids ... 1017
dl-β-Pyridylalanines, 3 isomeric ... 1678
β-(3-Pyridyl)-ethylamine, prepn. of ... 2288
Pyrimidine-5-carboxylic acid, synthesis of ... 794
Pyrimidines, sulfanilamido-, as chemotherapeutics, 567; 2-thio-5-keto-4-carbethoxy-1,3-dihydro-, and related compds., 1511; optical properties of 2-sulfanilamido, 2230; N^1-sulfanilylamino-alkyl-, 2340; some new thiazolidino-, of barbituric acid type ... 2709
Pyrogallol trimethyl ether, behavior toward Grignard reagents ... 2085
Pyrolysis. (See also *Isomerization; Paraffins; Rearrangements.*) of 5-membered rings, 896; of acetaldehyde by H_2S, 1707; of amylsodium, 2247; of ketene acetals and orthoesters ... 2525
Pyrrole, prepn. of D derivs. of, 1543; rearrangements of, in oxidation of dipyrrylmethanes ... 2106
Pyrrylmethanes, synthesis of unsym. N-Me di-, 922; substituted di-, 1267; detn. of bridge structure of di-, 2098; rearrangements of pyrrole rings in oxidation of di- ... 2106
Pyrrylmethenes, steric influences on aromaticity of di- ... 593
Pyruvic acid, prepn. of aceto- ... 874

QUANTUM mechanics, orientation of substituents in aromatic mols ... 900
Quassin ... 2883
Quaternary salts, some new ... 2231
Quinaldine, derivs. of 4-amino-6-methoxy- ... 1309
Quinolines, 5-amino- and 1-aminobenzo(f)-, and derivs., 540, (corrn.) 3069; 2,4-disubstituted, derivs., 1357; use of alkoxy ketones in synthesis of, by Pfitzinger reacn ... 1897
Quinones, tetrahydroxy-, from inositol–HNO_3 oxidation, 67; enolate–, reacn., 528; behavior of, related to vitamin E at dropping Hg electrode, 644; Grignard reagent action on pentacene, 1253; prepn. of some peri-hydroxy-, inner complexes, 1649, (corrn.) 3071; alkylation of para, with acyl peroxides ... 2060
Quinonimine, reacns. of retene-, and phenanthra-, with aldehydes, 2567; and with Schiff bases ... 2569
Quinoxalines, synthesis of dihydroxy-, isomeric with "luminol" ... 2644

RADICALS, production by illumination of diacetyl, 717; dipole moment of a, 1179; reactivity of, in carboxylation, 1621; instability of org.-metallic ... 1727
Radiochemistry, effect of strong elec. fields on, decompn. of NH_3 ... 1908
Radioelements, exchange with I, 940; synthesis and oxidation of fumaric acid with C, 948; tracer studies with H, 948; halogen exchange with Br, 1342; tracer studies with H, 2293, 2294; tracer studies with Fe, 2297; exchange expts. with, tracers, 2297; tracer studies with C, 2299; tracer studies with H, 3037; C as tracer in Arndt–Eistert reacn., 3043; tracer studies with, C—exchange between acetic anhydride and NaAc ... 3050
Radio exchange, halogen exchanges in P halides ... 850
Radiography, iodinated org. compds. as contrast media for, diagnoses ... 1436
Raman spectra. (See also *Spectra.*) of some aromatic carbonyl and nitro compds., 1181; of thiophenol solns ... 1230
Rays, Roentgen. (See also *Crystal structure; Spectra.*) diffraction spacings of collagen, 727; study of Ca–Sr alloy series, 1226; significance of the "V," diffraction patterns of starches, 1388; diffraction patterns of Pb oxide mixts., 1637; diffraction

measurements on biotin, 1742; examn. of the isomeric gluconitriles, 1950; measurements on β-lactoglobulin 2504
Reactions. (See also *Arndt–Eistert reaction; Bart reaction; Cannizzaro reaction; Catalysis; Diels–Alder reaction; Friedel–Crafts reaction; Heat of reaction; Menschutkin reaction; Oxidation; Pfitzinger reaction; Reformatsky reaction; Willgerodt's reaction; Wurtz reaction.*) mechanism of "aromatizing" diene, in nitrobenzene, 176; exchange, between simple alkyl iodides and iodide ion, 940; ionic competition in base-exchange, 954; role of neighboring groups in replacement, 2780, 2787, 2791, 2792, 2796; mechanism of cyclization 2894
Reaction velocity. (See also *Catalysis.*) photochemistry of isobutene, 1; sapon. of acetylsalicylic acid, 77; photochem. decompn. of cyclic ketones, 80; oxidation of cellulose by NO_2, 121; production of at. I by peroxides with I^-, 161; of *n*-BuBr with Na salts of phenol, thiophenol and *n*-Bu mercaptan, 226; catalytic reacn. in coal hydrogenation, 230; nuclear substitution of benzene derivs., 297; association of ferric ions, 335; equations for consecutive reacns., 465; of periodate oxidation of 1,2-glycols, 552; of toluene–*t*-BuCl reacn., 648; of Br–vinyl bromide reacn., 704; of Br–allyl chloride reacn., 709; decompn. of NH_3, 745, 751; action of NO on pentaphenylethane, 860; decompn. of dimethyl ether and acetaldehyde, 994; of 2,6-diiodotyrosine formation, 1147; O absorption by dioxolane and methyldioxolane, 1354; reduction of V_2O_5 in concd. acid solns., 1462; effect of Ag on autoxidation, of photographic developers, 1561; kinetic studies on copolymerization, 1675; of thermal reacn. of H and cyanogen, 1880; of *t*-Bu nitrate and benzyl nitrate with water and hydroxyl ion, 1928; allylic conversion of crotyl and methylvinylcarbinyl chlorides, 2157; absorption of O by glutathione, 2282; of carbinol formation of phenolphthalein, 2312; acid catalyzed hydrolysis of Ph substituted aliphatic esters, 2362; of diacetone glucose, diacetone galactose and diacetone sorbose with *p*-toluenesulfonyl chloride in pyridine soln., 2463; of the reacn. $O_3 + Br^- \rightarrow$, 2468; of transformation of hydrazine cyanate into semicarbazide, 2777; Equil. and Kinetics of Gas Reacns. (Pease, book review) 3064
Reactivity, effect of structure on, 297; of *o*-terphenyl 1365
Rearrangement. (See also *Isomerization; Mutarotation.*) use of D as tracer in Claisen, 2302; allylic 2157
Reduction. (See also *Hydrogenation; Polarography.*) bimol., of hindered aldehydes, 30; of vitamin C, 358; enyne and dienyne, 363; electrolytic, of strychnine, 790; electro-, of water, 833; of salts by metals in NH_3 solns., 1187; catalytic, of some carbonyl compds., 1456; of unsatd. hydrocarbons at dropping Hg electrode, 1765, 2365; of iodate and bromate in neutral and basic media, 1970; of salts in liquid NH_3 soln. by metals, 2715; catalytic, of cholesterol α-oxide 2723
Reformatsky reaction, enolization in 2131
Refraction. (See also *Electrons; Rays.*) of free and bonded ions 3023
Refractive index, temp. and compn. coeffs. of, of MeOH–dioxane system, 1207; of normal satd. fatty acids in liquid state, 2739; of cumene 3056
Relativity, Special Theory of (Dingle, book review), 189; Introduction to Theory of (Bergmann, book review) 2517
Renin, prepn. and properties of 561
Resin acids, from pine tar, 871; structure and configuration of podocarpic acid and ferruginol 928
Resins, Technology of Natural (Mantell, Kopf, Curtis, Rogers, book review) 1491
Resonance. (See also *Isomerism; Spectra.*) as basis for classification of dyes, 199; in heterocyclic mols., 1130; in substituted biphenyls, 1350; effect in some substituted benzenes, 2212; in nitroethane and chloronitroparaffins 2829
Resorcinols, vicinal substituted 1313
Retenequinonimine, reacn. with aldehydes, 2567; reacn. with Schiff bases 2569
Retronecine, structure of, and related bases, 2593; proof of primary and secondary hydroxyl groups in 2597
Rhenium compounds, polarographic investigation of 1001, 2182
Rheology. See *Fluidity.*
Rhodanine-oxindoles, keto and mercapto derivs. of cinchoninic acid from 1669
Rhodizonic acid, prepn. of, from inositol–HNO_3 oxidation 67
Riboflavin, estimation in fruits and vegetables 1980
Ricinelaidic acid, geometric configuration of 2253
Ricinoleic acid, geometric configuration of 2253
Riddelliine, structure of 2760
Rigidity, of system polystyrene–xylene 1323
Rings, stereochemistry of hydrogenation of aromatic 1985
Ring compounds. See *Cyclic compounds.*
Rotation, isomers of isopentane due to hindered, 1034; restricted, in aryl amines, 1475; restricted, in aryl olefins 1786, 1791, 1795
Rubber, electrophoretic study of proteins in, latex serum 2628
Rubidium hexafluogermanate, structure of 1233
Rubidium sulfate, activity coeff. of 550

SACCHARIDES, reacns. relating to poly- 1957, 1959
Salicylaldehyde, prepn. of 4-nitro- 825
Salicylic acid, sapon. of acetyl-, 77; rearrangement of O-crotyl-3,5-dichloro-, and related compds., 607; heat of reacn. between methemoglobin and, 1472; basic In salicylates 2234
Salicylyl disulfide, prepn. of acetyl-, and 1486
Sapogenins, 147, 180, 221, 468, 481, 721, 809, 813, 818, 1283, 1653, 1655, 1843, 2581, 3047; structure of the side chain in dihydro-pseudo-, 1655; synthesis of tectorigenin dimethyl ether 2737
Saponification. (See also *Hydrolysis.*) of acetylsalicylic acid 77
Saponins 2581, 3047
Sarsasapogenin, oxidation products of, and keto- 813
Sarsasapogenoic acid, permanganate oxidation of anhydro-, 147; and acid obtained from this reacn. 180, 721
Saururine, and derivs. 968
Schiff bases, reacns. of retene- and phenanthraquinonimine with 2569
Selenic acid, secondary ionization and activity coeffs. of 1054
Selenium, d. of 2679
Selenium compounds, crystal structure of diphenylselenium dichloride, 508; spectrophotometric detn. of dissocn. consts. of diphenyl 2673
Selenium dioxide, oxidation of β-pinene with, 1008; reacn. of β-pinene with, in AcOH 1807
Selenium tetracysteine 1742
Semicarbazide, kinetics of transformation of hydrazine cyanate into, 2777; some allyl nitrophenyl thio-, and their anal. properties 2873
Senecio Riddellii, riddelliine, the alkaloid in 2760
Serological properties, of simple substances 2994, 3003, 3010, 3015
Shellac, nature and constitution of 1902
Silicon compounds, electron diffraction investigation of mol. structures of $SiBr_4$, tribromosilane and dibromidifluorosilane, 62; structure of $(NH_4)_2SiF_6 \cdot NH_4F$, 633; high temp. heat content of $MnSiO_3$. 1769
Silicon tetrachloride, elec. moment of 2076
Silver, contact angles of water against, and Au, 494; potential of AgBr–, electrode in MeOH, 517; molal electrode potential of AgCl–, electrode, 1478; effect of, on autoxidation of photographic developers, 1561; interfacial contact angles between water

and org. liquids on, surfaces, 1530, 1641; adsorption of gases at low temp. and pressure on, 2545; change in potential of AgCl–, electrodes with time ... 3053
Silver acetate, reacn. of some dihalides and acetoxyhalides with, 2780; effect of water on reacn. of, with some butene and cyclohexene derivs. ... 2787
Silver arsenate, parameters in ... 354
Silver bromide, potential of Ag–, electrode in MeOH ... 517
Silver chloride, molal electrode potential of Ag–, electrode in EtOH–H_2O mixts., 1478; change in potential of Ag–, electrodes with time ... 3053
Soaps. (See also *Saponification.*) inhibition of proteolytic action of trypsin by ... 487
Sodium, action of hexamethylacetone, 554; detn. in beidellite membranes, 1814; condensations by ... 2239, 2240, 2242, 2247, 2250, (corrn.) 3073
Sodium acetate, molal vol. of ... 761
Sodium alkyls, action on aliphatic chlorides ... 1783
Sodium carbonate, soly. in fused NaOH ... 1053
Sodium chlorate, some isotherms of the system Na_2CrO_4–H_2O– ... 2746
Sodium chloride, system: $FeCl_3$– ... 241
Sodium chromate, isotherms of the system $NaClO_3$–H_2O– ... 2746
Sodium dichromate, sp. gr. of, solns. ... 175
Sodium hydroxide, conductance of aq. ... 621
Sodium nitrate, system: dioxane–water– ... 2474
Sodium sulfate, isopiestic ratios for Rb and Cs sulfates with ... 550
Solids, elec. properties of, 283, 2389; energy states of ... 1346
Solubility, nephelometric detn. of low, 101; water, of carcinogenic hydrocarbons, 108; of Org. Compds. (Seidell book review), 1014; measurements of some V systems, 2810; effect in benzene ... 2822
Solubility studies ... 2742
Solution, theory of, of high polymers ... 1712
Solvents, photodissocn. in rigid ... 2801
Solvolytic reactions, catalytic effect of electrolytes on, 2498; of *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate ... 2796
D-Sorbitol, 1,2,3,4-dibenzylidene- ... 1493
Sorbose, rate of reacn. of diacetone, with *p*-toluenesulfonyl chloride in pyridine soln. ... 2463
Sorption. (See also *Absorption; Adsorption.*) of CO by metals ... 2610
Specific heat. See *Heat capacity.*
Spectra. (See also *Raman spectra.*) structure and absorption, 72, 76; absorption, of para- and diamagnetic Ni complexes, 181; assocn. of ferric ions with chloride, bromide and hydroxyl ions, 335; infrared, of ammonium halides, 857; formation of conjugated material during bleaching of vegetable oils, 988; ultraviolet absorption, of coronene, 1485; ultraviolet absorption, of nitrogenous heterocycles, 1604; absorption, of the isomeric gluconitriles, 1950; of carotenoids of yellow corn grain, 2603; dissocn. consts. of diphenylselenium compds., 2672; evidence of intermol. transfer of protons, 2684; absorption, of some double salts containing $CoCl_2$, 2748; effects of solvents on absorption, of dyes ... 2923, 2937
Spectrophotometer, studies of complex ions ... 1630
Spectroscopy, Spectrochem. Analysis of Metals and Alloys (Twyman, book review) ... 1745
Spinasterol, isolation of β-, and δ- ... 2488
Spirocyclopentane-1,1′-tetralin ... 1719
Starch, oxidation with HIO_4, 585, 589; "V" X-ray diffraction patterns of, 1388; products from, by action of the amylase of *Bacillus macerans*, 2139; nature of fatty acids associated with, 2144; fractionation of, by selective pptn. with BuOH, 2957; non-carbohydrate substances in cereal, 2954; action of *macerans* enzyme on a component of corn ... 3044
Stearic acids, diastereoisomerism of the 9,10,12-trihydroxy-, 2253; *n* of normal satd. fatty acids from caproic to ... 2739
Stereochemistry, studies in, 325, 2557, 2563; of catalytic hydrogenation ... 1985, 1991, 2003, 2006, 2009, 2014, (corrns. 3071) 2022
Stereoisomers. See *Isomers.*
Steric hindrance, in neopentyl halides, 543; in aliphatic carbonyl compds., 1242, 1247, 1251, 1618, 1619, 2964; Friedel–Crafts acylations of some, alkylbenzenes, 2421; mechanism of reacn. between hindered carbonyl compds. and the Grignard reagent ... 2875
Sterols, 147, 180, 210, 213, 216, 219, 221, 468, 481, 720, 721, 809, 813, 817, 818, 822, 1228, 1273, 1276, 1280, 1282, 1283, 1653, 1655, 1842, 1843, 2089, 2093; prepn. of some Δ-cholestadienes, 140; steryl sulfates in, sepn., 361, 471, 482; prepn. of 3,5,6-cholestantriol-I, 471; location of double bond in clionasterol, 473; 7-benzoxy-, and their use in prepn. of 7-dehydro-, 1177; mono- and di-alkyl ethers of stilboestrol, 1625; structure of fuco-, 1732; 7-dehydrocampesterol, 1900; prepn. of 6-methoxy-*i*-norcholenyldiphenylcarbinol, 2115; chem. behavior of cafe-, 2235; derivs. of estrone, 2235; studies on cholesteryl oxides, 2317; epimeric 7-hydroxycholesterols, 2453; of alfalfa seed oil, 2488; catalytic reduction of cholesterol α-oxide 2723
Steryl sulfates ... 361, 471, 482
Stilbene, α-(9-phenanthryl)-, 69; unsym. cyano-, 885; synthesis of 4,4′-dicyano-, 1482; synthesis of 4,4′-diamidino-, hydrochloride, 1487; sepn. of *cis* and *trans*, by chromatographic brush method, 1919; sym. cyano- ... 2486
Stilbene-2-acetic acid, synthesis of ... 2962
Stilbenediol, an amino ... 2152
Stilboestrol, mono- and di-alkyl ethers of ... 1625
Stoichiometry, Higher Chem. Calcns. (Mee, book review), 1012; Thermochem. Calcns. (Wenner, book review) ... 1237
Strontium, X-ray study of Ca–, alloy series ... 1226
Strontium chloride, activity coeffs. of ... 244
Strontium nitrate, system: $Ca(NO_3)_2$–H_2O– ... 1301
Strychnine, electrolytic reduction of ... 790
Styrene, rigidities of system xylene–poly-, 1323; viscosities of system xylene–poly-, 1330; vapor pressure of, 2501; polymerization of, catalyzed by *p*-bromobenzenediazonium hydroxide ... 2508
β-Styrylacetaldehyde, cyclization of ... 1007
γ,γ′-Suberodilactone, *dl*- and *meso*-γ,γ′-diphenyl- ... 2727
Succinic acid, Ca α-tocopheryl succinate ... 1084
N-Succinyl compounds, N-succinyl-1-Me-amino-2-Me-naphthalene and N-succinyl-1-Me-amino-4-chloro-2-Me-naphthalene, 1475; prepn. of N-succinyl-N-Et-3-bromomesidine and 5-alkoxy-4-N-succinyl-4-amino-1,3-dimethylbenzenes, (corrn.) ... 3069
Sucrose. (See also *Sugars.*) bacterial synthesis of dextran from, 1959; invertase activity in, hydrolysis ... 2577
Sugars, *d*-glucopyranose 1-phosphate, 23; dibenzylidene dulcitols, 132, 136, 137; polymorphism of *d*-galactose diethylmercaptal pentaacetate, 183; mutarotation of glucose in aq. MeOH, 236; D-manno-D-gala-heptose and derivs., 247; transformation of tetramethylglucoseen-1,2 into 5-(methoxymethyl)-2-furaldehyde, 265; constitution of arabo-galactan, 302, (corrn. 3069), 1507, 2838; enzymic hydrolysis of alkyl β-D-glucosides, 369; almond emulsin and populin action on Ph 2,4,6-Me_3-β-D-glucoside, 374; prepn. and rearrangement of phenylglycosides, 690; anhydro deriv. of D-mannosan<1,5>β<1,6>, 925; structure of diacetone-L-fucitol, 982; structure of dimethylene dulcitol, 986; mutarotation of α-D-glucose, 1010; Phys. and Chem. Methods of, Analysis (Browne, Zerban, book review), 1014; new glucose and gentiobiose derivs., 1110; synthesis of cellobiose, 1289; *l*-glycidol, 1291; sulfanilyl-2-amino-α-D-glucose, 1371; alkyl glucosides, 1482; D-mannosan

<1,5>β<1,6> from β-phenyl-D-mannoside, 1483; lactose synthesis, 1490; 1,2,3,4-dibenzylidene-D-sorbitol, 1493; azoyl derivs., 1501; L-glucoheptulose, 1606, 1609; configuration of aldonic acids, 1612; 1,3:4,6-di-*o*-nitrobenzylidenedulcitol, 1614; temp. effect on Hudson's isorotation rules, 1626; mol. wts. of Schardinger α- and β-dextrins, 1651; action of diazomethane on acyclic, derivs., 1701; *d*-allulose, 1740; syntheses of epi-lactose and lactose, 1852; fractionation of partially methylated glucosides, 1957; bacterial synthesis of dextran from sucrose, 1959; O-pentaacetyl-*d*-gluconates of polyhydric alcs. and cellulose, 2026, (corrn.) 3071; products obtained from starch by action of the amylase of *Bacillus macerans*, 2139; action of diazomethane on acyclic, derivs., 2329; structure of dextrins isolated from corn sirup, 2331; studies on D-galactosan<1,5>β<1,6>, 2435; rates of reacn. of diacetone-glucose, -galactose and -sorbose with *p*-toluenesulfonyl chloride in pyridine soln., 2463; a new fructosan isolated from *Yucca mohavensis*, Sarg., 2501; invertase activity in, hydrolysis, 2577; prepn. of *d*-fructose-1,6-diphosphate, 2722; synthesis of 5-D-glucosido-D-arabinose, 2731; stability of β-methylmaltoside toward hot alkali.. 2871

Sulfadiazine, optical properties of..... 2230

Sulfanilamide, soly. of..... 2464

Sulfanilamide derivatives, 2763; of D-glucose, 1371; of N bases from Calif. petroleum, 1499; certain naphthylidene, 2230; N–C–N system in N^1 heterocyclic, 2532; heterocycles as chemotherapeutics, 2902; theory of relation of structure to activity of..... 2905

Sulfanilamidopyrimidines, as chemotherapeutics, 567; optical properties of 2-..... 2230

Sulfanilylamidine..... 2763

N^1-Sulfanilylamino-alkyl-pyrimidines..... 2340

Sulfanilylcyanamide, and related compds..... 1682

Sulfanilyl-*l*-cystine, N,N′-di-acetyl-, and N,N′-di-.. 1488

Sulfobenzoic acids, identification of *o*- and *p*-, as their S-benzylthiuronium salts..... 3040

Sulfonamides, dicarboxylic acid derivs. of, 1572; substituted, 2516; 4-nitrodiphenyl ether-4′-..... 3056

2-Sulfonamido-5-aminopyridines, substituted..... 1695

p-Sulfonamidophenylarsonic acid, derivs. of..... 1287

Sulfonic acid, antihemorrhagic activity of sulfonated 2-Me-naphthalenes..... 1096

Sulfonyl chloride, 4-nitrodiphenyl ether-4′-..... 3056

Sulfonyl urea, prepn. of *p*-aminobenzene-..... 2225

Sulfur, dipole moment and resonance in heterocyclic mols. containing, 1130; studies, 1165; The Stone that Burns (Haynes, book review), 2521; formation of insol., in presence of gases other than SO_2..... 3041

Sulfur compounds. (See also *Thio compounds.*) 2-thio-5-keto-4-carbethoxy-1,3-dihydropyrimidine, 1511; synthesis of *p*-hydroxyphenyl amyl sulfide. 2322

Sulfur dioxide, non-peroxide catalysts for olefin–, reacn..... 1229

Sulfuric acid, action on 2-butanol, 1025; apparent mol. vols. of aq., solns..... 1878

Supercooling, of chlorobutanes and chloropentanes.. 737

Surfaces. (See also *Adsorption; Catalysis; Films.*) reproducible contact angles on reproducible metal, 494, 1530, 1641; adsorption and energy changes at crystalline solid..... 2383

Surface tension, of aq. solns. of dodecylamine acetate, 2067; relative, of KCl solns. by a differential bubble pressure method, 2476; of aliphatic nitroparaffins, 2540; of electrolyte solns. as function of the concn..... 2744

Sympathomimetic amines, color reacns. of, with diazonium compds..... 1318

Systems, dineric distribution in liquid ternary, 347; ternary, involving cyclohexane, water, and isopropyl and *n*-propyl alcs..... 1886

D-TALOSAN<1,5>β<1,6>, 3,4-anhydro-, derived from D-mannosan<1,5>β<1,6>..... 925

Tanning, mechanical influence on, 868; chem. constitution and the, effect..... 2274

Tannins, constitution of natural..... 1101

Tantalum tribromide..... 1740

Tautomerism, character of imidazole ring..... 1167

Tectorigenin dimethyl ether, synthesis of..... 2737

Temperature. (See also *Equation of state; Heat.*) Measurement (Weber, book review), 475; heat capacities of red and yellow Pb monoxides at high, 617; high, vapor pressures of satd. salt solns., 841; effect of, on validity of Hudson's rules of isorotation, 1626; coeff. of conductance of KCl solns..... 2517

Ternary systems. See *Systems.*

Terpenes, phys. properties of..... 2978

o-Terphenyl, chemistry of.....1365, 2639

Tetralin, spirocyclopentane-1,1′-, 1719; reacn. of furoic acid with..... 2601

Tetronic acid, dissocn. const., dipole moment and structure of α-nitro-..... 1948

Thallium salts, oxidation–reduction potentials of thallous–thallic salts—formation of chlorothallate complex ions..... 1644

Thermochemistry, Calcns. (Wenner, book review).. 1237

Thermodynamics. (See also *Entropy; Heat of Reaction.*) of N at high pressures, 44; of the dithionite ion, 398; of KCl solns., 513; of Sn–Bi system, 1392; magnetism and 3rd law of, 1535; theory of electrocapillarity, 1548; Treatise on Phys. Chemistry. Atomistics and (Taylor, Glasstone, book review), 1743; The Nature of (Bridgman, book review)..... 2524

Thiamin. See "B" and "B_1" under *Vitamins.*

Thiazine, f. p. of pheno-..... 461

Thiazoles, 2-phthalimido-Me-4-N-diethylamino-Me-, 90; some quaternary salts containing aryloxyethyl and aryloxypropyl groups, 2234; researches on.....2709, 2712

Thiazolines, phenylmercapto-..... 2487

α-Thienylaminoalkanes..... 477

Thioamides, reacn. between, and primary amines... 2722

Thiocyanic acid, reacn. of ferric ion with orthophosphate in acid soln. with, ester as indicator for ferric ions, 291; As, Sb, and P salts of..... 1757

Thiodiglycol, some ester of..... 908

Thiophene, condensations with..... 451

Thiophenol, kinetics of *n*-BuBr–, reacn., 226; assocn. effects in Raman spectra of, solns..... 1230

Thiophosphoryl triamide, prepn. of..... 1553

Thiopyran, addn. compds. of tetrahydro-..... 1232

Thiosemicarbazides, some allyl nitrophenyl, and their anal. properties..... 2873

Thiourea, elec. moment of, 1944, (corrn.)..... 3071

Thiuronium chloride, identification of alcs. and alkyl H sulfates with S-benzyl-..... 1978

Thiuronium salts, S-benzyl-, of octadecenoic acids, 1061; identification of *o*- and *p*-sulfobenzoic acids as their S-benzyl-..... 3040

Thorium chloride octahydrate, purification of..... 1009

Thorium oxide, photoactivation of adsorption of H on..... 1731

Thymol, some quaternary salts containing aryloxyethyl and aryloxypropyl groups..... 2234

Thyronine, synthesis of 3′,5′-diiodo-..... 1070

Tigogenone, bio-reduction of 4-dehydro-..... 818

Tin, thermodynamics of Bi–, system..... 1392

Tin chloride, elec. moment of $SnCl_4$..... 2076

Tin compounds, tri-*o*-tolyl-, 1727; prepn. of K oxalatostannate, 1759; complex dioxalatothiometastannates..... 1762

Tin oxide, soly. of SnO in $HClO_4$..... 719

Titanium dioxide, adsorption of Co ions on..... 2820

Titration. (See also *Acidity; Analysis.*) potentiometric, of dibasic acids..... 1153

Tobacco mosaic virus, concn. and purification of, by

Sharples super-centrifuge, 1804; basic amino acids in strains of ... 2734
Tocols, the 3 dimethylethyl- ... 445
α-Tocopheramine, a new vitamin E factor ... 1082
Tocopherols, 3,5-dinitrobenzazide in prepn. of, 433; synthesis of α-, 440; behavior of, at dropping Hg electrode, 447; amperometric titration of α-, with auric chloride, 646; crystalline natural, acetate ... 1487
α-Tocopheryl succinate, Ca ... 1084
Toluene, kinetics of *t*-BuCl–, reacn., 648; heat capacity of ... 2375
Toluenesulfonate, solvolysis of *trans*-2-acetoxycyclohexyl-*p*-, 2796; 4-, of the nitro-4-phenylphenols ... 3057
p-Toluenesulfonyl chloride, rate of reacn. of diacetone -glucose, -galactose and -sorbose with, in pyridine soln ... 2463
p-Toluidine, reacn. of BCl_3 with ... 1584
o-Tolylmethane, tri- ... 1837
Tolyltin, tri-*o*- ... 1727
Tosyl. See *p-Toluenesulfonate.*
Toxic principles, of poison ivy ... 3058
Transference numbers. See *Ions,* electrolytic; and such headings as *Chlorides; Hydrogen ion; Sulfates.*
Triazene, reacns. between *sym*-diphenyl-, and Hg (II) salts ... 935
Trillium erectum, new sapogenins from ... 2581
Trillogenin, a new sapogenin ... 2581
Trimethylene esters, chain structure of ... 154
Tripterine, identity of ... 182
Triptycene ... 2649
Triterpenoid sapogenins, some color reacns. of ... 3047
Tritium oxide, H exchange with ... 2503
Trypsin, inhibition of, proteolysis by soaps ... 487
Tungsten compounds, catalyst from, in oxidation of naphthalene ... 2917
Tyrosinase, factors influencing the cresolase activity of ... 2344
Tyrosine, sp. rotation of *l*-, 724; kinetics and mechanism of 2,6-diiodo-, formation ... 1147

UNSATURATED compounds, hydration of ... 1117, 1122, 1953
Uracil, action of ketene on 5,5-dibromoxyhydro- ... 306
Urea, effect on electrophoretic patterns of serum proteins, 1090; hydantoins from reacn. of phenylglyoxal and, 1434; dipole moment and structure of, and thio-, 1944, (corrn.) ... 3071
Urea, prepn. of *p*-aminobenzenesulfonyl, 2225; some unsym. disubstituted, 2233; synthesis of aminobenzoylene- ... 2644
Ureido derivatives, cyclization of, of iminodibasic acids ... 1686
Urethan, optically active Ph-, anesthetics, 1112; acidic and basic catalysis in, formation ... 2229

n-**V**ALERIC acid, prepn. of α,γ-diketo- ... 874
Vanadium, heterogeneous equil. on tetravalent, sulfate solns ... 2810
Vanadium pentoxide, reduction of, in concd. acid solns ... 1462
Vanillin, from lignin materials ... 1429
Vapor phase, esterification equil ... 36
Vapor pressures, of Me mercaptan, 165; of dimethyl sulfide, 169; of isobutene, 546; high temp., of satd. salt solns., 841; partial, of HCl from org. solvents, 951; hysteresis of liquid isopentane, 1034; of isopentane, 1039, (corrn.) 3069; temp.–, relations of $Mn(NO_3)_2$–H_2O system, 1445; activity coeffs. of bivalent metal nitrates from isopiestic, measurements, 1469; of indene, styrene and dicyclopentadiene, 2501; of phenylhydrazine as a function of temp., 2776; of phenothiazine ... 3035
Vapors, heat capacity of org ... 1224, 2372, 2375
Vasopressor amines, optically active ... 1449
Vegetable fats, isolation of new antioxidants from ... 2337
Veratrole series, studies in ... 2983
2-Vinylacetylene, identity of pirylene with 1-Me- ... 2693
Vinyl alcohols ... 2886, 2888
t-Vinyl amines, basicity studies of, 2588 (corrn.) ... 3073
Vinyl bromide, reacn. between Br and ... 704
Vinylcarbinyl chloride, conversion of Me-, to acetate and Et ether ... 2157
Vinyl chloride, viscosities of solns. of poly-, 277; elec. properties of plasticized poly-, 283; structure of copolymers of ... 2356
3-Vinyl-4-methylpyridine, synthesis of, 1093, (corrn.) ... 3071
Vinylnaphthalene, nitro- ... 1739
9-Vinylphenanthrenes ... 69
Vinyl polymers, structure of ... 92
Virial coefficients, 2nd, of gaseous mixts ... 2816
Virus, centrifugal concn. of tobacco, prepns., 1804; basic amino acids in strains of tobacco mosaic ... 2734
Viscosity, of polyvinyl chloride solns., 277; temp. and compn. coeffs. of, of MeOH–dioxane system, 1207; of system polystyrene–xylene, 1330; temp. and solvent effects on, of high polymers, 1557; of *cis*- and *trans*-decahydronaphthalene, 1912; of dil. solns. of long-chain mols ... 2716
Vitamins. (See also *Biotin; Carotene.*) chemistry of, E, 433, 435, 440, 445, 447, 644, 646, 1082, 1084; oxidation and reduction of, C, 358; 7-dehydrocampesterol, a new pro-, D, 1900; cocarboxylase and related esters, 2279; crystalline aliphatic esters of, A, 2407; crystalline, A, 2411; Chemistry and Physiol. of the (Rosenberg, book review), 2522; water-soluble compds. with antihemorrhagic activity ... 2657
Vitrification, of chlorobutanes and chloropentanes ... 737
Volume. See *Molecular volume.*

WALDEN inversion, malonic ester synthesis and ... 2606
Water, contact angles of, again Ag and Au, 494; anomalous electroreduction of, at dropping Hg electrode, 833; effect on photochem. bromination of acetophenone, 887; vapor pressures of, solns. at high temps., 841; interfacial contact angles between, and org. liquids on Ag and Au surfaces, 1530, 1641; effect of, on reacn. of AgAc with butene and cyclohexene derivs ... 2787
Willgerodt's reaction, new modification of ... 3051
Wurtz reaction, action of Na alkyls on aliphatic chlorides and relation to, 1783; products from, and the mechanism of their formation, 2039, (corrn.) 3071; general theory of ... 2239, 2240, 2242

XANTHINS, interconversion of fuco- ... 1235
Xanthol, absorption spectra of neocrypto-, and 2 neozea-, isomers ... 2603
Xylene, rigidities and viscosities of system polystyrene–, 1323, 1330; alkylation of *m*- ... 1662
2,6-Xylil, reacns. of ... 2152
Xylitol, crystalline ... 1739
o-Xyloquinone, dibromo-, and Na malonic ester ... 528

YEAST, prepn. of *d*-fructose-1,6-diphosphate by means of baker's ... 2722
Ytterbium, sepn. of, from accompanying rare earths by means of its amalgam, 1009; potential of the ytterbic–ytterbous ion electrode, 1133, (corrn.) ... 3071
Yucca mohavensis, Sarg., a new fructosan isolated from ... 2501

ZANTHOXYLUM *clava-herculis,* insecticidal principle in bark of ... 187
Zinc iodate, soly. in dioxane–water mixts ... 2305
Zirconia, time of set of hydrogel of ... 110